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Contents

389 Unpublished data on the founder of Romanian Neurosurgery – Professor Dumitru Bagdasar – 75 years from his passing to eternity

Horia Berceanu, Stanislav Groppa, Horia Pleș

403 T- configuration stent assisted coiling treatment of a complex wide-necked basilar tip aneurysm

A. Chiriac, N. Dobrin, Georgiana Ion, Z. Faiyad, A. Iencean, I. Poeata

408 Clinicopathological features, imaging characteristics and surgical management in a novel tumour entity - aggressive meningiomas

G. Popescu, Francesca Paslaru, A.C. Paslaru, M. Apostol, M.C. Zaharia, T. Corneliu, M. Mitrica, M. Popescu, R.M. Gorgan

412 The importance of Nuclear Magnetic Resonance (MRI) in the diagnosis of cerebral cavernomas. Case presentation

Dan Bentia, Andrei Alexandru Marinescu, Florin Papagheorghe, Georgeta Popa, Alexandru Vlad Ciurea

417 Giant, primary, hydatid cyst of the gluteal region. Case report

G. Iacob, R. Rosiu, Mihaela Luchian, G. Simion

422 Important controversies in lumbar spine surgery: which patients benefit from lumbar spinal fusion and who should be fused? Literature review

F. Urian, G. Iacob, A.V. Ciurea

428 Imaging characteristics, histopathological features and surgical considerations regarding aggressive meningiomas. Case series and review of the literature

G. Popescu, Francesca Paslaru, A.C. Paslaru, M. Apostol, M.C. Zaharia, T. Corneliu, M. Mitrica, M. Popescu, R.M. Gorgan

434 Postoperative lumbar spondylodiscitis. A systematic review

Arsene Anamaria-Alexandra, Iacob Gabriel, Ciurea Alexandru Vlad

444 Postoperative complications in endoscopic frontal transcortical surgery of lateral and third ventricle tumours. Speech disorders

Orest I. Palamar, Andriy P. Huk, Dmytro S. Teslenko, Ruslan V. Aksyonov, Dmytro I. Okonskyi, Nazarii V. Lazko

452 The complementary multimodal treatment of recalcitrant cerebral aneurysms. Two centres experience

Mohamed Adel Deniwar, Mohamed Kassem, Ashraf Ezzeldin, Jafar J. Jafar

457 Outcome of patients undergoing posterior spine fixation and decompression for posttraumatic thoracolumbar spine fractures and the factors predicting it

Geo Paul K. Jose, Tinu Ravi Abraham, P.K. Balakrishnan, Irphan Muhammed P.S, Haris T.P., Vala Parth Prakashbhai

468 A very rare fact occurring after V/P shunt in the surgical treatment of Pseudotumor Serebri Syndrome. Liver subcapsular pseudocysts

Mehmet Akif Ambarcioglu, I. Burak Atci, Okan Türk, Veysel Antar, Nail Demirel, Nuriye Güzin Özdemir, Emre Eğilmez, A. Can Karaoğlu, Özgur Baran

472 Ferrans and powers quality of life index for spinal cord injury: to adapt in local language

T.V.S. Divyalasya, A. Kiran Kumar, N.R. Sahana Bhat, M. Jahnavi, Ranjan Kumar Jena, Ram Lakhan, B.V. Subrahmanyam, Amit Agrawal

475 Reperfusion injury in brain stroke

Sabrina Rahman, Moshiur Rahman

478 Surgical smoke, neurosurgical practice and coronavirus: a few words of caution

Adesh Shrivastava, Noor-Ul-Huda Maria, Rakesh Mishra, William Florez-Perdomo, Amit Agrawal, Luis Rafael Moscote-Salazar

483 Basic considerations on growth hormone deficiency in traumatic brain injury

Ivan David Lozada-Martinez, Michael Gregorio Ortega-Sierra, María Milagros Daza-Vega, Leidy Natalia Cárdenas-Hormiga, Jorge Eduardo Contreras-Saldarriaga, Carlos Eduardo Garcia-Moron, Juan Santiago Serna-Trejos, Jorge Alberto Nuñez-Gamez, Daniela Gómez-Murillo, Mary Elena Rosero-Burgos, Luis Rafael Moscote-Salazar

490 Schwannoma of the digital nerve. A rare case report

Vuk Aleksić, Jovana Prelić, Matija Radojević, Radmila Ćulafić

493 Endoscopic third ventriculostomy versus ventriculoperitoneal shunt for treatment of hydrocephalus in infants in a tribal population in India. A single centre experience

Patel Pratik Bipinbhai, Lodha Krishna Govind, Jaiswal Gaurav, Gupta Tarun Kumar, Yadav Kaushal, Rai Abhinav Kumar

499 Cerebral amyloid angiopathy: early presentation in a patient with prior neurosurgical interventions. Case report

Alec Clark, Arnav Barpujari, Brandon Lucke-Wold, Ken Porche, Dimitri Laurent, Matthew Koch, Matthew Decker

503 Correlation of neutrophil lymphocyte ratio to clinical outcomes based on 6 months surveillance on traumatic brain injury patients at Haji Adam Malik General Hospital (2018-2020)

Nindi Lizen, Ridha Dharmajaya, Abdul Gofar Sastrodiningrat, Mahyudanil

508 Congenital sphenoid wing defect with lateral angular dermoid presenting with CSF leak after orbital surgery

Mohammad Sarwar, Laxminarayan Tripathy, Ejaz Ahmed Bari

511 Postoperative complications in endoscopic frontal transcortical surgery of lateral and third ventricle tumours. Speech disorders

Orest I. Palamar, Andriy P. Huk, Dmytro S. Teslenko, Ruslan V. Aksyonov, Dmytro I. Okonskyi, Nazarii V. Lazko

518 Recent descriptions on physiological concepts of the pineal gland: what's new?

Dany Leonardo Contreras-De La Hoz, Germán Camilo Viracacha-López, Julieth Vivian Sarmiento-Palma, Loraine Llerena-Gutierrez, Julio César Mantilla-Pardo, Guillermo Andre Blanco-Fernandez, Criss Madeley Millan-Puerto, Rodrigo Alberto Caicedo-Lozada, Anderson Fabian Guerrero-Ceron, David Eduardo Espinosa-Ortiz, Ivan David Lozada Martinez, Luis Rafael Moscote-Salazar

526 Aneurysmal subarachnoid haemorrhage in the context of a patient with traumatic brain injury

William Florez-Perdomo, Laura Acevedo-Aguilar, Laura Mass-Hernández, Michael Gregorio Ortega-Sierra, Jhoyner Alberto Jiménez-Filigrana, Luis Jose Payares-Celins, Roberto Andrés Ramos-Cordoba, Jorge Alberto Nuñez-Gamez

531 Multimodal neurological monitoring in neurotrauma. Theoretical considerations for a practical approach

Randy Reina-Rivero, Maria Manuela Rodriguez-Gutierrez, Michael Gregorio Ortega-Sierra, Diego Fernando Jamioy-Cabrera, Juan Felipe Villegas-Lora, Daniela Margoth Caycedo-Montiel, Juan David Balanta-Perea, Richard Adrian Vergara-Trujillo, Fernando Bellera, Yelson Alejandro Picón-Jaimes

538 Tumefactive multiple sclerosis. A rare but serious variable in multiple sclerosis

Michael Gregorio Ortega-Sierra, Raul David Delgado-Marrugo, Cristian Camilo Campo-Bedoya, Geraldine Marín-Pérez, Rhonald Gómez-Caballero, Bryan D. Hernández-Nieto, Gabriel Fernando Gutiérrez-Castillo, John Fredys Bello-Cordero, Mónica Alejandra Torres-Báez, Rafael Ricardo Ramirez-Morales, Ivan David Lozada-Martinez, Luis Rafael Moscote-Salazar

544 Guidelines for authors

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Unpublished data on the founder of Romanian Neurosurgery – Professor Dumitru Bagdasar – 75 years from his passing to eternity

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education and training in neurology (Gh. Marinescu, D. Noica), surgery and neurosurgery (M. Butoianu, W. Cushing), reports of the first neurosurgical procedures, connections with leading medical experts (N. Paulescu, I. T. Niculescu, P. Bailey, Ch. Frazier, J. F. Fulton, Th. de Martel, W. Freeman etc.), the first professor of neurosurgery in Romania (1945)

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ABSTRACT

Dumitru Bagdasar, who is indisputably considered as the founder of neurosurgery on the Romanian territory during the interwar period, was born in Roșiești, the former Fălciu County, in 1893. In 1913, after having completed his primary and secondary education, he enrolled at the Faculty of Medicine of Bucharest and, in the summer of 1916, at the end of his third university year, he transferred to the Medical Military Institute. From 1916 to 1918, **D. Bagdasar** dealt with the whole array of illnesses arising from the world conflict, including firearm-related injuries to the nervous system. After the war, he was transferred to the Neurology Clinic of the Colentina Hospital where, under the supervision of Professor **Gheorghe Marinescu**, he elaborated and completed his doctoral dissertation entitled: *Contribuțiuni la studiul Sindromului Parkinsonian-postencefalitic* (Contributions to the Study of Postencephalitic Parkinsonism), which he defended in 1922. From 1922 to 1926, at the Military Hospital of Bucharest, he completed his neurology internship under the guidance of the eminent neurologist Dumitru Noica and his initiation to surgery under Professor Mihail Butoianu. In 1927, after giving up his military contract, he was transferred to the Jimbolia Hospital by the Ministry of Health to work as an attending neuropsychiatrist. At the end of the same year, with a recommendation from Professor **Nicolae Paulescu**, he earned a neurosurgery specialisation scholarship under Professor **Harvey Cushing** in Boston. There, under the guidance of Professor **Cushing** and Doctor **Bailey**, he wrote two papers: *Le traitement Chirurgical des gommes cérébrales* and *Intracranial Chordoblastoma*, which were published in presti-

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gious medical journals. In 1929, he returned to the Jimbolia Hospital where, in 1930, he performed his first neurosurgical procedures. At the end of 1931, he transferred to the Cernăuți Hospital, again as a neuropsychiatrist, and in the following two years he performed a number of 149 operations on the central nervous system, which are described in the surgical reports written by Doctor **Bagdasar** himself. In 1934, he transferred to Bucharest, where he performed neurosurgical procedures in two hospitals (Emergency Hospital and Central Hospital) and, at the end of the same year, he was tenured as an attending neurosurgeon at the Central Hospital, following a contest organised by the Ministry of Health. From 1935, he worked primarily in the aforementioned hospital but he also performed operations in other hospitals (Emergency, Colțea, Military etc.). Alongside his surgical activity, he was also interested in the histopathology of the operated tumours, he wrote scientific papers based on his own case reports, participated in medical congresses (Bucharest, Bern, Chisinau etc.) and became interested in the social-political issues of the time..., joining the Communist Party in 1943. In 1940, just before the outburst of World War II, he wrote *Acute craniocerebral trauma* and published it in *Probleme de Medicină de Război*u (War Medicine Issues). During the war, due to his over a decade long experience in neurosurgical procedures, he assisted the injured (both militaries and civilians), while also managing common neurosurgical cases in Romania and the adjacent countries and even in Palestine, as a member of the so-called *"golden team"* (**C. Arseni, I. Ionescu, Irina Ogrezeanu-Ionescu**). In 1945, he was appointed Minister of Health and at the end of the same year, he became the first professor of neurosurgery in Romania. Unfortunately, his life came to an abrupt end on 16 July 1946 because of a metastatic brain tumour probably caused by primary lung cancer.

Dumitru Bagdasar (1893-1946) was born in Roșiești, the former Fălciu County, currently Vaslui County, on 17 December 1893, in a family of peasants of Armenian origin[1], being the fourth of twelve children. He attended primary school in the nearby town of Indricii de Sus, having an exceptional schoolteacher, Gh. Balaur and completing all five primary school years as best pupil of his class. Then, he enrolled to the renowned secondary school „Gheorghe Roșca Codreanu" of Bârlad, where he graduated from the humanities program in 1913. Given the difficult financial situation of his family, which had been economically destabilized by his mother's death (while giving birth to her thirteenth child, during her son's high school years), when he enrolled at the Faculty of Medicine of Bucharest, Dumitru Bagdasar also took a position as an educator at the Sfântul Sava High School, thus having free meals and accommodation. He managed to pay his university fees and other expenses (books, lectures and so on) through tutoring. This complex situation (being concomitantly a student, an employee and a tutor) went on for his first two university years – from 1913 to 1915 – without negative consequences on his university exam results. During his 3rd year of medical school, he gave up his educator job and started to work at the Zerlendi Sanatorium (a tuberculosis sanatorium) as an intern – according to A. Kreindler – probably a voluntary intern whose job was to perform the patients' sputum tests[2] from 7:30 PM to 10:30 PM, against meals, accommodation and the monthly wage of 5 lei. At the end of his 3rd year of studies, as Romania was preparing to enter into World War I, due to the tempting conditions offered by the Medical Military Institute, he accepted to be transferred to that institution, where he was given the rank of sublieutenant and a corresponding salary which enabled him to continue his medical education without the financial concerns he had previously had. At the same time, he was enlisted in the 41st Regiment of Infantry (Cf. Dr. V. Lavrov, *Oameni și fapte din istoria medicinei militare românești*, vol. I, Editura Pro Transilvania, 2005, p. 401, where it is stated that he was enlisted in the 66th Regiment of Infantry, the 17th Division, as an ambulance military doctor), which gave him the opportunity to become familiar with the whole array of illnesses arising from the world conflict, in particular, injuries caused by firearms, chemical substances or infective diseases, including disorders of the central and peripheral nervous systems. Except for a period when he suffered from exanthematous typhus and a period of reformation of the regiment in 1917, Sublieutenant Dumitru Bagdasar participated in all the military war campaigns, from August 1916 until his demobilisation in November 1918 (Cf. Dr. V. Lavrov, Ibidem, *"For his devotion and self-sacrifice proven during the war, he was decorated with the* 1916-1918 Commemorative Cross*, the* Romanian Crown Order as a knight *and the* Cross of Medical Merit 2nd class"). It should be noted that, in June 1918, during his military leave, he took all his 4th year examinations at the Faculty of Medicine of Iași, with excellent results[3].

After the war, in 1921, he wrote two papers in cooperation with Doctor Dem Paulian, entitled *A propos du traitement du Parkinsonisme (Considerație asupra tratamentului în Parkinsonism)* (On Parkinsonism Treatment) published in the Revue

Neurologique, June 1921, 703[4] and *Chist hidatic al creierului* (Hydatid Brain Cyst), published in Spitalul, July 1921, 55[5]. From 1921 to 1922, he attended the Neurology Clinic run by Professor Gheorghe Marinescu, where he was transferred from the Medical Military Institute for specialisation[6]. In 1922, he was awarded the Doctor of Medicine and Surgery degree, upon completion of his dissertation entitled: *Contribuțiuni la studiul Sindromului Parkinsonian-postencefalitic* (Contributions to the Study of Postencephalitic Parkinsonism), coordinated by Professor Gheorghe Marinescu[4].

After defending his doctoral dissertation in 1922, Doctor Bagdasar did his internship in neurology and psychiatry at the Regina Elisabeta Military Hospital of Bucharest, where his mentor was the renowned physician Dr Dumitru Noica. Under his guidance, from 1922 to 1927, he wrote 12 scientific papers on neurology (which are listed and commented in his work *Titluri, lucrări științifice*, Bucharest 1934[7]).

At the same time, during his neurology internship, the professional collaboration between the two doctors, D. Noica and D. Bagdasar, doubled by a personal/spiritual bond between master and disciple, was decisive for Dr Bagdasar's path in neurosurgery. At that time, Dr Bagdasar was interested in gathering sound knowledge on the histopathology of the nervous system, working in the laboratory of pathologic anatomy led by professor Șt. Beznea, alongside the latter's assistant, Dr I. T. Niculescu, who was back from his specialisation in histology in Paris; their fellowship soon turned into a strong friendship. After discovering his vocation for neurosurgery that he later developed into a profession, Dr Dumitru Bagdasar started to work on growing his education in surgery (which had started during the war, from 1916 to 1918) at the Military Hospital, under the guidance of General Mihail Butoianu[8]. Alongside his activity in neurology, from 1923 to 1926 he worked in the surgery unit of the same hospital, which was led by Professor Butoianu, and where he was initiated to general surgery. This surgical practice was, undoubtedly, the foundation of his training in neurosurgery, knowing that Professor Butoianu was one of the pioneers of neurological surgery in Romania[9].

The year 1927 has a triple importance for Doctor Dumitru Bagdasar, being the year when he married Florica Ciumetti (of Armenian origin), was assigned the position of attending neuropsychiatrist at the Hospital for Mental and Nervous Diseases of Jimbolia (after he resigned from the army) and, following the recommendation of Professor Nicolae Paulescu, he earned a 2-year scholarship from the Ministry to Health to specialise in neurosurgery at Professor Harvey Cushing's clinic within the Peter Bent Brigham Hospital of Boston. It should also be noted that a beautiful professional and personal relationship developed between Professor Paulescu and Doctor Dumitru Bagdasar, which grew closer and closer in time, from the period of Bagdasar's medical studies and until the premature end of Professor Paulescu (see the correspondence between master and disciple)[10]. Regarding this beautiful friendship in the Romanian medical environment of the early 20th century, it should also be noted that the same kind of relationship existed between two great medical scientists born in the same year (1869) and, though living on two different continents (North America and Europe), connected by mutual esteem due to the experimental research on the subtemporal removal of the hypophysis in dogs, which had been successfully performed by Nicolae Paulescu ever since 11 March 1903 when, with the help of Doctor Ion Bălăcescu, *he performed the first hypophysectomy with temporal access*. The procedure involved the following *sequence*: temporal drilling, opening the dura mater, gently lifting the temporal lobe to expose the Sella turcica, from which the surgeon: *„could pick the hypophysis like a fruit from a tree"* (cf. Nicolae Paulescu). This technique was first described in the Journal de Physiologie et de pathologie générale of 1907[11] and then it was detailed in the monography of hypophysis physiology, also published in Paris in 1908[12]. The method was superior to all the other existing methods and its advantage was that it allowed to avoid the dreaded complications of the previous attempts (trauma, haemorrhage and meningitis), since it was accompanied by histological checks for the absence of residual gland tissue in the Sella turcica and provided all certainties for its application in humans. That is why Harvey Cushing, when talking about the Romanian physiologist's method in 1910, stated that it was *"...by far the most important contribution to the subject matter"*[13] and adopted *"the method in his ground-breaking neurosurgical work that made him famous"*[14]. The correspondence between Cushing and Paulescu regarding Bagdasar goes back to 1926, following a letter written in German from

Bagdasar to the illustrious American neurosurgeon. In Cushing's positive response to Bagdasar on 21 August 1926 send to the address of the Military Hospital of Bucharest, the former promised he would give the applicant *"an Arbeit"* and would have him work in the clinic; at the same time, he thought he could arrange for him to have his meals at the hospital but he did not have funds to provide him with accommodation at the clinic. Professor Cushing concluded his letter as follows: *"I wrote to Professor Paulescu to see if you might want to apply for a Rockefeller scholarship. In case you do, it would be better if you asked him to write to Mr Clifford Wells, the scholarship advisor, Rockefeller Foundation, 61 Broadway, New York City, stating that he wants you to come here to work with me for a year and they will probably accept you as one of their itinerant fellows"*[15]. Though the two leading medical experts of those times communicated their thoughts to each other through mutual correspondence or through their mutual connection, D. Bagdasar, never managed to meet because of the geographic distance or the Romanian professor's illness... The last but one attempt was at the International Congress of Physiology in Boston, 1929, when Nicolae Paulescu could have met both Harvey Cushing and Ivan Petrovici Pavlov, the renowned Russian physiologist, a recipient of the Nobel Prize for Medicine and Physiology in 1904. The last possibility would have been at the International Congress of Neurology in Bern (Switzerland), 31 August – 3 September 1931 but unfortunately the Romanian professor had died the previous month (17 July 1931).

The recommendation letter written by Professor Nicolae Paulescu to Professor Harvey Cushing, alongside the deep knowledge of neurology, the determination and diligence of the young doctor Dumitru Bagdasar, were the main advantages that gained the latter the appreciation he benefited from throughout his professional specialisation in the United States. Professor Cushing stated that, *"My door is always open for Paulescu's students"*[16]. Since Professor Cushing's reputation at the peak of his career attracted disciples from all over the world (Europeans: H. Olivecrona, H. Cairns, N. Dott, S. Obrador; Americans: E. Cutler, G. Horax, L. Davidoff, W. Wagener), his clinic had become a point of maximum interest and pilgrimage for those who wanted to specialise in neurosurgery. In 1928, Professor Harvey Cushing's secretary, Madeline Stanton, stated that, *"...we're toiling to receive 200 visiting surgeons"*[17]!

But let us see what the daily schedule of the Romanian doctor D. Bagdasar at the clinic of the renowned American neurosurgeon H. Cushing looked like:

> I get up at 5:30 AM every day and I read in English until 9:00 AM, when I leave for the hospital. I go into the operating room every day to see one or two procedures which end at about 2:00 or 3:00 PM. After the operating schedule is over, I go to the laboratory where the extracted pieces are analysed and discussed until about 7:00 PM. I spend 9 to 10 hours at the hospital every day. When I get home, I read in English until 11:00 PM[18].

In professor Cushing's clinic, the master placed Bagdasar under the wing of one of his closest collaborators, the renowned anatomopathologist, neurologist, neurosurgeon and psychiatrist Percival Bailey, who introduced him to the standard procedures of the main neurosurgical operations performed in the clinic, alongside the techniques for the preparation and anatomopathological analysis of the intraoperatively extracted pieces[19]. During his training in neurosurgery under Professor Harvey Cushing of the Peter Bent Brigham Hospital of Boston – as a voluntary assistant – Doctor Bagdasar wrote two significant papers on neurosurgery: *Le traitement chirurgical des gommes cérébrales (Tratamentul chirurgical al gomelor cerebrale)* published in Rev. Neurologie, 1929, 2 (1), 1-30 and *Intracranial chondroblastoma (Cordoblastoamele intracraniene)* published in Amer J Path., 1929, 5 (5), 429. The first paper had a single author, while the second one had two authors (the second being the renowned P. Bailey), both papers having the approval of the scientific mentor in neurosurgery of those times, the great Harvey Cushing[20]:

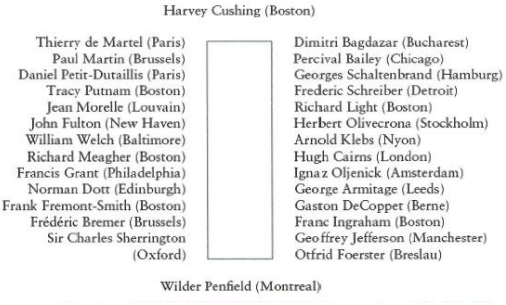
After a continuous working schedule of 14 hours a day, of which 9 to 10 hours were in the neurosurgery clinic, added to the fact that Bagdasar was a heavy smoker (like his mentor at that time), after 14 months of activity, both Bagdasar and his wife Florica Bagdasar fall ill of tuberculosis. Due to Cushing's network of friends, the Bagdasars are treated in two of the best American pneumology sanatoriums: the Sarnac Sanatorium in the Anderadaks Mountains and then the Troudeau Sanatorium[21].

The appreciative characterisation made by the intransigent and authoritative H. Cushing regarding Dumitru Bagdasar remains remarkable – in one of the annual reports of the Surgery Clinic (*Report of the Surgeon-in-Chief of the Peter Bent Brigham Hospital*, reprinted from the Fifteenth Annual Report 1928, p. 102): *"Dr Dumitru Bagdasar from Bucharest fell ill and had to temporarily suspend his stay with us. We deeply feel his absence, not only for personal reasons but also for his sharp understanding of neurological matters and his unusual working capacity"*[22]. It has to be mentioned that during the antituberculosis therapy in the abovementioned clinics, the family-like connection – one might say – between Cushing and Bagdasar continued through an amiable correspondence (found in the personal archives of the two families), where the Bagdasars talked about the favourable outcome of their illness and Cushing encouraged them or replied affirmatively to their polite requests[23].

We shall conclude this very important chapter in the training of the Romanian doctor Dumitru Bagdasar in neurosurgery at the American Professor Harvey Cushing's clinic by mentioning the correspondence that Bagdasar had throughout that period with his friends in Romania, namely: Professor N. Paulescu, Doctor I. T. Niculescu, his colleague, a distinguished neurologist and close friend D. Noica (head of the Neurology Unit of the Military Hospital in Bucharest), as well as the renowned physiologist J. Fulton, with whom he had become friends in the USA. In the autumn of 1929, Doctor Bagdasar was relatively stabilised from a pneumological point of view and returned to work in the Jimbolia Hospital where, with the help of his wife (who had a degree in Medicine and had joined him in the USA where, with Professor Cushing's support, earned a Fulbrait scholarship which enabled her to specialise in social medicine), performed the first 27 neurosurgical procedures in Romania in 1930: 15 ventricular punctions, 9 frontal parietal flaps, two subtemporal decompressions, one cerebellar decompression, as well as 18 procedures not involving the central nervous system: 12 vasectomies, four femoral sympathectomies and two frenectomies[24].

In 1930, Doctor Dumitru Bagdasar reports all the cases of medullary tumours published and operated in Romania up to that date: four had been operated by Professor Amza Jianu upon recommendation from Doctor State Drăgănescu (information from the doctoral dissertation of L. Dragomirescu), two had been operated by Professor I. Iacobovici and three by the associated professor Iancu Jianu[25].

In late August-early September 1931 (31 August - 3 September), Doctor Dumitru Bagdasar attended the First International Congress of Neurology in Bern, Switzerland, where Professor Harvey Cushing presented his memorable paper based on a personal statistic on 2,023 operated brain tumours. The presentation remained famous in the medical world because, for the first time, none of the participants (of which 25 were Cushing's disciples) was left outside the presentation room. During the congress, the American professor organised a festive dinner at the Bellevue Hotel, where he invited some of the leading experts in neurosurgery that were present. The disposition of the 29 seats at the table was prepared by the very host. The image below shows the honourable spot occupied by Bagdasar, at Cushing's left, facing the head of French neurosurgery, professor Thierry de Martel and near Doctor Percival Bailey, his second mentor in neurosurgery during his American traineeship[26, 27].



From June 1931 to December 1933, he worked as an attending psychiatrist at the Hospital for Mental and Nervous Diseases "Carol al II-lea" of Cernăuți. Here, assisted by his wife, Florica Bagdasar, by Miss Brenner and others, Dumitru Bagdasar performed 28 neurosurgical procedures in his first year and 31 in his second year[28,29]. The procedures performed in 1932 were as follows:

The first two procedures were performed on patient Karl A. (the age is not specified), the surgeon was Doctor Bagdasar, the name of the assistant is not mentioned and under "Anaesthesia" the first procedure mentions: local with novocaine, and the second one: local with novocaine 5%. The diagnosis for the first procedure of 11 January 1932 was:

cerebellar tumour and for the second one: Tumour of the left cerebellar hemisphere and vermis. Under "Procedure", the following is stated for the first operation: right ventriculography, and for the second operation: tumour ablation. Description of the first procedure[30]:

> Classical incision. Drilling. A ventricular needle is inserted into the right lateral ventricle on the first attempt; the fluid streams out at first, then drips rapidly. After draining about 65 to 70 cc, filtered air in the amount of 20 cc is introduced. The needle is removed gently (the patient reports slight headaches after receiving the first 15 cc of air). The wound is closed in two layers. Dressing with Mastisol". Description of the second procedure[31]: "The procedure begins at 9:30 AM and carries on until 8:00 PM; heart beat 120-130, does not answer any questions. The procedure is suspended for 15 minutes (2 cc of caffeine and 10 cc of camphor oil are given). The patient starts to recover, answers questions, the procedure is resumed without further incidents until the end. Crossbow (Cushing-style) incision. At the level of decompression, the dura is covered with a very think fibrous layer and cannot be separated through cleavage. The dura is opened with the help of a crochet on the left side, the entire left half of the bone breach is under heavy pressure and painful at the slightest movements. After opening the dura for a 2-cm length, a brown neoplastic tissue comes out. The incision is widened beyond the median line. After lifting several bone residues that were forming a bridge on the median line, the neoplastic tissue having a surface equal to the thenar eminence is dissected with a blunt instrument after having delimited the tumour; two stitches are applied on its most convex part and the dissection is continued while applying slight traction on the silk threads. Several haemorrhages are stopped with muscle tissue taken from another patient and silver staples. The tumour slightly exceeds the median line to the right side. After lifting the central part of the tumour (the size of a plum), smaller tumour pieces are lifted with a clip, continuing to dissect with blunt instruments. Healthy cerebellar tissue becomes visible on the lower side. When several tractions were performed on the lower side of the capsule, the patient felt pain in the left eye and had a strong shake (felt as if electrocuted), probably because of the irritation of the pyramidal fascia. Some capsule residue remains on the bottom and becomes heavily excavated, like half of an egg shell. During the procedure, the wound was flooded twice by an enormous quantity of cerebrospinal fluid which probably had drained from the ventricles through the cerebral aqueduct. After the first part of the tumour was lifted, the whole left hemisphere of the cerebellum remained depressed and stayed that way until the end of the procedure. The neoplastic tissue was placed on a pad that absorbed most of the liquids and, at the end of the procedure (several hours after it had been removed – 2 or 3), the tumour weighed 15 g. The dura was closed using the regular method. Dressing with gold sheets and Mastisol. Saline 400 cc is delivered subcutaneously on the surgical table. After the procedure, the patient feels well, no longer reports headaches, is slightly pale. The heartbeat is 130, normal, regular breathing.

On 15 February 1932, Doctor D. Bagdasar, assisted by his wife, Florica Bagdasar, performed a procedure under local anaesthesia with novocaine in a patient suffering from Jacksonian epilepsy, through a left temporal parietal flap. Description of the procedure:

> After cutting the flap, the dura appeared to be under tension, without pulses. An incision was performed on the dura parallelly to the bone and 1 (one) cm inside the bone, leaving an upper pedicle. Clips were applied on the smaller veins of the dura. When cutting the dura, adherences were seen between the dura and the cortex at the upward parietal level. The adherences were very thin and broke easily. The arachnoid mater appeared in the upper-front half of the infiltrated breach as superplastic, with several whitish nodules the size of a pin head and a spermaceti-like appearance. At the level of the adherence, that is at the upward parietal level, in the centre of the hand, there is a yellowish, well-delimited nodule near two large veins. The nodule is the size of a bean. Two clips are placed on the veins and then the nodule is detached through blunt dissection, also lifting part of the healthy substance in the brain. The bleeding is stopped with muscle tissue. A cotton pad immersed in formalin 10% is pressed on the cavity remaining after the nodule extraction (Cushing style). Several separated stitches are applied on the dura. Then, the bleeding is stopped with several pieces of temporal muscle – haemorrhagic on one half. The flap is put back in place and sutured the regular way[32].

One month later, on 15 March 1932, Doctor Bagdasar, again assisted by Florica Bagdasar, performed a procedure under local anaesthesia with novocaine in a patient suffering from spinal arachnoiditis, through an explorative laminectomy of the 2nd, 3rd and 4th lumbar vertebrae. Description of the procedure:

> *The muscle tissues are separated with great difficulty because of the contraction. After lifting the spinal apophyses, drilling is carefully performed and the breach is widened at the level of the 2nd, 3rd and 4th lumbar vertebrae. An incision is performed on the dura which has some adherences to the arachnoid, along a 3–4 cm distance. The arachnoid is very much thickened and slightly translucid. There is nothing else of notice. The spinal cord is normal. The wound is closed with a continuous suture on the dura and 4 additional layers. Dressing with Mastisol"*[33].

Of the 28 surgical procedures performed by Doctor Dumitru Bagdasar in 1932, we shall also stop on the one performed on 1 June. This involved a female patient (Gertrude T.) operated by the same operating family team, under general anaesthesia with avertin 2 g 3% sol. + local anaesthesia with novocaine 2%. The patient diagnosed with a right cerebellar cystic tumour (pontopeduncular) was subjected to cerebellar exploration. Description of the procedure:

> Crossbow incision. Craniotomy under the occipital protuberance, the dura appeared to be destroyed, without pulses. The VLD is punctured, the fluid flows with a slight pressure but stops flowing after 5–6 cc of fluid. An incision is performed on the dura and the right cerebellar hemisphere comes out through the breach; the vermis is punctured with the same result. Region V IV is examined but nothing is found. Given the appearance of the cerebellum, we suspect the presence of a deep tumour, probably located on the front side of the right cerebellum which is inaccessible for our surgical methods. The musculocutaneous flap is closed without suturing the dura (500 cc of saline is given on the table). The surgery lasted from 9:30 AM to 1:40 PA.
>
> Autopsy: A cystic tumour was found under the right cerebellum, between the cerebellum and the pontopeduncular area; it was the size of a large walnut, containing haemorrhagic brown fluid whose appearance was identical to that of the fluid drained through the suboccipital puncture (15 May 1932). The cystic cavity was covered with gliomatosis tissue from which several pieces were collected for anatomopathological examination[34].

Summing up the surgical procedures performed by Doctor Dumitru Bagdasar in Cernăuți in 1932, based on the protocols of the 28 procedures, one can conclude that 21 procedures were for brain diseases and the remaining (7) were for spine disorders (CT=1; T=3; L=3, of which one was a medullary tumour).

The experience acquired in the Boston clinic, in the Jimbolia Hospital and the Cernăuți Hospital materialises in 1932 with the publication of three scientific papers and the presentation of two communications on neurosurgery[35].

From 10 to 18 September 1932, Doctor Bagdasar participated in the 9th International Congress on the History of Medicine in Bucharest, whose main topic was "The evolutions of medicine in the Balkan countries". Among the 137 personalities coming from 23 different countries and representing 48 universities (Cf. Răzvan Constantinescu, *Carol al II-lea și congresul din 1932*, Viața medicală din 18 iulie 2014), there was also Doctor John Fulton, a friend of Bagdasar's since they had both trained in neurosurgery in the clinic led by professor Cushing; the congress was an occasion for them to meet and reconnect.

An important aspect of the neurosurgical activity carried out by Doctor Bagdasar in Cernăuți from 1931 to 1932 was his application to the Healthcare Inspectorate where he requested that a psychiatry unit be converted into a neurosurgery unit. Through its official communication no 4429 of 2 November 1932, the Inspectorate expressed its approval and thus the first official neurosurgery unit in the country was founded; Doctor Herbert Urban of the surgical clinic of the Vienna University asked to be informed on how this unit had been organised so that the same model could be implemented in Vienna[36].

In 1933, 31 neurosurgical procedures were performed by Doctor Dumitru Bagdasar assisted by his wife, Doctor Florica Bagdasar, as well as by Ms. Stofer, Sava, Sorodoc, Pokai (nurse). These procedures included: cerebral decompressions, explorative or decompressive drillings, cerebellar explorations, abscess opening through the cerebellum, trigeminal neurotomies, laminectomies, cordotomies and decompressions or sutures of the peripheral (median/cubital) nerve traumas[29].

Summing up the activity carried out at the Hospital for Mental and Nervous Diseases of Cernăuți, Doctor Bagdasar states that, from 1931 to 1933 he admitted 639 patients to the Neurology Unit, many of which required neurosurgical treatment: 24 ventricular punctions, 33 subtemporal decompressions, 17 Rolandic decompressions, 28 FP flaps, 5 F flaps, 18 cerebellar explorations, 4 retrogasserian neurotomies, 20 laminectomies (tumours, arachnoidites, rhizotomies and cordotomies). Besides the aforementioned procedures on the central nervous system, he also performed procedures on the peripheral nervous system: two pericarotidal sympathectomies and a suturing of the median nerve. He also performed 16 vasectomies in patients with mental disorders[37].

The four scientific papers published in 1933 reflected the neurosurgical issues Bagdasar had faced during that year, beginning with *Cerebro et Ventriculoscopie*, continuing with two papers on trigeminal procedures and concluding with one paper on a cystic cerebellar tumour[38].

In 1934, Doctor Bagdasar returned to Bucharest, with the support of Professors Iacob Iacobovici and

Nicolae Minovici, where he carried out his neurosurgical activity in two hospitals: the Emergency Hospital founded by Professors Minovici and Iacobovici within the Ambulance station[39] on Independence Street and the Central Sanatorium[40]. In 1934, he performed 41 neurosurgical procedures at the Emergency Hospital[41] and 23 procedures at the Central Sanatorium.

The neurosurgical pathology he dealt with during that year led Doctor Bagdasar to write and publish six scientific papers[42].

At the end of 1934, Doctor Dumitru Bagdasar published the paper entitled: *Titluri, lucrări științifice și activitate* (Titles, scientific papers and activity) including 28 pages, which we mentioned in the bibliographic references.

In the chapter *Surgical activity*, he underlines the fact that, alongside his activity in neurology, he also worked in the Surgery Unit of the same hospital, led by Professor Mihail Butoianu, where, for three years, says the author: "I was given the freedom to operate and I performed a relatively significant number of procedures", "This surgical traineeship which lasted for three years was useful in my approach to neurosurgery and is the foundation of my training in that field"[19].

The chapter *Neurosurgical activity* is divided into four parts: the United States, the Jimbolia Hospital (27), the Hospital for Mental and Nervous Diseases of Cernăuți (149), the Emergency Hospital and the Central Sanatorium of Bucharest (60), and mentions the types and number of procedures (236) performed in the hospitals of Greater Romania from 1930 to 1934. He also makes brief notes on the surgical techniques used and the difficulties he faced in the preoperative radiological exploration of patients[43]. We previously stated that the surgical report archive of the two hospitals in Bucharest (the Emergency Hospital and the Central Sanatorium) where Doctor Bagdasar performed procedures in 1934 contains 64 reports, representing – most certainly – the correct number of procedures performed (the four additional procedures were performed by Doctor Bagdasar after the publication of that volume).

The activity carried out by Doctor Bagdasar at the Emergency Hospital of Bucharest, since returning to Bucharest and until early autumn was described by one of the hospital leaders, professor Iacobovici in a certificate of activity, probably required for the enrolment in a contest for an attending neurosurgeon position at the Central Sanatorium which was approaching.

> Dr Bagdasar has been working in the Emergency Hospital since its founding. He took on 38 cases of non-traumatic injuries and led the treatment of all the skull fractures and all the traumatic nervous injuries. [...] Anyone who has experience in nervous surgery would see in Mr Bagdasar the maximum level of knowledge in this special branch of surgery, an impeccable technique and rare operating dexterity. Humble, hard-working, absolutely unbiased, Mr Bagdasar works with his own personnel, trains other practitioners of the Emergency Hospital and he brings all his own instruments every time. After surgeries, he attends to each patient day by day with extreme care until the end. [...] I have seldom had a collaborator with such exquisite education, such deep scientific insight and who worked with more self-sacrifice for science and the ill[44].

In late 1934, from 30 November to 2 December, the first contest in Romania for the position of attending neurosurgeon at the Central Hospital for Mental and Nervous Diseases took place in Bucharest. The three practitioners who enrolled in this contest, doctors Bagdasar, Moruzi and Vasiliu had completed their specialisation in important centres of the United States or Europe. Details about this contest are provided by Dumitru Bagdasar in a so-called Diary[45] that we had access to thanks to the efforts of Professor Ștefan I. Niculescu (son of I. T. Niculescu). The author of the diary concludes the description as follows: *"The ranking was decided as follows: since Moruzi and I had equal grades, I was ranked first because the rules set forth that seniority in the Ministry was decisive in case of equal grades"*.

Since 1935, Doctor Dumitru Bagdasar's surgical activity was carried out predominantly in one hospital, the Central Hospital for Mental and Nervous Diseases of Bucharest, where he earned his position following the contest for attending neurosurgeon. In that hospital, he performed 17 neurosurgical procedures in 1935[46]. The working conditions in the operating unit of this hospital that was under refurbishment from the second half of 1934 are described in a very plastic but truthful way by the one who assisted him in a large number of neurosurgical procedures throughout 7 years of activity (1934-1940) – Doctor Maria I. Niculescu. She describes the shocking working conditions of D. Bagdasar and his team in those early days of neurosurgery in Bucharest: *"the patients were naked,*

kept behind bars and, in that eerie atmosphere, outstanding surgical procedures were performed on an improvised wooden table, using a vacuum cleaner for home use adapted for surgeries and most instruments bought or made based on Bagdasar's instructions, thus following Cushing's example but without comparable financial resources"[47]. At the same time, he continued to perform procedures at the Emergency Hospital[48] or even other hospitals in Bucharest, such as the Colțea Hospital[49] as well as the Military Hospital[50] and the French Sanatorium or Paul Vincent Hospital[51], using a portable surgical instrument case that he sterilised in the hospital unit where he performed the procedure.

Alongside his surgical activity in the abovementioned hospitals, Doctor Bagdasar would attend the histology laboratory of the Medical School led by Professor Ștefan Besnea and then by Ion T. Niculescu each week: *"Every week, the microscopic sections of all the operated tumours brought in in countless cups and containers were discussed in depth by Brătianu, Ion Bazgan, later C. Arseni and occasionally Emil Crăciun and Maria Niculescu, drawing up reports including the macroscopic description, size, weight, microscopic description, diagnosis and synthesis of the discussions"*[52].

Throughout the years, he participated in various congresses, scientific meetings on neurology (The 1931 Bern Congress), the history of medicine (The 1932 World Congress of Bucharest), neurology, psychiatry and endocrinology (Chisinau, 1935), surgery (The National Congress of Surgery, Bucharest, 1939) etc.

In 1936, Doctor Dumitru Bagdasar wrote a report mentioning all the cases of primordial medullary tumours published and operated in Romania up to that date: 12 cases operated by professor Amza Jianu at the recommendation of Dem Paulian, two cases operated by Doctor Constantin Leonte at the recommendation of the same doctor and 13 cases operated by Doctor Alexandru Moruzi under the supervision of Professor Leon Ballif. (Apud Ștefan Balmez, *Tumori medulare – studiu anatomo-clinic și terapeutic* (Medullary tumours – anatomic, clinical and therapeutic study) (doctoral dissertation)[53].

From 1931 to 1941, summing up his activity in a report, Dumitru Bagdasar stated:

> During the years before the current war (1941), besides the domestic patients, I also received patients from Hungary, Bulgaria and Palestine. From 1931 to date – therefore during a time span of 10 years – I performed 1,800 surgical procedures on the nervous system, divided as follows: 473 ventriculograms having the purpose to diagnose the existence and location of neoplasms, 988 large craniocerebral procedures, 259 laminectomies, 83 procedures on the peripheral nerves[54].

From 1939 to 1940, after the death of Professor Marinescu, with his successor, Professor Nicolae Ionescu-Sisești and with the approval of the Council of the Faculty of Medicine and the Civil Hospital Board, a plan was drawn up to oversee the fitting of a modern neurosurgery ward with a capacity of at least 80 patients near the Neurology Clinic of the Colentina Hospital that could rival similar services abroad... In a report from 1941, after the beginning of the war, Doctor Bagdasar stated with disappointment: *"[...] In February this year, however, I found out that, for reasons unknown to me, the ward had been given a different destination.*

> The war caught me by surprise in a totally insalubrious building and the available personnel that had been trained for these procedures was made up of Doctor Arseni C. with a 5-year experience in the speciality and 3 nurses who had trained in the neurosurgery unit for the previous years.
>
> Doctor Arseni was mobilized and kept on the battlefront since the beginning of the war, although I had made countless attempts through the Ministry of Health and the military authorities to have him brought back to the hospital, where he would have been incomparably more useful to the army than on the battlefront. Such reasons have not been understood and my requests remained unanswered. [...]
>
> During the months of July and August, the injured started to come in as neurological patients with much more serious injuries than those in the general surgery units: complete irreversible palsies of the lower limbs through sectioning of the spinal cord, half-body palsies through brain injuries, brain abscesses, meningitis etc."[55]

From 1942 to 1946, according to the reports of Doctor Sofia Ionescu-Ogrezeanu[56]:

> Doctor Dimitrie Bagdasar would come to the hospital from the Cotroceni neighbourhood before 5 AM. Doctor Constantin Arseni would walk several kilometres on Calea Văcărești on any weather to be in the hospital at 5 AM. The family Ionel and Sofia Ionescu lived at the hospital.
>
> Professor Bagdasar was renowned for his incredible work capacity. A handful of people had to cater to all the needs of the patients occupying the 80 beds the ward had at that

time. An ambulance would bring in a war injured or a neurosurgical emergency every minute.

Professor Bagdasar started his day by visiting the patients in the injured ward. Then he visited everybody else. Once he entered the operating room only God knew when he would come out. He would keep his cool even in the most difficult circumstances in the operating room. He had the lightest hand when operating. At the end of each procedure, he filled in the surgical report for the operating register very meticulously. His notes were a priceless study material for anyone who read them. His writing was easily readable, clear, accompanied by drawings, sometimes using colours. He would describe the key moments of each procedure with extreme meticulosity for his collaborators. Any patient in a deep coma was cared for by Bagdasar's team until the very last moment. In Doctor Bagdasar's ward, no patient passed away without a doctor by their side. Inoperable cases and inane complications caught his interest. He had real talent as a researcher.

Every case was a lesson learned. In 1946, the neurology professor Ionescu Sisești, speaking about the activity in his ward, said: it was not only a hospital where surgical procedures were performed, it was a centre of relentless scientific research"[57].

His left-wing political orientation was a characteristic of his views throughout the years, being materialised through his membership of the Romanian Communist Party since 1943, by signing the memorandum of April 1944 through which the intellectuals demanded the exit of Romania from the war, through his activity in the board of "Apărarea Patriotică" and his tenure as Ministry of Health in the Petru Groza Government since 6 March 1945. This orientation was analysed, accepted and classified – after o period of 60-70 years – by his daughter, a world-renowned mathematician, Professor Alexandra (Bagdasar) (Bellow) Calderon[58] and by Doctor Mihail Mihailide[59].

My father's life was a continuous struggle. He had nothing «for free». Extreme poverty marked his childhood and adolescence years. When he thought he had overcome the «money issue», World War I broke out and he was sent to the battle front as a military doctor; there he fell ill of typhus and struggled to survive. His desire to learn and his prodigious work capacity were to a great extent also fed by his strong desire to contribute to the fight against poverty and human suffering which he had personally faced since a young age". [...] "Of course, my parents were not «professional revolutionaries». They were not made for a political career, power games and political scheming. The fight for privileges and benefits had nothing to do with them. But my father grew up seeing a lot of poverty and human suffering in the rural areas. In a country where the majority of people were peasants, he was acutely aware of the situation in the rural environment: illiteracy was spread to a shocking extent, the lack of hygiene and medical care, the huge rate of child mortality were all issues he felt deeply and first-hand. Humanistic ideas attracted him instinctively, because social injustice and racism, chauvinistic and exclusivist nationalism revolted him (see his diary from 1934 to 1935). He was, by his nature, on the side of the needy, so his left-wing orientation was natural. My mother, who was devoted to him and passionately believe in him, embraced his ideas"[60].

Being well informed and endowed with the scientific rigour of his profession, Doctor Mihail Mihailide managed to extract – from a history of communism in Romania – the parts that refer to Doctor Bagdasar, drawing up his own motivated presentation after what Alexandra Bagdasar[59], [61] had written before him, in two substantial articles of medical history published in the weekly paper "Viața Medicală" which he ran at that time and of which we shall quote a small part[49]:

[...] "For his unconditional support to the new Government, Dumitru Bagdasar was appointed Minister on 6 March 1945. He travelled across the country, becoming, according to the existing documents, an excellent propagandist, due to his increasing medical prestige and rhetoric qualities. Several speeches he held on various occasions have been preserved in his own writing: agitator messages, some of which used a wooden language that was quickly adopted by the speaker, including reverences to the Great Eastern Friend, filled with slogans and concluded with the invariable "Long live...!"

Regarding the awarding of his professor title, reader Dumitru Bagdasar, who had been recently appointed Ministry of Health in the Petru Groza Government, there are memorial documents that are considered unique in Romanian higher education, where a reader refuses the title of professor on the first proposal and accepts it unwillingly on the second nomination. I shall quote those testimonies left for posterity for the elegant expression and argumentation of the two parties at the dawn of the new democracy through: the request sent to the dean of the Faculty of Medicine, Professor Gr. T. Popa by Bagdasar and the reply that the latter received: *"Mr Dean, please be my interpreter with the Faculty professors, to whom I thank with all my heart for the care they show to our higher education or for the efforts they make to accomplish something in our*

field. The political position I hold at the moment does not allow me to accept this honour. During the dictatorship, I heavily criticised the tendency of certain high dignitaries to secure benefits for themselves or their friends in higher education. The professors and the public opinion of the time shared this view"; professors C. I. Parhon, C. I. Urechia replied to this request on 1 November 1945: *"We, the members of the advisory commission for position holders, have been aware for several months of your refusal to accept this title [...] However, considering the need to have a neurosurgery department in our institution, we and all our colleagues are asking you to please not deny our Faculty the honour to have the first department in our country for this branch of medicine and to accept our recommendation"!*[62]

He died on 16 July 1946 after an illness that lasted several months and forced him to give up his ministerial assignment on 24 April 1946, as well as the nomination for ambassador of Romania in the United States[61]. Before that date, following a medical examination in Vienna, he had found out his primary diagnosis (inoperable lung/digestive cancer)[62] and he established his secondary diagnosis on his own (brain metastasis) once apraxia settled in... *"With his extraordinary common sense, professor Bagdasar did not tell the truth to anyone. He retired to the town of Breaza to await his end. On his deathbed, in his very last moments, he called his collaborators: Dr Constantin Arseni, Dr Ionel Ionescu, Dr Sofia Ogrezeanu Ionescu. What were his last words?*

> Do everything in your power for this speciality to evolve. Be as one. Continue what you started with the same energy, the same passion and, especially, with the highest ethics.

He also wanted Doctor Constantin Arseni to be appointed manager of the ward"[63].

He became a *post-mortem* member of the Academy of the Popular Republic of Romania in 1948[64].

After he won the contest for the position as attending neurosurgeon, during one decade (1935-1944), he published 28 scientific papers in medical journals and he presented three reports at specialist congresses. Two other papers to which he had contributed substantially were published *post mortem*:

D. Bagdasar, Gh. Pasăre, *Sindromul senzitivo-motor de tip periferic după traumatismele parietale*, Spitalul, 1947, An. 67, Nr. 5-8/Mai-August, p. 106-108[65].

D. Bagdasar, C. Arseni, *Traité de neurochirurgie*, Introducere de C. I. Parhon, Editura Academiei R. P. R., București, 1951, 601 [603] p., cu 1 [4] f. (translated in French by Doctor Maria Niculescu)[64].

For the 10-year anniversary from the death of Professor Dumitru Bagdasar, Professor I. T. Niculescu, a correspondent member of the Academy of the Popular Republic of Romania, made a magnificent description of Bagdasar starting from their first encounter in 1914, continuing with the time spent in Professor Marinescu's clinic and up to the time in Doctor Noica's ward at the Military Hospital of Bucharest where lifelong friendships had been built between co-workers who shared the same spiritual values...:

> In 1914, I first met a young man with smiling and kind eyes but at the same time endowed with a subtle irony. It was Mitică Bagdasar. He was the pride of the people of Bârlad who had joined him at Medical School. His wide general knowledge, his kindness and loyalty had immediately earned him the high esteem and fondness of his colleagues. An original note was his travel wear, with a wide hat and floating lavaliere that completed his appearance as a young man with a mind full of verses and good reading, which had always been his spiritual delight. [...]
>
> Bagdasar's first years as a student were impacted by the war of 1916-1918, when he did his duty as a doctor. After the war, I had the privilege to get to know Bagdasar better when we worked together in Professor Marinescu's clinic in Colentina, as well as later, when he worked with the great clinician, Doctor Noica. Mitică Bagdasar approached this distinguished person, follower of Dejerine, Babinski and Pierre Marie, with fondness and attachment, learning everything from Doctor Noica's experience in the admirable French clinic. The intellectual respect for Noica was doubled by a rare lifetime friendship between the two. Thus, through his long and diligent work alongside Noica and Marinescu, Bagdasar set the foundation of a deeply eradicated neurologic culture which later turned him into one of the most erudite neurologists in Romania.
>
> Since Bagdasar knew very early that he was going to become a neurosurgeon, he integrated his activity with extensive work in surgery within Professor Butoianu's unit at the Military Hospital. [...]
>
> Bagdasar was the founder of modern neurosurgery in Romania. Romanian science owes him a lot. He transplanted a difficult but very useful science into our country. He brought in all the scientific and technical knowledge in neurosurgery of the great Harvey Cushing, he applied all the novel scientific breakthroughs in this field

with discernment and seriousness, bringing important personal contributions and showing at all times the utmost respect for the ill whom he helped with love, delicacy and a sense of humanity. He was a gentle and understanding master for his followers.

Throughout his tragically ended life, Bagdasar was a great doctor and a good man, whom all good people should remember with love and kindness"[66].

The disciple and successor of Professor Dumitru Bagdasar as leader of the neurosurgery school in Bucharest, professor Constantin Arseni, on the occasion of the 30-year anniversary from his master's death, wrote in a prestigious journal of the time:

Doctor Bagdasar lived in a golden era of the Romanian medical school. That was for him an advantage because he had examples to emulate but also a disadvantage because it is obviously more difficult to shine in the light than in the shade. But – though it was more difficult – ha managed to shine in the light. [...]

Doctor Bagdasar's personality as a doctor was necessarily and harmoniously doubled by the finest personality as a person. He was a good and generous man, showing endless understanding towards human suffering, he had an unusual sense of justice and therefore of revolt in front of injustice. He was a deeply honest person, having a real cult for honesty, human values and respect for people, for the liberties of the individual and society. He was harsh on himself and would not accept any moral compromise. These ethical principles developed his activist side. It is known that he was one of the initiators and signatories of the 1944 memorandum through which intellectuals requested the exit of Romania from the war and after 23 August 1944, as Doctor Bagdasar was continuing his activity as a neurosurgeon, he found new resources to participate in the leadership of "Apărarea Patriotică" and in 1945 he was appointed Minister of Health in unimaginably difficult circumstances of neediness, hunger, epidemics, destruction and disorganisation. With the same perseverance and selflessness, Doctor Bagdasar did all his duty and gave his whole self.

In 1946, he died knowing he had completely honoured his duty[67].

Notes

1. Simion Tavitian, Armeni de seamă din România, vol. I, p. 55, in: www.ziuaconstanta.ro,
2. Acad. prof. dr. A. Kreindler, Viața și opera profesorului dr. Dumitru Bagdasar, Societatea pentru răspîndirea științei și culturii, București, 1960, p. 4.
3. Dumitru Bagdasar, Muncă și caracter, Scrisori-jurnal-portrete-discursuri-evocări. Introducere, selecție, prezentare și aparat critic de Ștefan I. Niculescu, Editura Eminescu, București, 1987, Mărturii de Nicolae Bagdasar, p. 351-353.
4. Dr. D. Bagdasar, Titluri, lucrări științifice și activitate, București, 1934, p. 4.
5. Dr. D. Bagdasar, op. cit., p. 4-5.
6. Dr. D. Bagdasar, op. cit., p. 3: "From 1921 to 1922, I attended the Neurologic Clinic of Professor Marinescu, being transferred there by the Medical Military Institute for specialisation".
7. Dr. D. Bagdasar, Titluri, lucrări științifice și activitate, București, 1934, p. 5-11.
8. Dr. D. Bagdasar, op. cit., p. 12.
9. M. Butoianu, I. Gilorteanu, Cranioplastie tardivă cu placă metalică pentru pierderi mari de substanță craniană, Spitalul, 1922, p. 310.
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all the action taken up to that point and gave its approval for the fitting of an emergency surgery hospital within the head office of the Ambulance Society on Splaiul Independenței. Unofficially but partially, the hospital starts to operate immediately, thus preceding the official opening of the 50-bed hospital on the 5th of May 1934 (Apud, Mircea Beuran, Benone Dutescu, Rodica Dutescu-Zăvoianu, Asistența urgențelor chirurgicale din București, Certitudini și speranțe, Editura Academiei Române, București, 2014, p. 30-31).

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T- configuration stent assisted coiling treatment of a complex wide-necked basilar tip aneurysm

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ABSTRACT

The advancement of intracranial stent technology and techniques has extended the applications of endovascular coiling methods for complex intracranial aneurysms. Coiling of wide-necked and complex bifurcation aneurysms usually requires double stent implantation. Different configurations for double stent-assisted coil embolization have been described. The T-configuration stent-assisted coiling procedure was recently described as a feasible, effective, and relatively safe endovascular technique used to treat wide-necked complex bifurcation aneurysms. In this article, we present the successful management of a complex wide-neck basilar tip aneurysm using a slightly modified T-configuration stent-assisted coiling technique

Keywords
T-configuration,
double stent assisted coiling technique,
intracranial aneurysm

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INTRODUCTION

Stent-assisted coiling is an increasingly used technique for the treatment of wide-necked intracranial aneurysms. Stents offers technical stability and durability of coil placement to prevent coil prolapse into the parent artery. However, a single-stent technique it can still be a challenge for the treatment of complex wide-necked aneurysms especially those in which the base of the aneurysm directly involves both bifurcation branches. Thus, in the case of these particular anatomical situations, endovascular treatment in optimal conditions requires the use of a double stent technique. The efficacy and safety of various configurations, such as X and Y stenting have been reported in the endovascular treatment of the complex intracranial aneurysm. In this study we describe the use of a particular T-configured double stent–assisted coiling technique for the treatment of wide-necked and complex basilar tip aneurysm. The efficacy and safety of this technique were also discussed referring to the few cases already presented in the literature [1,2].

CASE PRESENTATION

A female patient of 44-year-old was addressed to our emergency department for a subarachnoid haemorrhage revealed on cranio-cerebral CT scan. At admission she was in unconscious status with mild nuchal rigidity. The family declare severe headache suddenly installed a day ago. Her past medical history included hypertension with no regular treatment. The brain CT and CT angiography demonstrated a mild hydrocephalus and a complex basilar tip aneurysm as source of haemorrhage. The patient was intubated and immediately transferred to neurosurgery department for an external ventricular drain implantation.

The patient was proposed for an endovascular aneurysm occlusion for the next day. A written informed consent was signed by patient family after discussions with the operating team.

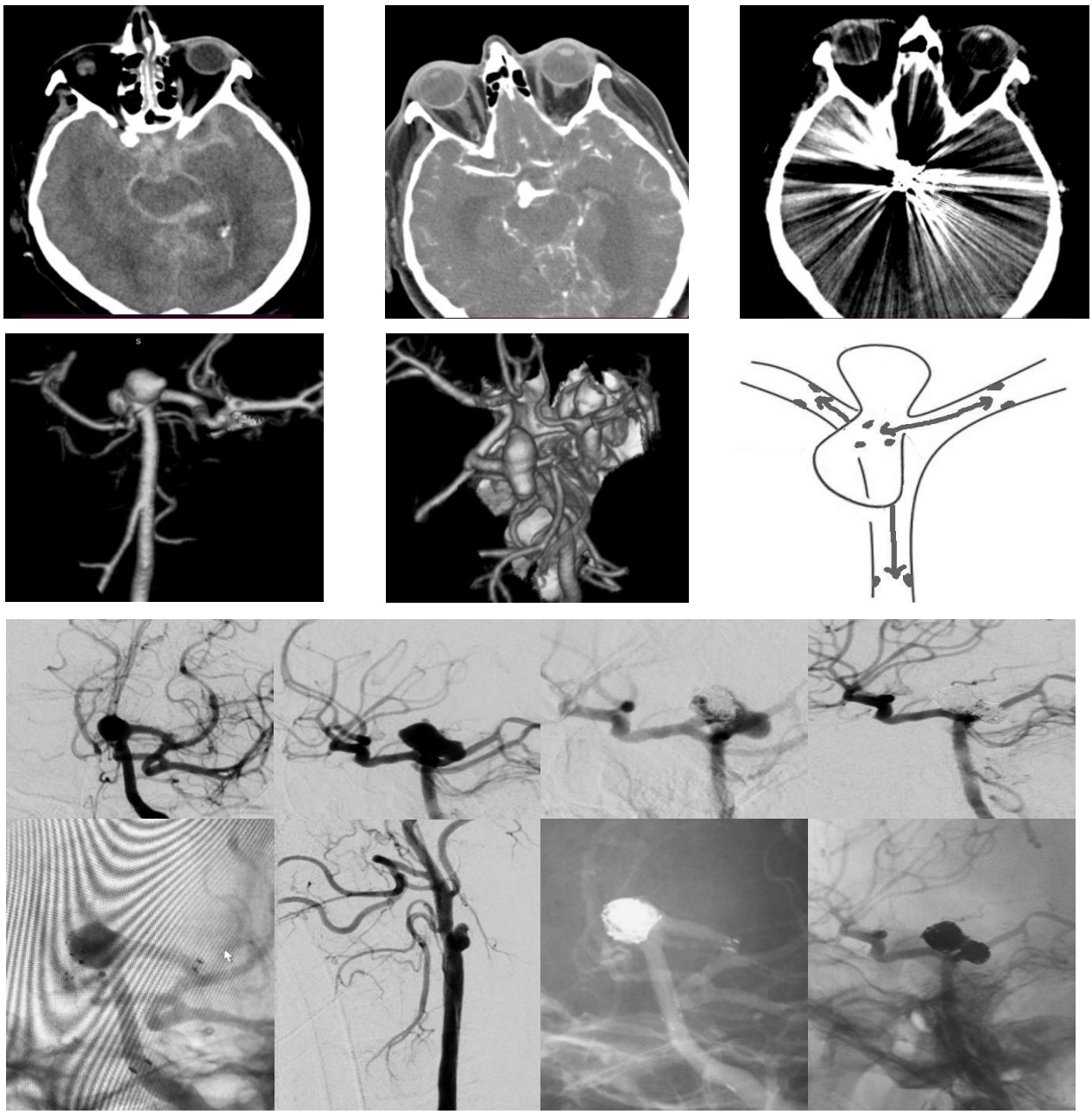

Figure 1. A, B - Brain CT diagnosis highlighting SAH and the aneurysm lesion; C - Post interventional barin CT control; D,E – Vascular 3D reconstruction showing the bilobate basilar tip aneurysm; F – Schematic image of the T-configuration double stent arrangement; G-N – Intraprocedural DSA images.

The procedure was performed on a biplane angiography system (INFINIX, Toshiba, Canon Medical System) and started with evaluation of both carotid and vertebral artery. The left ICA was founded obliterated and a total compensation of this vascular territory provided by the posterior circulation via a large left posterior communicating artery. The 3D DSA reconstruction image showed a large complex basilar tip aneurysm with two lobes in an hourglass anatomical configuration, a very wide neck involving both posterior cerebral artery junctions, originating from an asymmetric relation with the aneurysm sac. A dual stent support technique was deemed necessary for a safe endosaccular coiling and both PCA preservation (Fig 1).

The patient was premedicated with 150 mg aspirin before procedure and 5000 UI heparin after 6F femoral sheath (Merit Medical) placement. With the patient under general anaesthesia, the distal cervical part of left vertebral artery was catheterized with 6F Chaperon guiding catheter (Microvention) carefully advanced over 0.035 glidewire. A bolus dose of 2 mg of nimodipine (Nimotop, Bayer Health Care AG) diluted in 140 ml of 0.9% NaCl solution was infused through the guiding sheath for 10 minutes to prevent the development of vasospasm during the procedure. 3D angiographic imaging working projection was used for the guidance on roadmap images. We slightly modified the already reported T-configuration stent–assisted coiling technique by step-by-step catheterizing of the daughter branches and the aneurysm sac to avoid multiple catheter manoeuvring through the basilar trunk.

A Prowler Select Plus microcatheter (Codman J&J) was then very carefully advanced over a 0.014 Transed microwire (Boston Scientific) and positioned into the left posterior cerebral artery. At that point, the proximal end of the first stent, forming the short arm of the T configuration, was placed at the aneurysm neck, incorporating the corresponding daughter vessel. This branch was chosen for detachment of the first stent due to its closest relationship to the aneurysm neck and the tip of the basilar artery. Thus, the circumference of the distal end of this stent will be positioned so as not to overlapping (be under) the orifice of the second vascular branch of the bifurcation. To place the second stent, the right posterior cerebral artery was achieved carefully passing between the proximal end of the first deployed stent and the uncovered/unprotected aneurysmal neck of the Prowler Select Plus microcatheter over .014-inch microwire. The longer second stent was then fully deployed in the other daughter vessel, extending proximally into the basilar artery trunk. After the full deployment of the stents, a Prowler 10 microcatheter is placed into the aneurysm the anterior lobe of the aneurysm. After its complete angiographic occlusion, the microcatheter is positioned to the posterior lobe and the coiling of the aneurysm was continued until no further coils could be safely deployed within the aneurysm sac. Ffinal DSA images demonstrated a “Raymond class I” complete aneurysm occlusion with no neck remnant, coil herniation, clot formation or branch occlusion, and with no perioperative or perspective complications. The patient's evolution was slowly progressive, with suprimation of endotracheal intubation at 2 days postoperatively, and of the external drainage at 7 days. She was transferred to neurological recovery unit at three weeks presenting gait difficulties, dizziness and nystagmus.

Discussion

The endovascular treatment of wide-necked and complex bifurcation aneurysms which incorporates both vascular branches is still a challenge for endovascular neurosurgeons. Despite the progressive development of the new techniques for wide-necked aneurysm like double-balloon remodeling method or double-stent–assisted coiling technique, there are still complex anatomical situations that require continuous adjustment of them. In 2005 Chow et al. were among the first to describe the Y-stent–assisted coiling technique that greatly improved the ability to treat the wide-necked basilar bifurcation aneurysms. With this, the double-stent–assisted coiling procedures began to be used for wide-necked bifurcation aneurysms with various locations. However, subsequent studies have shown that Y-stenting may be associated with some technical risks and difficulties, especially when using 2 closed-cell stents. Thus, the need for catheterization of the second daughter vessel and passage of the second stent through the interstices of the first deployed stent may cause migration, dislocation, or deformation of the first stent. The occurrence of an hourglass-like deformation or stent narrowing at the point of intersection of the two

stents may induce thromboembolic events. Also, the intersection of the two stents at the level of the aneurysm neck may create technical difficulty for a possible subsequent catheterization of the aneurysm. Moreover, studies have shown that intraluminal crossing struts of 2 stents in a Y configuration are less susceptible to the progression of the endothelialization phenomenon, and may constitute a source of delayed thromboembolic complications [1,2,3].

Cho et al. reported for the first time the use of the T-configuration in the double stenting technique for the endovascular coiling treatment of wide-necked basilar bifurcation aneurysms. Inspired by the T-stent configuration used to treat coronary atherosclerotic bifurcation lesions, they attempted to resolve the safety issues associated with Y stenting. Thus, one of the main technical advantages of T stenting is represented by the elimination of risk of dislocation for the initial stent during the second stent passaging and deployment. Also, the T-stenting technique does not require any attempt of microcatheterization through the interstices of a crossing stents for coils placement in to the aneurysm. Furthermore, the presence of a total conformability with vascular anatomy and complete wall apposition of the stents increase proliferation of the endothelialization phenomenon on the entire surface of the implants, decreasing the risk of structural stenosis over time [2,5,6].

Generally, the technique of placing stents in T-configuration, means the deployment of a stent from one bifurcation branch to the wide aneurysmal neck and the second stent from the other opposite branch of the bifurcation into the parent trunk vessel. However, the technique of double T-stenting is a technical challenge, sometimes difficult or impossible to achieve, as in the case of large complex aneurysms with unfavorable anatomical configurations (sharp angles in the relationship between bifurcation vessels-carrier vessels - wide neck) as so called “arrow configuration”. The "anatomical T-shaped configurations" of the bifurcation aneurysms are the most accessible to use the double T-stenting technique even in the case of an asymmetry between the two origins of the bifurcation vessels towards the neck and the parent trunk vessel. However, of course, the placement of the stent in T-configuration should be reserved for patients with well-sized P1 vascular segments. Otherwise, placing a single stent in the large P1 is the option for patients with P1 hypoplasia / aplasia on one side. The simultaneous use of multiple microcatheters in the double stenting procedures may create a potential risk of thromboembolism. The possibility of application of a staged stenting by using a single microcatheter in the case of T-configuration stenting followed by the placement of coils only through the passage of the microcatheter through the interstices of a single stent can reduce this potential complication risk [2,3,4,6].

There are limited data in the literature regarding the safety and efficacy of the T-stent–assisted coiling technique. Aydin et all published in 2019 the largest series of patient treated by double T-stent–assisted coiling technique. They also present the successful applicability of T-stent–assisted coiling for the treatment of anterior circulation aneurysms. The immediate complete aneurysm occlusion rates reported was relatively high 83.3% compared with Y-stent–assisted coiling and close to the results of conventional single-stent–assisted coiling studies. At the last follow-up examinations, the complete occlusion was documented in 90.0% of patients. Regarding periprocedural complications, these were highlighted in 13.7% of cases, while delayed complications, generally represented by thromboembolic phenomena, were reported in only 3.9% of cases. Of these, only 1.9% led to permanent morbidity, and the death being registered in only 1% [1,2].

Conclusions

The T-configuration double stent–assisted coiling technique is a feasible and relatively safe endovascular procedure for the treatment of complex wide-neck cerebral aneurysms located at different bifurcation sites. However, a few aspects like the anatomy, angulation and take-off of the vessels may play a role in which technique to choose. Through this case report we showed that T-configuration stent-assisted coiling is an alternative successfully treatment for selected cases with favourable clinical outcomes and satisfactory midterm results.

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Clinicopathological features, imaging characteristics and surgical management in a novel tumour entity - aggressive meningiomas

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Keywords
aggressive meningiomas, clinicopathological features, imaging characteristics, surgical management

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ABSTRACT

Meningiomas are common neoplasms of the central nervous system, comprising between 24 and 30% of primary intracranial tumors, most commonly affecting females in their middle age or later adult life [1] [2].

Meningiomas are classified as benign, atypical or anaplastic meningiomas depending mostly on histopathological criteria known to be associated with worse prognosis in terms of tumor progression, recurrence risk after surgery and overall survival. The 2016 edition of World Health Organization (WHO) classification of Central Nervous System (CNS) tumors recognizes brain invasion as an independent criterion for diagnosing an atypical grade II meningioma [3]. Meningioma grading based on the WHO classification of CNS tumors thoroughly impacts therapeutic management and tumor prognosis.

Aggressive meningiomas, a different phenotype of tumors, characterized by rapid growth and involvement of adjacent brain tissue, blood vessels and bone, was not previously listed as an independent entity in the WHO classification of meningothelial-cell tumors.

Regarding the increasing importance of tumor grading in meningioma treatment

strategies, the authors here provide an overview of clinicopathological and radiographic features, surgical management and long-term prognosis of this novel meningothelial tumor entity, the aggressive meningioma. In particular, we aimed to describe pre-, intra- and postoperative methods for recognizing aggressive meningiomas and explore the implications of this diagnosis on both surgical strategies and adjuvant therapy.

Patients and methods

We performed a single-center retrospective study. We reviewed the files of all patients diagnosed with primary intracranial meningioma at the 4th Clinical Department of Neurosurgery, Bagdasar-Arseni Clinical Emergency Hospital, between January 2013 and December 2018. Inclusion criteria, primary based on preoperative imaging and confirmed by histopathological examination, consisted of either: invasion into the brain parenchima, involvement of the major blood vessels, cranial vault bone lysis without involvement of the outer table of the skull or complete bone destruction and aeshthtic diformity.

Results

A total of 25 patients, 16 female and 9 male patiens, with a gender female:male ratio of 1.7:1, met the required imagistic/histopathological criteria and were included in the present study. Age at diagnosis ranged from 29 to 74 year old, with a median of 53.8 years. Figure 1 shows the distribution based on the tumor location. We found 11 frontal meningioma, 6 skull base tumors, 5 parietal meningiomas and one of each: temporal, occipital and posterior fossa (comprised in Figure 1 as "others").

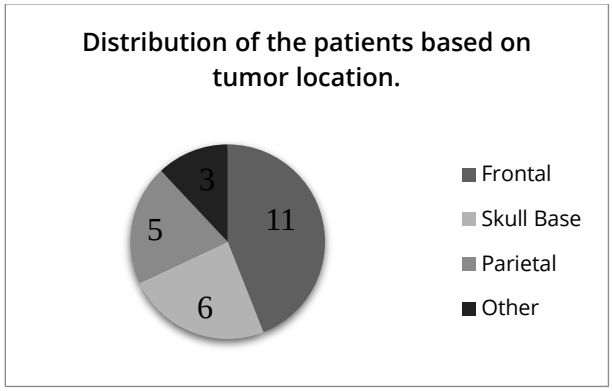

Figure 1. Distribution of the patients based on tumour location

Most frequent symptoms at diagnosis were: headache, progressive motor weakness and seizures. Regarding the tumor size, based on the largest diameter as measured on preoperative imaging, tumors ranged from 30 mm to 80 mm diameter. Figure 2 shows the distribution based on the involvement of the neighbouring structures. Bone lysis (Image 1, IMage 2) was observed in 9 cases (36%), major blood vessels involvement in 8 cases (32%), invasion into the brain parenchima in 8 cases (32 %) and complete bone destruction with cosmetic diformity (Image 2) in 6 cases (24%).

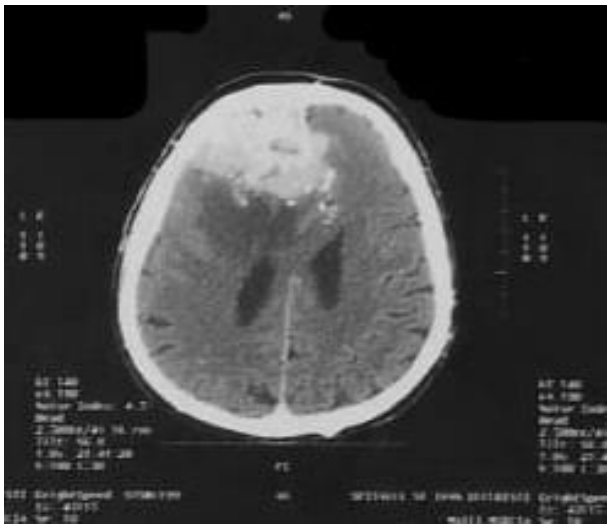

Image 1. Contrast enhanced computed tomography scan showing a large extraaxial lesion with frontal bone involvement and peritumoral edema

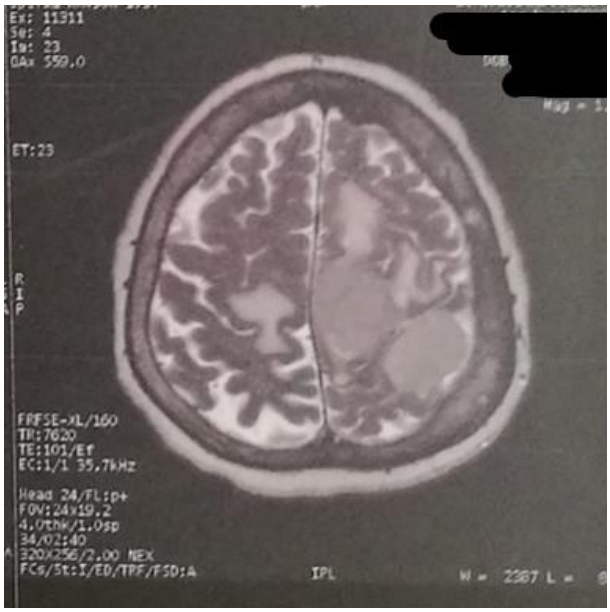

Image 2. Non-enhanced magnetic resonance imaging scan, T2 sequence, axial section, showing a left parietal tumor extending into the corpus callosum, with perilesional edema and bone invasion

Figure 3 shows the distribution of the patients based on the extent of resection. All but one patient were operated on, achieving a gross total resection in 16 cases (64%) and a subtotal resection in 8 cases (32%). In the single case where conserative management was chosen, it was because of the patient`s associated diseases.

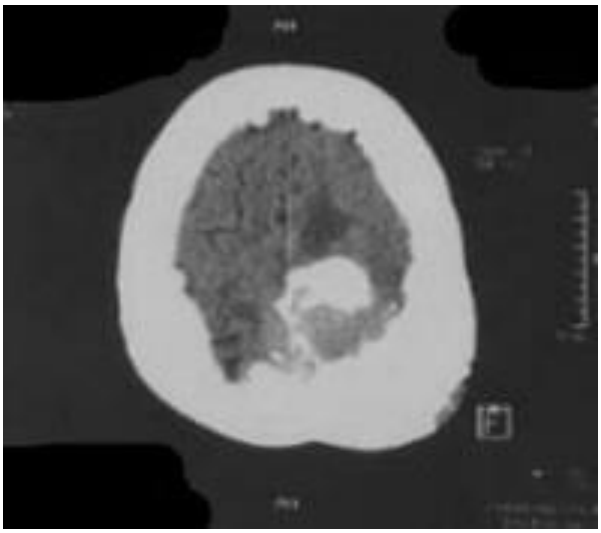

Image 3. Contrast enhanced cmputed tomography scan showing a large extraaxial lesion with complete parietal bone destruction and cosmetic diformity

FIgure 4 shows the patients distribution based on the histopathological variants, using the current WHO classification of tumors of the meninges. We found 13 atypical (WHO grade II) and 12 WHO grade I tumors: 5 transitional (mixed), 4 meningothelial, one psamomatous, one fibrous (fibroblastic) and one angiomatous meningioma.

Postoperative recurrence rate was 16% (4 cases). Perioperative mortality rate was 4% (1 case).

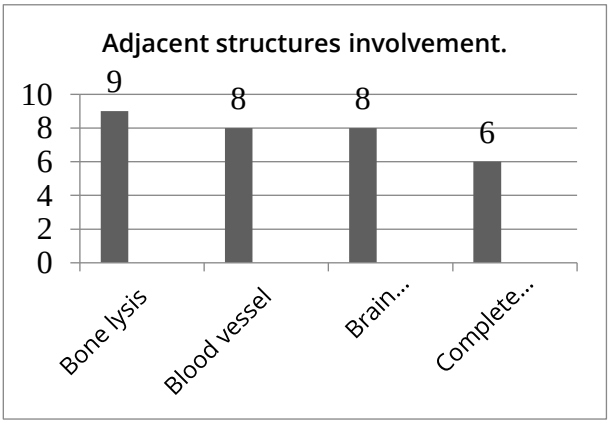

Figure 2. Adjacent structures involvement

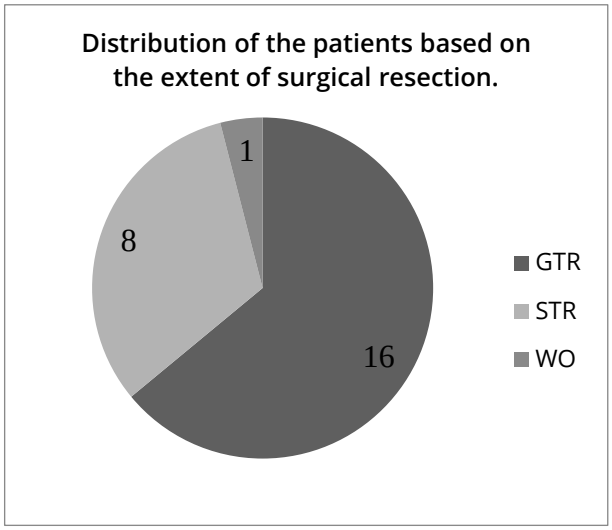

Figure 3. Distribution of the patients based on the extent of surgical resection

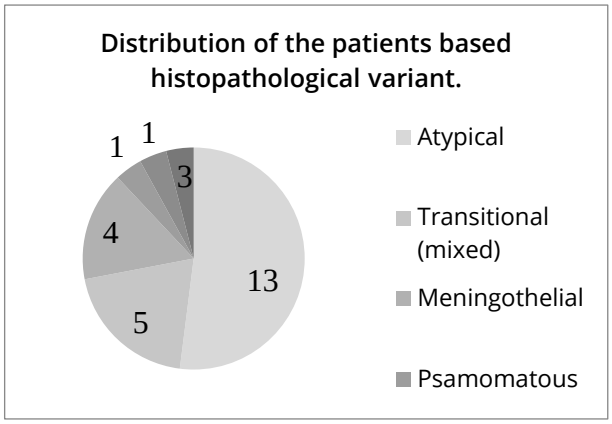

Figure 4. Distribution of the patients based histopathological variant

Discussion

Intracranial tumors can be divided into primary and secondary lesions, intra-axial or extra-axial. Most common origin structures for extra-axial tumors are cranial nerves and meninges [4]. Meningiomas, tumors arising from arachnoidal cap cells, comprise between 24 and 30% of primary intracranial tumors and most commonly affect females in their middle age or later adult life [1] [2]. These tumors are a heterogenous group, commonly defined by histopathological classification based on the WHO grading scale. However, it has been reported that the clinical aggressiveness of intracranial meningioma does not always correlate with WHO grading, some tumors displaying early recurrence and invasion, despite maximal surgical resection with of without

adjuvant radiotherapy [5]. The 2016 edition of World Health Organization (WHO) classification of Central Nervous System (CNS) tumors has integrated infiltrative growth of meningioma into the adjacent brain parenchima as a stand-alone criterion for diagnosing and atypical meningioma [3]. Behling et al. studied the prognostic significance of intraoperative detection of infiltrative growth of primary meningioma and reported that the combination of intraoperative detection and histopathological assesment of central nervous system invasion is an independent prognostic factor for recurrence and gives a better risk-adapted tumor classification [6]. Brain invasion could also be predicted based on preoperative MRI scans. Ong et al. reported that large peritumoral edema was significantly higher in invasive meningioma and enlarged pial feeding arteries, a rare finding, was only seen in brain-invasive meningiomas, while a complete cerebrospinal fluid cleft was only found in non-invasive meningiomas [7]. Joo et al. published an imaging-based model that combines interface radiomics and peritumoral edema, in order to predict brain invasion by meningioma [8]. In our study, we found brain parenchima invasion in 8 out of the 25 patients with aggressive meningioma (32%). The primary treatment of intracranial meningioma remains safe maximal surgical resection, being an independent prognostic factor for tumor recurrence [9]. Diagnosis of meningioma is based on histopathological examination of the surgical or biopsy sample. However, Karabagli et al. studied the prognostic significance of histopathological features of aggressive meningioma regarding the recurrence rate and found that no feature could be used to predict the recurrence rate [10].

Conclusions

Aggressive meningiomas, characterised by rapid growth and involvement of adjacent brain tissue, blood vessels and bone, can be considered a different phenotype of tumors, not previously mentioned in the WHO classification, with a distinct pattern of evolution and postoperative recurrence. Further studies are needed to better asses the criteria for diagnosing this type of tumors.

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The importance of Nuclear Magnetic Resonance (MRI) in the diagnosis of cerebral cavernomas. Case presentation

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Keywords
cavernomas, GKS, neurosurgery

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ABSTRACT

Introduction: Cavernomas are one of the four types of vascular malformations which develop in the central nervous system. From an imaging point of view, they are low flow small vessel malformations that cannot be seen on conventional angiography and are rarely visible on CT. They can be seen on MRI because of the para-magnetic haemoglobin break-down products within them.

Case presentation: A 35 years old male presented at the emergency room following a tonic-clonic seizure, without urine emission. After a clinical exam, it was decided to perform a cerebral MRI with contrast substance and angiographic sequence. Clinical and imagistic results showed a superficial left temporal cavernoma, which showed signs of recent bleeding. After the surgery, the patient has no neurological deficits and is discharged afebrile and without any other symptoms. At 6 weeks after the surgery, the patients returned for neurosurgical reevaluation in perfect neurological condition, without motor deficit or intracranial hypertension.

Conclusions: Cavernomas are angiographic cryptic vascular lesions that need an MRI investigation in order to appreciate them correctly.

INTRODUCTION

Cavernomas are one of the five types of vascular malformations which develop in the central nervous system, representing about 5-15% in

total. Cerebral cavernomas are cryptic angiographic lesions, classically defined as dilated vascular structures, with thin walls, located in the CNS (central nervous system), without any cerebral parenchyma interposed. [1,2]

In 1984, McCormick presented a study in which out of 5734 autopsies, only 19 cavernomas were discovered. This results in an incidence of 0.34%. A few years later, Otten et al report 131 cases of cavernomas out of a group of 24,535 autopsies. Thus, the incidence was 0.53%. [3]

According to McCormick's 1966 classification, neurovascular malformations can be divided into 5 large categories: [4]

- Telangiectasias
- Varicose veins
- Cavernous malformations
- Arteriovenous malformations (AVM)
- Venous angiomas

This classification was later modified: varicose veins were combined with venous malformations/venous angiomas and were put together in the category of venous developmental abnormalities (ADV). Several pathological classification criteria for each malformation have been suggested in the literature, but their nomenclature and structuring criteria are ambiguous and variable. In addition, cases of mixed forms and transitions from one form to another have been reported. Also, in the literature there are cases of coexistence of these malformations. The most common malformation associated with cavernomas is ADV. Another common combination is capillary telangiectasia. A few similarities such as pontin damage, the presence of a family form and multiplicity are reasons to consider telangiectasias a precursor to cavernomas. [3]

The term "cavernoma" was used for the first time by Rokitansky in 1846 and it was referring to a vascular lesion located in the brain. Later, in 1956 Rudolf Virchow made for the first time a histopathological description of these lesions. In 1956, Crawford and Russel introduced the term cryptic, to describe an arterio-venous pathology or venous hamartomas located in the encephalon and which often led to hemorrhage. Later, this term was used for the cerebrovascular lesions which couldn't be observed on angiography, along with the term „angiographically occult vascular malformation". The current nomenclature includes the following terms: cavernoma, cavernous angioma, cavernous hemangioma or cavernous malformations.[5]

The use of MRI leads to the diagnosis of cavernomas even before the histopathological diagnosis. The right treatment of these lesions requires a good knowledge of epidemiology, histopathological characteristics and of their natural evolution.

The clinical picture of cavernous angiomas varies significantly, by including asymptomatic forms which are discovered on CT or MRI examination (performed for a headache syndrome or after a traumatic event), but also forms discovered during autopsy after a fatal intracranial hemorrhage.

NEUROIMAGING DIAGNOSIS

Today, the advances in neuroimaging allow the diagnosis of cavernomas even before the histopathological exam.

The CT examination shows a spontaneously hyperdense lesion, given the inhomogeneous hemosiderin impregnation, with a round well-defined contour or irregular shape. After administering the contrast substance, cavernomas have different behaviors, in some cases appearing filled with contrast substance, especially if the examination is performed tardy. It is worth noting that these lesions are characterized by a slow flow and that in some cases, calcifications can be seen at this level.

The MRI examination represents the „gold standard" for the diagnosis in most cases. The typical image for a cavernoma is a well-circumscribed lesion, with an inhomogeneous "popcorn" appearance and an hypointense ring on the outside which represents the hemosiderin impregnation. Traces of older or more recent microhemorrhages can be seen in the lesion or in the adjacent areas. Rarely, a draining vein can be seen. In the T2 sequence of MRI we can see a hypointense area at the periphery of the lesion due to the edema of the parenchyma. (Figure 1)

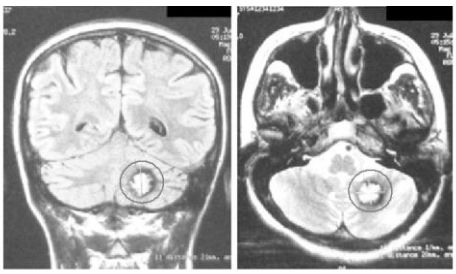

Figure 1. Cerebral MRI: left infratentorial cerebellar

cavernoma. (From the personal collection of Prof. Alexandru Vlad Ciurea, MD. PhD.)

Cerebral angiography is negative in most of the cases, cavernomas representing most of the occult vascular malformations. Rarely, it can show an avascular area or a capillary cluster. Usually, it is not indicated for cavernomas diagnosis unless it is necessary to obtain information regarding the vascular anatomy of the region or if an association with another vascular malformation is suspected.

Therapeutic attitude

Cavernomas, being by their nature well-defined lesions, with feeding vessels with a reduced blood flow, offer the premises for a total surgical resect Currently, there is a general attitude of extending surgical indications even in young patients, minor symptoms, thus removing the risk hemorrhage and its consequences. therapeutical attitude is possible thanks to advances in neuroimaging and the introductio neuronavigation, it is worth noting complications may occur in lesions with critical locations: cortical or subcortical cavernomas of eloquent areas or deep regions, such as the basal nuclei, thalamus, corpus callosum, paraventricular or brainstem.

Case presentation

Male patient, 35 years old, with no neurological pathology associated, came in the Emergency Room of Sanador Clinical Hospital following a tonic-clonic seizure, without urine emission. Following the neurological and neurosurgical consult, it was decided to perform a cerebral MRI with contrast substance and angiographic sequence. (Figure 2)

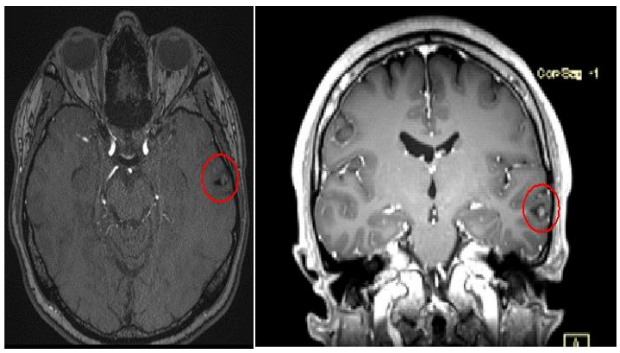

Figure 2. Cerebral MRI with contrast substance which shows a left temporal cavernoma, with recent haemorrhage.

Clinical and imagistic evaluation of the patient showed a superficial left temporal cavernoma, which showed signs of recent bleeding. Together with the neurosurgical team from Sanador Clinical Hospital, it is decided to perform the total ablation of the cavernoma using Kinevo 900 operating microscope and neuronavigation.

After the surgery, the patient has no neurological deficits and is discharged afebrile and without any other symptoms. At 6 weeks after the surgery, the patients returned for neurosurgical reevaluation in perfect neurological condition, without motor deficit or intracranial hypertension. This is confirmed by the postoperative MRI with contrast substance. (Figure 3)

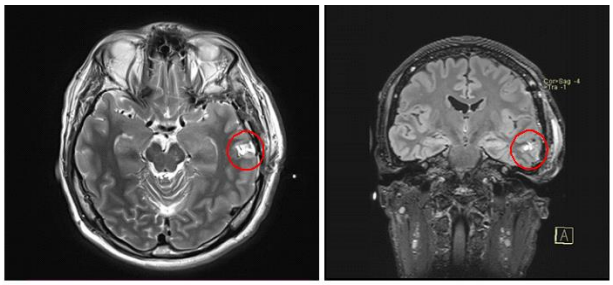

Figure 3. Postoperative cerebral MRI with contrast substance which shows total ablation of the left temporal cavernoma.

Discussions

Cavernomas are low flow small vessel malformations that cannot be seen on conventional angiography and are rarely visible on CT, so if we want to be certain of the diagnosis, we must perform an MRI. This type of imaging can show us the cavernous malformations because of the para-magnetic hemoglobin break-down products within them.

Over time, it has been debated what is the best treatment for cavernomas, between surgical approach, radiotherapy (GKS) and conservative treatment. According to the literature, the best approach is the neurosurgical one in the case of symptomatic, superficial lesions that are not located in the eloquent area. For the other cavernomas (asymptomatic, multiple, located in eloquent or deep areas) the risk-benefit ratio must be balanced. So, it will be decided together with the patient, between the surgical approach and the conservative treatment.

H. Bertalanffy et al. (2001) presented an analysis that consist 72 patients operated in 5 years, of which 24 had the lesion located within the brainstem, 18

within the deep white matter of the hemispheres, 12 in the basal ganglia or thalamus, 11 in superficial areas of the hemispheres and seven within the cerebellum. They reinforce the fact that angiography was the first imaging study used to see cerebrovascular malformations, but it shows no pathological changes. In the mid-1970s, the computed tomography (CT) became available and the detection of symptomatic cavernomas increased significantly, but this kind of imaging study has poor specificity. The most important and with the highest accuracy imaging study is MRI.[6] Rigamonti et al., being one of the firsts to describe the MRI features of cavernomas, are recalled in this study for their article in which they presented the differences between CT scan and MRI. From 10 patients, CT scans detected 14 lesions, while MRI detected 27 distinct lesions, so it can be seen how specific is MRI besides CT scan for the cavernous malformations diagnosis.[7]

D. Cavalcanti et al. (2011) described that genetics have an important part in cavernous malformations. Cavernomas can be both sporadic and familial. According to them, "half of CCMs are familial, and they inherited in an autosomal dominant fashion with variable penetrance". The most of familial CCMs are identified on MRI as multiple lesions. This multiplicity of lesions is characteristic in up to 84% of familial cases, whereas it is reported in 10%-33% of supposed sporadic cases. Annually, up to 6.4% of familial cavernomas can bleed and become symptomatic. To date, 3 distinct loci have been mapped in different families, CCM1, CCM2 and CCM3. These 3 loci account for 70%-80% of all cases of familial CCMs. Multilocus linkage analysis showed 40% of inherited cases that CCM1 account, 20% for CCM2 and 40% for CCM3.[8]

The radiotherapeutic approach for cavernomas has been in constant debate since the invention of Gamma Knife Surgery. Still, this controversy reached a conclusion when one of the founders of GKS, Ladislau Steiner published his comprehensive comparative study on this subject. L. Steiner et al. (2010) came to the conclusion that GKS it is not an effective approach for cavernous malformations and the surgical approach remains the best choice in treating this pathology.[9]

J. K. Liu et al. (2010) found in their article about cavernous malformations that the CT scans showed the OPH CMs as suprasellar hyperdense masses. Cerebral angiography did not reveal any arterial feeding vessels. MRI was performed at 88% of cases and the cavernomas could be seen as heterogenous with mixed signal intensities suggestive of different ages of blood, this appearance often described as a "popcorn-like" lesion.[10]

In another case presentations similar to ours, P. Feizi et al. (2020) described that a 50 years old woman has presented to the emergency room following new onset seizures and express her symptoms as right arm jerking, drooling, and encephalopathy. CT scans without contrast were effectuated and the results were multiple supratentorial and infratentorial hyperdensities measuring up to 8 mm, which were concerning for possible hemorrhagic metastases in the setting of history of malignancy. [11]

An MRI was performed too, with and without contrast, and was demonstrated that some of the lesions had peripheral vasogenic edema, and internal hyperperfusion. Based on those imaging and clinical data and the patient`s known history of thyroid carcinoma, the first diagnosis was "possible multiple hemorrhagic brain metastases". Three-month follow-up MRI of the brain demonstrated vasogenic edema and left parietal lesion with a surrounding hemosiderin ring and heterogeneous internal signal now able to be visualized. So, the diagnosis of cavernous malformations became evident.[11]

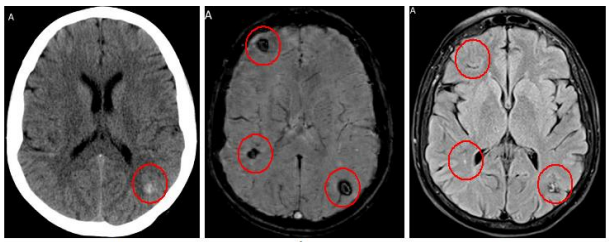

Figure 4. (a) CT scan; (b) MRI with SWI sequence; (c) T1 MRI
Image source: Feizi P, Lakhani DA, Kataria S, et al. Multiple cerebral cavernous haemangiomas masquerading as haemorrhagic brain metastases. Radiol Case Rep. 2020 Aug 20;15(10):1973-1977. Licensed under CC BY-NC-ND 4.0; © 2020 The Authors

CONCLUSIONS

Cavernomas are angiographic cryptic vascular lesions which need an MRI investigation in order to appreciate them correctly. In the case of small cavernomas, such as the one presented, the CT examination does not reveal the lesion. Thus, MRI is a valuable investigation for neurosurgical

emergencies, especially if the patient has a new comitial seizure, is young and does not have other neurological pathologies associated.

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Giant, primary, hydatid cyst of the gluteal region. Case report

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ABSTRACT

Background: Primary hydatid disease in the muscle is extremely rare, resulting in either the spread of cysts spontaneously or after operations for hydatidosis in distant regions.

Methods: Report of an unusual case of primary hydatid cyst in the gluteus muscle, behaving as enlarging soft-tissue tumour, with a review of the literature.

Results: Magnetic resonance imaging revealed an intramuscular cyst in the gluteus muscle; and no cyst existed in any other location. The cyst was excised totally, and the diagnosis of muscular cystic hydatidosis was confirmed by histopathologic examination. In follow-up of two years after the operation, there has been no recurrence in either patient.

Conclusion: The involvement of the gluteus maximus muscle without the evidence of hepatic or pulmonary disease is rare, characterized by slow development, but a major local extension must be considered in the differential diagnosis of a cystic mass with well-defined margins in the extremities of individuals from endemic regions. Physical examination, serology results and radiological findings should be interpreted with care, especially in hydatid cyst endemic countries. Surgery is still the treatment of choice, with total cyst excision.

Keywords
cystic echinococcosis, primary musculoskeletal location hydatid cyst, gluteal region hydatid cyst

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INTRODUCTION

Human echinococcosis is a zoonotic disease, caused by ingestion of ova of the cestode Echinococcus granulosus (Eg) and formation of the larval stage in different organs and tissues. Cystic echinococcosis (CE) has become an important burden on human population in endemic area and no endemic countries, by infected people migration and livestock exchange (1). CE is responsible for the loss of 1–3 million disability-adjusted life years per annum and severe economic losses to the livestock industry probably amounts to US$ 2 billion (2). Romania was listed in 1995 among the countries with the highest prevalence of CE worldwide. Nevertheless, latest study Heracles FP7 EU Project oct 2013 - sept 2018 confirm that CE has a prevalence of 0.41%000 in

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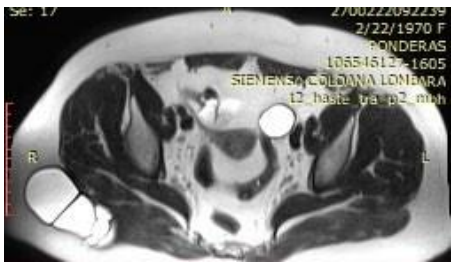
Romania (3). Molecular characterization belonged to the G1-G3 complex (E. granulosus), which contains the most widespread and infective strains of the parasite, also a non-G1-G3 genotype of E. granulosus, likelihood, a G7 genotype, which is often found in pigs and dogs in most countries of eastern and south-eastern Europe (4). Primary musculoskeletal location hydatid cyst are rare: only 2 to 3%, possibly most affected sites are the neck, thigh and the paravertebral region, the psoas muscle, the thoracic wall muscles, sartorius, and quadriceps muscles. On the gluteal region hydatid cyst are very rare (5-19). Clinical, diagnosis and therapeutic considerations are discussed.

Case presentation

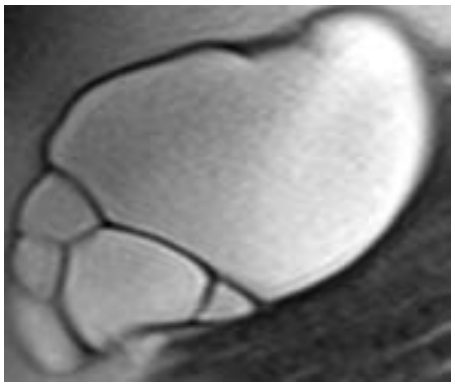
A 53 years old woman, seamstress in town, presents to his primary care provider with a 6 months history of lower back pain, stiffness. The pain was intermittent, improves after rest without medication, worse with activity and in the morning when changing the position of the body from supine position to orthostatism, at the effort of coughing, sneezing, defecation, sometimes with right irradiation on the back of the buttocks, thighs, left calves to the heels; but she was able to lean forward. Also, the patient has been reporting for about 4 months a painful mass installed insidiously at the right gluteal region, firm consistency, normal skin, which has progressively increased in the last 2 weeks before admission. She does not have any known chronic medical conditions, also she has never smoked, but she does drink an occasional glass of wine with dinner. No significant family history of disease is reported. She has not noted any other masses on his body with self-examination, no history of rash, fever, malaise, anorexia, no weight loss, neither she nor other family members came in contact with pets.

Upon physical examination, this patient has a blood pressure of 131/75 mm Hg and a heart rate of 65 beats/min. His respiratory rate is 7 breaths/min and his temperature is normal at 98°F (36.7°C). His cardiovascular and respiratory findings are normal; specifically, no murmurs or rubs are detected. The patient has no photophobia, eye redness, or decreased visual acuity. Upon examination of the back, flexion of the lumbar spine is possible, without limited range of motion with rotation and lateral flexion at the lumbar spine. The right buttock is painful to the touch. On clinical examination we found a painful mass in the posterior lateral region of the upper third of the right thigh, with normal looking skin on top, of firm consistency, 30 cm long axis, 18 transversal axis, fixed to muscle with no evidence of local inflammation. No motor, sensitive deficit or abnormal hip mobility were encountered. The remainder of the physical examination is within normal limits.

The biological assessment was unremarkable: it reveals a white blood cell count of 4.6 × 103 cells/μL (reference range, 4.5-11 × 103 cells/μL), a hemoglobin level of 13.7 g/dL (reference range, 13.5-17.5 g/dL), a hematocrit of 43% (reference range, 41% to 50%), eosinophilic count of 2.8 (reference range, 0.8-8.1 %), a platelet count of 120 × 103 cells/μL (reference range, 150-450 × 103 cells/μL); electrolyte values are within normal limits, only the erythrocyte sedimentation rate was 35 mm/hr (reference range, < 10 mm/h). The diagnosis was made by lumbar and pelvic magnetic resonance (MRI) which brought into evidence of lumbar disc protrusions at L2-L5, without root conflict, lumbar vertebral marginal osteophytes; multiple cystic formations, single or partitioned cysts, on the posterior and lateral surfaces of the root of the right thigh and the gluteal region, mainly occupying the gluteus maximus and sub- aponeurotic fat. They had a thin wall in enhanced T2 hypo-intense after injection of gadolinium with variable signal fluid content, the largest measured 13 x 12 cm (Fig.1).



A.



B.

C.

Figure 1. Primary, multiple hydatid cysts of the right gluteal region MRI, enhanced T2 hypo-intense after injection of gadolinium: A axial section, B & C coronal sections.

A total resection under general anesthesia was performed by an extended posterior lateral approach of the thigh. Intraoperative finding highlighted a very thick hydatid pericyst with tight adhesion to the gluteus maximus muscle bundles, composed of inflammatory tissue, the hydatid exocyst and the hydatid endocyst with irregularly shaped daughter cysts of different sizes and hydatid fluid. Despite our anatomical exposure and delicate dissection of the cyst, a minimal breach with hydatid fluid exteriorization was found. The cyst content was appropriately evacuated and the surgical field was soaked with hypertonic saline (Figure 2).

A B C D E

Figure 2. Intraoperative pictures: A. General aspect of the hydatid cyst during dissection, B&C several irregularly shaped daughter cysts of different sizes, D the hydatid exocyst, E thick hydatid pericyst with tight adhesion to the gluteus maximus muscle bundles completely dissected.

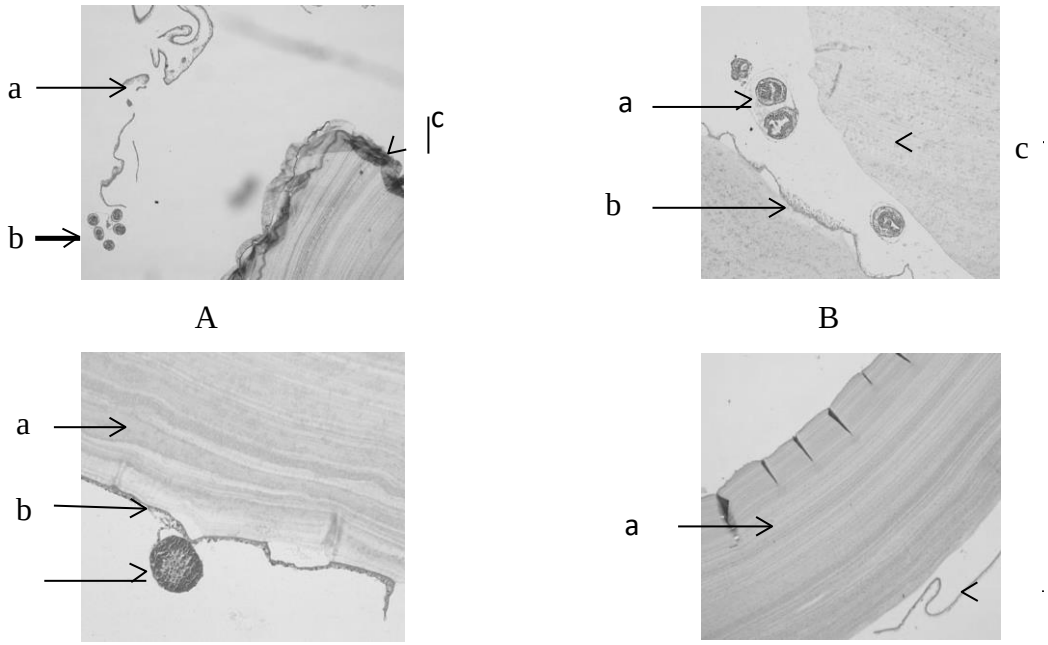


Figure 3. The histopathologic examination in our case:
A H.E col. obj. 20 X 10, a. the inner germinal layer, b. protoscolices, c. the middle-laminated membrane;

B H.E col. obj. 20 X 20, a. protoscolices, b. the inner germinal layer, c. the middle-laminated membrane;
C H.E col. obj. 20 X 20, a. the middle-laminated membrane, b. the inner germinal layer, c. daughter vesicle, attached by a pedicle to the germinal layer;
D H.E col. obj. 20 X 10, a. the middle-laminated membrane, b. the inner germinal layer.

The serology was positive for E.g., and the extension assessment: cerebral MRI, pulmonary and abdominal CT were normal.

The histopathologic examination (Figure 3) confirmed the diagnosis of hydatid cyst.

Results

The post-operative evolution was uneventful. The patient had completed a chemotherapy with an anti-helminthic agent Albendazole (Zentel) 15 mg / kg /day, for the next 3 months postoperatively; 6 months after, there was no evidence of recurrence or complications.

Discussion

Hydatid cysts result from infection by the Echinococcus tapeworm species and can result in cyst formation anywhere in the body. Typically, the primary cyst locations hydatid are the liver and lungs. This can be explained by the significant vascularization of these structures that can be filters. Rarely, the hydatid cyst occurs at the musculoskeletal tissues, with slow and relatively asymptomatic evolution, without hepatic involvement, as in our case. Primary hydatid disease in the muscle is extremely rare, resulting either from the spread of cysts spontaneously or after operations for hydatidosis in distant regions.The most reported sites are the neck, thigh and the paravertebral region, very rare at the gluteal region (5-7)(10-20).

In general recognition of hydatid disease is possible, sometimes even when serologic tests had been non-conclusive (9). In endemic areas the etiological diagnosis of the cyst can be difficult in some cases. Accurate diagnosis could be made using pelvic radiograph, the USG exam, the first-line radiological examination - in our case could have highlighted multiple hydatid cysts, within the stage 2 – septated cystic lesion and stage 3 - cystic lesion with the daughter lesion, see the Gharbi ultrasound classification (9). CT scan rarely shows typical characteristics of the hydatid cyst, possible wall calcifications, other hydatid cyst localizations and MRI – the reference examination as in our case is useful, especially in the case of giant cysts, assessing the size of the mass, relationships with neighboring tissues and nervous and vascular structures (8), recognizing complications (e.g., rupture, infection of cysts)(6), correlated to macroscopic and microscopic pathology (20). Also MRI should be considered for differential diagnosis between slow-growing tumors, hematomas, myositis, and abscesses (19). Total cyst excision is the primary treatment method, avoiding in suspected hydatid cysts biopsy and aspiration to prevent rupture and spread (8)(14)(20). In case of the hydatid cyst rupture hypertonic saline irrigation of the surgical field is the best method to prevent recurrences by antigens spreads to the muscles, inflammatory reaction complicated by a secondary bacterial infection (6)(20). As a particularity of the presented case there was a concomitant lesion generated by lumbar protrusions with right root irritation phenomena and buttock hydatid cyst.

Conclusions

The involvement of the gluteus maximus muscle without the evidence of hepatic or pulmonary disease is quite rare, characterized by a slow development, but a major local extension must be considered in the differential diagnosis of a cystic mass with well-defined margins in the extremities of individuals from endemic regions. Physical examination, serology results and radiological findings should be interpreted with care, especially in endemic areas. Surgery is still the treatment of choice, with total cyst excision, followed by chemotherapy with an anti-helminthic agent.

Abbreviations

echinococcus granulosus (Eg)
cystic echinococcosis (CE)
ultrasonography (USG)
tomograph computer (CT)
magnetic nuclear resonance (MRI)

Conflicts of interest

There are no conflicts of interest.

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Important controversies in lumbar spine surgery: which patients benefit from lumbar spinal fusion and who should be fused? Literature review

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Keywords
lumbar spinal fusion, surgical outcomes, conservatory & surgical treatment, instability, spondylolisthesis, lumbar spinal stenosis, Oswestry disability index

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ABSTRACT

Considering the rising tendency in the application of lumbar spine devices, a rigorous selection of candidates for lumbar spinal fusion must follow the benefit of the patient in terms of a better outcome than classical techniques or conservatory treatment. We pulled essential information from scientific sources regarding the clinical results of patients who underwent fusion surgery to sift patients who do better from fusion.

We found out that imagistic proof of instability such as spondylolisthesis associated with lumbar spinal stenosis and refractory pain takes the most from spinal fusion procedures. Oswestry disability index improvement along with restoring the function and reduction of pain remained the postoperative desires of a successful fusion. Clinical amelioration with bracing test prior to intervention was a predictor of better results after fusion. Exclusion criteria like psychiatric disorders and prior lumbar spine surgery were highlighted since studies demonstrated that they are bad predictors of outcome in spinal fusion surgery.

Laminectomy was nowhere implemented in the literature as to be urgently fused since only about 20% of patients manifest instability after this classical procedure. Iatrogenic segmental instability after laminectomy, radiologically proven should be a candidate for spinal fusion. These procedures have high costs and high rates of complications putting the patient's functional status and quality of life at uncertainty since there is still a lot of debate in this area of spinal neurosurgery.

Motto: "Outcome may be improved by more careful selection of patients and by performance of an adequate surgical decompression" (Deen Jr, 1995)

INTRODUCTION

"Which patients should be fused?" remains a big controversy. Lumbar surgical interventions for disc herniation, lumbar stenosis, with or without scoliosis, spondylolisthesis are more frequent, especially for

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older patients, who request for a bigger autonomy (2-4). For several patients, on the medium and long term outcome, evolution may be complicated by postsurgical instability after extensive multilevel surgery, osteoporosis; the more rapid progression of degenerative changes, the suboptimal decompression of the contralateral side because of the impaired view of the target area and a slower postoperative rehabilitation may accentuate compression, especially to older patients, affecting their request autonomy (1)(5).

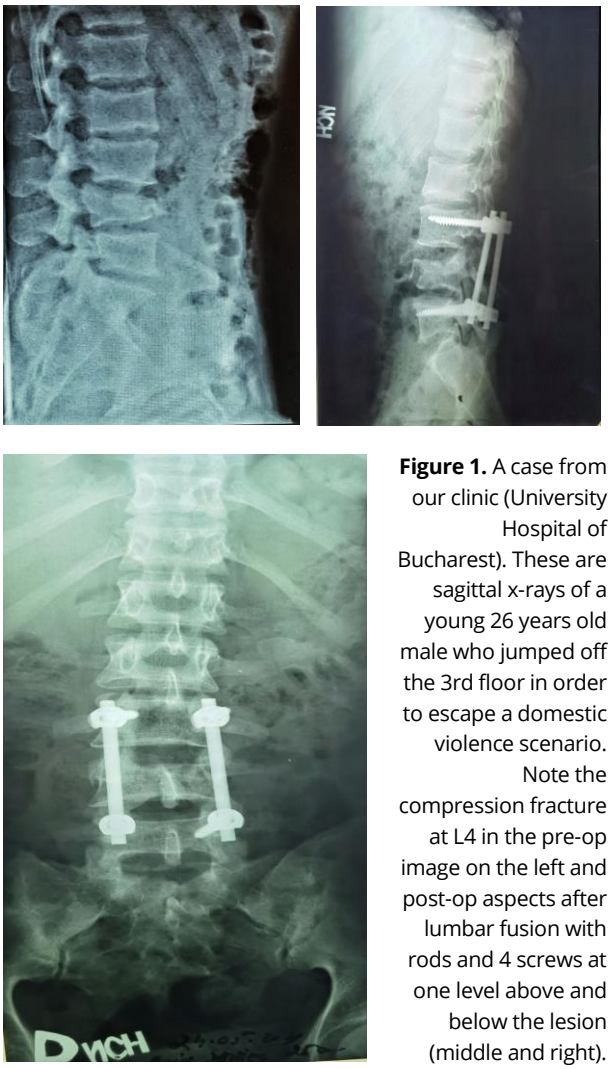

Figure 1. A case from our clinic (University Hospital of Bucharest). These are sagittal x-rays of a young 26 years old male who jumped off the 3rd floor in order to escape a domestic violence scenario. Note the compression fracture at L4 in the pre-op image on the left and post-op aspects after lumbar fusion with rods and 4 screws at one level above and below the lesion (middle and right).

Material and methods

Radiological and clinical pictures of instability are key features in stratifying patients who gain the most from fusion procedures. Spinal spondylodesis is suitable for deformities and instability but lacking proof of effectiveness in primary disc herniation and lumbar spinal stenosis without instability (3).

Spondylolisthesis represents the classical x-ray feature of spinal instability (6)(7). A meta-analysis made in 2017 on 302620 patients with LIF demonstrated a major clinical improvement of individuals who were fused, while the complications and reintervention risk compared with simple decompression limited the benefits brought by spinal fusion in lumbar stenosis with RR of 1,17 for CI of 95% - 1,06-1,28 compared with spondylolisthesis RR 0,75 for CI 95% - 0,70-0,80 (8).

Authors and Year	Class of evidence	Summary
SPORT – 2007 2009 & 2018	II	Randomized (n=304) and observational (n=303) spondilolysthesis surgical vs. conservatory. Fusion offered a better outcome after 2, 4, and 8 years of follow-up.
Ghogawala et. al. – 2016	I	66 patients with spondylolisthesis grade I. Simple decompression vs. decompression and LIF. Fusion improved the quality of life (4 years follow-up)
Chou et al. – 2009	II	A systematic review of 24 articles on fusion vs. conservatory for L LBP and spondilolysthesis Surgery was equivalent to intense PM&R

Table 1. Lumbar fusion in spinal canal stenosis with spondylolisthesis, modified after (9).

Lumbar back pain is common, unfortunately it's a vague symptom and determining what patients benefit from fusion surgery can be delicate. About 20% of patients with LBP are unable to work (10). A detailed clinical exam and PHI are essential in determining patients who have bigger chances of recovery after spinal fusion.

Multiple studies have demonstrated improvement after fusion in patients with lumbar stenosis and spondylolisthesis (tab.1). A multi-centered randomized study with a 2 year follow-up on 294 subjects with chronic LBP and imagistic evidence of lumbo-sacral degeneration found that all surgical fusion procedures used reduced pain, Oswestry score (tab.1) and improved function (10). Exclusion criteria were: radiologically proven

radicular compression, history of surgical intervention on lumbar spine and those with psychiatric disorders in treatment. All patients were refractory to conservatory treatment. Another randomized study conducted in 2003 on 64 patients with DDD and LBP for more than 1 year demonstrated improvement of ODI score similar to cognitive therapy and exercises (11).

While patients with mild spondylolisthesis do well from postero-lateral fusion with no instrumentation, degenerative disc disease gains the most from postero-lateral fusion with instrumentation, therefore type of surgical treatment should be in relation with the diagnosis (12). A common outcome predictor of fusion in everyday practice is bracing test. Important alleviation of pain after using a TLSO indicates a good outcome for lumbar spinal fusion vs. conservatory treatment. This test has value only in patients with chronic low back pain with no prior spine surgery (5).

0%-20% minimum disability	Activities of daily living are performed normally. No special treatment is required
21%-40% moderate disability	Patient has pain when standing, sitting or lifting weights. Normal activities are still performed well Conservatory treatment is nedeed.
41%-60% severe disability	Daily activities are affected as pain is increasing and becoming constant
61%-80% infirmity	Daily activities are interrupted Surgical intervention is mandatory
81%-100% "stuck in bed"	Patient lies in bed all day or dissimulates

Table 2. Interpretation of Oswestry disability index after filling a special questionnaire, modified after (4).

Discussions

Numerous descriptions regarding the stability of spinal column have been made still no defining consensus was reached. According to White-Panjabi (13)(14): instability means a loss of spine's ability to maintain under physiological conditions it's normal anatomical relationships at risk causing signs of irritation spinal cord/nerve root, pain or crippling deformities and to Louis (15) spinal stability is the cohesion of vertebral structures in all physiological positions. In contrast, spinal instability it's an important cause of lumbar back pain and important disability.

Diagnosing spinal instability can be challenging. Use of imaging like X-rays in flexion-extension and side-bending, standardised lumbo-sacral X-rays along with lateral flexion and extension radiographs – defining spinal instability as sagittal plane translation of 4 mm or more (13)(14), fluoroscopy, MRI(standard and dynamic) and CT scans can provide useful information. Dynamic X-rays in flexion and extension should not be replaced by MRI and CT scans in the assessment of spinal instability (16). Radiological documentation of instability should be performed preop, at 6 months and 3 years post op to demonstrate evidence of progressive segmental instability (2).

Instability could be responsible for stenosis; it could be associated with LSS symptomatic with intermittent mechanical pain; iatrogenic with symptomatic instability or without clinical signs (17)(18).

Spondylolisthesis, lumbar scoliosis may generate instability (19-21), also after decompression, the possibility of segmental instability should always be considered. Fusion procedures, especially those involving instrumentation are associated with increases in cost and complications, are used for pre-op, intraoperative instability or postop listhesis (22-24). Still there are several debatable aspects - subject of controversy: the criteria of instability, the spondylolisthesis or scoliosis grade, what kind of stabilization should be used with or without motion preservation, minimally or invasive intervention, the approach used: posterior, anterior or "circumferential", instrumentation increases the fusion rate?, implant failures and adjacent joints degeneration (25).

Spiking if stabilisation is needed, even if is better to stabilise without decompression, there are several aims to respect (2)(26):

- *treat a dynamic component* - patients with severe symptoms and radiographic evidence of excessive motion, greater than 4 mm translation or 10^{o} of rotation, who fail to respond to a trial of nonsurgical treatment;
- *prevent postoperatory instability* - stabilization is needed for confirmed preoperatory instability, large resections and abnormal articular orientation;
- *fusion* should be made to obtain a stabilization after arthrectomy, to correct a deformity, to avoid

a hypermobility, maintaining lordosis and foraminal size;
- *arthrodesis & instrumentation* there are several options: open - rigid stabilization systems with pedicle screw fixation, percutaneously, motion preservation: dynamic stabilization systems, facet arthroplasty - TFAS® Total Facet Arthroplasty System;
- *lumbar interspinous implants:* - Colfex, Wallis, Diam, X-Stop, a.s.o.

Current guidelines reject stabilization by default on the basis of an extensive literature search (2)(23)(24). Even after a laminectomy only 20% of cases need a fusion procedure (22). The reactive degenerative changes obviously prevent manifest segmental instability, even after decompression if more of 50-66% of articular process or isthmus are conserved, without discal space violation (25). There are several surgical alternatives (27-32):

- *Open:* bone deposition, iliac bone graft, instrumentation rigid or dynamic with pedicular screws, inserted with the help of a spinal navigation system, interbody cages;
- *Microscopic;*
- *Percutaneously;*
- *Facet arthroplasty;*
- *Interspinous spacers* (X-STOP, DIAM, COFLEX, HELIFIX) with 45% improvements after two years, an intermediate option between conservative and surgical treatment - "does not burn bridges", for patients with mild symptoms, to those that can't undergo or refuse more extensive surgery, as a temporary solution, "addressing the problem within the canal without entering the canal". Interspinous spacers advantages are: disc not removed, no pedicles used, opening of foramens, unloading of the posterior part of the disc, of the facets. There is also less risk of significant complications, no direct manipulation adjacent to the neural structures; the risk of neurological deficit (paralysis; dural tears; etc) decrease to a minimum. Such interspinous spacers can't be used in the following anatomic variants: markedly decreased interspinous distance (kissing spine–like), with concomitant facet joint hypertrophy, a posterior V-shaped interspinous area, limited accessibility of the space between the base and the tip of the spinous process because of facet joint hypertrophy and variations in the shape of the inferior surface of the spinous process.

Combined LSS with degenerative spondylolisthesis and posterior arthrosis at one or several levels. In such cases it's more frequent lateral LSS associated with disc hernia. Spondylolisthesis in itself is not an indication, except if there is > 4 mm translation in sagittal plane and 10° angulation flexion/extension. For such cases foraminal decompression, discectomy and fusion to all affected levels should be made (33). It is uncertain whether instrumentation: use of pedicle screws or metal cages help to fuse adjacent vertebrae or biologic agents - bone morphogenetic protein should be used to enhance osseous fusion (2).

Combined LSS with degenerative listhesis and posterior arthrosis at one or several levels. From the surgical point of view decompression in LSS may affect isthmus and generate iatrogenic instability because of arthrectomy, especially in a LSS with degenerative listhesis and posterior arthrosis. We should treat only the instable level (25). Several complications could be seen: overlying stenosis (by recurrence of a degenerative spondylolisthesis, hypertrophic flavum ligaments), disassembly of osteosynthesis by fracture instrumentation on a short and medium term, as a sign of pseudarthrosis.

Conclusions

Interbody lumbar fusion indication should be established on imagistic proof of instability and substantiated by perpetual clinical suffering refractory to conservatory methods. It's already demonstrated that large laminectomies should be avoided, lumbar decompression with fusion, at the symptomatic level should be made if medical treatment fails.

There is still a lot of work to do in this field of research since there is a lack of randomized studies that compare surgical outcomes with natural history of lumbar pathologies, classical techniques and conservatory measures.

On the other hand, there are some encouraging positive results of surgical fusion in patients with lumbar spine instability and associated degeneration, as a promising alternative detrimental to conservatory treatment, although psychiatric background and prior history of lumbar surgery should rise the alarm of surgeon, since the latter

were proved to be negative predictors of outcome in spinal fusion.

Abbreviations

CI Confidence interval
CT Computed tomography
DDD Degenerative disk disease
LBP Low Back Pain
LSS Lumbar Spinal Stenosis
LIF Lumbar Interbody Fusion
MRI Magnetic Resonance Imaging
ODI Oswestry Disability Index
PHI Personal History of Illness
PM&R Physical Medicine and Rehabilitation
RR Relative Risk
TLSO Thoracic Lumbar Sacral Orthosis

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Conflicts of interest

The authors declare no conflict of interest.

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Imaging characteristics, histopathological features and surgical considerations regarding aggressive meningiomas. Case series and review of the literature

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Keywords
aggressive meningiomas, clinicopathological features, imaging characteristics, surgical management

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ABSTRACT

Meningiomas are tumors of the meninges that arise primarily from arachnoidal cap cells, but they can also occur rarely as primary tumors in other localizations, such as within the ventricles. They stand for 24-30% of primary intracranial tumors and affect mostly women in their middle age or later adult life [1, 2]. Meningiomas can be classified, according to World Health Organization (WHO) classification of Central Nervous System (CNS) tumors, as benign (grade I, most frequently encountered type), atypical (grade II) or anaplastic (grade III), based mostly on histopathological criteria known to be associated with tumor progression, recurrence risk and survival. Since meningioma grading based on the WHO classification is the most important factor determining therapeutic management and tumor prognosis, there has been an increasing interest in adding new criteria for better characterization of these tumors. Thus, the 2016 edition of WHO classification recognized brain invasion as an independent criterion for atypical (grade II) meningioma diagnosis [3]. However, meningiomas that display aggressive features such as rapid growth and higher recurrence rate, can also involve blood vessels and bone. Hence, the authors aim to describe a different entity, aggressive meningiomas, not previously listed as a tumor

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phenotype in the WHO classification of meningothelial-cell tumors, with regard to pre-, intra- and postoperative methods for diagnosis and explore the implications on surgical strategies and adjuvant therapy.

Materials and methods

We performed a single-center retrospective study. We reviewed the files of all patients diagnosed with primary intracranial meningioma at the 4th Clinical Department of Neurosurgery, Bagdasar-Arseni Clinical Emergency Hospital, between January 2013 and December 2018 and identified the cases of aggressive meningiomas, characterized by either: invasion into the brain parenchyma, involvement of the major blood vessels, cranial vault bone lysis without involvement of the outer table of the skull or complete bone destruction and aesthetic deformity, as showed by preoperative imaging and confirmed by histopathological examination.

Results

We identified 291 patients with tumors meeting the required imagistic/histopathological criteria, from which we selected 2 representative cases for the current articles, aiming to better describe this tumor entity regarding pre-, intra- and postoperative aspect and therapeutic strategy.

FIRST CASE

A 65-year-old male was admitted to our department complaining of refractory headache ongoing for more than 3 months. His past history consisted of high blood pressure, permanent atrial fibrillation, type 2 diabetes mellitus, grade II obesity and chronic anticoagulant treatment. He denied any episodes of seizures or loss of consciousness, limb weakness, paresthesia, visual deficits, speech disturbances or vomiting. Clinical examination showed a small swelling in the right frontal region. Neurological examination showed no deficits.

Contrast-enhanced CT scan revealed a large hyperdense extra-axial lesion in the right frontal region, measuring 64/46 mm in cranio-caudal diameter, with a small area of important contrast uptake and associated bone lysis, producing mass effect on midline structures that appear displaced 6 mm to the left side.

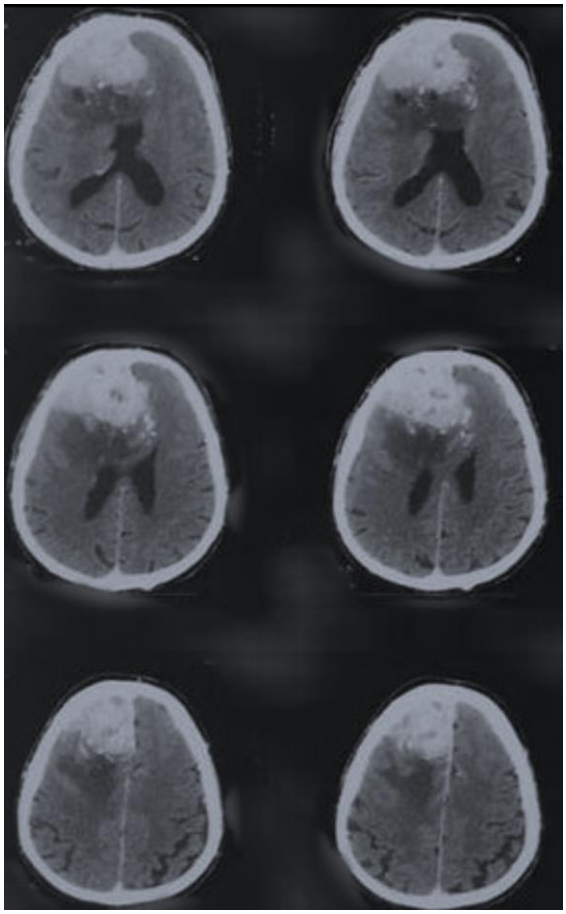

Image 1. Contrast-enhanced CT scan, axial section, showing a large hyperdense extra-axial lesion in the right frontal region, with a small area of important contrast uptake, bone lysis, and mass effect displacing midline structures.

Gadolinium-enhanced MRI scan revealed a large right fronto-basal extra-axial lesion displaying central necrosis and displacing the right lateral ventricle, anterior cerebral artery, falx cerebri and the superior sagittal sinus.

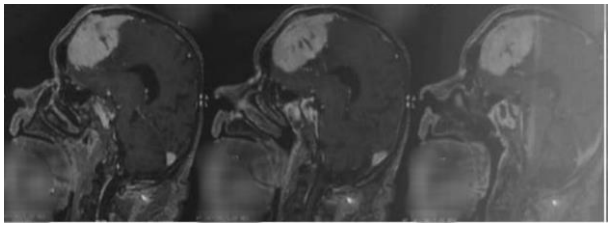

Image 2. Gadolinium-enhanced T1-weighted MRI scan, sagittal section, showing a large fronto-basal extra-axial lesion eroding into the adjacent bone.

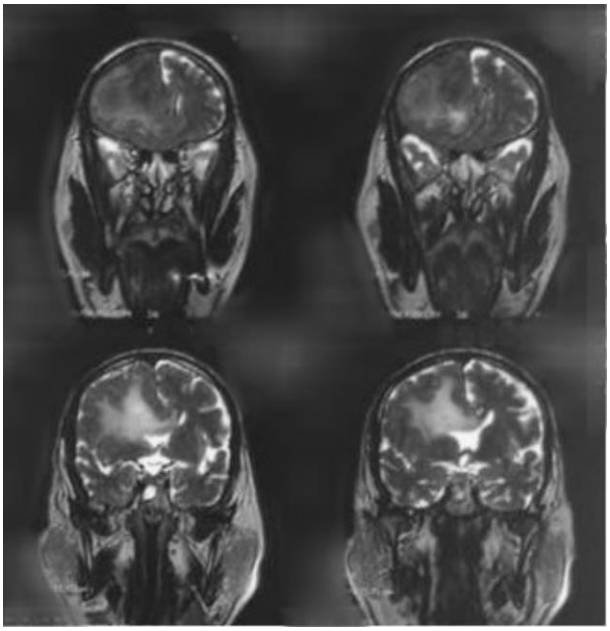

Image 3. Non-enhanced T2-weighted MRI scan, coronal section, showing a right frontal lesion with extensive perilesional edema and displacement of the midline structures.

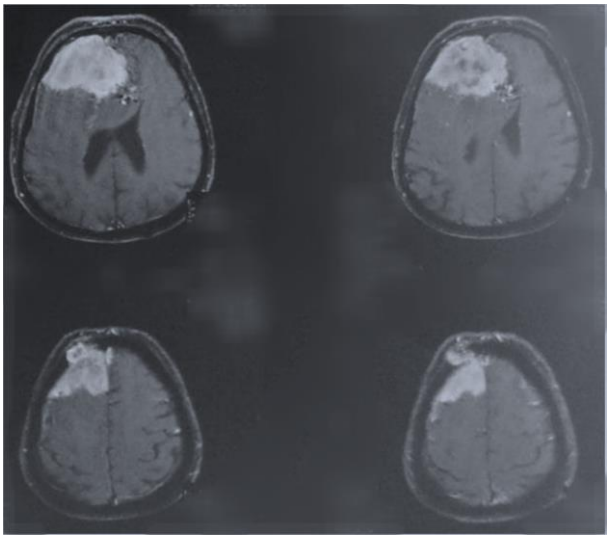

Image 4. Gadolinium-enhanced T1-weighted MRI scan, axial section, showing a large frontal extra-axial lesion eroding into the adjacent bone.

The lesion produced erosion of right frontal bone and showed homogenous gadolinium uptake. Angiography was performed in order to better describe the vascular supply of the tumor.

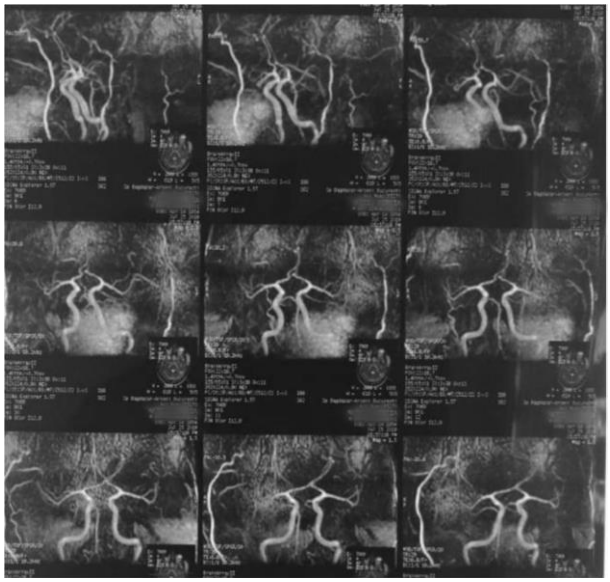

Image 5. Digital-substraction angiography showing prolonged vascular blush.

The surgical approach was aimed at gross total resection, as well as obtaining enough tissue sample for an accurate histopathological diagnosis with subsequent appropriate adjuvant therapy. A right fronto-temporal craniotomy was performed, revealing a reddish, well vascularized, firm tumor. Postoperative CT-scan (Image 6) showed gross total resection of the right fronto-basal meningioma.

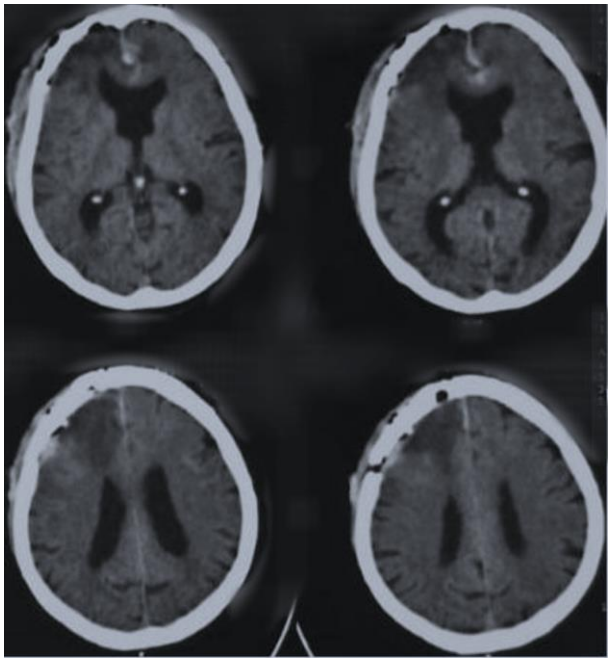

Image 6. Non-enhanced CT scan showing a right fronto-temporal craniotomy and no tumoral remnant.

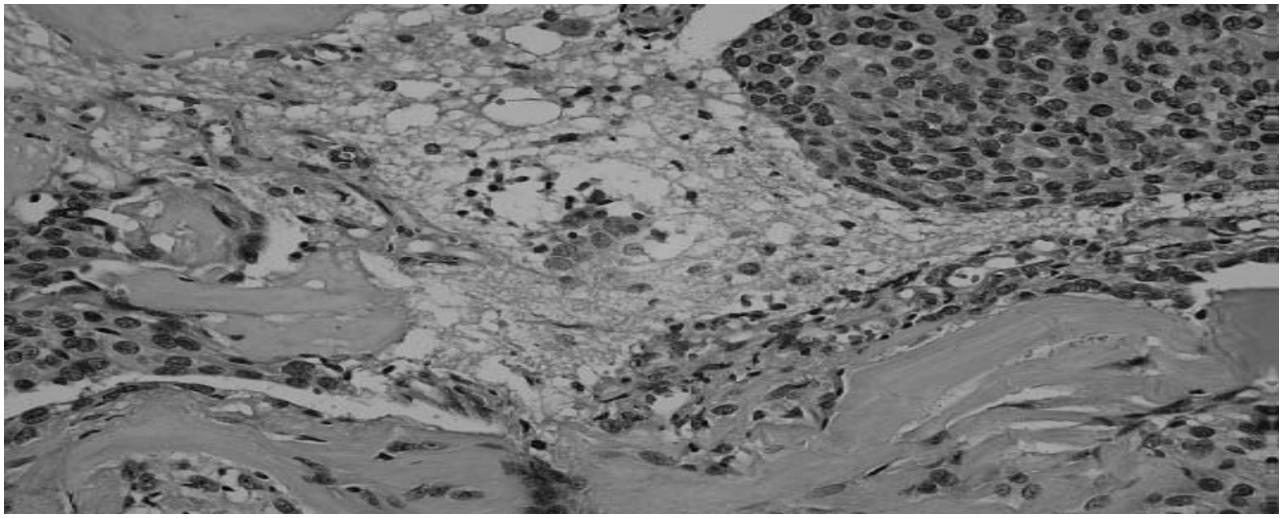

Image 7. Optic microscopy view of the intraoperative tumor sample, showing meningioma cells with atypical features and invasion into the adjacent parenchima and bone.

Postoperative evolution was favorable and the patient was discharged 7 days later

Second case

A 74 years old female was admitted to our department for progressive right upper and lower limb weakness. Her past history consisted of high blood pressure, ischemic heart disease, grade II obesity and bilateral lower limb venous insufficiency. She denied any episodes of seizures or loss of consciousness, visual deficits, speech disturbances or vomiting. Neurological examination showed right hemipharesis. Contrast-enhanced CT scan revealed a left parasagittal parietal extra-axial lesion, partially calcified and displaying homogeneous contrast uptake, measuring 56/33 mm in diameter, with perilesional edema that displaced median structures 6,65 mm towards the right side. The lesion seemed to be inserted on the meninges and determining osteosclerosis of the surrounding bone (Image 8).

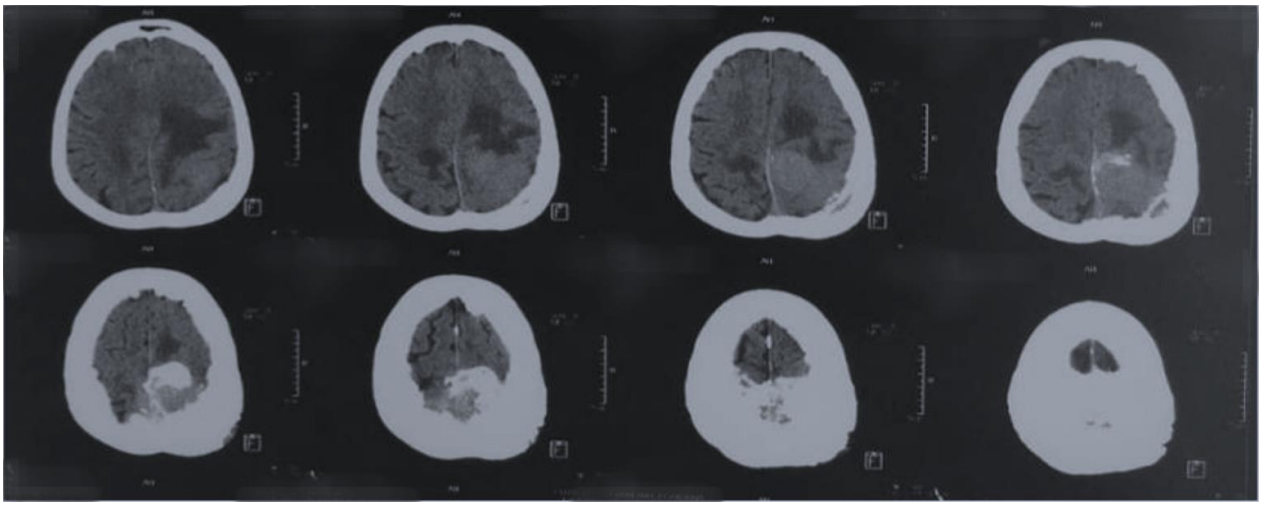

Image 8. CT scan showing a left parietal extra-axial lesion, partially calcified, with perilesional edema and displacement of the midline structures towards the right side.

MRI scan revealed a large left parietal lesion extending towards the right side, with perilesional edema, left lateral ventricle displacement and adjacent bone invasion (Image 9).

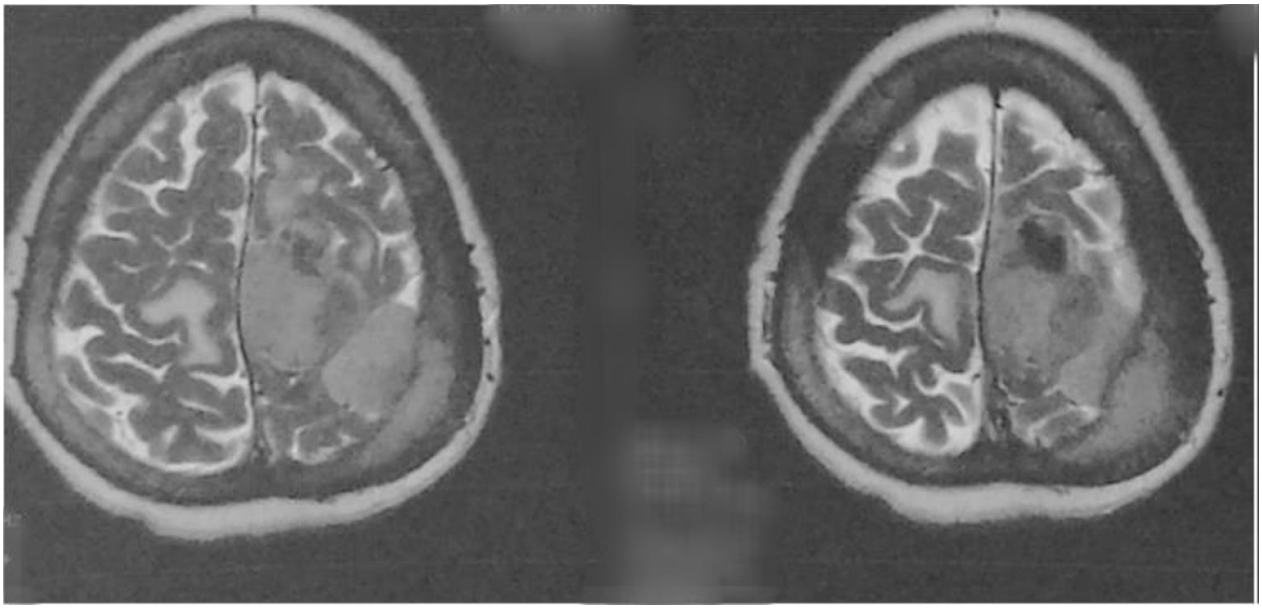

Image 9. T2-weighted MRI scan, axial section, showing a large left parietal lesion extending towards the right side, with perilesional edema, left lateral ventricle displacement and adjacent bone invasion.

Histopathological examination showed atypical meningioma cells, with invasion into the nervous and destructive infiltration of adjacent bone tissue (Image 10).

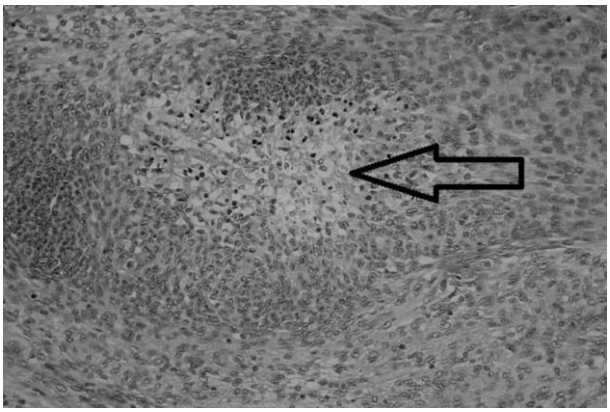

Image 10. optic microscopy view of the intraoperative tumour sample, showing meningioma cells with atypical features and direct invasion into the adjacent brain parenchima and bone.

Postoperative evolution was favorable and the patient was discharged 7 days later.

Discussion

Meningiomas are a heterogenous group of lesions that can be classified, based mostly on histopathological criteria, as benign (grade I, most frequently encountered type), atypical (grade II) or anaplastic (grade III), according to WHO classification of CNS tumors. However, other characteristics have started to be recognized as independent criteria for diagnosing higher-grade meningiomas. Nazem et al. studied the genomic alterations supposed to be encountered in many meningiomas patients, such as losses on chromosome 22 (WHO grade I), losses on chromosomes 1p and 14q (WHO grade II) or modifications on chromosome 9p and 17q (WHO grade III), but these changes have yet to be listed as independent diagnostic criteria (4). The 2016 edition of WHO classification stated that brain invasion can be considered an independent criterion for atypical (grade II) meningioma diagnosis (3). Meningiomas that display aggressive features such as rapid growth and higher recurrence rate, can also involve adjacent blood vessels and bone. Karabagli et al. reported that no distinct histopathological feature could be used to predict the recurrence rate of meningiomas (5). Behling et al reported that intraoperative detection and histopathological assessment of CNS invasion can be an independent prognostic factor for recurrence, giving a better risk-adapted tumor classification (6). However, aggressive meningiomas, a tumor phenotype, characterized by rapid growth and involvement of adjacent brain tissue, blood vessels and bone, was not previously recognized as a separate entity in the WHO Classification of CNS tumors of the meninges. The involvement of so many important adjacent structures makes it more difficult to achieve a gross total resection, thus

making this type of tumors more prone to recurrence.

Conclusions

Aggressive meningioma, a different phenotype of tumor, characterised by rapid growth and involvement of adjacent brain tissue, blood vessels and bone, although not previously mentioned in the WHO classification, has a distinct pattern of evolution and postoperative recurrence rate. Surgical procedures are challenging due to the implication of various tissues and the outcome depends on the location, size, grade of invasion and associated pathology.

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Postoperative lumbar spondylodiscitis. A systematic review

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Keywords
postoperative lumbar spondylodiscitis, septic and aseptic spondylodiscitis, conservative and surgical treatment, implants, biofilms

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ABSTRACT

Background. Several causes that can trigger POD can be incriminated: the patient's immune status, surgical technical errors, intra-operative contamination, foreign materials microfilm. Extensive analysis is required to eradicate the limited or diffuse infection and manage the optimal therapeutic attitude conservative or by surgery to get: faster recovery time, to improve symptoms, to allow mobilization, to offer a good quality of life and to reduce the average length of hospital stay.

Objectives. To perform a systematic review of POD outcomes via retrospective analysis of current studies based on the mechanism, the pathogenesis, the management of patient's immunological status, aetiology (microorganism involved, foreign material applied for hemostasis, application of spinal instrumentation, cement, screws, spinal devices), laboratory (TLC, ESR, CRP), MRI/CT-scan, antibiotherapy guidelines and the type of surgery performed: classical or minim-invasive, length of procedure, intraoperative accidents, the experience of the neurosurgeon, post-operative stay in ICU, etc.

Methods. Several data were taken into account regarding lumbar infections using a comprehensive review of the literature published studies from 1998 to 2021. Demographic data, clinical variables, length of hospital stay, duration of antibiotic treatment, and post-treatment complications were assessed.

Results. We performed a systematic review concerning 31 studies regarding clinical status, diagnosis and treatment.

Conclusions. Based on our systematic analysis, training and continuous education in spine surgery are necessary to prevent POD. The diagnosis of lumbar POD is based on history and physical examination, biochemical markers, neuroradiologic studies, using appropriate MRI imaging. Most cases of lumbar POD can be managed by conservative treatment with antibiotics after causative germ isolation and antibiogram. Surgery is performed on patients with conservative treatment failure - resistant to antibiotic therapy, as those with neurological complications: acute paraplegia, pain resistance to analgetics, acute sepsis, abscesses, spinal instability, severe kyphosis. Early surgery with wound irrigation/debridement is more readily able to disrupt biofilm formation and facilitate penetration of systemic antimicrobials to allow for resolution of the infection, vacuum-assisted closure facilitates wound healing and eradicates spinal infections, decrease the rate of complications, permit

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rapid pain relief while preserving the instrumentation/stability, better clinical outcomes, infection control before extensive destruction of the vertebrae, spinal instability and kyphotic deformity appear. Instrumentation can usually be preserved in patients with early infections (e.g., <6 weeks), but instrumentation removal should be considered for infections presenting in a delayed fashion (e.g., >6 weeks to even years) PSII. Patients should be adequately followed for one postoperative year, to ensure that the infection has been fully eradicated. Implant sonication provides cultures for direct identification of active and/or persistent biofilm, while the introduction of enzymes that dissolve the biofilm matrix (e.g., DNase and alginate lyase) and quorum-sensing inhibitors that increase biofilm susceptibility to antibiotics may further help manage postoperative infection (2) (27-31).

Introduction

Postoperative lumbar infection, after adult spine surgery may interest the degenerated spinal disc: septic or aseptic - spinal disc infections generating post-operative discitis (POD), the adja- cent vertebral bodies infections known as osteomyelitis (OM), or both osteo-discitis (OD). In general these pathologic spinal entities rarely occur separately and are known under the term spondylodiscitis (SD); but also postoperative lumbar infection may extend epidural and/or to facet joint arthropathy, paravertebral spaces. Semantically POD - a rare complication, representing 3-5% of cases should be differentiated from primary vertebra endplate infection with secondary involvement of the disc; be- cause of this is more accurate to use the term spondylodiscitis (SD) or vertebral osteomyelitis (VO) (1), and surgical site infections (SSIs) after adult spine surgery, generated by preoperative, intraoper- ative, or postoperative factors that contribute to the risk of infection following spinal fusions - which varies from 0.7% to 20% (2). The diagnosis of POD must be based on a combination of clinical symptoms, laboratory tests, bacteriological cultures from disc puncture, and radiological findings (3- 6). It's a severe complication which can lead to severe impairment of quality of life, neurological deficits, deformities, segmental instabilities (4-6). A recent study in Denmark showed that the inci- dence of spondylodiscitis increased from 2.2 to 5.8 per 100.000 people per year between 1995 and 2008, and the incidence of age in Germany was estimated at 30 to 250.000 per year based on data provided by the Federal Statistical Office 2015 (7), in the West it is <1%, and in India from 4% to 10% (8).

Methods

15 studies, published from 2003-2021, are analysed, out of which two: Ahsan K. (3) and Jain M.(8) publications were referring to postoperative osteodiscitis were considered (Table 1).Patients were diagnosed clinically, by laboratory investigations such as: complete blood count (CBC) erhrytrocites sedimentation rate (ESR), C reactive protein (CRP) and coagulation levels, and radiological lumbar studies: X-rays, CT, MRI. Demographic data, clinical variables, length of hospital stay, duration of antibiotic treatment, and post-treatment complications were assessed. Inclusion and exclusion criterias are presented below (Table 1).

Authors and Year	Class of evidence	Summary	Criteria for inclusion in the study	Criteria for exclusion the study
Ahsan K. et. al. - 2020	I	Prospective study (n * = 38). Conservative Vs. operative management of postoperative lumbar discitis. Fusion status offered the best outcome after 1,3,6 to 12 months of follow-up, with no risk. The study was conducted from January 2017 till May 2020.	Patients with POD are diagnosed after lumbar discectomy at a single level. Back pain appeared 1-6 weeks after surgery. Bridge with radiculopathy.	Patients with spontaneous discitis. Patients with multilevel discectomy. Patients who lost follow-up during the 12 months after discharge. Patients who started medical management before switching to surgical treatment due to inadequate response. Patients with severe spinal instability.
Jain M. et. al. - 2019	II	Descriptive study (n = 12), 10 own and 2 referred. Postoperative lumbar Pyogenic spondylodiscitis. Fusion status offered a good outcome after 12 to 18 months of follow-up, with moderate risk. A study was conducted from January 2015 till January 2017.	Patients with lumbar discectomy at one level.	Patients with multiple discectomies. Patients with spontaneous discitis. Patients with implant-associated discitis.

n*= number of patients

Table 1. Study of fusion for conservative and interventional treatment of lumbar osteodiscitis, modified after (3)(8).

Results

The patients were followed for 12-24 months by Ahshan K. (3). Thus, they divided the patients into two groups A and B, respectively in the conservative and operative group and it was found that after primary discectomy, the pain-free interval was 1-6 weeks for the conservative group and 1-8 weeks for the operative group and the duration symptoms before admission were 5-21 days for group A and 7-21 days for group B. Patients experienced moderate to severe pain, radiculopathy, mild fever, paravertebral muscle spasm, positive SLR test, and pseudo Gower sign. Demographic characteristics in both groups showed no significant differences in age, sex, clinical presentation, pain-free interval for the development of disc symptoms, duration, disc level, and associated risk factors. ESR and CRP values, were elevated in all patients in both groups. After treatment, the values in some patients decreased in one to two weeks, and the values that remained

elevated returned to the initial preoperative value in 1-3 months. Values returned to normal in all patients within six months. Biopsy reports showed a mixture of inflammatory cells, including neutrophils, plasma cells and lymphocytes but no granulomatous lesions. Simple x-ray imaging investigations in antero-posterior and lateral incidence were recommended in all patients. Six to eight weeks later, patients in the first study had localized osteopenia, narrowing of the disc space, erosion of the final plaque, cavitation, and kyphotic deformity. Dynamic X-rays were used for patients who experienced pain in the first study, and in the second study no dynamic X-rays were performed due to severe pain on mobilization. CT showed that the final plate erosion had formed 3-6 weeks before the discitis. MRI showed hypointensity on T1- weighted images and hyperintensity on T2-weighted images with improved diffuse and continuous heterogeneous contrast of discs, end-plate, and adjacent bone marrow in all patients in both studies. Severe pain, after a painless interval, after lumbar discectomy increases the possibility of a recurrent disc herniation but the distinction is made after 6 months after surgery, between a recurrent disc with postoperative changes and scar tissue by MRI. Ahsan K (3) observed that after treatment with group A (conservative) the condition of patients improved after 4-6 weeks. Intravenous antibiotics were given for 4-6 weeks, followed by five weeks of oral administration until the pain improved, ESR and CRP returned to normal. The administration of antibiotics lasted 69 -92 days. In group B (operated patients) the good condition was found in two to three weeks of intravenous administration of antibiotics and followed by 3-4 weeks of oral administration. The duration of antibiotics was 34-50 days. Empirical antibiotics were initially prescribed for all patients (example: ceftriaxone, which was resistant to 40% of cases) and then culture-specific: Staphylococcus aureus, S. epidermidis (Meropenem, Flucoxacillin, Linezolid, fusidic acid). Ciprofloxacin and Tobramycin were administered for the culture in which E. coli, Enterobacter, Pseudomonas were present. Jain M. (7) treated group A (conservative) with antibiotics, analgesics, orthoses and physiotherapy and group B (operated patients) only with debridement surgery; debridement with postero-lateral fusion by autogenous bone graft and stabilization by screw and pedicle stem; inter-body lumbar transforaminal debridement with fusion through titanium cage and autogenous bone graft and stabilization by screw and pediculated stem. Serial ESR and CRP returned to baseline values in about three weeks. The condition of all patients improved in eight weeks. Patients were followed by a blood or x-ray test after 1,3,6 and 12 months after discharge and then once a year. The state of fusion was assessed at 6-12 months by X-ray and CT. No patients during the conservative and surgical treatments suffered neurological damage. The satisfaction rate was higher in the operating group than in the conservative group at the end of the one year. The operating group required significantly shorter hospitalization with bed rest and a shorter period of antibiotic administration and reduced discomfort symptoms. The costs of procedures and blood transfusions were higher for the operating group, but the complication rate was also higher.

Discussion

POD is a complication, extremely serious and rare today, after surgery on the intervertebral disc. Such entity was first described by Frank Turnbull in 1953 as a clinical entity (9-11). POD occur more commonly in the lumbar spine: a single level involvement 65%, multiple contiguous levels 20% and multiple non-contiguous levels (10%); appear after about 6-7 weeks mainly after discectomy, see an insufficient operation or a recurrent disc herniation (2-9); may present septic (more frequent as a postoperative complication involving skin flora such as Staphylococcus aureus) and aseptic forms (due to disc trauma and vascular compromise during surgery, involving spinal tuberculosis - spread along spinal ligament to involve the adjacent anterior vertebral bodies, causing angulation of the ver-tebrae with subsequent kyphosis (18). POD may also be caused by hematologic spread from a distant infection site has been identified in almost half of spondylodiscitis patients, as a remote infection (14). Common distant infection sites include the genito-urinary tract (17%), the heart (endocarditis, 12%), skin and soft tissue (11%), intravascular devices (5%), gastrointestinal tract (5%), respiratory tract (2%) and oral cavity (2%). POD has a male predominance, significant morbidity - especially in developing countries it has a high incidence (16) and mortality (17)

The most important risk factors (2-12)(15) in the development of POD are:

- preoperative: advanced age, male sex, obesity, long-term systemic administration of steroids, organ transplantation, diabetes mellitus, tobacco/alcohol use, malnutrition, coronary and severe vascular diseases, liver cirrhosis, chronic kidney disease, rheumatic disease, also concomitant infections (sep- sis, extra-spinal infections of the skin, teeth, lungs, ascending infection, e.g. from urogenital tract), immunocompromised patients especially to AIDS, intravenous drug abuse, organ transplantation, preoperative hospital stay, prior poly-trauma, tumor/malignancy, high ASA score, previous spinal surgery (16), multiple lumbar surgeries, suboptimal timing of prophylactic antibiotic therapy, ele- vated preoperative serum glucose levels.
- intraoperative: large blood loss, use of cell savers, operations that last very long > 5 hours, increased wound exposure to air (longer surgical duration), greater soft tissue dissection, and increased mus- cle/skin retraction devascularize the para-spinal muscles, increases the potential for blood loss, and results in larger dead spaces, which also contribute to the risk of infection, open interventions, number of levels operated, postoperative incontinence following laminectomy and/or fusion, but also mini- mally invasive spinal and endoscopic procedures, posterior vs. anterior spinal instrumentation, fu- sions, implant material (titanium vs stainless steel), use of allograft, use of microscope/O-arm/C-arm, fluoroscopy, intraoperative computed tomography, many people in the operating room (two or more residents on a case), open suction drainage, the failure to drain wounds correlates with a significantly higher risk of delayed spinal infections. The timing of administration of preoperative antibiotics is strongly correlated with an increased risk of POD. Ideally, preoperative prophylactic antibiotics should be administered within an hour of surgery (e.g., cephalosporin except in penicillin allergic patients); administration up to 15 minutes prior to the incision may be even more effective, spinal surgery for tumor resection is also independently associated with an increased risk of lumbar POD (2)
- postoperative urinary/faecal incontinence, poor wound care, postoperative ICU stay, elevated post- operative serum glucose levels

As an aetiology, POD mono-microbial or poly-microbial infection in 10-50% of cases (2) - contiguous infection spread (12)(14):

- pyogenic - bacterial: Staphylococcus aureus (60% of cases, methicillin-sensitive Staphylococcus aureus MSSA, still the predominant aetiologic agent in drug users), Streptococcus viridans (VDU, immunocompromised), Staphylococcus epidermidis is associated with implant- related infections, whereas coagulase-negative Staphylococci and Streptococcus viridans may be a cause of indolent infections, due to their low virulence, gram-negative organisms: Enterobacter spp. Escherichia coli (11% -25%) is the most common pathogen in this group, followed by Proteus, Klebsiella and Enterobacteriae spp. occur in the elderly, in states of immunosuppression and diabetes, Brucella spp.(6-12%) (common in the Mediterranean and Middle Eastern countries) (13), Salmonella, Pseudomonas aeruginosa in cases associated with intravenous drug abuse Enterobacter, and Acinetobacter, Burkholderia pseudomallei (i.e. melioidosis): diabetic patients from northern Australia and parts of Southeast Asia, Brucella spp.; in patients with sickle cell disease Salmonella spp... There are also common organisms implicated in POD with spinal instrumentation like S. aureus, coagulase negative Staphylococcus and Propionibacterium, have a predilection for biofilm formation (after seroma or hematoma who can alter the surface properties of an implant thereby impacting the overall susceptibility of bacterial adherence) with some protection for microbial organisms against antibiotics, phagocytes, and other cellular and humoral immune responses by an altered phenotype with regard to growth rate and gene transcription (both of which can impact diagnostic and management strategies (2).
- granulomatous: Mycobacterium tuberculosis (Pott disease) (7)(12)(13) is more frequent in developing countries, accounting for 46% of cases.
- fungal among immunodeficient people: Cryptococcus neoformans, Candida spp. Histoplasma capsulatum, Coccidioides immitis, Burkholderia pseudomallei (ie melioidosis) to

diabetics patients from northern Australia and parts of Southeast Asia
- parasitic - Echinococcosis (12)(14)
- 1/3 of patients the implicated organism may not be isolated (1)

In lumbar POD, infection extending to the adjacent disc and vertebra may generate extensive vertebral destruction, deformity, compromise stability, formation of paravertebral abscesses or may spread into the spinal canal causing epidural formation, neurological impairement with spinal cord or cauda equina compression, with high morbidity and mortality rates. There are three main ways of contamination (2) (12):

- iatrogenic by direct bacterial inoculation, direct open traumas of the spine responsible for 14% to 26% of spinal infections, by biofilm at the surface of the implants where certain bacteria can adhere with altered phenotype with regard to growth rate and gene transcription - both of which can impact diagnostic and management strategies (2);
- hematological dissemination are the most common cause of spondylodiscitis and is mainly arterial, allowing bacteria from distant sites to contaminate the spine in the setting of bacteremia;
- non-hematological, extension from a contiguous infectious site.

Clinical POD diagnosis is based on: continuous, deep-seated, throbbing low-back back pain the most common symptom (over 90% of patients), located at the site of infection, which worsened at night or gradually increased from mild pain to severe pain, associated with morning stiffness. POD pain appear early within 1-8 weeks of surgery, after an initial post-surgical relief of pain, aggravated by defecation, coughing, and sneezing, also at the slightest touch of the bed. Pain is accompanied by severe paravertebral muscle spasm that radiates to the buttocks, thighs, groin, perineum or abdomen; fever (less common - under 20% of patients, unreliable parameter, and often absent), fatigue, a general malaise may be seen in 11% - 68% of cases. Examination revealed severe restriction of movement, loss of lumbar lordosis, a positive pseudo-Gower sign, radiculopathy, less common neurologic defi- cits, wound drainage is common, may be present in up to 90% of patients (1-3)(9). Delayed lumbar POD relate to those infections occurring 3-9 months postoperatively (2), especially to those patients with spinal instrumentation typically present several months to years later with chronic pain - in- creased pain at the incision site and tenderness to palpation of the soft tissue under the incision, wound drainage, implant failure, or lack of adequate spinal fusion. Delayed infections are more often culture negative vs. early infections because as they are frequently caused by less virulent pathogens (e.g., Propionibacterium acnes, coagulase negative Staphylococcus epidermidis, bacillus, and micrococcus species), facultative anaerobe pathogens (2), favored by a postoperative sterile inflammatory pro- cesses who may create a favorable environment for the growth of low virulence organisms such as Propionibacterium.

Biochemical markers used to diagnose POD are:

- TLC - may be elevated, unsteady (9);
- ESR - normal at the time of admission (1)(7), is elevated during the first 2 weeks after lumbar discectomy (10) and slowly returns to baseline between 21-42 days;
- CRP the most important, normal at the time of admission(1)(7), reaches its maximum on the second day after discectomy and returns to normal between within 6 days, if no complication occurs (4), has also high sensitivity compared to cultures if there is only one germ. An elevated CRP after the first postoperative week thus indicates a bacterial infection, also higher postoperative CRP levels are can be find after instrumented spinal surgery vs. simple decompressions (2). A high CRP 2 weeks after surgery should make the neurosurgeon think (1)(3)(7)(16-18);
- blood culture positive in 17% of cases, in specimens from the intervertebral disc space at surgery and 12% showed a positive culture that came from the operation by microscope itself (6);
- blood investigations (blood glucose, serum albumin, liver, and renal function tests) (3)(8)
- aerobic, anaerobic, fungal and mycobacterial liquid and tissue samples, blood and urine cultures, as well as histology (14);
- biopsy, useful in the diagnosis of polymicrobial infections, if the blood cultures were negative; performed 48 hours after antibiotic treatment only if the patient is stable (6);

- CT- guided percutaneous biopsy for unidentified POD;
- technique of vortexing and sonification, followed by generally negative culturing scraped from the implant, in case of biofilm infection in POD with spinal instrumentation (2);

Neuroradiologic studies were done after hospitalization, before starting empirical treatment with antibiotics (3)(8) They relate to:

- x-rays performed in the anteroposterior and lateral incidence of the lumbosacral spine to observe in advanced cases, only after 2-4 weeks from the onset of the infection, to notice the extent of bone destruction, but also abnormalities of the infected spine: irregularity or ill definition of the vertebral endplates, cavitation, reduction of disc space, and instability in about 90% of cases, bony sclerosis may begin to appear in 10-12 weeks. In pyogenic POD, the first observation is narrowing of the disc space, followed by blurring and end-plate irregularity. In TB, the integrity of the disc is usually preserved, but after 8-12 weeks, significant bone destruction is evident.
- lumbar CT scan is more sensitive to plain film but are more sensitive to earlier changes: end-plate destruction, surrounding soft tissue swelling, intervertebral disc enhancement with contrast, collections (paraspinal, psoas muscle abscesses, even epidural abscesses), disc hypodensity. Bone necrosis and pathological calcification that occurs in TB are detected. CT is most commonly used for guided biopsy or if MRI is contraindicated. CT-guided aspiration, was performed using a needle or trocar for microscopy, culture, and biopsy were performed to identify pathogens. The culture from a fine-needle aspiration was positive in 1 patient and negative in 5 (19).
- serial lumbar MRI with gadolinium contrast enhancement, is the investigation of choice in lumbar POD, due to its very high sensitivity and specificity, also to evaluate the response to treatment (21). In the early stage of POD, MR imaging can not differentiate between the septic and aseptic forms (6), vertebral end-plate erosion is found in the majority of cases in both forms of discitis. POD that develops at a disc level with pre-operative degenerative type 2 or 3 changes may give some diagnostic problems owing to its variations from typical MR findings (6).

Signal's characteristics (1) include:

- on T1-weighted images irregular intensity with low signal in disc space, in adjacent endplates (bone marrow edema) and in (fluid) pyogenic infections;
- on T2 (fat saturated or STIR especially useful): high signal in disc space (fluid), in adjacent endplates (bone marrow edema), in paravertebral soft tissues, in the psoas muscle (imaging psoas sign): this finding is ~92% sensitive and ~92% specific for spondylodiscitis (Fig. 1) (Fig. 2)

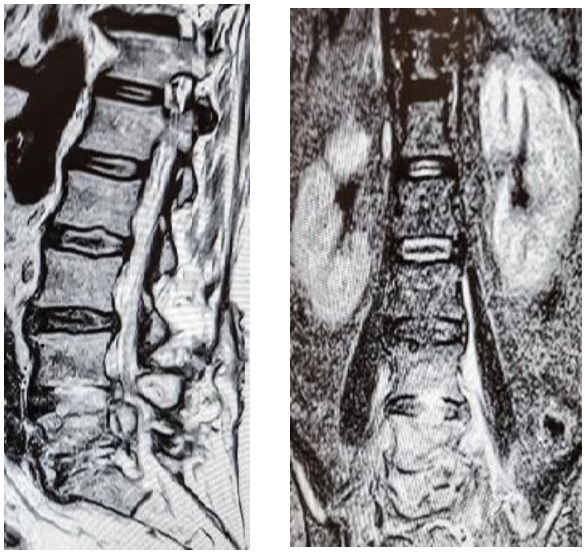

Figure 1. Imunocompromised patient with uncontrolled diabetes type 2. After 2 months post-fenestration at L4/L5 level presented with severe low back pain, elevated inflammatory markers. Sagittal (A) and coronal MRI T2-weighted (B) revealed massive height reduction of L5 vertebral body, edema and T2 hyperintensities at L4/L5 and L5/S1 along disc spaces and adjacent endplates suggestive for POD. Note the epidural abcess at the same level (A).

- after contrast administration (Gd) in T1: the enhancement of the disc, the narrowing of the disc space, the development of erosions in the vertebral endplates, peripheral enhancement around fluid collection(s), paravertebral soft tissues, around low-density center indicates abscess formation (hard to distinguish inflammatory phlegmon from abscess without contrast).
- on DWI sequences: hyperintense in the acute stage, hypointense in the chronic stage.

- positive MR imaging and elevated CRP should be followed by disc puncture and optimal antibiotic therapy.

Figure 2. 55 years old, man, known with a lumbar polidiscopathy and decompensated diabetes presents spastic paraparesis installed one week after lumbar paravertebral infiltrations. Examination of lumbar spinal MRI (T2-weighted sequences A in the sagittal plane, B and C in the axial plane, D in the coronary plane) revealed a T11-T12 POD, spinal epidural abscess of the posterior vertebral body T11. Operated in an emergency, the dural sac and the T11-T12 disc space are decompressed, isolating Staphylococcus aureus MRSA +, 1 month postop. the motor deficit remits.

If the bacteriological culture is negative, it is appropriate to choose antibiotics against S. aureus, the most frequent cause of POD (21). In the absence of signal increase on T2-weighted images and undetectable or low improvement after the introduction of the contrast substance a fungal infection should be considered, also a diffuse vertebral infection with Brucella may be difficult to differentiate with TB (21). In the absence of specific MRI characteristics, insignificant values of ESR and CRP, it suggests a non-infectious aseptic etiology or a malignant tumour, in such case a biopsy is used. The intranuclear cleft sign described by Aguila (20), cited by (6) is not relevant indicator for POD (linear enhancement within the disc, seen as two thin bands parallelling the end-plates) appears in 20% of patients without post-operative complications at 3 months after lumbar discectomy, the annular enhancement in the most posterior aspect of the disc at the site of surgical curettage is a normal post-operative finding.

- if MRI is inconclusive or contraindicated, three-phase bone scintigraphy with technetium-99m, Gallium-67 (2), scintigraphy with single-photon emission CT (SPECT) and Fluorine-18 fluorodeoxyglucose positron (F-18-FDG PET) can be used, which has higher accuracy in POD, but is not widespread (14). If MRI is contraindicated or hampered by artifact, dual imaging with PET/CT could become the imaging modality of choice; also promising results in pilot studies/small series has shown Non-FDG PET/CT with Ga-68 citrate (24).
- labeled leukocyte imaging less sensitive for processes in which the predominant cellular response is not neutrophilic (e.g., tuberculosis) (2).

POD treatment means antibiotics after biopsy, depending on the pathogen involved, cultures, sensitivities; also strict bed rest, nutritional diet, analgetics, orthosis, physiotherapy, reducing the mobility of the affected region, either with a back brace or a plaster cast, recommended about two weeks until the acute pain subsides. Many studies have shown that long-term conservative treatment has a success rate of 70% -83% (3)(4)(9)(21-23). Anti-staphylococcal penicillin or a first-generation cephalosporin is the best choice in the treatment of methicillin-sensitive staphylococci infection. If the germs - Staphylococcus epidermidis are resistant to methicillin, Vancomycin is administered and alternatively Linezolid and Quinupristin-dalfopristin. Penicillin G is of choice in the treatment of infections with Streptococcus spp., Cephalosporin or a quinolone is administered for gram-negative bacteria and metronidazole or clindamycin is given in cases with anaerobes. The classic regimen in TB includes isoniazid, rifampicin, ethambutol and pyrazinamide because it has a higher resistance. Amoxicillin and streptomycin or gentamicin are useful in Brucella infection, and amphotericin B or

azole are needed in fungal osteodiscitis (14). If the patient is not stable, antibiotic treatment is performed and the biopsy should be performed approximately 48 hours after the most recent dose of antibiotic (12)(14)(25). The duration of antibiotic therapy varies from case to case, mean time 6-8 weeks of intravenous therapy, others propose 6-8 weeks of intravenous antibiotics followed by 2 months or more of oral therapy, depending on clinical and laboratory responses, up to a year, depending on the complexity of the infection, its resistance to antibiotics, to prevent recurrence and to allow complete healing of POD, especially in immunocompromised patients (3)(12)(14). In cases where treatment begins within 2 weeks of the onset of symptoms, 6 weeks of treatment is considered sufficient. If treatment is delayed 6-7 weeks after the onset of symptoms, then antibiotic therapy for 4-8 weeks is associated with an increased recurrence rate compared to treatment for 12 weeks or more (3-5)(7)(24). Failure of medical treatment should be considered in patients with prolonged back pain, increased inflammatory markers after treatment, important destruction of the vertebral body, damage to the nerve root, progressive kyphosis. It is to avoid prolonged rest leading to skin ulcers, colitis, kidney failure, allergic reactions, deep vein thrombosis, pulmonary embolism, pneumonia, pseudoarthrosis, instability with spinal deformities, chronic pain back, also unwanted psychosocial aspects (11).

Some authors argue that early surgical debridement, followed by antibiotics, is superior to conservative antibiotic-only treatment. In cases where treatment begins within 2 weeks of the onset of symptoms, 6 weeks of treatment is considered sufficient. If treatment is delayed 6-7 weeks after the onset of symptoms, then antibiotic therapy for 4-8 weeks is associated with an increased recurrence rate compared to treatment for 12 weeks or more (3-5)(7)(24).

Surgery is performed to patients with conservative treatment failure - resistant to antibiotic therapy, as those with neurological complications: acute paraplegia, pain resistance to analgetics, acute sepsis, anterior abscess larger than 2.5 cm on lumbar MRI and epidural abcesses, spinal instability, severe kyphosis. Lumbar POD are positively associated with extended hospitalizations, increased morbidity and healthcare costs, poorer long-term outcomes, and greater dissatisfaction with the initial operative procedure (2); for these reasons early surgery permit rapid pain relief, infection control before extensive destruction of the vertebrae, spinal instability and kyphotic deformity appear (3-8)(13)(21-24). Especially in piogenic POD exploration by a posterior approach, debridement of all inflammatory tissues, the epidural abscesses are evacuated, the disc space should be irrigated with gentamicin mixed with normal saline (0.9% NaCl), betadine irrigation, dispersing powdered Vancomycin into the wound just prior to closure (2), followed by interbody fusion with titanium banana cage, autogenous spongy bone grafts or posterolateral fusion by graft bone, posterior instrumentation - antimicrobial coated implants, with pedicle screws and rods, vertebral bodies were included above and below the affected segment, then perioperative smears and tissue samples were taken for histological and microbiological evaluation. (3) Instrumentation of the spine has a higher success rate after complete debridement and concomitant antibiotic therapy (12). After surgery, patients received 2-3 weeks of broad-spectrum intravenous antibiotics consisting of ceftriaxone/meropenem with flucloxacillin for gram-positive and gram-negative organisms and metronidazole for anaerobic coverage.The dose and duration of treatment were based on the patient's weight, kidney, and liver condition, followed by 3 weeks of oral antibiotics or until ESR and CRP levels improved or back pain decreased significantly (3)(8). POD surgical treatment offer more patient satisfaction because the duration of healing and the administration of antibiotics was shorter than in the case of those treated conservatively, but it can also be risky because there are cases of postoperative recurrence of the infection. The duration of the procedure, which lasts more than five hours, the attempt of a minimally invasive intervention, a more aggressive operation, delayed or incomplete debridement, diabetes, smoking, the advanced age of the patients led to serious postoperative complications (3)(8)(12). Surgery at L4 / L5 and L5 / S1 by anterior approach are quite difficult, morbidity being increased and therefore POD was operated by posterior approach. Even if there is an active infection, instrumentation after radical debridement will not lead to an increased risk of recurrent infection, as it speeds up the healing process. Percutaneous transpediculary discectomy and drainage lead to rapid pain relief (3)(8)(10).

However, in lumbar POD suited by prostheses-based biofilm, especially most infectious disease physicians now recommend removal of the underlying spinal instrumentation (2), increasing the chance of eradicating the infection. Nevertheless, this potential advantage must be weighed against the risks of prematurely removing spinal instrumentation, essential for maintaining normal spinal alignment and preserving spinal stability.

Conclusions

The diagnosis of lumbar POD is based on history and physical examination, biochemical markers, neuroradiologic studies, using appropriate MRI imaging. Most cases of lumbar POD can be managed by conservative treatment with antibiotics after causative germ isolation and antibiogram. Surgery is performed to patients with conservative treatment failure - resistant to antibiotic therapy, as those with neurological complications: acute paraplegia, pain resistance to analgetics, acute sepsis, abscesses, spinal instability, severe kyphosis. Early surgery with wound irrigation/debridement are more readily able to disrupt biofilm formation and facilitate penetration of systemic antimicrobials to allow for resolution of the infection, vacuum-assisted closure facilitates wound healing and eradicates spinal infections, decrease the rate of complications, permit rapid pain relief, while preserving the instrumentation/stability, better clinical outcomes, infection control before extensive destruction of the vertebrae, spinal instability and kyphotic deformity appear. Instrumentation can usually be preserved in patients with early infections (e.g., <6 weeks), but instrumentation removal should be considered for infections presenting in a delayed fashion (e.g., >6 weeks to even years) PSII. Patients should be adequately followed for one postoperative year, to ensure that the infection has been fully eradicated. Implant sonication provides cultures for direct identification of active and/or persistent biofilm, while the introduction of enzymes that dissolve the biofilm matrix (e.g., DNase and alginate lyase) and quorum-sensing inhibitors that increase biofilm susceptibility to antibiotics may further help manage postoperative infection (2) (27-31).

Abbreviations

POD postoperative discitis OM ostemyelitis
OD osteofyscitis SD spondylodiscitis
OD vertebral osteomyelitis SSIs surgical site infections IVDU intravenous drug users
ASA American Society of Anesthesiology score ICU intensive care unit
TLC total leukocyte count CRP C reactive protein
ESR erhrytrocites sedimentation rate
CT tomograph computer
MRI magnetic nuclear resonance
PSII postoperative spinal implant infections

Conflicts of interest

There are no conflicts of interest.

Authors contributions

All authors contributed equally.

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Postoperative complications in endoscopic frontal transcortical surgery of lateral and third ventricle tumours. Speech disorders

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Keywords
endoscopic,
lateral ventricle,
mutism,
third ventricle,
transcortical approach

Abstract
Neurosurgical approaches to lesions of the lateral and the third ventricles are divided into two fundamentally different groups: transcortical neurosurgical approaches, including - endoscopic and interhemispheric transcallosal micro-neurosurgical approaches. Complications in surgery of lateral and third ventricle tumours are often associated with the specific approach technique and could be transient. We analyzed postoperative neurological complications and the approach criteria on MRI or CT scans in the postoperative period such as localization of corticotomy, distance from corticotomy to the coronal suture, "angle of attack" after the frontal transcortical approach to the lateral and third ventricle based on 54 cases and presume transient nature of specific to approach complications and approaches' factors that have a role in postoperative mutism.

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Introduction

Neurosurgical approaches to the tumors of the lateral and the third ventricles are divided into two fundamentally different groups: transcortical neurosurgical approaches, including - endoscopic and interhemispheric transcallosal microneurosurgical approaches. Two different approaches to the ventricular system cause distinct brain injuries: tightly compressed commissural fibers of the corpus callosum are injured by the interhemispheric transcallosal approach, while the transcortical approach damages gray and white matter of the brain on its way [1,2].

Complications in surgery of lateral and third ventricle lesions are often associated with the specific approach technique and today is a widely discussed problem [3,4]. When applying the abovementioned approaches, the most common complications are aphasia, mutism,

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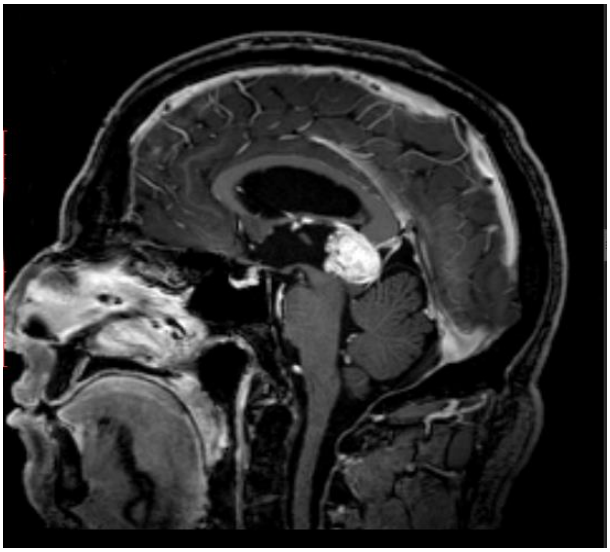
hemiparesis, seizure, memory impairment, apatheia/abulia, endocrinopathy, subdural hygroma, etc. [1, 16].

Manifestations of mutism, which are currently little studied in the context of the use of these neurosurgical approaches, constitute a field of particular scientific interest. Mutism is a clinical state, in which a conscious patient is unwilling to or unable to speak, resulting in the absence or marked paucity of verbal output. The patients can be mute while their ability to write or comprehend spoken language is intact [1,11]. Mutism can occur as a result of damage to the Broca area, premotor cortex, and supplementary motor area of the dominant hemisphere, association fibers of white matter, the anterior part of the cingulate gyrus, commissural fibers of the corpus callosum, damage of the cortical-bulbar fibers bilaterally, bilateral thalamotomy and damage of reticular formation of the midbrain [7,5].

Materials and methods

A retrospective analysis of 54 patients with neoplasms and lesions of lateral (anterior horn, body, atrium) and third ventricles who underwent surgery in the period from October 2015 to May 2021. Male – 26 patients, the mean age was 44.5 years (range: 20-71 years), female – 28 patients, the mean age was 42.4 years. (range: 15-74 years). Mean preoperative Karnofsky Performance Statuse Score (KPS) was 76.37.

Localization of neoplasm: the third ventricle - 41 (75.9 %) patients; lateral ventricular tumors - 13 (24.1 %) patients. Histological distribution depending on the location is given in Table 1.



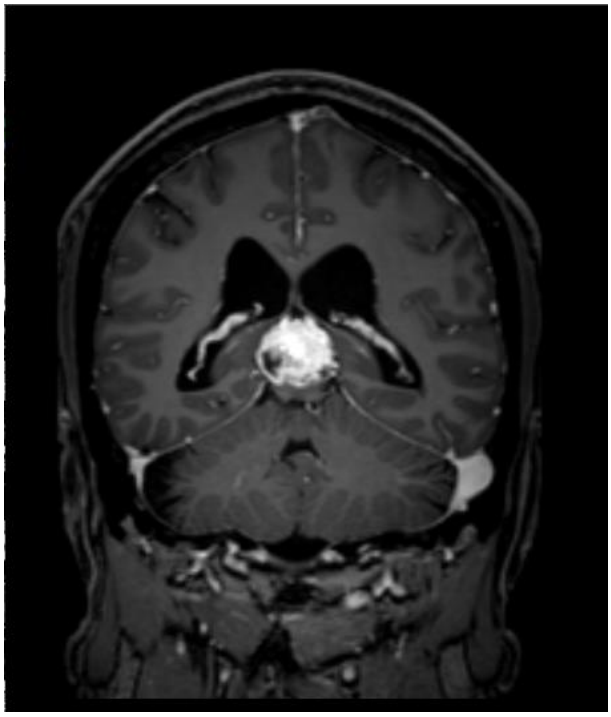


Figure 1. A-B. Tumor in the posterior part of the third ventricle (Glioblastoma), preoperative contrast-enhanced, T1W images.

Histopathological evaluation of these 54 neoplasms and lesions indicated 15 distinct diagnostic entities including brain tumors of glial origin with invasion in the ventricular system (diffuse and anaplastic astrocytoma, glioblastoma, oligodendroglioma, and anaplastic oligoastrocytomas) accounted for 35,2% (Fig. 1), subependymoma and ependymomas varying degrees of malignancy – 14,8%, colloid cysts - 13%, central neurocytomas - 11.1%, craniopharyngiomas 11.1%, germinomas - 7.4%, others - 7.4%

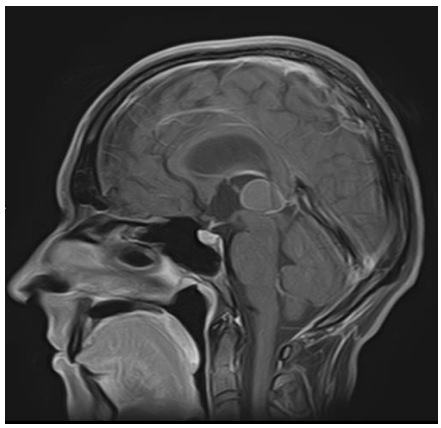
Histopathology	Lateral ventricles (n-13)	Third ventricle (n-41)
Pilocytic astrocytoma, WHO Gr I	-	1
Diffuse astrocytoma, WHO Gr II	2	3
Anaplastic astrocytoma, WHO Gr III	-	3
Glioblastoma, WHO Gr IV	1	5
Oligodendroglioma, WHO Gr II	1	2
Anaplastic oligoastrocytomas WHO Gr III	1	-
Subependymoma, WHO Gr I	1	1

Typical and atypical meningiomas, WHO Gr I та II	2	-
central neurocytomas, WHO Gr II	4	2
Pineoblastoma, WHO Gr IV	-	1
Ependymoma, WHO Gr II, anaplastic ependymoma WHO Gr III	1	5
Craniopharyngioma, WHO Gr I	-	6
Colloid cysts	-	7
Germinomas	-	4
Mature teratoma	-	1

Table 1. Histopathology of intraventricular neoplasms.

Preoperative symptoms include: cephalalgia - 49 (90.7 %) patients, sings of elevated ICP - 32 (59.25 %) patients, neurocognitive disorders and psychoorganic syndrome - 10 (18.5%) patients, oculomotor dysfunction - 10 (18.5%) patients, motor deficits - 9 (16.6%) patients, short term memory loss- 8 (14.8%) paients, decreased visual acuity and loss of peripheral vision - 7 (12.9%) patients, endocrinopathy - 4 (7.4%) patients, seizures - 2 (3.7%) patients.

Preoperative contrast-enhanced magnetic resonance imaging (MRI) (Fig.2) of the brain and computer tomography (CT) were also used for the preoperative planning of the approach side, optimal for the resection of the neoplasm and minimization of postoperative complications. We analyzed the localization of the neoplasms in the ventricular system, the side with greater distribution, signs of occlusive hydrocephalus, the side with the wider interventricular foramen of Monro, localization of estimated corticotomy ("entry point"), and the best "angle of attack ".



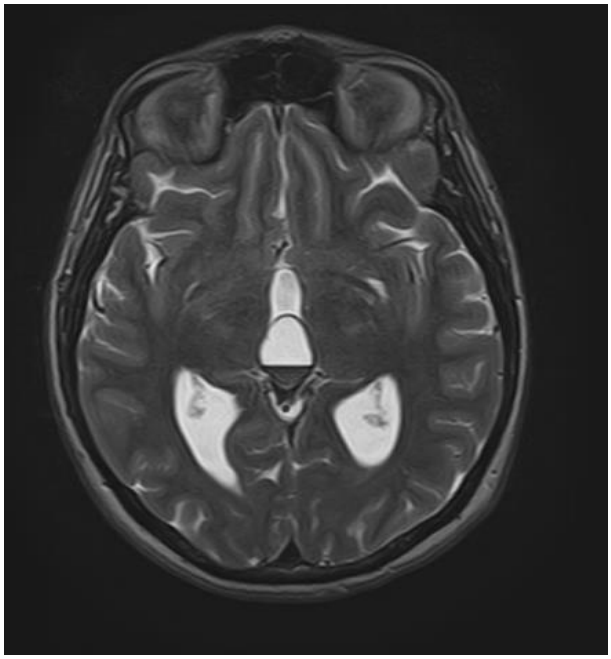


Figure 2. A-B. Tumor in the posterior part of the third ventricle (ependymoma), preoperative contrast-enhanced T1W images and T2W images.

In surgery of neoplasms of the lateral (anterior horn, body, atrium) and third ventricle, we use endoscopic frontal (craniotomy over the frontal lobe) transcortical (corticotomy through the upper or middle frontal gyrus) approache. We perform an endoscopic frontal transcortical approach via parasagittal craniotomy over the non-dominant hemisphere of the brain (or over the priority hemisphere for approach) with the centration at the Kocher's point. Corticotomy up to 2.2 cm. is carried out through the top of the middle or upper frontal gyrus. The next stage is white matter fibers dissection to the front horn of the lateral ventricle and the subsequent introduction of intracerebral retractors.

Depending on the location of the tumor or lesion in the third ventricle, its size, and available hydrocephalus we used transventricular (through the cavity of the lateral ventricles) approach and further transforaminal (approach to the third ventricle through the interventricular foramen of Monro) or extended transforaminal transchoroidal approach (approach to the third ventricle through the interventricular foramen of Monro with the anterior choroidal dissection). Surgery was performed using an endoscopic stand based on the HD- endoscope "Image-1HD" (Karl Storz, Germany).

Rigid endoscopes "Karl Storz" 4 mm in diameter with viewing angles of 0 and 35 degrees were used as the main tool for visualization of the operating field.

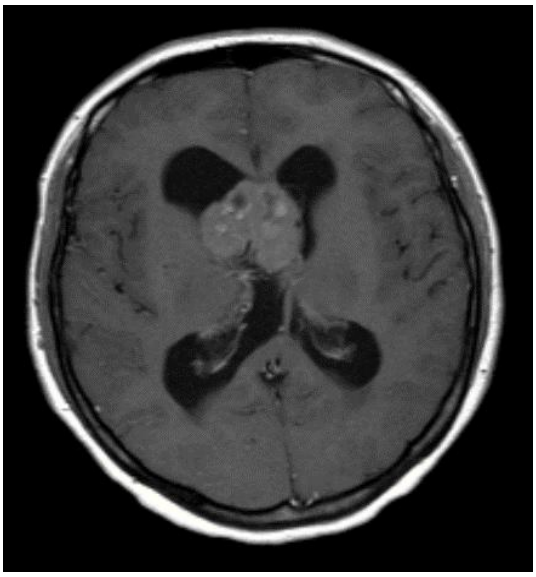
Approach through the right hemisphere has been performed in 38 (70.4 %) cases and through the left one in 16 (29, 6 %) cases. Endoscopic frontal transcortical approach to the lateral ventricles was used in 13 (24.1 %) cases; endoscopic frontal transcortical transentricular transforaminal approach to the third ventricle - 13 (24.1 %) cases, extended transforaminal transchoroidal approach - 28 (52%) cases. In all cases, a 100% endoscopic technique (" fully endoscopic resection ") was performed.

In case of clinical and MR signs of occlusive hydrocephalus and with the purpose of preventing the progression of hydrocephalus in 22 (40.7%) cases with simultaneous resection of tumor we performed endoscopic third ventriculostomy.

In the early postoperative period, all patients underwent contrast-enhanced CT or MRI in order to detect residual component of the tumor, potential postoperative ischemia and bleeding, and evaluations of the ventricular system.

The follow-up ranged from 3 to 42 months, at average 12.5 months. During the follow-up examination of patients, which was performed approximately 2-4 months after the surgery, we assessed the overall health status, neurological status, contrast-enhanced MRI of the brain (Fig. 3). On MRI we evaluated the presence of residual component of the tumor or tumor growth, ventricular system (presence of hydrocephalus), expansion/narrowing of the transcortical channel in the matter of the frontal lobe.

A.



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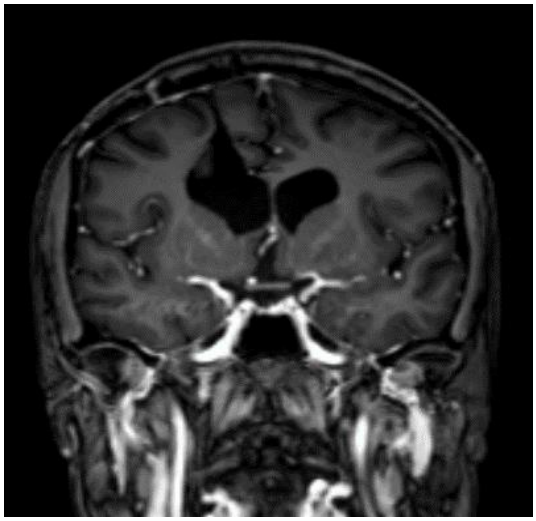

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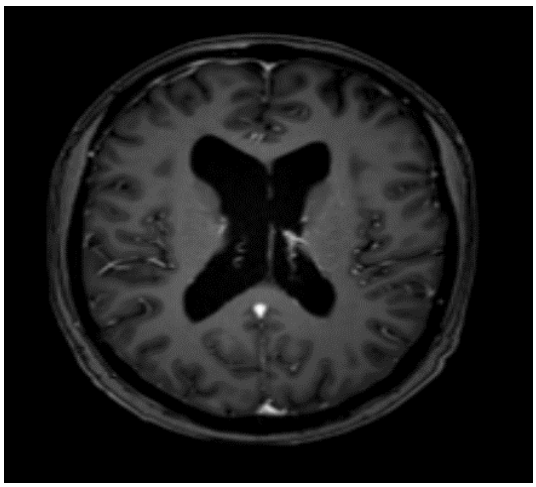


D.

Figure 3. A-B. Tumor in the right lateral ventricle (ependymoma), preoperative T1W images.
C-D. 5-month postoperative contrast-enhanced T1W images depicted gross total resection of the tumor.

RESULTS AND DISCUSSION

Extent of resection in our series: gross total resection/near total resection - 34 (63 %) patients, subtotal/partial resection - 15 (27.7 %) cases, biopsy - 5 (9.2 %) cases.

39 (72.2 %) patients had no postoperative complications, 15 (27.7 %) patients had at least one postoperative complication. Postoperative complications included:

- speech disorders such as mutism - 6 (11.1 %) patients and apathia/abulia - 5 (9.2%) patients. We observed that 4 patients with postoperative manifestations of apathia/abulia also had concomitant mutism. In the postoperative period, at the follow-up examination 2-4 months after the surgery, a complete or partial regression of both mutism and apathia/abulia was observed in all 6 patients;
- short term, "fixation" memory loss - 5 (9.2 %) patients. In all 5 cases the endoscopic transcortical transventricular transforaminal or extended transforaminal transchoroidal approach to the third ventricle was applied. In the postoperative period, at the follow-up examinations during the next 2-6 months after the surgery, a complete or partial regression was observed in 3 patients;
- oculomotor dysfunction - 5 (9.2%) patients. Oculomotor dysfunction included paresis of n. oculomotorius and/or Parinaud syndrome and in all 5 cases have been associated with tumor resection of the posterior part of the third ventricle. In the postoperative period, complete or partial regression was observed in 1 patient;
- motor deficits - 4 (7, 4%) patients. In our series, we associate the occurrence of this complication either with resection of the glial tumor (originated in close proximity to corticospinal tracts) with the invasion in the third ventricle or with the premotor cortex and supplementary motor area injury. We observed the complete regression in 2 patients during the next 4 months after the surgery;
- neurocognitive disorders - 4 (7.4%) patients which regressed in 1 patient 4 months after the surgery;
- endocrinopathy - 3 (5.5%) patients. We associate this complication with the resection of tumors that have been tightly fused to the hypothalamic area of the bottom of the third ventricle. Regression was observed in 1 patient after 3 months;
- postoperative hemorrhage – 2 (3,7%) patients;
- postoperative wound infection occurred in 1 (1.85%) patient;
- postoperative meningitis - 1 (1.85%) patient.

In our series, seizures, as a postoperative complication, did not occur.

Postoperative mortality - 1 (1.9%) patients due to hypothalamic dysfunction, leading to acute electrolyte shifts, after the resection of craniopharyngioma with the significant spread in the third ventricle.

Compared with the series Brian D. Milligan at al in the group transcortical approach, short-term memory loss in the postoperative period was recorded in 6 (12 %) patients, that is 2.8% higher than in our series. Motor deficits were recorded in 18 (35%) patients, that is 27.6 % higher than in our series. Neurocognitive disorders were 4.6% higher than in our series, and the percentage of patients with endocrinopathy was the same as in the series Brian D. Milligan at al. [16]

The average KPS on the day of discharge was 83,35%.

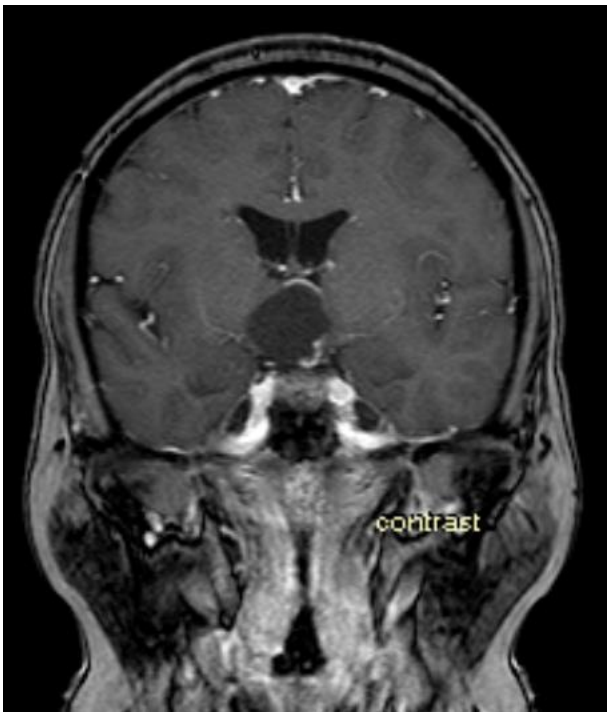
In the early postoperative period, all patients underwent contrast-enhanced CT or MRI of the brain and, among other things, we evaluated the following approach criteria (Table. 2) using RadiAnt DICOM Viewer software:

1) localization of corticotomy, "entry point" (upper/middle frontal gyrus (upper parts);
2) the distance from the coronal suture to the corticotomy in front;
3) "Angle of attack " (the angle between the sagittal plane and plain "entry point" - the point of entry into the frontal horn of the lateral ventricle). (Fig. 4)

Localization of corticotomy	Right hemisphere n-38 (70,4%)	Left hemisphere n -16 (29,6%)
Upper frontal gyrus	12 (31,5 %)	7 (43,7%)
Middle frontal gyrus, upper part	26 (68,5 %)	9 (56,3%)
Distance from the coronal suture to	2,8 cm, min- 1,2, max- 3,6	2,8 cm, min- 0,5, max- 2,9

the corticotomy (mean, min-, max).		
"Angle of attack" (mean, min-, max).	27,4°, min-17°, max-35°	26,7°, min-21°, max- 34°

Table 2. Approach criteria.



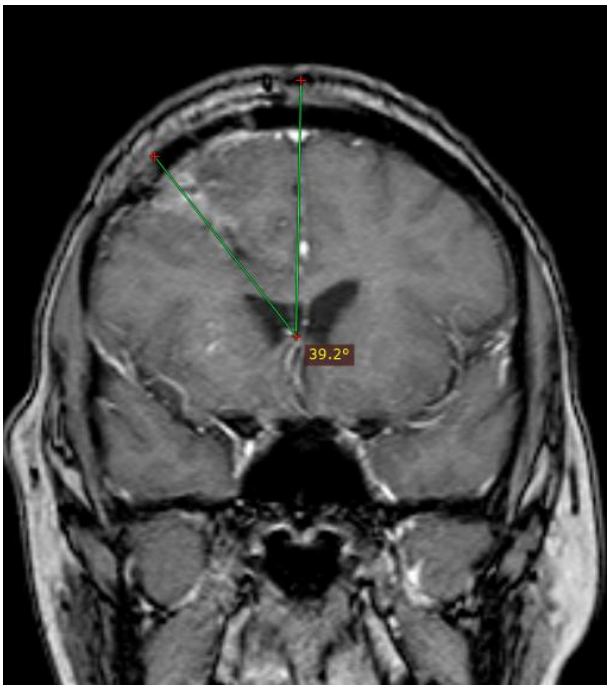


Figure 4. A. Tumor of the third ventricle (craniopharyngioma), preoperative, contrast-enhanced T1W image.

B. 4-month postoperative contrast-enhanced T1W images, "angle of attack" calculation using using RadiAnt DICOM Viewer software.

In our series, mutism, as a manifestation of specific speech disorders caused by the frontal transcortical approach to the lateral and third ventricles, was observed in the postoperative period in 6 (11.1 %) patients (approach on the left - 6 patients). This clinical condition was transient and regressed within 4 months after the surgery. We indicate that corticotomy in patients who had postoperative mutism was performed in the upper frontal gyrus – 4 patients, in the middle frontal gyrus – 2 patients. We presume that postoperative mutism is related to the following features of the approach:

1) the approach side - dominant hemisphere.
2) corticotomy in the upper frontal gyrus and at a distance of less than 2 cm. from the coronal suture.
3) "angle of attack" less than 26.7○.

In their series, S. Asgari et al reported that when applying the transcortical approach, transient mutism occurred in 11% of patients, while via interhemispheric/transcallosal approach in 18% of patients, that equals and is 8.2% higher compared to our series respectively [7]. R. G. Ellenborg concluded that speech disorders are a fairly common complication when applying a transcortical approach through the dominant hemisphere and occur in 10-30% of patients [13]. In the article by Brian D. Milligan et, when comparing transcortical and interhemispheric approaches, mutism is not distinguished as a complication, instead this clinical condition is classified as a separate group of complications - aphasia/abulia, which occurs in 31% and 25% of cases, respectively, when applying transcortical and transcallosal approaches [16]. In our series of cases, aphatia/abulia manifested in the postoperative period in 5 (9.2%) patients, in all cases - together with mutism. It is uncertain whether there is a direct link between apathy, abulia and mutism. However, there is some evidence that the medial part of the frontal lobes, especially the cortex and fibers of the anterior cingulate gyrus, may play a role in manifestations of aphatia/abulia along with signs of mutism, as well as akinetic mutism [12]. The anterior part of the cingulate gyrus has a complex relationship with the limbic structures, other parts of the frontal cortex and periaqueductal gray matter of

the midbrain. It is involved in interaction between the decision-making process and the "emotional" world of the limbic system, which is considered crucial for the start of speech and vocalization [6,19].

Functionally, the corpus callosum is closely related to speech function [9,20]. Mutism often occurs in the postoperative period after the interhemispheric approach with callosotomy [8,18]. Jin Hong et al suggested that damage to the corpus callosum can lead to speech disorders [15]. Ishizaki et al describe that transcallosal diaschisis is a possible mechanism of aphasia [14]. In our opinion, the commissural fibers of the corpus callosum and forceps minor fibers injury while applying the transcortical approach to the ventricular system, may play a role in the development of transient mutism.

Utilizing magnetic resonance diffusion-tensor tractography and comparing two different localizations of corticotomy (through the middle frontal gyrus and through the upper frontal gyrus) applying transfrontal transcortical access, T. Szmuda et al concluded that the application of access through the upper and middle frontal gyrus one way or another leads to trauma, including the upper longitudinal fascicles II, which is partially responsible for the relationship between the fields of Brock and Wernicke [21]. Although most of the fibers involved in the speech network and connecting the middle and lower frontal gyrus and posterior part of superior temporal gyrus are a part of the so-called upper longitudinal fasciculus III (anterior fibers of arcuate), they are located more caudally to the potential injury of the white matter via frontal transcortical approach in our cases [17].

Injury to the supplementary motor area and the premotor cortex, especially of the dominant hemisphere of the brain, can also cause mutism. Penfield and Welch used cortical stimulation to identify the boundaries and functions of this area. The connections of this cortex are quite branched and include the upper temporal gyrus, the intraparietal sulcus, the caudate nucleus, the thalamus, and other. [10]

Conclusions

The endoscopic frontal transcortical approach in surgery of neoplasm and lesions of the lateral and third ventricle is effective and minimally invasive approach. The transient nature of postoperative complications is due to the gentle manipulations of anatomical structures when applying this approach. Specific surgical approach complications such as mutism, apathia/abulia, motor deficits (due to the injury of the premotor cortex and supplementary motor area) were mostly transient and had a tendency to regress immediately in the postoperative period and most of them completely regressed from 2 to 4 months after the surgery.

The nature of mutism as a manifestation of speech complications when applying endoscopic frontal transcortical approach is multifactorial. The development of postoperative speech complications, namely of transient mutism when applying the endoscopic frontal transcortical approach is not a frequent complication and according to our observations regresses within 4 months. In our opinion, in order to reduce the risk of mutism in the postoperative period, endoscopic frontal transcortical approach should be performed via the non-dominant hemisphere (unless otherwise specified during preoperative planning) and in the upper part of the middle frontal gyrus at a distance more than 2 cm from the coronal suture. Corticotomy should be gentle and based on our series no more than 2.2 cm in length, "angle of attack" should be no less than 26.7○ which reduces cerebral cortex and white matter injury and the risk of postoperative complications associated with the application of this approach, including manifestations of mutism.

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The complementary multimodal treatment of recalcitrant cerebral aneurysms. Two centres experience

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Abstract

Background: The main treatment of cerebral aneurysms is the direct surgical clipping or endovascular coil embolization. However, some cerebral aneurysms that we reviewed in the literature are still not susceptible to a single treatment approach. These aneurysms can be referred to as complex aneurysms.

Objective: We aim to report these aneurysms and share our clinical experience with their treatment and diagnosis.

Methods: All cases of cerebral aneurysms treated in New York University and in Mansoura University from 2010-2021 were retrospectively reviewed.

Results: 18 patients with 21 cerebral aneurysms were treated by combined surgical and endovascular modalities. Aneurysms associated with arteriovenous malformations (AVMs) in 3 patients, associated with vasospasm in 7 patients, and 3 patients had double aneurysms. A total of 18 patients with aneurysms were treated with combined endovascular and microsurgical therapy. Early angiogram (< 1 week) reveled; complete obliteration of 19 aneurysms (90%) out of total 21 aneurysms, residual filling was observed in 2 aneurysms (10%). Late radiological follow up (> 3 months- 2 years) reveled; a stable residual filling in one and the other case underwent retreatment.

Conclusions: The recalcitrant or complex cerebral aneurysms can be better referred to as diseases rather than lesions as many clinical and anatomical factors make their treatment difficult. Endovascular and microsurgery could be complementary to each other and create a multimodal approach for treating them.

Keywords
complex aneurysms, cerebral, multimodal, complementary treatment

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Background

Direct surgical clipping or endovascular coil embolization is the most common treatment for cerebral aneurysms. (4) Despite significant advancements in microsurgical techniques and equipment, as well as endovascular devices in a parallel direction, some brain aneurysms that we evaluated in the literature are still not susceptible to a single treatment approach. These aneurysms can be referred to as recalcitrant or complex aneurysms. (6,8,10-12,21)

We aim to report these challenging aneurysms and share our clinical experience with their treatment and diagnosis.

METHODOLOGY

After IRB approval for both New York University and Mansoura University, all cases of cerebral aneurysms treated in New York University and in Mansoura University from 2010-2021 were retrospectively reviewed.

Inclusion criteria

Patients proved radiological (CT or MR Angiogram or digital subtraction angiography) to harbor cerebral aneurysms that was treated by both endovascular and open surgery with any of the following criteria:

1. Ruptured or unruptured
2. Single or multiple
3. Giant and/or widely necked aneurysms
4. With or without AVMs
5. With or without vasospasm
6. Compressing or involving origin of adjacent arteries.
7. Aneurysms were primary managed with surgery or endovascular embolization and showed residual or recurrence on follow-up.

Exclusion criteria

Aneurysms that were treated by one modality only (endovascular or open surgery).

Patient demographics, aneurysm characteristics, procedural details, clinical outcome (Glasgow outcome scale) and radiological follow-up were analyzed. The radiological follow-up was achieved using digital subtraction angiography (DSA) and/or magnetic resonance angiography (MRA) and/or CT scan angiography (CTA).

RESULTS

18 patients harboring cerebral aneurysms were found to be treated by combined surgical and endovascular modalities.

Patient demographics

There were 11 females and 7 males. The mean age was 58 years (age range, 40–70 year).

Characteristics of aneurysms

In total, there were 21 aneurysms in 18 patients. Three patients had aneurysms linked with arteriovenous malformations (AVMs), seven patients had vasospasm, and three patients had double aneurysms (Figure1).

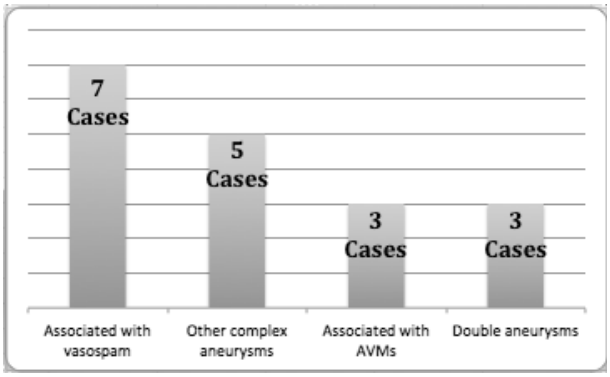

Figure 1. Diagram illustrating the included aneurysm cases.

Aneurysmal rupture and/or bleeding from associated AVMs were the commonest presentation, in 14 patients. The admission Hunt and Hess (HH) grade distribution of this patient group was as follows: Grade I, II 9 patients; and Grade III or more, 5 patients. The other 4 patients with unruptured aneurysms were as follow: incidentally discovered 1 patient during screening for familial aneurysm; 1 patient presented with third cranial palsy; 1 patient presented with agitation and confusion and another patient with aneurysm associated AVM was presented by convulsions.

The mean aneurysm size was 8.5 millimeters (mm). There were 16 small aneurysms (up to 10 mm diameter), and 5 large aneurysms (15–28 mm in diameter). 9 aneurysms had a wide neck (>3mm in width), 6 were saccular in shape and 4 were lobulated. The most common locations of the aneurysms were the posterior communicating artery (PComma) and middle cerebral artery (MCA) and for the AVMs associated with the aneurysms were as follows: 2 cerebellar and 1 temporal. (Table 1)

Table 1. Aneurysmal location

Parent artery	Number (n)
PComm	5
MCA	4
AComm	3
ICA –bifurcation-	3
ACA	2
PICA-AICA complex	1
SCA	1
Anterior choridal	1
Ophthalmic	1
PComm, posterior communicating; AComm, anterior communicating; PICA-AICA, posterior inferior cerebellar artery anterior inferior cerebellar artery; SCA, Superior cerebellar artery.	

Treatment techniques

A total of 18 patients with aneurysms were treated with combined endovascular and open surgery. 1 case with residual aneurysmal neck following surgical clipping underwent coil embolization. 3 cases with recurrent aneurysm following pervious coil embolization underwent surgical clipping. 3 cases of double aneurysms underwent coil embolization and surgical clipping. 4 cases of AVM flow related aneurysms underwent partial embolization of the nidus and coil embolization of aneurysm followed by surgical resection. 7 cases developed cerebral vasospasm following surgical clipping underwent balloon and pharmaceutical angioplasty. To facilitate surgical clipping: preoperative balloon occlusion test (BTO) and intraoperative DSA was applied in 3 and 7 cases receptively. (Figure 2 and 3)

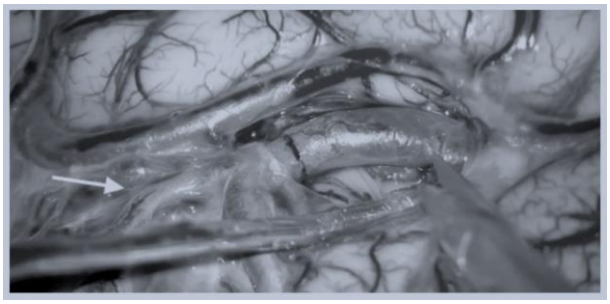

Figure 2. An intraoperative image showing complementary surgical resection of AVM after pervious endovascular onyx embolization of the AVM associated with an aneurysm. A white arrow points to onyx in the nidus.

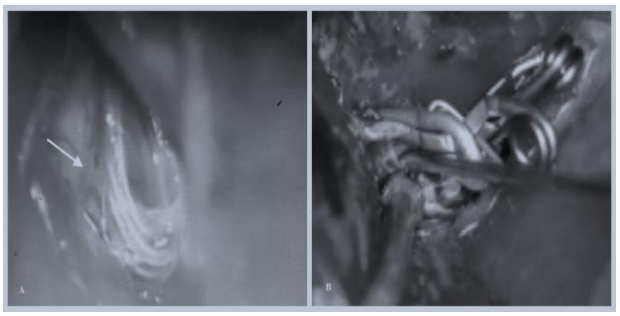

Figure 3. (**A**): An intraoperative image showing a pervious coiled aneurysm that developed significant recurrence (white arrow points to the coil in the aneurysmal sac). (**B**): An intraoperative image showing clipping of the same aneurysm in figure 3A with two clips after removal of the coils.

Outcome

The average radiological and clinical follow-up intervals were 13 and 16 months, respectively. All patients had an early (one week) postoperative radiological follow-up. An early angiography revealed full obliteration of 19 aneurysms (90%) out of a total of 21 aneurysms, with residual filling found in 2 aneurysms (10%), which were followed up on. Late radiological follow up (> 3months- 2 years) was done for the patients on follow-up visits. A stable residual filling in one case and the other underwent retreatment (clipping with intraoperative DSA guidance). (Table 2)

Table 2. Summary of the clinical outcome

Patients	Clinical outcome prior to discharge (< 1 month) (N)*			Late outcome (>3 months)
	Neuro logically intact	Same neurol ogical deficit post-manag ement	New neurologi cal deficit post-manage ment	
Individual Aneurysms	17	0	1**	No significant change
Aneurysms associated with AVMs	2	0	1***	Complete improvement

Neurological status factors: Glasgow coma score, motor, cranial nerve and cognitive functions; other psychological and intellectual assessment were not included.

* Number of patients.

** 1 patient developed monocular blindness post ophthalmic artery aneurysmal clipping postoperative angiogram revealed patent ophthalmic and orbital branches though ophthalmology consult revealed no optic disc abnormalities, but diagnosis was posterior ischemic neuropathy with poor prognosis.

*** 1 patient developed right lower limb weakness grade 4+ and positive Romberg, patient had avulsed PICA during AVM embolization and sacrifice the vertebral artery was done, later developed massive cerebellar infarction later on, however gradual improvement was not noticed during outpatient clinic visits in 6 months.

Discussion

Complex and recalcitrant aneurysms

Many researches had attempted to categorize recalcitrant aneurysms in some way. Hacin-Bey et al., as a combination of anatomical aneurysm variables and clinical factors describe complex aneurysm characteristics. These characteristics are summarized in a table in his study. (8) (See Table 3)

Table 3. Hacin-Bey et al. table of features that define recalcitrant or complex aneurysms (7).

Aneurysm anatomy (best assessed by 3D aneurysm reconstruction from DSA or CTA data)	**Clinical features (detailed clinical risk stratification important)**
Size: large or giant, too small for a clip or coil	Clinical grade at presentation: HH_3.
Shape: fusiform, serpentine, pseudoaneurysm, dissecting aneurysm.	Timing: vasospasm at the time of presentation.
Content: filled with thrombus, calcified wall, dysplastic vessel wall.	Medical comorbidities: cardiovascular, pulmonary, renal or endocrine comorbidity.
Neck: difficult surgical access, broad, calcified, involving perforator vessels, and other branching vessels.	Advanced age.
Perianeurysmal environmental: aneurysm embedded ineloquent brain tissue, bone, edema, scar from previous surgery.	
3D, three dimensional: DSA, digital subtraction angiography: CTA, computed tomography angiography; HH, Hunt and Hess. Used Table from with permission from Wolters Kluwer Health with modifications.	

The ISAT (International Subarachnoid Aneurysm Trial) requires subjective agreement that an aneurysm might be treated by endovascular or open surgery (5). Many aneurysms, however, did not fit the requirements, such as: 1- patients with life-threatening intracerebral or subdural hematomas; 2- incompatible neck-to-dome ratios; 3-parent artery or branch artery incorporation into the dome; 4-fusiform aneurysms; 5-thrombotic aneurysms; 6-giants; 7-blisters; 8- pseudo/traumatic aneurysms; 9-those with mass effect; and 10-those that had failed repeated endovascular treatment (16,20).

Complementary multimodal therapeutic approach

Choudhri et al described the Stanford neurosurgical experience with the combination of endovascular and open surgery in 67 cases. The aneurysms in all of the individuals in the study were completely obliterated, with no mortality. (2) The combination method was used to treat a total of 96 aneurysms, according to Lawton et al. The aneurysms were enormous or giant in size in 43% of the cases, and fusiform or dolichoectatic in 34%. In 91 aneurysms, the angiographic obliteration was complete (95%) (15).

Chen et al. and Cockroft et al., both had reported the treatment of recalcitrant cerebral aneurysms by surgical reconstruction of aneurysm neck followed by endovascular coiling on a planned concept. Cockroft et al. also reported in his series the initial coil embolization of ruptured basilar tip aneurysm to reduce the risk of rebleeding followed by permanent surgical clipping (1,3).

The radiological and clinical out come of this multimodal treatment in these reported studies and our study was favorable. These good results of combing both surgical and endovascular techniques encouraged the evolution of a new treatment modality, which is the hybrid cerebrovascular surgery.

Hybrid cerebrovascular surgery era

In several subspecialties, hybrid surgery is regarded as a cutting-edge technique. The term "hybrid" refers to a combination of standard surgical and endovascular methods. Actually, it's a multimodal technique that may be done in one session or over a period of time (scheduled). The use of hybrid surgery in the treatment of cardiovascular disorders has ushered in a new era in disease management.(18,19)

In the same direction for the cerebrovascular diseases, hybrid operative theatres have been innovated in the neurosurgical institutes in last few years. Between November 2003 and August 2011, Muryma et al. and Kurtia et al. published two case series of patients with intractable complicated cerebrovascular lesions who were treated with a combination strategy (endovascular and surgical). (14,17) Other case reports were documented in the literature too. (5,7,9,13) A furthermore studies are expected be conducted on a larger scale concerning the hybrid cerebrovascular surgery in the nearby future.

Conclusion

The recalcitrant or complex cerebral aneurysms can be better referred to as diseases rather than lesions; of which many clinical factors in add to the anatomical one define their complexity and make their treatment difficult. Endovascular and open surgery could be complementary to each other and create a multimodal or combined approach for treating these aneurysms, and that concept has

evolved to what known nowadays as the hybrid cerebrovascular surgery.

Contributorship statement

Mohamed Deniwar, Mohamed Kassem and Ashraf Ezz Eldin designed the study. Mohamed deniwar, Mohamed Kassem, Ashraf Ezz Eldin and Jafar J. Jafar, participated in data extraction, analysis, writing and drafting of the manuscript, Jafar J. Jafar critically revised the manuscript and all authors approved the final version.

IRB approval

After IRB approval for both New York University (i14-01394) and Mansoura University (R.21.03.1240), all cases of cerebral aneurysms treated in New York University and in Mansoura University from 2010-2021 were retrospectively reviewed.

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Outcome of patients undergoing posterior spine fixation and decompression for posttraumatic thoracolumbar spine fractures and the factors predicting it

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ABSTRACT

Background: Posterior spine fixation and decompression for thoracic and lumbar spine fractures have the advantage of stabilization of the fracture, decompression of neural canal, early mobilization and rehabilitation of the patient. The study aimed to find out the postoperative outcome and complications following posterior spine surgery and the factors affecting the outcome.

Methods: A retrospective study was carried out among 44 patients who underwent posterior spine decompression and fusion for thoracic and lumbar spine fracture. The data regarding patient presenting symptoms, comorbidity, associated injuries and imaging finding in CT and MRI were collected. The postoperative outcome of patients after surgery was assessed using ASIA impairment scale, KPS, VAS scale for pain are noted at the preoperative and postoperative period. Other factors like improvement of bowel and bladder symptoms, back stiffness and return to the job after surgery were also found out.

Results: There was a significant improvement in ASIA impairment scale (mean =0.74 grade), KPS score (mean = 40) and VAS pain scale (mean = 6.7) at 6 months follow up after surgery. Improvement in ASIA impairment scale was more in the patient with severe canal compromise (mean = 1.62 grade), patients with translational/ distraction injuries (mean= 1.01grade) and patients with paraparesis (mean=1.06). Only one-third of patients with bowel and bladder involvement improved after surgery. Around 56.8% of patients were able to return to jobs at 6 months follow up. Patients who were paraplegic at the initial presentation were mostly not able to return to jobs. The most common reported complication in the study was intraoperative pedicle breakage.

Conclusion: Decompression of the spinal cord plus posterior spine fixation is a safe, reliable and effective method in the management of thoracic and lumbar fractures with significant improvement in outcome in terms of motor power, pain and quality of life.

BACKGROUND

Thoracic and lumbar spine fractures occurring as a result of trauma can lead to pain, neural compromise and deformity. The appropriate

treatment for these fractures ranges from conservative management with thoracic lumbar corset to surgical management with anterior/posterior instrumentation for fixation plus decompression[1,2].

Surgical management for these fractures has the advantage of stabilization of fracture with fixation, decompression of neural canal, early mobilization and rehabilitation of the patient[3]. Though there are both anterior and posterior approaches for thoraco-lumbar spine fractures most spine surgeons advocate posterior fusion and decompression as the treatment of choice for unstable fractures as the approach is less extensive[1,4,5]. Various posterior stabilization procedures are there which include hooks, wires, transpedicular screw and rod fixation, of which transpedicular screw and rod fixation is the preferred technique now[6].

In traumatic spine fractures the outcome following posterior spine decompression and fusion depends on various factors which includes timing of surgery, patient comorbidities, general condition of the patient, associated injuries. The outcome following the surgery is measured based on the extend of pain relief, to be able to mobilize the patient early, return to work, neurological recovery and development of any postoperative complications.

This study was done to find out the factors affecting the post-operative outcome following posterior spine decompression and fusion surgery in patients with traumatic thoracolumbar spine fractures. The study also aimed to find out the postoperative outcome and complications following posterior spine surgery.

Methodology

A retrospective observational study was carried out among 44 patients admitted with thoracic and lumbar spine fracture who had underwent posterior spine decompression and fusion in the department of Neurosurgery, in a tertiary care center in central Kerala, India during the period from 1st January 2019 to 31st December 2020.

Study involved collecting data regarding those patients who were admitted and operated for traumatic thoracic and lumbar spine fracture using the standard surgical protocol followed in the department. This involved laminectomy and decompression of the spinal cord +/- neural foraminal decompression and posterior spine fixation two levels above and below using polyaxial screws and rods. The data regarding presenting symptoms, comorbidities, associated injuries and imaging finding in CT and MRI was collected (like type of fracture, canal compromise and level of injury). Type of fractures were divided into posterior element only fractures, anterior wedge compression fracture, burst fracture and translation/ distraction injury. Canal compromise was divided into no/ mild (obliteration in CSF space is <50%), moderate (>/=50% obliteration in CSF space, but not deforming the cord), severe (compressing and deforming the cord). Level of injury was divided into upper dorsal(D1-D6), mid dorsal (D7-D9), dorso-lumbar junction (D10-L2) and lower lumbar(L3-L5). Other details like interval between trauma and surgery, and complications following surgery were also recorded.

The post-operative outcome of patients after surgery was assessed using ASIA (American Spine Injury Association Scale) impairment scale (Table.1b), KPS (Karnofsky Performance Status) scale (Table.1a) and VAS (Visual Analog Scale) of pain (from 0-10), all of which were noted at the preoperative and post-operative (immediate,1 month and 6 months) periods from the data available in the department. Other factors like improvement in bowel and bladder symptoms, back stiffness and return to job after surgery were also found out.

A) Karnofsky Performance Status Scale[7]		B) ASIA scale[8]	
Score	**Findings**	**Grade**	**Findings**
100	Normal no complaints; no evidence of disease.	**A** (Complete)	No Sensory or Motor Function is preserved
90	Able to carry on normal activity; minor signs or symptoms of disease.	**B** (Sensory Incomplete)	Sensory but not Motor Function is preserved below the neurological level and No Motor Function is preserved more than three levels below the Motor Level on either side of the body
80	Normal activity with effort; some signs or symptoms of disease.		
70	Cares for self; unable to carry on normal activity or to do active work.		
60	Requires occasional assistance, but is able to care for	**C** (Motor Incomplete)	Motor Function is preserved below the Neurological Level and More

	most of his personal needs.		than half of key muscle functions below the Neurological Level of Injury have a muscle grade less than 3 (Grades 0-2)
50	Requires considerable assistance and frequent medical care.		
40	Disabled; requires special care and assistance.		
30	Severely disabled; hospital admission is indicated although death not imminent.	**D** (Motor Incomplete)	Motor function is preserved below the neurological level and At least half (half or more) of key muscle functions below the NLI have a muscle grade ≥ 3
20	Very sick; hospital admission necessary; active supportive treatment necessary.		
10	Moribund; fatal processes progressing rapidly.	**E** (Normal)	If sensation and motor function as tested are graded as normal in all segments
0	Dead		

Table 1. showing a) Karnofsky Performance Score b) ASIA Impairment Scale[7,8]

In the end of the study the post-operative clinical, radiological and functional outcome in patients undergoing thoraco-lumbar posterior spine fixation and decompression was determined. The factors affecting post-operative outcome in patients undergoing thoraco-lumbar posterior spine fixation and decompression were also determined. The common complications following thoraco-lumbar spine fixation and decompression were also found out.

Data Management and Statistical Analysis*:* The data collected was entered in Microsoft Excel sheet. Percentage were calculated for categorical data, whereas numerical data represented as mean+/-SD. Statistical analysis was done to determine significant relationship between clinical and radiological factors to post-operative outcome. Paired T- test was used to compare preoperative and postoperative outcomes. Probability </=0.05 (p</=0.05) was considered significant.

Inclusion Criteria*:* Diagnosed cases of post traumatic thoracic and lumbar spine fracture who had undergone posterior spine decompression and fusion

Exclusion Criteria:

i) Cases without proper history and clinical examination
ii) Cases without proper imaging
iii) Cases without follow up
iv) Children below 13years of age

RESULTS

Mean age affected by traumatic thoraco-lumbar spine fracture is 44.30 +/- 11.87yrs. Most common age group affected was between 30-50 yrs – (26 patients,59.1%) (table.2, fig.1). The age of the study population ranged from 21yrs to 69yrs.

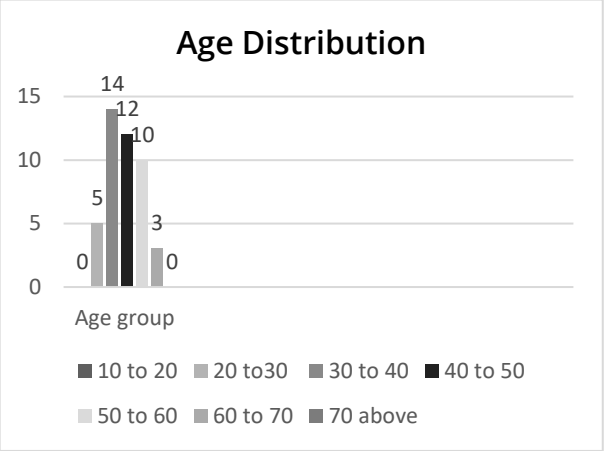
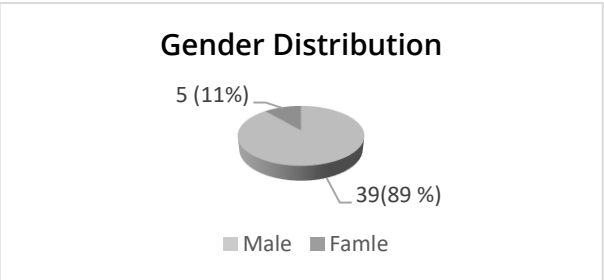


Figure 1. showing age distribution.

Age groups	10 to 20	20 to 30	30 to 40	40 to 50	50 to 60	60 to 70	70 to 80
No. patients (%)	0 / 0.0 %	5/ 11.3 %	14 / 31.8 %	12 / 27.3 %	10 / 22.7 %	3 / 6.8 %	0 / 0.0 %

Table 2. showing age distribution

Figure 2. showing gender distribution



Traumatic thoracolumbar spine fractures mainly affect males (39 patients ,88.6%). Male to female ratio is 7.8:1 (fig.2).

Table 3. showing distribution of patients according to a) fracture type, b) canal compromise, c) Level of fracture and d)interval between injury and surgery.

a) Fracture	No. of patients	b) Level	No. of patients
Only Pars #/ posterior element	0 (0.0%)	D1- D6	7 (15.9%)
Anterior wedge compression	11 (25.0%)	D7-D9	6 (13.6%)
Burst	19 (43.2%)	D10-L2	25 (56.8%)
Translational injury/subluxation / Burst # + PLC injury	14 (31.8%)	L3-L5	2 (4.5%)
Total	44 (100.0%)	Multiple levels	4 (9.1%)
C) Canal Compromise	**No. of patients**	**d) Interval between injury and surgery**	**No. of patients**
No / mild	8 (18.2%)	(</=2weeks	16 (36.4%)
moderate	23 (52.3%)	2-4weeks	14 (31.8%)
severe	13 (29.5%)	1-3months	14 (31.8%)
Total	44 (100.0%)	> 3months	0 (0.0%)

Most common fracture type involved in the study was burst fractures (19 patients, 43.2%) (table.3a). Most of the patients (23patients, 52.3%) in the study had moderate canal compromise (more than 50% obliteration of subarachnoid space, but not deforming the spinal cord) (table .3c). Most common level involved was D10 to L2 level (Thoraco-lumbar junction) 25 patients (56.8%) (table.3b). For most of the patients in the study surgery was done within 4weeks duration, (30 patients, 68.2%). For 14 patient surgery was done between 1-3 months duration (table.3d).

Patients who underwent surgery for traumatic thoracolumbar spine fractures showed a mean improvement in grade of 0.43 and 0.76 in ASIA impairment scale postoperatively at 1month and 6 months respectively compared to preoperative status. These findings were found to be statistically significant (table.4a). Patients with paraparesis and paraplegia showed an improvement ASIA impairment scale of 1.06 and 1.25 grade respectively compared to preoperative scale, which was statistically significant Ttable.4b).

a) Parameter	Mean	N	Std. Deviation	Difference	t	p value
Pre ASIA	3.27	44	1.633	+0.43	5.25	.000
Post ASIA1*	3.70	44	1.579			
Pre ASIA	3.33	43	1.614	+0.76	6.22	.000
Post ASIA6*	4.09	43	1.306			

b) Symptom	Parameters	Mean	N	Std. Deviation	mean difference	t	p value
Paraparesis	PreASIA	3.60	15	.632	+1.06	6.95	.000
	Post ASIA6	4.67	15	.488			
Paraplegia	PreASIA	1.00	12	.000	+1.25	4.48	.001
	Post ASIA6	2.25	12	.965			

c) Parameter	Canal Compromise	N	Mean	Std. Deviation	F	P value
Pre ASIA	No/ mild	8	4.38	.744	17.278	.000
	moderate	23	3.83	1.370		
	severe	13	1.62	1.193		
Post ASIA6	No/ mild	8	4.75	.463	.463	.001
	moderate	23	4.43	1.080		
	severe	12	3.00	1.477		
d) Parameter	**Level**	**N**	**Mean**	**Std. Deviation**	**F**	**P value**
Pre ASIA	D1- D6	7	3.14	1.676	2.255	.081
	D7-D9	6	1.67	1.633		
	D10-L2	25	3.48	1.584		
	L3-L5	2	4.00	.000		
	Multiple levels	4	4.25	.957		
Post ASIA	D1- D6	7	3.86	1.676	1.449	.237
	D7-D9	6	3.17	1.169		
	D10-L2	24	4.21	1.285		
	L3-L5	2	4.50	.707		
	Multiple levels	4	5.00	.000		

e) Parameters	Fracture type	N	Mean	Std. Deviation	F	P value
Pre ASIA	Anterior wedge compression	11	4.27	1.009	7.29	.002
	Burst	19	3.53	1.467		
	Translational injury/subluxation / Burst # + PLC injury	14	2.14	1.657		
Post ASIA6	Anterior wedge compression	11	4.73	.467	6.38	.004
	Burst	19	4.37	.955		
	Translational injury/subluxation / Burst # + PLC injury	13	3.15	1.725		

Table 4. showing a)preoperative and post operative - ASIA impairment scale, . (I 1*-post operative at 1month, 6*- post operative at 6month), b))preoperative and postoperative - ASIA impairment scale among paraparesis and paraplegic patients c) relationship of canal compromise with preoperative ASIA (PreASIA) , and postoperative ASIA at 6month (Post ASIA6), d)relationship of level of injury with Pre ASIA and Post ASIA score at 6month, e)relationship of fracture type to Pre operative ASIA (PreASIA) ,Post operative ASIA at 6months (Post ASIA6).

Table 6. showing a)pre operative and post operative KPS score (I*-immediate post operative, 1*-post operative at 1month, 6*- post operative at 6months), b) relationship of fracture type to post operative KPS at 6months (PostKPS6) , c)relationship of canal compromise with preoperative KPS (PreKPS) and postoperative KPS at 6months (Post KPS6).

a) Parameter	Mean	N	Std. Deviation	Difference (improvement)	t	p value
Pre KPS	39.8	44	11.91	+5.7	6.03	.000
Post KPS I*	45.5	44	11.30			
Pre KPS	39.8	44	11.91	+25	13.09	.000
Post KPS1*	64.8	44	15.77			
Pre KPS	40.0	43	11.95	+39.8	15.76	.000
Post KPS6*	79.8	43	18.32			

b) Parameters	Fracture type	N	Mean	Std. Deviation	F	P value
Post KPS6	Anterior wedge compression	11	90.9	13.75	7.73	.001
	Burst	19	82.6	15.93		
	Translational injury/subluxation / Burst # + PLC injury	13	66.2	17.58		

c) Parameter	Canal Compromise	N	Mean	Std. Deviation	F	P value
Pre KPS	No /mild	8	46.3	10.61	7.136	.002
	moderate	23	42.6	12.51		
	severe	13	30.8	4.94		
Post KPS6	No/ mild	8	92.5	13.89	10.766	.000
	moderate	23	83.9	14.06		
	severe	12	63.3	17.75		

Table 8. a) showing distribution of all patients return to job after surgery, b) showing distribution of patients having weakness returning to job after surgery.

a) Job	No	Modification	Old same Job	Total
No. Of patients	19 (43.2)	17 (38.6)	8 (18.2)	44 (100.0)

b) Weakness		Job			Total		
		No	Modification	Old same Job		x^2	P VALUE
	No weakness	4 (26.7%)	4 (26.7%)	7 (46.7%)	15 (100.0%)	30.755	.000
	monoparesis	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (100.0%)		
	paraparsis	3 (20.0%)	11 (73.3%)	1 (6.7%)	15 (100.0%)		

	paraplegia	12 (92.3%)	1 (7.7%)	0 (0.0%)	13 (100.0%)		
Total		19 (43.2%)	17 (38.6%)	8 (18.2%)	44 (100.0%)		

Pre ASIA	**Post ASIA6**					
	A	**B**	**C**	**D**	**E**	**Total**
A	3	4	4	1	0	12
B	0	0	0	1	0	1
C	0	0	0	2	2	4
D	0	0	0	3	10	13
E	0	0	0	0	13	13
Total	3	4	4	7	25	43

Table 5. showing comparison of preoperative ASIA score (pre ASIA) to postoperative ASIA score at 6 months (post ASIA6).

None of the operated patients had deterioration in ASIA score at 6month follow up. Of the total of 12 patients operated with preASIA grade A, only 3 patients remained at grade A, whereas 4 patients each had improved to ASIA grade B and C (table 5) on post-operative follow up at 6months.

Preoperative ASIA impairment score showed significant relation to fracture type, with patients suffering from translational /distraction injury having a poorer grade (mean ASIA score of 2.14 = grade B to C) whereas anterior wedge compression fracture having better grades (mean ASIA score of 4.27= grade D to E). Post operatively ASIA impairment scale at 6 months showed significant relations to fracture type, with patients having anterior wedge compression fracture (mean ASIA score of 4.73= grade D to E) having better scores than patient with translational injury (mean ASIA score of 3.15= grade C to D) (table.4e).

Considering canal compromise, patients with severe canal compromise were having poor ASIA score both preoperatively and postoperatively when compared with patients having mild / moderate canal compromise (table.4c).

Regarding the level of involvement, patient with D7-D9 involvement were having lowest preoperative ASIA score (mean ASIA score was 1.67= A to B), but these finding didn't have and statistical significance (table. 4d). Interval between injury and surgery failed to find any statistically significant relation in terms of outcome.

When compared to preoperative KPS there was significant improvement in mean postoperative KPS score at 1month and 6 months as 25 and 39.8 respectively. (table.6a). Though preoperatively KPS failed to show any significant relation to fracture type, post operatively KPS at 6 months showed significant relation to fracture type, with patients having anterior wedge compression fracture (KPS=90.9) having better scores than patient with translational injury (KPS= 66.2) (table.6b).

Considering canal compromise, patients with severe canal compromise were having poor KPS score both pre-operatively (mean=30.8) as well as post operatively (mean=63.3) when compared with patients having mild (mean preKPS =46.3, mean post KPS6 =92.5)/ moderate (mean preKPS =42.6, mean post KPS6 = 83.9) canal compromise (table.6c). KPS score didn't have any significant relation with the level of injury.

Considering the VAS pain scale, there was again significant decrease VAS pain scale in post-operative period (Immediately, at 1month and at 6 month scores being 1.65, 4.88 and 6.7 respectively-table.7). However, VAS pain scale didn't show any significant relations to fracture type, canal compromise or the level of injury.

Parameter	Mean	N	Std. Deviation	Difference (Decrease in pain)	t	p value
PreVAS	7.70	44	.851	-1.65	7.975	.000
PostVAS I*	6.05	44	1.613			
PreVAS	7.70	44	.851	-4.88	26.899	.000
PostVAS1*	2.82	44	.995			
PreVAS	7.70	43	.860	-6.7	36.423	.000
PostVAS6*	1.00	43	1.024			.

Table 7. showing preoperative and postoperative VAS pain score. (I*-immediate post operative, 1*-post operative at 1month, 6*- post operative at 6 months).

Of the 44 patients operated, 25 patients (56.8%) were able to return to job. 8 patients (18.2%) were able to return to their old job (table.8a). Among the 13 patient operated with paraplegia only 1 patient (7.7%) was able to return to work with job modification and none of them were able to return to old job. But among 15 patients with paraparesis 12 (80%) were able to return to job (1 patient returned to the same job, rest 11 had to modify their job) (table. 8b).

Bowel was involved in only 12 patients, of which 4 patients improved after surgery (33.3%) and in the

rest 8 patients symptom remained same. Bladder was involved in 14 patients of which 4 patients improved (28.6%) and rest 10 patients remained symptomatically same. There was no worsening of bowel or bladder symptom following surgery (Table 9).

Symptom	Outcome after surgery			
	Not involved	worsen	Same	Improved
Bowel	32	0	8	4
Bladder	30	0	10	4

Table 9. showing ouctome of bowel and bladder symptom following surgery.

No significant relationship was found out between associated injuries or comorbidities to post-operative outcome.

Intraoperative complication like pedicle breakage was seen in 3 patients. Other intraoperative complications like nerve root injuries were not observed. Postoperative complications like surgical site infection was seen in only 2 patients, discitis/ abscess and DVT was observed in 1 patient each. Other postoperative complications like implant failure were not observed. Post-operative complaint most commonly observed was stiffness in back at the operative site and was present in 25 patients (56.8%).

Discussion

This retrospective study was done during the study period from 1st January 2019 to 31st December 2020, including 44 patients admitted for thoracic and lumbar spine fracture who had underwent posterior spine decompression and fixation. The study had 39 male patients (88.6%), with male to female ratio 7.8:1. The mean age of presentation was 44.30+/-11.87yrs and most common age group of presentation was 30-50 yrs (59% patients) this again point to the fact that traumatic fractures mainly affects physically active age group and population (males). In a similar study done by Hariri O R et al between 2005 to 2015 among 46 patients, 93% patients were male and mean age of presentation was 36.8 years [9]. Another comparative study done by Petr V et al in thoraco-lumbar spine fractures among 35 patients, again had 28 male patients and mean age of presentation as 42.4years[10].

As the study included only patients undergoing surgery for thoracic and lumbar fractures most common fracture type included in the study was burst fracture 43% (even though posterior element fracture and anterior compression fractures are far more common, as they are commonly managed conservatively, they are lesser in number in this study).

In the study population thoraco-lumbar junction (D10-L2) was the most commonly involved fracture level (56.8%), probably due to the relative instability of transition zone. In the study of 66 patients by Roop Singh et al from 2007 to 2011 had reported similar results with about 57.6% (38 patients) thoracolumbar fracture occurring at D12, L1 levels[11]. Petr Vet al again had reported 80% of thoracolumbar fractures from D12, L1 levels[10].

Regarding the postoperative outcome the study showed improvement in ASIA impairment scale of 0.74 grade at 6 months postoperatively when compared with preoperative status. Among 43 patients followed up at 6 months (1patient lost in follow-up at 6month) no patients had deterioration in ASIA score. On post-operative follow up of 12 patients operated with preoperative ASIA grade A at 6 months only 3 patients remained at grade A , 4 patients each had improved to ASIA grade B and C, 1 patient to grade D and non to grade E (table.5). Among patients with paraparesis and paraplegic mean preoperative ASIA were 3.6 (ASIA grade C to D) and 1 (ASIA grade A). Their post-operative grade improved to 4.67 (ASIA grade D to E) and 2.25 (ASIA grade ~B) (table.4b). Although there was post-operative improvement in paraplegic patients, it was not up to functional levels. So, we can infer from the study that both paraplegic and paraparesis patient can have significant improvement in ASIA scale, but chance of paraplegic patients able to walk after surgery is rare. The study by Roop Singh et al among 66 patients also had similar observations with an improvement of average 1.03 grades in neurological status as per ASIA Impairment scale from the preoperative to final follow-up at one year[11]. Among 34 patients having preASIA grade A, 14 patients improved to grade B , 2 patients to grade D and non to grade E. The study also showed that the patients having incomplete lesions of the spinal cord showed more neurological improvement (mean, 1.5 grade) than the complete lesion of the spinal cord (mean, 0.53 grade). Similar observations were reported in another study by Butt et al [12].

When ASIA score was assessed in terms of fracture type, as expected patients with anterior wedge compression fracture had better preASIA score (mean preASIA=4.27, ASIA D to E) compared to patient with translational /distraction injury (mean preASIA=2.14, ASIA B to C). This may be due to severe canal compromise / spinal cord injury associated with translation/ distraction injury. But postoperatively there was significant improvement in ASIA score at 6months for translation/distraction injury (post ASIA6=3.15, ASIA C to D) (mean improvement=1.01 grade) and burst fracture (post ASIA6= 4.37,ASIA D to E) (mean improvement = 0.84 grade). So we can expect a significant neurological improvement even in patients with translational / distraction injury on doing decompression + fixation.

Patients with severe canal compromise were having preASIA score 1.62 (ASIA A to B) and with no/mild canal compromise were having preASIA score 4.38 (ASIA D to E). Here also post operatively patients with severe canal compromise were having significant improvement at 6month (post ASIA6= 3.00, ASIA C) (Mean improvement =1.38 grade). Similar improvement was seen in moderate canal compromise patients. So, we can expect a significant neurological improvement in patients with moderate to severe canal compromise, on doing decompression + fixation.

There was no significant relation between level of injury and ASIA score but patients with D7-D9 level injury tend to have preASIA score very low (mean pre-ASIA =1.67, ASIA A to B) and 6month post-surgery there was significant improvement (mean post ASIA6= 3.17, ASIA C to D). Alessandro L et al in their study have reported poor ASIA score common for thoracic level vertebra fracture[13].

In our study, most of the patients underwent surgery within 4weeks of injury, (30 patients, 68.2%). For 14 patient surgery was done between 1-3 months duration (table.3d). Surprisingly there was no significant difference in improvement between early surgery group and late surgery group in terms of ASIA impairment scale. This is primarily because even in early surgery group most of the surgery were done after 1 week (partly because of lack of facilities for emergency stabilization of the spine and due to patient reporting late because of ignorance on the part of the patient or due to late referral from other centers). But study done on 27 patients between 2004 to 2006 by Sahika L C et al have reported surgical decompression and stabilization within 8 hours of spinal cord injury had better outcome than when operated between 3 and 15 days[14]. In the study by Roop Singh et al the patients of early surgery group showed slightly better improvement in mean ASIA score (1.2 grade) than the patients who had underwent surgery late (0.95 grade), which was not a statistically significant difference[11]. Chadha et al and Butt et al.had also reported a fair neurological recovery in cases were surgery was done late[12,15].

Compared to preoperative KPS score (mean PreKPS=39.8) there was significant improvement in mean post-operative KPS score at 1month (mean PostKPS1=64.8) and 6 months (mean post KPS6= 79.8) as 25 and 40 respectively. So, at 6months follow up on an average the patient in the study were able to carry out normal activity with signs and symptoms of disease (KPS=80). Similar results were seen in a study done by Mohsen K et al who compared the outcome after surgery and conservative management among 25 patients. In this study JOABPEQ (JOA Back Pain Evaluation Questionnaire) was used to assess the functionality in five domains including walking ability, lumbar function, low back pain, social life function and mental health at admission and at the interval of 3, 6, 12 months after treatment. In both surgery and conservatively managed patients there was improvement in outcome, but faster and better recovery was among post-surgery group[16].

In our study fracture type and KPS score didn't have significant relation in preoperative period. Postoperatively at 6months KPS showed significant relation to fracture type with patients with anterior compression fracture having mean KPS score as 90.9, and those with translation / distraction injury having mean KPS as 66.2. So, even though there was improvement in KPS score in all types of fractures, anterior wedge compression fracture followed by burst fracture tend to have best improvement in terms of KPS score after 6months of surgery. In terms of canal compromise, pre-operative KPS for no/mild, moderate and severe were 46.3, 42.6 and 30.8 respectively which improved to 92.5, 83.9 and 63.3 at 6month post operatively. So, improvement in KPS score in no/ mild, moderate, severe canal compromise were 46.2, 41.3 and 32.5 respectively. So, there was better improvement in KPS score in mild and moderate canal compromise patients compared to severe canal compromise patients.

These findings may be partly due to absolute bed rest advised for all patients prior to surgery, hence irrespective of fracture type and canal compromise preoperative KPS will be low for all, whereas postoperatively patients with less severe injury have far better improvement in KPS score.

Compared to preoperative status, postoperatively there was significant decrease in VAS pain scale - immediately post op, at 1month post op and at 6-month post op as 1.65, 4.88 and 6.7 respectively (table.4). VAS pain scale didn't find any significant relation in terms of fracture type, canal compromise both preoperatively as well as post operatively. Study by Rajdeep S B et al on 30 patients conservatively managed had mean VAS score of 9.77 ± 0.43, which decreased to 2.03 ± 0.90 at the end of 2 years[17]. Study by Roop singh et al had quantified pain using Denis pain scale and found out 48.48% patient had mild to no pain, and 42.42% patient had moderate pain at 1 year follow up[11].

Regarding outcome in terms of job, postoperatively at 6months follow up 19 patients (43.2%) were not having job, of which 12 were paraplegic initially itself.

Among 13 patient having paraplegia initially, only 1 returned to job (7.7%) with job modification, none of them were able to returned to same job. Whereas, of the 15 patients having paraparesis 12 (80%) of them returned to job, but 11 of them had to modify their job. In patients having no weakness, 11 patients (73.3%) were able to return to job, of which 7 patients (46.7%) were able to return to old job itself. So, paraplegia in initial presentation implies a very poor outcome in terms of job. Patients with no weakness or paraparesis in initial presentation tend to return to same job or to a modified job.

Study by Roop singh et al had reported 63.4% patients not returning to job (most of them were initially paraplegic) and 36.6% patients returning to work (half of them with job modification)[11]. Leferink et al. had reported, 50% of patients changed the intensity of their work or the kind of work they did, after thoracolumbar spine injury and treatment[18]. Study by Briem D et al also had reported a low work capacity after thoracolumbar spine fractures[19].

was involved in only 12 patients, of which 4 improved after surgery (33.3%) and rest 8 symptom remained same. Bladder was involved in 14 patients, of which 4 patients improved (28.6%) and for rest 10, symptoms remained same. There was no worsening of bowel or bladder symptom following surgery (table.7). So, there is around one third chance of improvement by surgical decompression when bowel and bladder is involved in thoracolumbar spine fracture. In literature review a study by Ping-Yeh Chiu et al among 8 patients from 2005 to 2012 with pure conus medullaris syndrome with thoracolumbar burst fracture, 5 patients regained self-voiding function[20].

In our study no significant relationship was found out between associated injury or comorbidity to post-operative outcome.

Complications observed in the study were intraoperative pedicle breakage in 3 patients, postoperative surgical site infection in 2 patients, discitis/ abscess and DVT was observed in 1 patient each. Other complications like nerve root injury and implant failure were not seen. Though there was no implant failure reported in 6-month follow up (which may be an advantage of fixation of 2 levels above and below the spine fracture), most of the patients (56.8%) complaint of stiffness in back at operative site. In transpedicular screw fixation it is recommended to include two spinal levels above the fracture level and one or two levels caudal to the fracture level[21]. Such long segment spinal fixation might result in significant loss of mobility and increased risk for adjacent level morbidity. In an attempt to lessen the problem arising due to decreased mobility, short segment instrumentation has been introduced, fusing only two motion segments. But it also has come up with mixed results and complications[22,23.] On literature review the study by Butt MF et al.says more than 50% of patients had one or more complications, including 18 cases of hardware failures, involving 20 pedicle screws[12]. Complications reported in study by Roop Singh et al were single level above and below the fracture site was fused had only one implant failure such as nut loosening (asymptomatic), 4misplaced screws (in 3 patients -asymptomatic)[11]. Chadha et al had reported misplacement of the screw in 3 cases, one case of screw loosening and one screw pullout[15].

Conclusion

From this retrospective study, we can conclude that laminectomy and decompression of the spinal cord and posterior spine fixation 2 levels above and below, using polyaxial screws and rods is safe, reliable and effective method in the management of thoraco-lumbar fractures. There was significant

improvement in ASIA impairment scale (mean improvement at 6months=0.74 grade) , KPS score (mean improvement at 6months= 40) and VAS pain scale (mean improvement at 6months= 6.7) at 6 months follow up after surgery.

Study was able to find out that the improvement in ASIA impairment scale was more in patient with severe canal compromise (mean improvement at 6months=1.62 grade), patients with translational/ distraction injuries (mean improvement at 6months= 1.01grade) and patients with paraparesis /paraplegia (mean improvement at 6months= 1.06/1.25 grade respectively).

Only one third patients with bowel and bladder involvement improved after decompressive surgery. Around 56.8% patients were able to return to job (either same job or with some modification) at 6 months follow up. Patients who were paraplegic at initial presentation, were mostly not able to return to job.

Most common reported complication in the study was intraoperative pedicle breakage.

Abbreviations

ASIA - American Spine Injury Association Scale
KPS - Karnofsky Performance Status Scale
VAS - Visual Analog Scale
MRI - Magnetic Resonance Imaging
CT - Computed Tomography

Declarations

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A very rare fact occurring after V/P shunt in the surgical treatment of Pseudotumor Serebri Syndrome. Liver subcapsular pseudocysts

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Keywords
V/P shunt, surgical treatment, Pseudotumor Serebri Syndrome, liver subcapsular pseudocyst

ABSTRACT

Introduction: In this study, it is aimed to present a very rare liver subcapsular accumulation of a patient after ventriculoperitoneal shunt surgery who was diagnosed with Pseudotumor cerebri syndrome with progressive sight loss.

Case: The patient is a 38-year-old female who was diagnosed with lomber spondylose and later operated with stabilization and fusion surgery. Seven days after the operation her headaches became clear and blackout in her left eye was seen and she was observed with medical treatment. CSF pressure of her was measured to be 25 cm/ water, so she was diagnosed as pseudotumour cerebri and taken to the operation immediately. On the 3rd day of post-operation, there occurred to be intense stomach ache and abdominal sensitivity of the case. After the scanning of abdominal CT, 7 cm of liquid collection was detected in the shunt distal of liver subcapsular area.

Discussion: Liver pseudocyst should be considered, even if it is a rare complication when back striking abdominal pain and high liver enzymes are seen in patients with shunt dysfunction. USG and abdominal bt tests should be made for these patients. The drainage of the cyst and then the removal of the abdominal catheter should be applied.

✉

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INTRODUCTION

Pseudotumor Cerebri Sydrome (PTSS), is characterized with hydrocefaly intracranial infection in the form of obstructive lesion situated in the brain with the increase of intracranial pressure without radiological findings (1). It is called Pseudotumor Cerebri or idiopathic intracranial hypertension at the same time. It was first defined by Quinke in 1897 and its Diagnostic criteria were determined by Dandy in 1937 but its Patophysiology has not been described completely (2). The biggest risk factors are female sex and obesity. Its clinical

symptoms are frequently seen as headache, loss of sight, dizziness, tinnitus and diplopy (3). Its most significant finding is papil oedema. However, cases without headache and papil oedema have rarely been found out. Treatment is priviliged with the retraction of secondery reasons of weight loss. If there are cases without any recovery then medical and surgical treatment can be used.

In this study, it is aimed to present a very rare liver subcapsular accumulation of a patient after ventriculoperitoneal shunt surgery who was diagnosed as Pseudotumor cerebri syndrome with progressive sight loss.

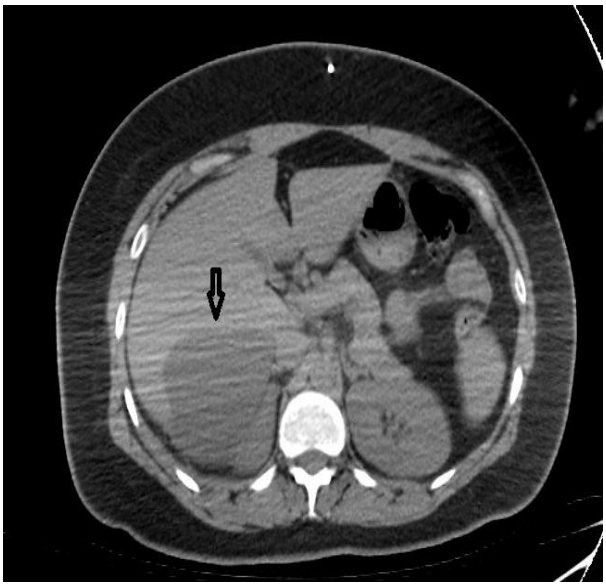

Figure 1. The enhanced CT after operation. (a) Axial CT showed water-like hypointense mass in the liver contour.

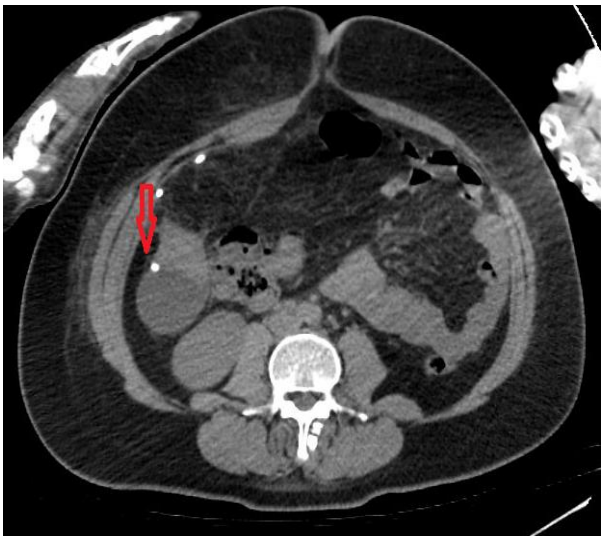

Figure 2. The enhanced CT after operation. (a) Axial CT showed water-like hypointense mass and catheter image in the liver contour.

CASE

The patient is a 38-year-old female who was diagnosed with lomber spondylose and later operated with stabilization and fusion surgery. Seven days after the operation her headaches became clear and blackout in her left eye was seen and she was observed with medical treatment. Opthalmology consultation was demanded as a result of sight loss in her left eye 15 days after the operation. In her consultation in left eye optical atrophy and in her right eye papil oedema was detected as a result of which she was sent to our clinic straightaway.When the patient was seen in our emergency service her conscious was clear koopere oryante ır +/- BMI which was not deficit neurologically. In order to exclude pseudotumour cerebri possibility, firstly cranial mrg, diffusion mrg, and venography were applied to her. As there were not any patological find-outs, CSF pressure of her was measured to be 25 cm/ water, so she was diagnosed as pseudotumour cerebri and taken to the operation immediately. Lumboperitoneal shunt was set in the surgery. She was discharged on the 4th day of post operation as her oedema in the right eye had drawn back and her headache had soothed.2 months later she came again with serious headache and sight loss in the right eye.CSF pressure measured to be 29 cm/ water via LP. She was consulted to opthalmology clinic with the diagnosis of Lumboperitoneal shunt dysfunction for the fenestration of optical nerve cover fact. There was not any extra pathology in the following of the operated case. After ‘ years, she applied to emergency service with the increase of sight loss, headache, tinnitus and dıplopy. After neuroimaging, CSF was measured to be 28 cm/water, therefore neuronavigation guided ventriküloperitoneal shunt was planned. After the operation, the complaints of the patient decreased. On the 3rd day of post operation, there occurred to be intense stomach ache and abdominal sensitivity of the case. After the scanning of abdominal CT, 7 cm of liquid collection was detected in the shunt distal of liver subcapsular area(fugure 1,2,3,4). When USG performed; dren was placed into the subcapsular area. The liquid not compatible to the CSF was discharged for three days.

Then shunt distal revision was made with reoperation.

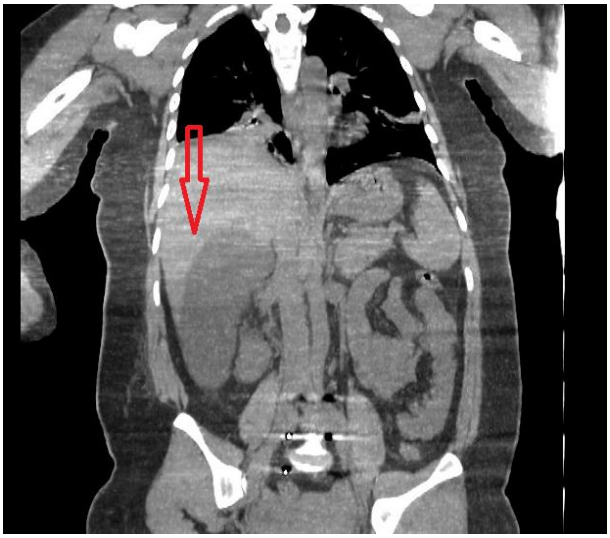

Figure 3. The enhanced CT after operation. (a) Coronal CT showed water-like hypointense mass in the liver contour.

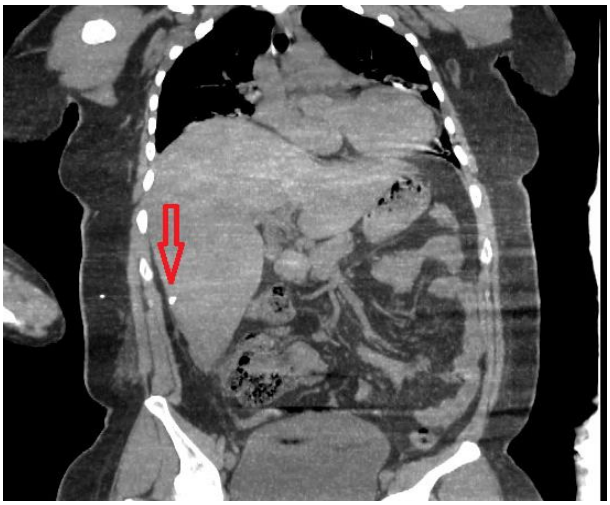

Figure 4. The enhanced CT after operation. (a) Coronal CT showed water-like hypointense mass and catheter image in the liver contour.

Discussion

Pseudotumor Cerebri is often seen in women, that is; the intensity of Pseudotumor Cerebri for general population is 0,9/100.000 while it is 19,3/100.000(1,2) for obese women who are at a childbearing age(4,5). It is essential to start treatment without delay as the sydrome causes headache and progressive sight loss. The aim of the treatment is to control headache and to protect seeing. During the treatment, making the obese patients lose weight helps most patients recover without any need of medication. The first option in medical treatment is a carbonic anhidraz inhibitor, asetolozolaid which is used to decrease the production of BOS pressure(6). Topiramat and Furosemid can be started at chosen cases as well(6). Optical nerve fenestration, shunt, venos sinüs stent and barıatrıc surgery are applied in surgeric operations.Ventriculoperitoneal or lumboperitoneal shunt are applied when the patients utilise from lomber ponction in case of no progress in medical treatment(7). In these operations, especially shunt obstruction, infection, intracranial hypotension, and mechanic complications due to the catheter can be observed. Obctruction that is one of the often seen reasons of shunt dysfunction can be a result of pseudocysts growing in abdominal part.

The frequency of mentioned complication is between 0,25% and 10 % among all v/p shunt complications in theory(8,9). Pseudocysts in liver subcapsular area is rarely seen in literature. 16 cases have been reported in all literature so far.the forming of pseudocysts in liver is defined as two kinds. In the first one, there occurs to be cyst existing in intraaxial in which the shunt dystal is within the liver parenchymal. The second kind happens to be in extraaxial and its catheter dystal is in the glisson capsul. As the capsul is sensitive to the pain, in extraaxial pseudocysts, heavy pain striking to the back in lower right dial and hard breathing due to dıaphragm irritation are seen (10).

In the cases there happens to be pseudoscysts, the increase of liver enzymes can be observed. In our case, the increase in sub ast ggt alp parameters as a result of intense cyst formation and the pressure of gallbladder were detected. In diagnosis, first abdominal USG among non invasive verifications and then for some cases the imaging of cyst size by abdominal tomography can be chosen. In the treatment, when the other 15 cases are examined , it is seen that shunt dystal revision is made when there is no infection is found in the content of the cyst after the aspiration of extraaxial cysts. Shunt dystal revision is suggested instead of cyst aspiration because of bleeding risk in liver cysts. In our case, shunt revision operation was applied as there were no cells in CSF after the drainage of catheter within the cyst for 3 days and the culture was negative.

Abdominal pseudocyst can repeat after revision surgery. The repetition rate can change from 7,1 % to 62 % in literature. On the other hand, there are no

reports on the recurrency of liver pseudocysts.

Conclusion

Liver pseudocyst should be considered, even if it is a rare complication, when back striking abdominal pain and high liver enzymes are seen at patients with shunt dysfunction. USG and abdominal CT tests should be made to these patients. The drainage of the cyst and then the removal of abdominal catheter should be applied. When the cell is negative in CSF and when 3 negative cultures were seen, then catheter should be set with reoperation. In these operations, cooperation with the general surgery staff should be made in order to remove the shunt dystal from the liver to a distant part by open surgery or laparoscopıc methods.

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Ferrans and powers quality of life index for spinal cord injury: to adapt in local language

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Keywords
spinal cord injury, quality of life, Telugu language, satisfaction

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ABSTRACT

Objective: To translate and culturally adapt the Telugu version of Quality-of-Life tool among Spinal Cord Injury patients.

Method: It's a prospective cross-sectional study conducted at a tertiary neuro centre care hospital. The English version was translated into Telugu by two expert medical professionals and cross-checked by three experts in Telugu vocabulary. Nursing students who had good proficiency in reading and writing in English and Telugu languages were chosen for checking tool reliability. Initially English language was administered on the satisfaction domain followed by the importance domain one month apart. After two months Telugu version was administered in the same way as the English version. The reliability analysis was done.

Results: The tool was administered to 50 nursing students. The Cronbach's alpha for the satisfaction domain was 0.97 and the importance domain was 0.91, indicating excellent reliability.

Conclusion: The Telugu version of the QOL tool had excellent reliability. Therefore it can be administered in the Telugu language for evaluating the quality of life of people with spinal cord injury.

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INTRODUCTION

Spinal cord injury (SCI) is a major public health issue. In India, due to rapid advancement in motorization and industrialization the SCI are

increasing every year. SCI results in motor and sensory impairment which may be temporary for short time or permanent throughout lifetime depending on the severity of injury and individual factors. [1, 2] Majority of SCI survivors will have permanent non-repairabledamage to spinal cord thus they will suffer from secondary complications which will have major effect on their daily activities. Quality of life (QOL) is an important parament of disabled patient, especially among SCIs. The parameter in QOL includes subjective and objective aspects of injured patient. [3] Therefore; evaluating QOL among SCI patients is a challenging issue. The tool has been widely adapted and translated in major languages across the world. As per the census of 2001, the Telugu is a first language of over 74 million people in India. At present, Telugu is a third major language that is spoken in the country. Hence it is very important to have QLI in Telugu language. Thus, there is lack of reliable studies addressing QLI tool in Telugu language. The objective of the present study is to translate and culturally adapt the Ferrans and Powers Quality of Life (QLI), Spinal Cord Injury-III in Telugu language.

Methods

It's a prospective cross-sectional study conducted at the department of Neurosurgery, Narayana Medical College, Nellore. Permission through email was sought from Farren to translate and validate this tool in Telugu language. The study was approved by Institute Ethical Committee. The tool was translated by two medical professionals who were proficient in reading, writing, and speaking of Telugu and English languages. All 37 items of both parts of health quality; satisfaction and importance were translated[4,5]. The translated items were read by three independent professionals. Independent readers have ensured that the translation in Telugu is accurate and flawless by giving their suggestions. The final draft of Telugu version was finalized after incorporation of suggestions and corrections of readers.

Fifty nursing students, well proficient in English and Telugu languages were chosen for the study. The informed written consent was obtained from all the participant. Participants did not receive any incentives for their participation in the study. Two interviewers (not know to each other) administered the tool in English language on all the participants. All standard procedures for administering the tool were followed. The questions of satisfaction and importance domains were administered with one month apart. The Telugu translated questionnaire was administered after 2 months of administering English language. A gap of one month was maintained between administration of satisfaction and importance domain.

Statistical analysis

The data was analyzed with the help of Statistical Package for the Social Science, version 18. The Cronbach's alpha and correlation were calculated for difference between interviewee responses on English and Telugu questionnaire.

Results

The Cronbach's alpha coefficient was calculated for QLI in Telugu language among Telugu speaking population. The domains of satisfaction and importance had a Cronbach's alpha coefficient of ≥ 0.9, indicating excellent reliability. Table 1 revels result of the reliability analysis.

Ferrans and Powers Quality of Life	No. of items	alpha
Satisfaction domain	37	0.97
Importance domain	37	0.91

Table 1. Reliability table for the Quality-of-Life tool

Discussion

There are many tools available but none are without limitations. The most accepted and commonly used tools are from developed countries and have been adapted in developing countries in their native languages. Among such tools the Ferrans and Powers Quality of Life (QLI) is very reliable and a valid tool that has been found very comprehensive and applicable in assessing the quality of life in SCI patients[3,6]. The QLI Spinal Cord Injury - Version III, is a specific version which was specifically designed for spinal cord injury[7].

The study result reports that satisfaction and importance domains of QLI in Telugu language had excellent internal consistency as reflected by Cronbach's alpha value (α≥0.9). The intercorrelation between satisfaction and importance domains of QLI in English and translated Telugu language is very high. The result of all the Telugu translated items of tool are all most same as English language, because intercorrelation between the translation and English

language is excellent. Hence both the satisfaction and importance domains of QLI in Telugu language have excellent reliability.

A study from Brazil translated QLI for SCI into Portuguese cultural vocabulary and reported that the kappa coefficient was statistically stable of all the items of the tool. 8 A study translated QLI in Norwegian version and reported excellent reliability with alpha value of 0.93. 9 Various studies have reported internal consistency reliability ranging from 0.73 to 0.93 for health and functioning domains of QLI. 10, 11 In order to adapt QLI for SCI in the Telugu speaking population their cultured vocabulary was used. Exact translation and substitution of English sentence with same meaning in Telugu was done by expert person. The present study results report that Telugu translated QLI have excellent reliability and can be used among Telugu population.

Conclusion

The Telugu translated Quality of Life Index Spinal Cord Injury - Version III showed that the tool is suitable from satisfaction and importance domain point of view and provides way for easy application to evaluate the QOL among SCI people.

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Reperfusion injury in brain stroke

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ABSTRACT

The occlusion of a cerebral artery by a thrombus accounts for about 80% of strokes. Reperfusion can save hypoperfused brain tissue from early cerebral blood flow restoration (CBF), thus limiting neurological impairment. The most successful treatments for stroke care have proven to be reperfusion techniques. One of the key drawbacks of these treatment methods is that early ischemic brain tissue reperfusion can lead to adverse effects, including blood-brain barrier breakdown, which can lead to cerebral oedema, haemorrhage of the brain, or both. Haemorrhages are especially devastating after reperfusion and are associated with exceptionally high morbidity and mortality. Fear of haemorrhage-related reperfusion greatly restricts the use of stroke therapies. Reperfusion injury, a mechanism that further damages brain cells, the ischemic arterial wall, and the microvasculature, is due to the deleterious effects of early restoration of cerebral blood flow following stroke. It seems clear that the brain will benefit from therapies to restore CBF to an ischemic region. The brain's reliance on normal CBF levels is underlined by the sensitivity of the brain to relatively short ischaemic cycles. Experimental and clinical data, however, suggests that tissue damage can be aggravated by organ reperfusion. [1] Studies have failed to prove that infarct size is increased by reperfusion. Reperfusion can aggravate the formation of oedema and lead to abnormal blood flow patterns and microvascular lesions within the reperfused areas.

Keywords
reperfusion injury,
brain stroke,
neurosurgery

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FOCAL CEREBRAL ISCHEMIA – REPERFUSION INJURY

It is characterized by a thick infarction center surrounded by a peripheral zone of penumbra-called potentially viable tissues. [2] This is a crucial region for the dissemination of ischemic lesions. Ischemia-reperfusion induces a cascade of molecular events that cause neuronal death that range from immediately to several days later in time. [3] Two different mechanisms of cell death are displayed by post-ischemic neurons: necrosis and apoptosis. During ischemia-reperfusion injury, several events occur, including Ca21-induced protease activation, glutamate toxicity, free radical development, receptor-mediated death signals, and altered pro-apoptotic and anti-apoptotic protein expression, eventually triggering the morphological result that can be either necrosis or apoptosis. [4] Apoptosis is spread predominantly in the penumbra. In focal or incomplete cerebral ischemia, propofol has

been shown to be effective in preventing cerebral injury. [5] But the propofol therapeutic window was not well explored.

In focal cerebral ischemia, infarction in the reperfused brain can extend into the peripheral region, and the degree of this expansion may be due to the penumbra cell outcome. [5] The acute penumbra is evanescent and deteriorates steadily, ultimately subsuming within the ischaemic heart. [2] The co-existence of apoptosis and necrosis indicates the pathological result of focal cerebral ischemia-reperfusion damage.

Reperfusion-related brain injury and melatonin

Melatonin is an interesting compound that, among other tissues in mammals, is mainly synthesized in the pineal gland. In response to environmental light-dark cycles, its secretion, primarily at night, is regulated circadically by the suprachiasmatic nucleus, and has been associated with several significant physiological phenomena that have been attributed to the timing of pineal melatonin secretion. [6] In addition to its related physiological functions, it is recognized that melatonin performs direct and indirect antioxidant activities both at physiological and endogenous concentrations and at concentrations exceeding physiological levels by many orders of magnitude. It is understood that overproduction of free radicals during cerebral ischemia and reperfusion leads to functional dysfunction and neuronal death, among other pathophysiologic mechanisms. As a consequence, in view of its antioxidant activities compared to the detrimental cellular actions of free radicals, attention was given to melatonin as a neuroprotective medication against ischemia/reperfusion brain injury. The key causes of permanent brain injury and damage are focal cerebral ischemia induced by thromboembolic occlusion of the major cerebral artery, often the middle cerebral artery, as well as global cerebral ischemia caused by cardiac arrest, extreme hypotension, or significant hemorrhage, leading to temporary or permanent interruption or decrease of blood flow in particular brain structures or the entire brain. [8] As a consequence of its specific biochemical features, the brain is particularly susceptible to oxidative damage. [9] Chemical substrates for further increasing cellular changes, neuronal death and neurological deficits can also include reperfusion and reoxygenation of the ischaemic tissue, which must be restored within minutes in an attempt to avoid serious neurological damage and facilitate the survival of individuals. [10]

NLRP3 and ROS in reperfusion Injury of the brain

It is well known that the brain damage initially caused by ischemia can be aggravated by reperfusion, causing an I/R injury. [11] Inflammation and oxidative stress are involved in the pathogenesis of brain I/R among the different underlying mechanisms of stroke, and adequate inflammatory level control can play a critical role in the prevention and treatment of stroke. [12] The role of inflammasomes, especially NLRP3, in postischemic inflammation after stroke has been recognized in recent years. Since inflammation is triggered by the inflammasome, NLRP3 inflammasome modulation can regulate the inflammatory response. However, from a molecular point of view, a number of molecular signalling systems in the I/R brain can activate the NLRP3 inflammasome pathway and several mechanisms have not yet been completely identified. Specifically, this cytokine is produced by macrophages or microglial cells during central nervous system disease or after brain injury [14], and molecular mediators such as mitochondrial ROS and lysosomal protease cathepsin B are essential for the development of interleukin-1β by microglial cells [14].

Reperfusion Injury treatments

In the post-ischemic environment, many pharmacological agents often protect the brain when given. (S)-emopamil, a novel blocker of the calcium channel and antagonist of serotonin S2, reduces infarct size when administered after permanent and temporary occlusion of MCA. Blocking of amino-3-hydroxy-5-methyl-4-isoxazole (AMPA) receptors by the 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F) quinoxaline (NBQX) blocker, a selective antagonist for the excitatory amino acid receptor subtype AMPA/kainate, has also been shown to protect both global and focal ischemia histopathologically. Most recently, when given after the first provocation, the non-competitive N-methyl-D-aspartate (NMDA) antagonist MK-801 protected the brain from the cumulative effects of repeated brief ischemic episodes. Ischemia-induced calcium ion treatment techniques and neurotransmitter disturbances are critical areas for ongoing study. In

the pathogenesis of reperfusion injury, several studies have implicated oxygen radicals. [13]

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Surgical smoke, neurosurgical practice and coronavirus: a few words of caution

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ABSTRACT
Surgical smoke also referred to as cautery smoke is a gaseous mixture produced during surgical procedures where there is ablation, cutting, coagulation, desiccation or vaporization of the tissue. In a true sense "surgical smoke" refers to surgically generated gaseous contents. The surgical smoke results from the destruction of bones and tissues, causing microscopic particles to get suspended in the environment.

Keywords
surgical smoke,
coronavirus,
neurosurgical practice

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Coagulation devices such as ultrasound, electrical instruments and laser generate nebulization of particles viral, carcinogens and toxic substances. [4, 6] The recent appearance of COVID19 infection has emerged as a risk factor for surgical practice. Surgical smoke contains particulate matter which passes the upper respiratory tract and gets deposited.7-9 The overall effect of surgical smoke is determined by the duration of the working hours in the operating room [5, 10] as well as safety measures adopted to protect from the surgical smoke. [5]

The global pandemic of Covid-19 has made surgeons rethink their strategies to maximize the safety of treating personnel. Neurosurgery is not untouched by the current situation of this pandemic. There are many concerns including the safety of health care workers, poor availability of resources etc. Many of the elective surgical procedures are postponed all-round the globe as a means to prevent transmission.[11] Since the majority of neurosurgical illness is progressive and can transform from elective to emergency with time. Also, like in other specialities, neurosurgery is benefitted with technological advances to maximize the efficacy and minimize

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the morbidity associated with neurosurgical procedures. There are concerns with the use of ultrasonic aspirator, drill system which potentially generates aerosols and surgical smoke. With ongoing pandemic, it is evident that these procedures cannot be postponed indefinitely and no alternative is yet available to ensure a better outcome. Even in neurosurgical emergencies and Neurooncological surgeries, it is of utmost importance to take cognizance of potential effects of surgical smoke and precautions while operating on patients who are suspected or proven Covid-19 positive. Neurological surgery comprises a versatile set of different surgical domains that include spinal surgery, cranial surgery, endoscopic surgery and minimally invasive surgical procedures which have their own biological and physical factors. Since the surgical smoke has heterogenous composition, it is not clear which surgical procedure has more potential to generate smoke containing viral products as particulate matter.

The surgical smoke thus generated consists of 95% water and 5% particulate matter consisting of chemical compounds, cell particles, bacteria, viruses and even drugs are taken by patients.[10, 12-15] Several chemical compounds (≥ 80 different toxic chemicals) have been found in surgical smoke. [16, 17] which have the potential to cause cell damage. [1, 16] Prolonged exposure to surgical smoke (with cumulative dose effect0 can cause mild symptoms like headache, irritability, mood changes to severe injuries like an injury to the lungs and in long term infections and a certain type of malignancies. 1, 9, 18 Particulate matter in surgical smoke is mostly less than 5 um in size. [12, 19] Although many regulatory bodies agree on the dangers of surgical smoke, the degree of hazard and methods to prevent is yet to be firmly established20. Electrocautery generates heat which damages the cell membranes and generates smoke containing mostly water vapour which gets aerosolized in the operating room. [2, 8, 21], In addition, it chars the neighbouring cells. This causes further thermal necrosis and releases carbonized cell fragments and gaseous hydrocarbons.[22] The byproduct of diathermy coagulation and biochemicals present in the smoke depends on the settings of diathermy and the tissue being burnt with the gray matter being low particulate matter tissues. [1, 18, 23-27] Similarly ultrasonic aspirators create aerosols by creating cavitation nuclei. The combined action of ultrasonic aspirators and diathermy electrocoagulation has potential to generate aerosols containing infective particulates. Electrocautery produces more particulate matter than lasers and ultrasonic devices, but because the smoke generated by lasers and ultrasonic devices is colder and has more biohazard with the risk of transmitting infection [1, 26, 27] as the smoke and aerosols can be inhaled and gets deposited in the respiratory system.28 Though, there is insufficient evidence for COVID-19 transmission through surgical smoke, data, existing studies and expert opinion suggests it a theoretical risk.29, 30 A review was done based on the existing studies suggested the methods to mitigate the potential risk of surgical smoke and COVID-19 transmission to OR personnel. [29]

The composition of this hazardous surgical smoke depends much on the type of surgical procedure, the duration, the devices/instruments used, the structure of the operating theatre, the expertise of the surgeon, the pathology operated upon and the precautionary measures taken during surgery. It is not hard to imagine that such surgical procedures carry the potential of a generation of heavy and potentially hazardous surgical smoke. While on the other hand, for brain surgery, a use of bipolar cautery, CUSA, ultrasonic probe, generation of biological particle including tumours and again infectious matter, bone dust because of bone drilling and craniotomy flap elevation, neuronavigation and laser contribute in the generation of the Surgical Smoke. Studies on biohazards of surgical smoke have shown the presence of viral DNA, activated Corynebacterium, Hepatitis B, Human papillomavirus. [1, 31-38] In a few studies, 80% of the surgical smoke from infected patients contained viral particles suggesting the potential risk of transmission to personnel in OR. [39-41] Bacteria and viruses can survive in the surgical smoke for up to 72 hours'[19] It has been shown that in aerosols SARS-CoV-2 can survive up to 3 hours and on the surfaces up to 72 hours.38 However, no data is yet available for transmission of SARS-CoV-2 through smoke produced in a surgical procedure. Majority of the literature available is related to laparoscopic surgeries. [11, 42] Even the biohazard potential is not very well established in other surgical specialities [42-44] SARS-CoV-2 has shown transmission potential through aerosols and fomites similar to SARS-CoV-1 in experimental conditions [38].

To reduce the risk of transmission of SARS-CoV-2 through surgical smoke, preventive strategies suggested by Zheng et al. seems appropriate and worth considering in neurosurgical patients.[11] Chow et al have mentioned the method to convert existing OR into negative pressure OR.45 Unilaminar airflow in OR is effective in removing 97% of particulate matter of size more than or equal to 0.3 um.46 Various filters can be used along with smoke evacuators in the OR like, charcoal filters, coconut shell charcoal, ultralow particulate air (ULPA) filters.29 these filters can retain particles up to 0.1 um in size. Different surgical societies all around the world have published guidelines involving comprehensive measures, changes in OR and filtration systems aimed to prevent the established and hypothetical risk of transmission. [47-49] Neurosurgical procedures are not immune to the production of surgical smoke given the usage of ultrasonic aspirators, high-speed pneumatic drills. In parallel to other surgical association, the neurosurgical community should assess the size of the risk to provide quality surgery to the patient and protection of the surgical team. The American National Standards Institute (ANSI) has established strategies for smoke reduction during laser surgery. 50 In the current pandemic of COVID-19, health care worker needs to have PPE and N95 masks. Available masks to prevent inhalation of surgical masks and its health hazards include Surgical mask, N85 masks and High filter masks.[51-53] Surgical mask doesn't provide tight face seal, positive pressure inside the facepiece and filter particulate matter less than 5 um in size and therefore may fail to protect from transmission of infective pathogens through surgical smoke.[21, 54] Surgical masks my provide > 90% protection and has been in use for a century and N95 mask may not offer adequate protection in these potential contagious procedures and activated carbon filters in addition to N95 may be more appropriate. [21, 55-58] However, N95 masks have their own challenges which includes CO2 build up, difficulty in breathing after a certain time and subjective symptoms of headache, light headedness etc. [59]

In summary, there is an increased need to create awareness regarding the side effect of surgical smoke, to train an individual to minimize the exposure and develop facilities for the safe evacuation of the surgical smoke in the operation theatre and thus to safeguard the personnel's in the operating theatre. [21]

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Basic considerations on growth hormone deficiency in traumatic brain injury

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ABSTRACT

Growth hormone is responsible for stimulating the growth and differentiation of cells of various tissues and cell types contribute to protein synthesis and the mobilization of fatty acids. At the nervous system level, it stimulates the regeneration of neurons, astrocytes, endothelial cells, oligodendrocytes, and even neuronal myelination. Traumatic brain injuries can alter the secretion of this hormone, due to the deformation of brain tissue and the alteration of neurometabolism by the subsequent ischemia. Knowing the basic aspects of pituitary disorders in this type of patient allows early identification and management to avoid complications.

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INTRODUCTION

Growth hormone (GH), synthesized in the adenohypophysis, is responsible for the stimu-lation of cell growth and differentiation, its

synthesis and release is related to growth hormone releasing hormone (GHRH) which is responsible for stimulating the process of synthesis and release of GH, while somatostatin hormone is responsible for inhibiting the synthesis and release, thus performing a negative feedback. It has been shown that the highest serum levels of this hormone are found during sleep [1,2] GH secretion occurs in the form of pulses, and its serum concentrations may vary according to sex and individual conditions [3]. Different brain injuries can alter GH metabolism, taking into account that different trauma mechanisms can produce damage to the brain parenchyma as inflamma-tory or ischemic damage [4,5]. Considering the relevance and impact of neuroendocrine disorders on neurological integrity and quality of life, the aim of this review is to present basic concepts for the understanding and early detection of growth hormone deficiency in traumatic brain injury.

GROWTH HORMONE GENERALITIES

GH is synthesized in the lateral zones of the adenohypophysis by somatotropic cells. This hormone is a protein consisting of 191 amino acids with an approximate weight of 22650 Daltons. The synthesis and release of this hormone depends on two neurohormones loca-ted in the hypothalamus: GHRH and somatostatin [2,3]. The first one has a stimulating character, while the latter has an inhibitory character. Its release is rhythmic and alterna-ting, occurring when the amount of GHRH in plasma predominates. The peaks of GH re-lease occur in the slow wave phase of sleep, with a maximum amplitude hypothalamic-pituitary rhythm [2].

GROWTH HORMONE SYNTHESIS

Growth hormone synthesis is directly influenced by hypothalamic and peripheral factors which act on somatotrophs. Both act by binding to specific receptors located on the surface of somatotroph cells [3,6]. GHRH binds to a metabotropic receptor, which are receptors with 7 transmembrane domains that couple to second messengers via G proteins, which upon ligand-induced activation causes intracellular stimulation of cyclic adenosine monophosphate (cAMP), leading to GH synthesis [2]. Hypothalamic somatostatin has five receptor subtypes (SSTR1-SSTR5). Among which SSTR2 and SSTR5 are responsible for signaling suppression of pituitary GH and thyrotropin secretion [7].

Other regulators have been described, such as IGF-1, which in addition to mediating the peripheral actions of GH, is also capable of inhibiting GH secretion. Nutritional status can also influence the synthesis and secretion of GH, since it has been described that it can be increased in malnourished or fasting individuals [3,8]. Although, in states of hyperglyce-mia, hormones such as leptin are able to inhibit GH secretion. It has also been found to be associated with ghrelin, which is an intestinal peptide responsible for the induction of GH secretion, its receptor is expressed in the anterior pituitary, this peptide is produced mainly in the stomach, although small amounts are obtained from intestinal tissue, pitui-tary, placenta and pancreas, it is of great relevance because it is a nutritional regulator of GH secretion, its function is to maintain blood glucose levels during starvation [3,8].

EXCRETION

GH excretion is pulsatile, its serum concentration can be detected if an ultrasensitive as-say is used. These pulses are regulated by the reduction of inhibition by somatostatin. Therefore, serum GH measurement should be done in a 20-minute sampling during 24 hours, which would allow accurate assessment of serum GH concentrations; it was found that on average, serum GH during the night ranges between 1. 0 ± 0.2 ng/mL, while day-time concentrations average 0.6 ± 0.1 ng/mL in unimpaired adults; these levels may be lower in adults and obese persons, and higher during puberty and in neonates [2,8,9].

The maximum serum GH concentration ranges from 4.3 ± 0.7 ng/mL at night to 2.7 ± 0.5 ng/mL during the day, with the highest peak GH excretion occurring 1 hour after the onset of deep sleep. Physical activity, trauma and septic states increase GH secretion in the ran-ge of 20 to 30 ng/mL (3).

RECEPTORS

GH acts by binding to a specific receptor which is a homodimer located mainly in the li-ver, and induces intracellular signaling through a phosphorylation cascade by the JAK/STAT pathway which are activators of signal transcription. Its main action is to sti-mulate hepatic synthesis and secretion of IGF-1, which contributes to cell growth and dif-ferentiation [2,3].

The GH receptor is a 70 kd protein, belonging to the cytokine/hematopoietin superfamily. It consists of a single extracellular ligand-binding domain which spans the membrane and a cytoplasmic signaling component. Circulating GH-binding proteins are fragments of the receptor that bind to GH [6]. It has been observed that a single GH molecule is able to form complexes with two GH receptor molecules, leading to rapid internal turnover and activation of the JAK2 tyrosine kinase, which allows phosphorylation of several cyto-plasmic signaling molecules that determine cell proliferation and differentiated function [6].

On the other hand, it has been observed that STAT proteins, which are cytoplasmic pro-teins, represent important signaling components for GH action. They are phosphorylated by JAK2 and translocate directly to the cell nucleus, triggering GH-specific target gene effects at this level by binding to the nucleotide DNA. Within this group of proteins, it has been observed that STAT 1 and 5 interact most directly with the GH receptor [10,11]. The function of this receptor can be directly inhibited by IGF-1, as well as GH secretion, which is due to negative feedback [2,5].

GH receptor mutations have been described to be associated with partial or complete GH insensitivity and growth failure (Laron dwarfism), which is associated with normal or high serum GH concentrations, decreased serum GH-binding protein concentrations, and decreased serum IGF-1 concentrations [2,3].

Physiological functions

Unlike the other hormones produced by the pituitary gland, growth hormone does not act in a specific gland, but in the whole organism. This hormone stimulates the growth and differentiation of cells of various tissues and cell types. Its anabolic effects are remar-kable, stimulating protein synthesis and the mobilization of fatty acids for use as a source of energy [3,6]. It is also known to promote a diabetogenic state by decreasing glucose uptake by peripheral tissue, stimulating glucose secretion in the liver, and in turn insulin secretion [3]. In bone, it promotes protein deposition by bone growth-inducing cells, con-tributes to the rapid growth of bone cell lines, and is known to stimulate the conversion of chondrocytes into osteogenic cells, resulting in the pre-dominance of the rate of bone ma-trix apposition over the rate of bone resorption [3,12]. At the level of the central nervous system, it has been proven that this hormone exerts important functions related to neuro-nal function and differentiation; its contribution to the regeneration of neurons, astrocytes, endothelial cells, oligodendrocytes, and even neuronal myelination has been studied. It has also been implicated in processes such as migration and survival of neurons [1].

The current concept of the diagnosis of growth hormone deficiency in the adult is based on the absence of growth hormone secretion following the administration of pharmacolog-ical agents, which normally trigger hormone secretion. This is due to the fluctuation of hormone over a 24-hour period. However, serum IGF-1 levels lack diurnal fluctuation and reflect the action of GH. Therefore, the usefulness of the latter has been investigated in the diagnosis of growth hormone deficiency [13]. In children in some cases, clinical risk factors are identified and taken into account, which may provide evidence of growth hor-mone deficiency, without the need for continuous stimulation testing. However, for con-firmation of the diagnosis in most countries of the world the latter test is required [14].

Traumatic Brain Injury

Pathophysiology

Primary and secondary lesions in traumatic brain injury divide the pathophysiology of trauma into two distinct phases. The first phase is characterized by mechanical deforma-tion of brain tissue and the second by brain biochemical changes that occur from the time of injury and last from days to months. The first phase is produced by the forces of accele-ration, deceleration, and impact forces, which will lead to loss of polarity of neurons, da-mage to blood vessels and axons. Ischemia is explained in the alteration of the architectu-re and functionality of the blood vessels, evidencing compromise in terms of tissue perfu-sion due to the lack of vascular bed density, added to other physiological phenomena such as arterial hypotension due to the loss of intrinsic capillary regulation, deficit of nitric oxide production and excess of prostaglandins, which will promote vasoconstriction [4,5,15]. Post-traumatic vasospasm is the result of an imbalance of vasodilator and vaso-constrictor factors, and is an aggravating factor of ischemia and hypoxia. Due to

the state of anaerobiosis, the increase in lactic acid will directly alter cell membrane permeability [4,5,15]. The water and electrolyte imbalance will contribute to the formation of cerebral edema, with subsequent endocranial hypertension. The second phase of traumatic brain injury will initiate an inflammatory cascade characterized by the presence of inflamma-tory cytokines and the presence of excitatory neurotransmitters that will alter calcium homeostasis and other electrolytes. The excess of intracellular calcium, together with an environment rich in inflammatory substances, will lead the neuron to the activation of internal pathways of self-destruction, represented by proteases and caspases that will de-grade the cytoskeleton proteins, irreversibly activating programmed cell death, or earlier, necrosis, with subsequent release of inflammatory substances into the extracellular environment [4,5,15].

Pathophysiology of hypopituitarism induced by traumatic brain injury

Although the exact pathophysiology of hypopituitarism following traumatic brain injury is unclear, several pathological mechanisms have been proposed as responsible for this dysfunction [16]. One of the main hypotheses is based on the argument of their anatomi-cal location. The pituitary gland, the hypothalamus and the vessels that irrigate these structures are fragile and vulnerable to significant changes in the characteristics of the environment in which they are located, which is the case in traumatic brain injury. Me-chanical alterations secondary to trauma can lead to different situations such as edema, rupture of blood vessels, hematoma, increased intracranial pressure, displacement of the hypothalamus, tearing and fracture of bones that destabilize the function of the gland [5].

Several studies have found genetic predisposition and immunity to be factors responsible for this condition. High levels of antihypophysis and antihypothalamic antibodies have been found in patients with this pituitary dysfunction after traumatic brain injury. Tanri-verdi et al [17], showed a strong association between the presence of high titers of anti-pituitary antibodies and anti-thalamic antibodies five years after traumatic brain injury [17]. Damage to the gland has been found, ranging from 26 to 86%, in patients who died after trauma. It is not uncommon to find infarcts in segments of the pituitary gland, such as anterior neocrosis of the gland in patients who died less than a week after traumatic brain injury. Mechanisms such as ischemia and intracranial pressure may be responsible for this damage to the pituitary gland [15]. The vascular hypothesis is supported by imaging studies that have demonstrated severe pathological changes in relation to vascular injury. This hypothesis is also related to patterns of hormone loss, through studies showing that the most frequent hormone loss is somatotropin and gonadotropins, excreted in specific sites irrigated by pituitary portal vessels. The genetic polymorphism could also be associated with hypopituitarism [18]. Medications used in the intensive care unit could be responsible for having an impact on endocrine function.

Growth hormone deficiency secondary to traumatic brain injury and its effect on quality of life

The prevalence of hypopituitarism and quality of life in patients who survive traumatic brain injury is subject to factors such as skull fracture, duration of ventilatory support, initial imaging related to Marshall's classification and coma [19]. Although head trauma is common in certain high-risk occupations such as military service, a clear association between pituitary hormone dysfunction and head trauma in the military has not been established, but a long-term negative psychological effect may possibly be generated [14,20,21,22]. In a meta-analysis it was also analyzed that 12 months after a head trauma, about one third of patients were at high risk of suffering post-traumatic pituitary deficien-cy [23]. In a prospective study, it was recognized that in children, unlike adults, the prevalence of hypopituitarism after traumatic brain injury remains controversial [16]. However, it has been established that children after trauma suffer a challenge in terms of rehabilita-tion and reintegration to their life as it was prior to the traumatic injury. This finding is directly related to the severity of the brain injury, which in turn affects the resilience of children after trauma [24-28].

Reduced growth hormone production in the context of pituitary dysfunction following head trauma is common. During a crossover, double-blind, placebo-controlled study, physical changes, resting energy expenditure, fatigue, sleep

disturbance and neuropsycho-logical status were observed in 18 patients with growth hormone deficiency secondary to trauma. Additionally, changes in anatomical features of the brain parenchyma were ob-served on MRI scans of these patients. However, when growth hormone was replaced, al-terations in brain morphology and connectivity were evident, as well as a reduction in fatigue and other related symptoms [29,30].

Growth hormone and its effect on bone mass loss induced by mild head trauma

It has been demonstrated that recurrent mild head trauma exerts certain effects on the vol-ume of trabecular bone at different scales depending on the affected skeletal site. In con-trast, cortical bone is unaffected [31]; it is believed that this is due to several mechanisms among which are: the site where bone remodeling takes place, regulatory mechanisms of trabecular and cortical bone formation, the site of the trabecular bone formation and the cortical bone formation [32,33]). Finally, neuroendocrine signals generated by trauma may affect trabecular bone formation and remodeling more than cortical bone formation and remodeling. Findings showed that low-dose growth hormone treatment was useful, as it partially rescued the loss of trabecular bone mass, which had been caused by the combi-nation of trauma and immobility generated by trauma. However, more research in humans is needed to confirm these effects [34].

Roles of GH/IGF-1 in non-severe traumatic brain injury

Normally IGF-1 exerts a neuroprotective and neurorepair mechanism after any brain inju-ry [35]. Rapidly after cranioencephalic trauma GH/IGF-1 levels are elevated, regardless of growth hormone status [36,37]. However, depending on which IGF-1 allele is present in the neurocritical-posttraumatic patient, neuropsychiatric symptoms and feelings of dizzi-ness or lightheadedness may be present or become chronic, so the final outcome of the traumatic injury is variable [38-40].

Alterations in the axis GH/IGF-1 - intestinal microbiota after traumatic brain injury

The rapid expansion in the field of interaction between different systems such as gastroin-testinal, immune, endocrine, neurological in relation to the intestinal microbiota, has led to the conclusion that the microbiota has an influence on any of these systems [41-43]. This leads to the discussion of an axis currently known as the microbiota-gut-brain axis [44,45]. Recent analyses have demonstrated a link between altered gut microbiota and altered neurocognitive, behavioral and neuropathological states [46-50].

Growth hormone deficiency in subarachnoid haemorrhage and cerebral ischemia

Subarachnoid hemorrhage (SAH) is a disease of acute onset and sudden onset consisting of three phases: acute rupture phase, vasospasm phase and recovery phase. The most fre-quent neuroendocrine abnormalities studied in SAH are disorders of the hypothalamic-pituitary-adrenal axis [51,52].

Endocrine disorders were found in 78% of patients with subarachnoid hemorrhage and in those with ischemic stroke. The most common findings were low IGF-1 levels compatible with growth hormone deficiency (45%), followed by hypogonadism (39%), thyroid dys-function (36%) and hypo-reactivity to cortisol (33%) [53].

The pathophysiological mechanisms of endocrine disruption in patients with brain injury following subarachnoid hemorrhage are not clear, however, it is believed that hypothala-mic and pituitary injury secondary to hematoma compression, ischemic injury or elevated intracranial pressure would be a logical explanation for the endocrine disorders generated [53]. Another explanation for these findings is the influence of proinflammatory cytoki-nes, such as IL-6, TNF α, IL-1B, present in acute brain injury processes of various kinds, which may exert inhibitory or stimulatory effects on pituitary and hypothalamic hormones [54].

Conclusions

Hypopituitarism secondary to brain lesions has not been fully described, it has been ob-served that traumatic brain lesions can deform the brain tissue and subsequently generate biochemical changes; Permanent lesions have been explained due to the alteration in the form and function of blood vessels, finding a compromise in cerebral irrigation, as a con-sequence of this and taking into account the anatomical location, the pituitary is an organ susceptible to ischemic changes, which happens in

brain lesions causing a hormonal loss, mainly of soma-totropin and gonadotropins, in conclusion, there is an alteration in the metabolism of GH.

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Schwannoma of the digital nerve. A rare case report

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ABSTRACT

Schwannomas are the most common benign tumours affecting the peripheral nervous system. They represent a benign proliferation of Schwann cells. Schwannomas and other peripheral nerve sheath tumours are common in the head and neck, spine, thorax, abdominal wall, and retroperitoneum. However, localization in hand is exceptional. We present a 22-years-old female patient diagnosed and operated on for schwannoma of the digital nerve (dorsal cutaneous branch originating from the palmar cutaneous branch of ulnar nerve). In the case of a palpable hand mass, one of the possible diagnoses is schwannoma, and since the operative technique is somewhat specific with tumour enucleation and internal neurolysis, it is necessary to preoperatively keep in mind schwannoma in the differential diagnosis.

Keywords
schwannoma,
digital nerve,
hand schwannoma

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INTRODUCTION

Schwannomas are the most common benign tumors affecting the peripheral nervous system (1). They represent a benign proliferation of Schwann cells. Schwannomas and other peripheral nerve sheath tumors are common in the head and neck, thorax, abdominal wall, and retroperitoneum. These tumors are rarely found in the hands, particularly the fingers (2). They are most frequent in adults between the ages of 30 and 60, and they affect both men and women equally (3, 4). Most schwannomas are asymptomatic however they can cause functional deficits and pain depending on which nerve is affected (5).

We present a 22-years-old female patient diagnosed and operated on because of left hand digital nerve schwannoma.

CASE REPORT

The 22-year-old female patient was admitted to the neurosurgery department for surgical treatment of a tumor in the dorsal region of the left hand, which was described as a scwannoma on ultrasound (Figure 1). Due to the suspicion of a ganglion cyst the tumor was punctured in another institution and aspiration was tried, however, no content was obtained, and subsequently reddening of the skin above tumor appeared few days later. The tumor has been present for several years and has begun to grow during the last year. Phisical examination

revealed small tumor between the third and fourth finger of the left hand on the dorsal side, messuring about 3 x 2 cm, mobile, painless, and percussion in the tumor region gave a positive Tinel sign. Based on the clinical picture and ultrasound findings, an indication for surgical removal of the tumor was set. The patient was operated under the conditions of local anesthesia and the tumor of the digital nerve in the region of the ulnar nerve branch was microsurgically removed. The change was irregular in shape, pearly white in color in cross section with significant adhesions for the surrounding tissues, so external and internal neurolysis were performed and all shown fascicles were preserved exept the fasciculus from which the tumor grew (Figure 2). The operation went smoothly, the patient was transferred to the ward. The postoperative period was uneventful, the patient was neurologicaly intact and was discharged on second postoeprative day. Histopathological examination confirmed suspected diagnosis of schwannoma (WHO grade I) (Figure 3). After 3 months, the patient is without symptoms, neurological deficit and with no signs of tumor recurrence.

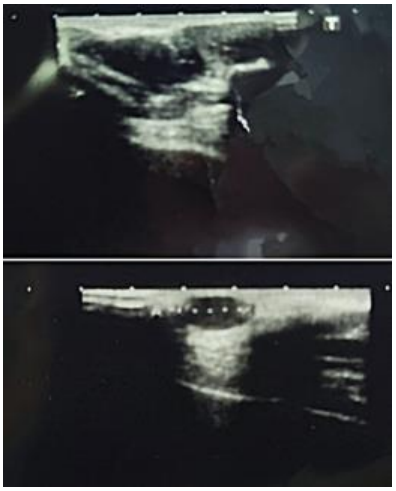

Figure 1. Ultrasound finding of the mass located in the dorsal region of the hand resembling schwannoma or ganglion cyst.

Discussion

Schwannomas are typically benign slow growing tumors of the peripheral nerve. Despite its low overall incidence, benign schwannoma is one of the most common peripheral nerve tumors. They are usually find in the head, neck and spine (3, 4). The hands, particularly the fingers, are rarely affected by these tumors (2). We present a rare case of the digital nerve (dorsal cutaneous branch originating from palmar cutaneus branch of ulnar nerve) schwannoma located on the dorsal side of hand.

Schwannomas are typically described as non-painful swellings that go unnoticed for years, making clinical identification and therapy more challenging (6). In the differential diagnosis neurofibroma, perineurinoma, ganglion cyst, giant cell tumors of the tendon sheath, fibroma of the tendon sheath, lipoma, extraosseous chrondroma and other soft-tissue masses should be considered (5). In our case ultrasound finding was described as ganglion cyst or schwannoma. Local finding was more suggestive of schwannoma, especialy since the lesion was punctured and no content was obtained. Positive Tinel's sign also indicated nerve (sheath) tumor.

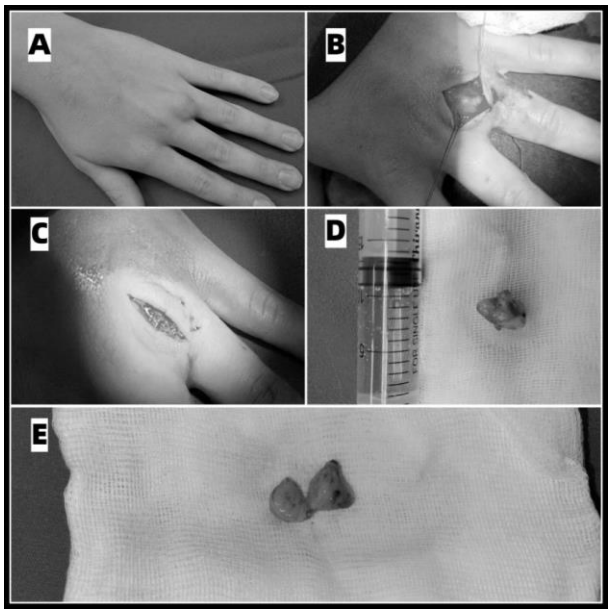

Figure 2. Intraoeprative findings: (A) preoperative aperance; (B) finding after skin incision; (C) local finding after tumor removal; (D) macroscopic apperance of the tumor after removal; (E) cros section fo tumor.

Wide spectrum of clinical symptoms such as parasthesias, hypoesthesia, tingling, motor defict, and positive Tinel's sign contribute to almost impossible clinical distinction between schwannomas and other peripheral nerve tumors or other soft-tissue tumors. The most common clinical scenario represents a patient with swelling that starts to hurt and grows a bit more after a few years of beeing an asymptomatic lesion. The appearance of pain and the fast growth of a tumor might signal a malignant transformation (7, 8). Our patient had

tumor for several years, but it started to grow during one last year.

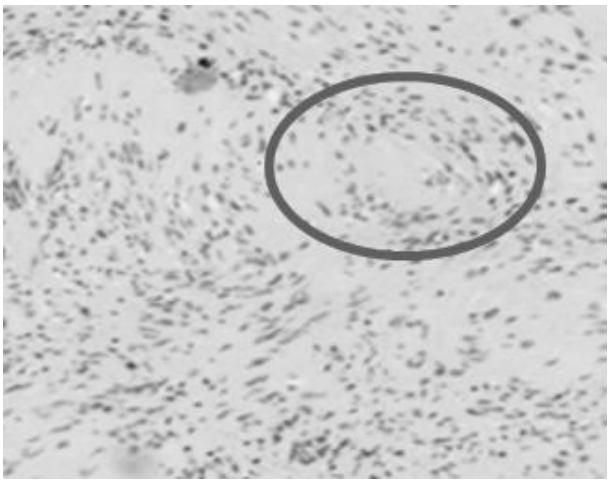

Figure 3. Pathohistological diagnosis confirmed schwannoma with typical Verocay bodies (rounded).

Additional diagnostic procedures are usualy required such as ultrasound and magnetic resonance imaging. On ultrasonography, a schwannoma is a homogeneous, hypoechoic mass with enhanced through transmission, target appearance, and pseudocystic appearance, similar to ganglion cysts. As a result, it's difficult to tell the difference between a schwannoma of the hand and a cystic lesion (9). In our case due to suspicion of ganglion cyst patient was first referred to another institution where puncture and aspiration were performed, however, no content was isolated. During the operation in our institution, the intraoperative finding was indicative of schwannoma, which was confirmed with histopathological analysis.

Treatment for schwannoma is determined by the location of the tumor, if it is causing pain, and how rapidly it grows. Sometimes observation is indicated, but surgery is essential if symptoms occur. Main goal is enucleating the tumor while avoiding nerve damage with internal neurolysis, so usage of operative microscope is strongly recommended (10). After performed operation our patient didnt have any postoperative complication nor neurological deficit.

Conclusion

Schwannomas are benign tumors that are rarely encountered in clinical practice. Ultrasound, MRI, and finally histological analysis of the tumor verify them. The tumors are normally benign, and the condition is rarely life-threatening, but depending on where they are located, they might cause a variety of symptoms. One of the possible diagnoses in the case of a palpable hand mass is schwannoma, which requires a special microsurgical approach in order to completely remove the tumor while preserving nerve function. Therefore, because operative technique is somewhat specific, it is essential to keep schwannoma as a possible diagnosis.

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Endoscopic third ventriculostomy versus ventriculoperitoneal shunt for treatment of hydrocephalus in infants in a tribal population in India

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Keywords
endoscopic third ventriculostomy, ventriculoperitoneal shunt, hydrocephalus, infants, tribal population,

ABSTRACT

Study design: Prospective long term follow-up study

Background: Hydrocephalus remains a common cause of admission in pediatric neurosurgery units. Of the two prevalent modalities of treatment for hydrocephalus in infants, i.e., endoscopic third ventriculostomy and ventriculoperitoneal shunt, which one is a better option, especially in a tribal setting, is a matter of debate.

Aim: To determine and compare the effectiveness of endoscopic third ventriculostomy versus ventriculoperitoneal shunt for the treatment of infants in a tribal population.

Methods: A prospective follow-up study was carried out on 70 patients of hydrocephalus with age less than or equal to 12 months during a period of 7 years from August 2014 to June 2021. A detailed history, physical examination, and computed tomography scan were done in all the cases. Based on patient condition, aetiology and parents' choice, 30 patients were treated by Endoscopic third ventriculostomy and 40 patients were treated by ventriculoperitoneal shunt. At enrolment, baseline clinical data were collected. Postoperative data were collected, including assessments of complications and treatment failures.

Results: A total of 70 infants with hydrocephalus were enrolled in the study and out of them, 30 (42.86%) underwent ETV and 40 (57.14%) underwent VP shunt for the initial treatment of their hydrocephalus. The mean age of patients was 6.4±1.2 months with a range of 18 days to 342 days. Clinical improvement was shown in 76.67% and 70% in ETV and VP shunt groups respectively. No significant difference (p=0.53) was observed in clinical outcomes in both groups. In the 1 to 6 months of age group, 07 (30.43%) clinically improved patients were from the ETV group, while in the VP shunt group, 10 (35.71%) patients showed improvement. In the 7 to 12 months age group, 16 (69.57%) clinically improved patients were from the ETV group and 18 (64.29%) patients were from the VP shunt group (p=0.69). Association of treatment success with gender, term of gestation and aetiology of hydrocephalus was not statistically significant (p>0.05). Out of 70 patients with hydrocephalus, postoperative complications such as infection, CSF leak, haemorrhage and blockage were found in 09 (12.86%), 08 (11.43%), 05 (7.14%) and 08 (11.43%) patients respectively. A significant higher proportion of infection (p=0.043) and blockage (p=0.023) was found in the VP shunt group than in the ETV group.

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Conclusion: Treatment success was high in both procedures. VP shunt was found to be more successful than ETV in terms of clinical outcome in both age groups. However, the results were statistically insignificant. A significantly higher proportion of complications was found with VP shunt than ETV therefore greater benefits can be achieved using ETV. Thus, for a tribal population, where patient compliance is poor and healthcare accessibility, as well as regular follow-up, is difficult, a procedure like ETV can be considered better than VP shunt.

Introduction

Hydrocephalus can occur at any age but is most common in infants and adults aged 60 and older.[2] Hydrocephalus in children remains one of the more common etiologies for admission in the pediatric neurosurgical units.[6] Hydrocephalus is characterized by excessive accumulation of cerebrospinal fluid (CSF), leading to ventricular dilatation, raised intracranial pressure and may be accompanied by secondary brain parenchymal atrophy.[8] The pathophysiology of hydrocephalus is complicated and remains unclear, which creates challenges in the management of patients.[1] Because of that, optimal treatment for infant hydrocephalus is yet to be definitively determined. Two main surgical options exist namely: endoscopic third ventriculostomy (ETV) and ventriculoperitoneal shunt.[3]

Ventriculoperitoneal shunt remains the conventional treatment for hydrocephalus due to its relatively high safety features.[8] Recently, endoscopic third ventriculostomy was deemed to be indispensable for treating obstructive hydrocephalus, on account of least complications because it avoids foreign body associated infections.[7,13,16] However there is ambiguity regarding the relative benefits of these two procedures. Ventriculoperitoneal shunting is technically simple and has a lower rate of failure immediately after surgery than does ETV, but it is more prone to failure over the long term and patients with shunt-dependent hydrocephalus may require urgent shunt-revision surgery due to obstruction of the shunt tubing or valve. In contrast, ETV is technically more difficult than shunting, but it has the advantage that virtually all failures occur within 6 months, after which the risk of failure is low.[9,15] Nevertheless, it remains unclear as to which of these two is more beneficial to patients because both methods have advantages and disadvantages. In resource limited settings, especially in tribal area, there are economic, cultural and geographic barriers to accessing treatment. Considering these factors, this study was planned to find out the effectiveness of endoscopic third ventriculostomy versus ventriculoperitoneal shunt in infants in a tribal population.

Aims and Objectives

To determine and compare the effectiveness of endoscopic third ventriculostomy versus ventriculoperitoneal shunt for treatment of infants in a tribal population.

Materials and Method

Study design: Prospective follow-up study conducted under the Department of Neurosurgery, RNT Medical College, Udaipur over a study period of 7 years (August 2014 to July 2021) for data collection, analysis and report writing, taking infants with hydrocephalus as the study population.

Inclusion criteria

1. Patients of hydrocephalus with age ≤ 12 months.
2. Both genders.
3. Consenting parents.

Exclusion criteria

1. Associated congenital anomalies such as spina bifida.
2. Dysmorphic brain anatomical features.
3. Known chromosomal abnormality.
4. Associated intra-ventricular or intra-cerebral hemorrhage
5. Non-consenting parents.

Method

A prospective follow-up study was carried out on 70 patients of hydrocephalus with age ≤ 12 months and admitted in the Neurosurgery department of RNT Medical College during August 2014 to July 2021. A detailed history, physical examination, and computed tomography scan was done in all the cases. Based on patient condition, etiology and parents choice, 30 patients were treated by Endoscopic third ventriculostomy and 40 patients were treated by ventriculoperitoneal shunt. At enrolment, baseline clinical data were collected. Postoperative data were collected, including assessments of complications and treatment failures.

Follow-up

Following the initial intervention, patients were regularly followed as per departmental and surgeon's practice with scheduled visits at post-op day 15, 1 month, 3months, 6months, 12 months and yearly thereafter. Adverse events were documented. All the information was recorded in individual case record sheets.

Procedures

1. Endoscopic third ventriculostomy - ETV was performed using a rigid pediatric endoscope (Karl Storz Tuttlingen, Germany), size 17F. The scope was introduced via anterior fontanels or a burr hole was placed just anterior to the coronal suture in the mid pupillary line in the patients with small fontanel. The floor of the third ventricle was punctured using a Fogarty catheter and the fenestration was enlarged using a Fogarty catheter balloon. Successful creation of stoma was confirmed by appreciating clap sign as the indicator of establishing CSF flow as well as visualization of basilar artery complex intra-operatively.

2. Ventriculoperitoneal shunt- The VP shunt involved creating a burr hole in the frontal or parietal regions and cannulating the ventricle with a silastic catheter. This was then attached to a slit and spring valve mechanism and distal silastic tubing of a medium pressure ventriculoperitoneal (MPVP) shunt which ran subcutaneously to the peritoneal cavity.

Outcome

Success of procedure was defined clinically (by the criteria of improvement in the patient neurological status) and surgically (if no further CSF diversion procedure required during the follow-up period of 1 year). Treatment failure was consider if further CSF diversion procedure was required or the patient dies. Because of very low socioeconomic status and affordability issues radiological parameters were not used to assess the success of procedures.

Complications of procedure such as intra-operative bleeding, postoperative infections, CSF leak and blockage leading to failure of procedure were evaluated and recorded.

Statistical analysis

Statistical analysis was performed with SPSS 20.0 (trial version). Data was presented in form of tables and graphs. Chi square test was used as test of significance and p value of <0.05 was considered statistically significant.

Ethical clearance

Enrollment of patients was started after taking ethical clearance from institutional ethic committee. Written consent was taken from all the parents.

Results

Total 70 infants with hydrocephalus were enrolled in study and out of them, 30 (42.86%) underwent ETV and 40 (57.14%) underwent VP shunt for the initial treatment of their hydrocephalus. Mean age of patients was 6.4±1.2 months with range of 18 days to 342 days. Male were 65.71% and female were 34.29%. Ten (14.29%) infants born preterm and all of them have low birth weight (<2500Gm). On the basis of clinical and radiological evaluation, cause of hydrocephalus was aqueductal stenosis among 51 (72.86%), arachnoid cyst among 06 (8.57%), Dandy–Walker cyst among 04 (5.71%) and Tubercular meningitis among 03 (4.26%) patients. (Table 1)

Table 1. Characteristics of study participants.

Patients' characteristics	ETV (n=30)	VP shunt (n=40)	Total (n=70)
Age in months			
1 -3	05 (16.67)	08 (20)	13
4 – 6	07 (23.33)	11 (27.5)	18
7 -12	18 (60)	21 (52.5)	39
Gender			
Male	20 (66.67)	26 (65)	46
Female	10 (33.33)	14 (35)	24
Term of gestation			
Preterm	05 (16.67)	05 (12.5)	10
Full term	25 (83.33)	35 (87.5)	60
Etiology			
Aqueductal stenosis	25 (83.33)	32 (80)	57
Arachnoid cyst	02 (6.67)	04 (10)	06
Dandy-Walker cyst	02 (6.67)	02 (5)	04
TBM	01 (3.33)	02 (5)	03

Clinical improvement was shown in 76.67% and 70% in ETV and VP shunt groups respectively. No significant difference (p=0.53) was observed in clinical outcome in both groups. There were two mortalities in ETV and three mortalities in VP shunt group and rest were required revision surgeries within one ear of follow-up. (Table 2 & Figure 1)

Table 3 depicts association of patient characteristics with treatment success of either

procedure. In the 1 to 6 months of age group, 07 (30.43%) clinically improved patients were from the ETV group, while in VP shunt group, 10 (35.71%) patients showed improvement. In 7 to 12 months age group, 16 (69.57%) clinically improved patients were from ETV group and 18 (64.29%) patients were from VP shunt group (p=0.69). This suggested better results in VP shunt group compared to ETV group, however the results are not statistically significant. (Figure 2) Association of treatment success with gender, term of gestation and etiology of hydrocephalus was not statistical significant (p>0.05).

Table 2. Distribution of participants according to type of treatment and clinical outcome.

clinical outcome	ETV	VP shunt	P value*
Successful	23 (76.67)	28 (70)	0.53
Failure	07 (23.33)	12 (30)	

Table 3. Distribution of study participants according to Clinical improvement.

Patients' characteristics	ETV (n=23)	VP shunt (n=28)	P value*
Age in months			0.69
1 -6	07 (30.43)	10 (35.71)	
7 -12	16 (69.57)	18 (64.29)	
Gender			0.84
Male	17 (73.91)	20 (71.43)	
Female	06 (26.09)	08 (28.57)	
Term of gestation			0.86
Preterm	01 (4.35)	02 (7.14)	
Full term	22 (95.65)	26 (92.86)	
Etiology			0.99
Aqueductal stenosis	21 (91.30)	23 (82.14)	
Arachnoid cyst	01 (4.35)	02 (7.14)	
Dandy-Walker cyst	01 (4.35)	02 (7.14)	
TBM	0 (0)	01 (3.57)	

Table 4. Distribution of study participants according to Clinical complications.

Clinical complications	ETV (out of 30)	VP shunt (out of 40)	Total	P value*
Infection	01 (3.33%)	08 (20%)	09	0.043
CSF leak	06 (20%)	02 (05%)	08	0.11
Hemorrhage	04 (13.33%)	01 (2.5%)	05	0.20
Blockage rate	01 (3.33%)	07 (17.5%)	08	0.023

*Chi square test was used as test of significance and p value of <0.05 was considered statistically significant.

Out of 70 patients of hydrocephalus, postoperative complication such as infection, CSF leak, hemorrhage and blockage was found in 09 (12.86%), 08 (11.43%), 05 (7.14%) and 08 (11.43%) patients respectively. Significant higher proportion of infection (p=0.043) and blockage (p=0.023) was found in VP shunt group than ETV group. (Table 4 and Figure 3).

Figure 1. Treatment outcome of study participants.

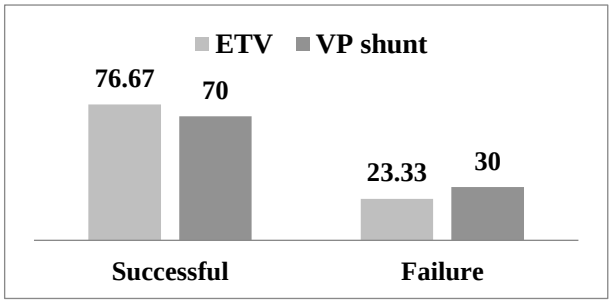


Figure 2. Comparison of clinical improvement in ETV and VP shunt as per age group of study participants.

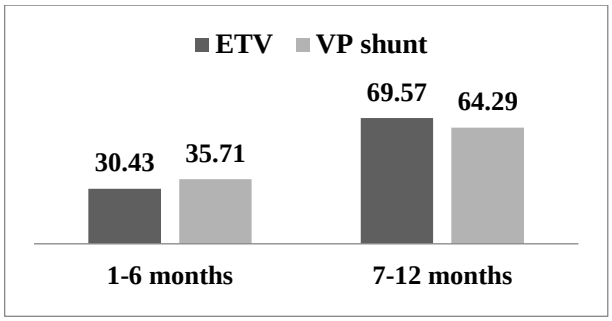
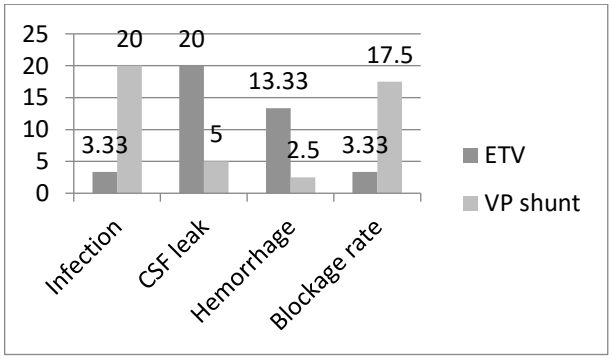


Figure 3. Comparison of complication rates in ETV and VP shunt groups.



Numbers shown in figure are percentages.

Discussion

The disturbance of CSF formation, flow or absorption on account of obstacles, congenital or acquired, leads to an increase in overall CSF volume in the central nervous system result in hydrocephalus. Based on patient's condition, two popular methods, ETV and VP shunt are available for infants. The impact of ETV compared to shunt on long-term outcome is not known and has been one of the most important questions in pediatric hydrocephalus. To compare effectiveness of these two procedures, a prospective follow-up study was conducted at Neurosurgery department of RNT Medical College.

In present study, out of 70 infants with hydrocephalus, ETV was performed in 30 (42.86%) and VP shunt was performed in 40 (57.14%) patients. Mean age of patients was 6.4±1.2 months with range of 18 days to 342 days. Male predominance was seen with 65.71%. Abhaya V. Kulkarni et al[11] study 78 patients hydrocephalus and found mean age 5.1 months and male to female ratio of 1.29:1. Out of 78 patients, 75.65% were treated by ETV and 24.35% were treated by VP shunt. Another study done by Abhaya V. Kulkarni et al[10] on 100 patients of hydrocephalus and found mean age of patients was 3.1 (2.6 to 4.1) months and among them 39 were female. Sarah C. Jernigan et al[8] conduct study on 872 infants (16.1%) initially underwent ETV and 4544 (83.9%) underwent ventricular shunt placement. The median infant age was 37 days (IQR 11–122 days) with male predominance.

In this study, most common cause of hydrocephalus was aqueductal stenosis (72.86%), followed by arachnoid cyst (8.57%), Dandy–Walker cyst (5.71%) and Tubercular meningitis (4.26%). Clinical improvement was shown in 76.67% and 70% in ETV and VP shunt groups respectively with no statistical difference in success rate. Pavlos Texakalidiset et al[14] study various study and published a meta-analysis report that also shows aqueductal stenosis as a common cause of hydrocephalus. In contrast to present study, Abhaya V. Kulkarni et al[11] reported that ETV success was 66.3% at 6 months and 64.1% at 36 months, while shunt success was 87.8 % at 6 months and 79.1 % at 36 months. These initial results suggest that shunting has a superior success rate compared to ETV, although the success rate for both was relatively high. Similar to this study, Pawan Goyal et al[4] found 68% of success rate in cases underwent VP shunt and 42% success rate among ETV group and there is no significant difference in success rate.

Treatment of choice was depending on many factors such as age, presence of complications, accessibility of treatment and follow-up. For a tribal population, where patient compliance is poor and healthcare accessibility, as well as regular follow-up is difficult, a procedure like ETV can be considered better than VP shunt.

In present study, association of treatment success was found insignificantly with age of patients, gender, term of gestation and etiology of hydrocephalus. Significant higher proportion of infection and blockage was found in VP shunt group than ETV group. Overall rate of infection and hemorrhage was 6.4% and 5.1% in study of Abhaya V. Kulkarni et al[11] although rate of infection and hemorrhage was not statistically different in both group. Similar to present study, result of Meta analysis done by Liang Lu et al[12] showed significantly lower postoperative infection, hemorrhage and blockage rates in the ETV group than VP shunt group.

Conclusion

Treatment success was high in both procedures (76.67% for ETV and 70% for VP shunt). VP shunt was found to be more successful than ETV in terms of clinical outcome in the in both age groups. However, the results were statistically insignificant. Significant higher proportion of complication was found with VP shunt than ETV therefore greater benefits can be achieved using ETV. Thus for a tribal population, where patient compliance is poor and healthcare accessibility as well as regular follow-up is difficult, a procedure like ETV can be considered better than VP shunt.

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Cerebral amyloid angiopathy: early presentation in a patient with prior neurosurgical interventions. Case report

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Keywords
cerebral amyloid angiopathy, glymphatic system, cranial surgery, haemorrhagic stroke

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Abstract

Background: Cerebral amyloid angiopathy (CAA) has classically been described as a disease of the elderly. Genetic predisposition has been linked to the APOE e3/e3 allele. Evidence suggests that brain insult in the form of injury, prior surgical intervention, or radiation can exacerbate the clearance of toxic proteins in patients susceptible to CAA.

Case: We describe a unique case of CAA in a 30-year-old male who had prior surgical interventions for spina bifida, Chiari malformation, and hydrocephalus as a child.

Conclusions: The case is used to teach important components regarding diagnosis, clinical suspicion, and highlight the need for further investigation regarding the emerging role of the glymphatic system and its role in clinical pathology.

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Background

Cerebral amyloid angiopathy (CAA) is characterized by the accumulation of amyloid fibrils along the walls of small to medium-sized arterial blood vessels (1). The pathogenesis of CAA remains unknown; however, in most cases of disease presentation, it is presumably caused by an irregular production or diminished clearance of amyloid beta protein (Aβ) (1). As a result, there is a significant buildup of Aβ protein levels, ultimately leading to its aggregation along the walls of small and medium sized leptomeningeal and cortical arteries (1). Impaired vasodilation and alteration in vascular reactivity have been

identified as early markers of the disease (1). Collectively, these phenomena bring about oxidative stress, which further propagates the accumulation of Aβ (1). A study conducted by Yamada et al., investigating amyloid deposition in the brain of human subjects between the ages of 55 to 101 found that the incidence of amyloid deposition increases over time with advancing age. As such, CAA is considered a disease of the elderly (2). Little is known however if prior intracranial surgery can accelerate CAA in predisposed individuals.

Surgical intervention has the potential to damage healthy brain tissue and can lead to neuroinflammation, which has been postulated to accelerate amyloid pathology. Specifically, early surgical interventions can damage the blood-brain barrier (BBB), inhibit neurogenesis in the hippocampus, and lead to neural progenitor cell death. In patients without genetic predisposition for CAA, it has been postulated that the glymphatic system helps regulate neuroinflammation and clear toxic protein aggregates. In patients with APOE e3/3, this system may become overwhelmed with insult and result in malfunction (3). Additionally, vascular changes may involve early damage to vascular endothelial cells (3). A study conducted by Sugihara et al. employed immunohistochemistry to examine 123 autopsy brains from patients aged 30 to 59 (4). In their findings, Sugihara and colleagues report that the prevalence of cerebral Aβ deposits was two times higher in the patients who had received brain surgical interventions (27.8%) as compared to those who had not (14.8%) (4). Moreover, findings from this study also demonstrate that amyloid angiopathy was significantly more evident ($P < 0.05$) (4). This case report highlights a 30-year-old male who had early childhood surgical intervention for Spina bifida, Chiari malformation, and hydrocephalus who subsequently developed early onset CAA. We postulate potential mechanisms that may have contributed and warrant further investigation.

Case

This case report is of a 30-year-old male who had shunted hydrocephalus, Chiari decompression, spina bifida, seizures, and cerebral palsy. He presented originally at age 29 with a right frontoparietal hemorrhagic stroke with multiple other small intracranial hemorrhages including a left thalamic hemorrhage. He required a right decompressive hemicraniectomy with subsequent cranioplasty. Workup at that time for Col4a and aortopathy was negative. Diagnostic angiography was negative for vascular lesion. He was eventually discharged to rehab and made good clinical improvement with return to baseline functioning.

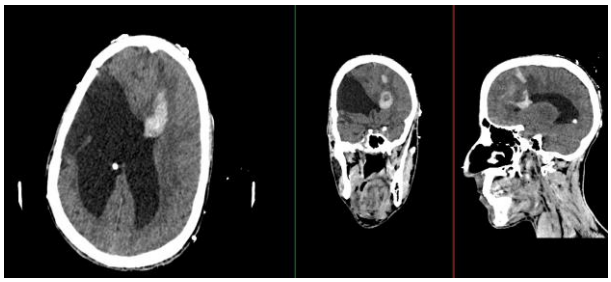

Figure 1. Prior encephalomalacia from previous right frontoparietal intraparenchymal hemorrhage. New acute left frontal hemorrhagic stroke.

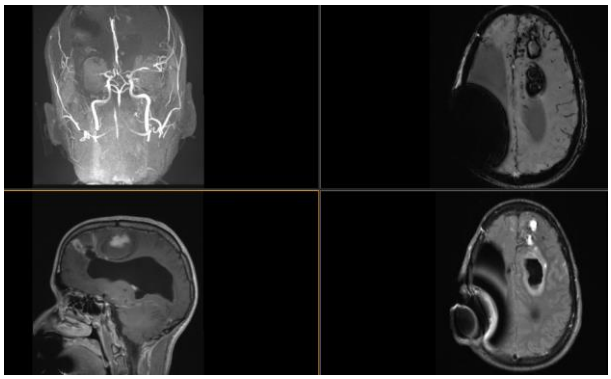

Figure 2. MRI/MRA consistent with cerebral amyloid angiography but not vasospasm. SWI imaging with classic presentation for CAA.

15 months after initial hemorrhage he developed symptoms of staring into space, right sided weakness, and aphasia. A left frontal intracranial hemorrhage was noted (Figure 1). Patient was admitted for further workup. Electroencephalography was done with abundant left frontal rhythmic delta activity but no seizures. Shunt tap was performed with no infectious or autoimmune etiology including negative findings for meningitis, JC virus, Varicella, fungal infection, malignancy panel, antiphospholipid battery, and ANCA. He was taken for diagnostic angiography where non-specific vasculopathy was noted. Magnetic Resonance Imaging with vasculitis protocol was done and concerning for CAA (Figure 2). Rheumatology was consulted and CT chest,

abdomen, and pelvis (CAP) was negative for vasculitis. Brain biopsy was completed and pathology was consistent with cerebral amyloid angiopathy and not acute vasculitis. APOE testing was positive for homozygous APOE e3/e3. He was discharged to long-term rehab and has been improving in strength and function. He remains non-verbal but is able to eat with assistance and smiles with family.

Discussion

CAA is associated with the accumulation of Aβ protein along the blood vessel walls in the brain. It is typically a disease presenting in elderly patients. Early-onset disease is generally associated with hereditary forms of CAA (5). However, history of prior brain surgery and/or radiation has also previously been shown to be associated with CAA in younger patients aged 30-59 (4). There are relatively few reported cases of biopsy-confirmed CAA years after initial surgical intervention. No cases have been associated with a specific childhood spina bifida, Chiari malformation, or shunted hydrocephalus. However, there has been documented vascular pathology after brain tumor radiation therapy that coincides with diagnostic criteria for cerebral amyloid angiopathy-related inflammation (CAA-RI), a subtype of CAA (6). Roongpiboonsopit et al. demonstrated evidence of cerebral microbleeds (CMBs) in 18/27 patients followed for a median of 4.1 years after craniospinal intervention (7). Five of these patients were children (median age 6.3 years). CMBs were primarily found in a lobar distribution which overlaps with the diagnostic criteria for CAA-RI, which suggests pathological and potentially functional similarity to CAA pathogenesis (6).

The exact correlation between history of prior cranial intervention and CAA remains unclear. A possible mechanism is decreased clearance of Aβ protein. Cerebral Aβ proteins are cleared through para-vascular pathways (8). The more recently discovered glymphatic system uses peri-vascular channels to facilitate excretion of central nervous system waste products, and has been suggested to play a direct role in Aβ protein clearance (9, 10). Early surgical intervention could theoretically impair lymphatic Aβ clearance, leading to an acceleration of CAA. McRobb et. al suggest another mechanism of early onset CAA is the downregulation of ADAM10, a protein that modulates the production of Aβ protein in the brain (11). Both of these topics warrant further investigation in pre-clinical studies with subsequent validation from clinical patient samples.

Conclusion

In summary, decreased clearance of Aβ protein by impaired glymphatic systems and downregulation of protein modulators may be a contributor to the pathogenesis of CAA and should be carefully considered in patients with APOE e3/e3 allele who had prior cranial interventions. Other sources of increased Aβ production should also be investigated.

List of Abbreviations: amyloid beta (Aβ), blood brain barrier (BBB), cerebral amyloid angiopathy (CAA), cerebral microbleeds (CMB), chest, abdomen, and pelvis (CAP)

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Correlation of neutrophil lymphocyte ratio to clinical outcomes based on 6 months surveillance on traumatic brain injury patients at Haji Adam Malik General Hospital (2018-2020)

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Keywords
traumatic brain injury,
neutrophils,
lymphocytes,
NLR,
Glasgow Outcome Scale

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ABSTRACT

Introduction: Traumatic brain injury is a major cause of disability, death, and economic loss in many countries around the world. The annual incidence in the United States is reported to reach 1.7 million sufferers, in Europe it is reported as 262 per 100,000 people per year, and in Indonesia, the incidence is increasing by 1% every year. Direct and indirect damage resulting from a traumatic brain injury can cause inflammation by activating glial cells and leukocytes, inducing the release of proinflammatory cytokines, and accelerating neurodegeneration and neuroinflammation. Recently, the neutrophil-to-lymphocyte ratio (NLR) has been proposed to be a predictor of clinical outcomes for various neurological diseases such as stroke and traumatic brain injury. To put it simply, elevated NLR levels in patients with intracerebral haemorrhage were independently associated with worse clinical outcomes. Researchers want to research the relationship between NLR and outcome based on 6 months GOS in traumatic brain injury patients at Haji Adam Malik General Hospital Medan.

Methods: An observational analytic study with a retrospective cohort design. Samples were selected based on inclusion and exclusion criteria from a traumatic brain injury at H. Adam Malik General Hospital Medan in 2018-2020.

Results: The research data were normally distributed and analyzed by the Pearson trial; the sig value was obtained. (2-tailed) of 0.798 ($P > 0.05$), which means there is no between NLR and 6 months GOS outcome in traumatic brain injury patients.

Conclusion: There was no relationship between *NLR* and outcome based on GOS 6 months of traumatic brain injury patients.

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INTRODUCTION

Traumatic brain injury is a major cause of disability, death, and economic loss in many countries around the world.[1] The annual incidence in the United States is reported to reach 1.7 million sufferers, in Europe it is reported as 262 per 100,000 people per year, and in

Indonesia, the incidence is increasing by 1% every year.2. based on RISKESDAS data in 2018 that the incidence of traumatic brain injury increases every year from 8.2% in 2013 to 9.2% in 2018. The highest prevalence is experienced by male patients (11%) with an average age of 15 – 24 years (12.2%) with the most locations in urban areas (9.4%). Road traffic accidents still account for the highest proportion (31.4%) with motorcycle riders being the most common cause of traumatic brain injury (72.7%).3 The incidence of traumatic brain injury is also a problem faced by many neurosurgeons, especially in the city of Medan. Based on data from patients served by SMF Neurosurgery, H. Adam Malik Hospital Medan in 2013 – 2017, traumatic brain injury sufferers were still listed as the most patients with the highest number reported reaching 32.64% in 2014 and the lowest figure found to be 15.83% in 2014. 2017.4 Direct and indirect damage resulting from a traumatic brain injury can cause inflammation by activating glial cells and leukocytes, inducing the release of proinflammatory cytokines, and accelerating neurodegeneration and neuroinflammation.5 Recently, the neutrophil-to-lymphocyte ratio (NLR) has been proposed to be a predictor of clinical outcome for various neurological diseases such as stroke and traumatic brain injury.[6]

Neutrophil Lymphocyte Ratio (NLR) is calculated as the ratio of neutrophil cell count to lymphocyte cell count in peripheral blood. NLR is an objective, readily available, inexpensive, and reproducible indicator of inflammation. NLR is also a sign of extensive secondary damage by neutrophils and their products to cerebral tissues and attenuation of cell-mediated immunity associated with systemic inflammation. Its prognostic role has been investigated in various neurological disorders such as stroke, multiple sclerosis, and traumatic brain injury. [7]

Evidence has suggested that patients with higher neutrophil cell counts, and lower lymphocyte cell counts have worse clinical outcomes. In addition, a higher NLR ratio was also associated with a worse clinical outcome at 1 year after traumatic brain injury.[8]

It has been found that NLR values in patients with severe traumatic brain injury on the first day of hospital admission are independent predictors of mortality and functional clinical outcome. The power of the NLR test to predict functional clinical outcome in these patients appears to be like the power of the Glasgow Coma Scale (GCS). There is a reported good correlation between NLR and GCS, where higher NLR is associated with lower GCS. However, the association between NLR and mortality was thought to be weaker than that of GCS, indicating the superiority of the GCS in predicting mortality in patients with traumatic brain injury.[9]

NLR examination has several benefits for predicting patient prognosis compared to GCS. First, the NLR is more objective than the GCS, and individual judgment is not involved in the NLR. Second, the slightest change in the patient's general condition related to the disease may not be directly reflected by the GCS, but the NLR is able to describe these changes. Third, GCS assessment is impaired if the patient is sedated or on mechanical ventilation. However, in emergency situations, NLR retrieval takes a long time, which is around 30-40 minutes to get results.[8]

To put it simply, elevated NLR levels in patients with intracerebral hemorrhage were independently associated with worse clinical outcomes. Researchers want to research the relationship between NLR, and outcome based on 6 months GOS in traumatic brain injury patients at Haji Adam Malik General Hospital Medan.

Methods

This study was an observational analytic study with a retrospective cohort study design to assess the relationship between neutrophil lymphocyte ratio and clinical outcome based on 6-month GOS in traumatic brain injury patients. Neutrophil Lymphocyte Ratio data from non-operative traumatic brain injury patients who came to Haji Adam Malik Hospital in Medan from 2018-2020 were compared to the clinical outcomes of patients based on the Glasgow Outcome Scale (GOS) at 6 months post-injury.

The independent variable in this study was the Neutrophil Lymphocyte Ratio of patients with non-operative traumatic brain injury on the first day of coming to Haji Adam Malik General Hospital, Medan, while the dependent variable included clinical outcomes of patients based on GOS 6 months after injury.

Inclusion criteria to be used as research samples are non-operative brain injury patients, head CT-

Scan criteria have features of Epidural Hematoma, subdural hematoma, Intraparenchymal hemorrhage, brain contusion, and subarachnoid hematoma, aged more than 10 years and less than 70 years, and have data neutrophils and lymphocytes on the first day of hospital admission. While the exclusion criteria in this sample were patients with penetrating brain injury, post-traumatic patients who had multiple injuries other than in the head region as evidenced by clinical and radiological findings, patients with a history of previous head injuries, patients with a history of comorbid diseases such as stroke, brain tumors, lung disorders. and heart disease, chronic kidney disease, and previous systemic infectious disease.

Sample is total sampling of the traumatic brain injury patients who were treated at Haji Adam Hospital Medan from 2018 to July 2020 who had met the inclusion and exclusion criteria. The study was conducted at H. Adam Malik Hospital using medical record data of non-operative traumatic brain injury patients from 2018-2020. Data collection was carried out after obtaining approval from the USU Medical Faculty ethics committee. Before starting the research, the researcher asked for ethical clearance from the Permanent Committee for Assessing Research Ethics, Faculty of Medicine, University of North Sumatra.

The data obtained were then collected for data processing using SPSS software version 25.0. To determine the characteristics of patients with traumatic brain injury and to determine the clinical outcome of patients 6 months after traumatic brain injury based on the Glasgow Outcome Scale, categorical data is presented in the form of a frequency distribution of n (%), tables and graphs, and numerical data is presented in the form of mean ± standard deviation. or median. The mortality rate is presented in the form of a rate.

To determine the relationship between Neutrophil Lymphocyte Ratio (NLR) on clinical outcomes of patients based on 6-month GOS in traumatic brain injury patients, Pearson correlation test analysis was performed if the data were normally distributed, or Spearman's Rank test was performed if the data were not normally distributed. Normality test using the Kolmogorov-Smirnov test (n>50), the data is said to be normally distributed if p>0.05.

RESULTS

In this study, 77 samples from the total sampling met the inclusion and exclusion criteria. The sample data are patients who experienced traumatic brain injury at Haji Adam Malik Hospital Medan from 2018 - 2020. The description of the characteristics of the research sample is described as follows:

Table 1. Distribution of samples by gender

Genders	Total	Percentage
Male	63	81,82%
Female	14	18,18%
Total	77	100%

Based on table 1, it was found that the male research sample amounted to 63 people with a presentation of 81.82% and the female research sample amounted to 4 people with a presentation of 18.18%. From these data, it was found that the male research sample was more than the female patient.

Table 2. Sample distribution based on GCS

GCS	Total	Percentage
13-15	29	37,66%
9-12	28	36,36%
< 9	20	25,98%
Total	77	100%

Based on table 2 get the research sample with GCS 13-15 totaling 29 people with a percentage of 37.66%, research samples with GCS 9-12 totaling 28 people with a percentage of 36.36% and research samples with GCS < 9 totaling 20 people with a presentation of 25 ,98%. From these data, it was found that the study sample with GCS 13-15 was more than the GCS 9-12 and <9.

Table 3. Sample distribution by trauma onset

Onset of Trauma	Total	Percentage
< 24 h	66	85,71%
> 24 h	11	14,29%
Total	77	100%

Based on table 3, the research sample with trauma onset less than 24 hours was 66 people with a percentage of 85.71% and the study sample with trauma onset more than 24 hours amounted to 11 patients with a percentage of 14.29%.

The data normality test was performed using the Kolmogorov-Smirnov test. Normality test was conducted to determine the difference test to be used next.

Table 4. Sample normality data using the One-Sample Kolmogorov-Smirnov Test

N		77
Normal Parameters[a,b]	Mean	,0000000
	Std. Deviation	1,94132437
Most Extreme Differences	Absolute	,318
	Positive	,274
	Negative	-,318
Test Statistic		,318
Asymp. Sig. (2-tailed)		,000[c]

From table 4, the results of the normality test of the research sample data with a significance value (P < 0.05) suggest that the data are normally distributed. Data with normal distribution will be tested for Pearson Correlation.

To determine the correlation between GCS and 6-month GOS outcomes in patients with traumatic brain injury at H. Adam Malik Hospital Medan, the Pearson correlation test was performed.

Table 5. GCS correlation test results data with 6-month GOS outcomes

GCS			GOS
GCS	Pearson Correlation	1	,783**
	Sig. (2-tailed)		,000
	N	77	77
GOS	Pearson Correlation	,783**	1
	Sig. (2-tailed)	,000	
	N	77	77

** Correlation is significant at the 0.01 level (2-tailed).

From table 5. obtained a sig. (2-tailed) value of 0.00 and a positive value on the Pearson Correlation, which means that there is a positive correlation between GCS and 6-month GOS outcomes, with a P value of < 0.05.

To determine the correlation between NLR and 6-month GOS outcomes in patients with traumatic brain injury at H. Adam Malik General Hospital Medan, the Pearson correlation test was performed.

Table 6. NLR Correlation Test Results Data with 6 months GOS clinical outcome

NLR			GOS
NLR	Pearson Correlation	1	-,030
	Sig. (2-tailed)		,798
	N	77	77
GOS	Pearson Correlation	-,030	1
	Sig. (2-tailed)	,798	
	N	77	77

From table 6. sig value is obtained. (2-tailed) of 0.798 (P > 0.05) which means that there is no correlation between NLR and 6-month GOS outcomes in traumatic brain injury patients.

CONCLUSION

The NLR correlation test has been carried out on the clinical outcome of traumatic brain injury patients based on 6 months GOS which obtained a sig value. (2- tailed) of 0.798 (P > 0.05) which means that there is no correlation between NLR and 6-month GOS outcomes in traumatic brain injury patients.

The results in this study are different another which stated that there is evidence of a correlation between high NLR and the worst functional clinical outcome and vice versa, lower NLR has a clinical outcome good functionality.9 An NLR value >15.63 at first hospital admission was a predictor of poorer clinical outcome and mortality at 28 days. Chen et al also reported that NLR levels with a cut-off value of 18.16 were correlated with clinical outcomes with a sensitivity of 74.3% and a specificity of 72.9%.8

In this study, different results were obtained from previous studies, where there was no relationship between NLR and clinical outcomes of traumatic brain injury patients. It is suspected that many factors can influence the results of this study. One of the types of intracranial lesions that occur due to impact on the head is thought to affect the NLR value itself. NLR values were seen to be significantly higher in brain injury patients with diffuse axonal injury than in patients with cerebral edema, intracerebral hemorrhage, subdural or epideral hematoma, and subarachnoid hemorrhage. In this study sample, there were heterogeneous types of intracranial lesions which were thought to have an impact on the results of the study. Thus, the same study can be carried out again with more homogeneous intracranial lesions from each study sample so that it can have maximum results.[10]

In addition to the type of intracranial lesion due to a blow to the head, the onset of trauma upon admission to the hospital and the time the patient's blood sample was taken were thought to also play a role in NLR levels. NLR levels peak in the first 24 hours of onset of traumatic brain injury. In the sample of this study, 14.29% of the sample with onset more than 24 hours after the incident of traumatic brain injury before routine blood tests were performed. This is thought to affect the results of this study.[6]

The research sample size is also suspected to affect the results of this study. Small differences in clinical outcomes can be statistically significant if the number of samples is very large. On the other hand, a very significant clinical difference may not be statistically significant if the sample is too small. Many studies are not published because the results are not statistically significant even though they are clinically important.11 From this study obtained 77 samples from the total sampling that have met the inclusion and exclusion criteria. There are many complicating factors experienced by researchers so that the number of samples obtained is too small. Thus, other methods in determining the number of research samples, such as using a probability formula with a high confidence interval, can be an alternative for the next research to obtain maximum research results.

Discussion: There was no relationship between NLR, and outcome based on GOS 6 months of traumatic brain injury patients. Further research is needed with a larger sample size to obtain optimal results.

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Congenital sphenoid wing defect with lateral angular dermoid presenting with CSF leak after orbital surgery

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ABSTRACT
Lateral angular dermoid may have associated bony defects which must be recognized before surgery. High-resolution 3-D CT scans and MRIs define these lesions very clearly. Total excision with attention to the bony defect is usually curative. CSF leak from the operative wound at the surgery or in the post-operative period signifies the intracranial connection or dural adhesion unnoticed by the Ophthalmologist before surgery.

Keywords
congenital sphenoid wing dysplasia,
CSF leak,
lateral angular dermoid,
sphenoid wing defect

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INTRODUCTION

Dermoid cysts are congenital benign tumours that originate from an embryonic ectodermal cell. Angular dermoid present at the outer angle of eye, beneath or in close proximity to the eyebrow. Various types of bony defects are associated with long standing dermoid in this location. Congenital sphenoid wing dysplasia (SWD) is a rare occurrence. It has a strong association with Neurofibromatosis type I (NF-1)[1], although it can occur alone. We present a case of a 3 years old male child presenting with orbital cellulitis, cerebrospinal fluid (CSF) leak after orbital surgery for lateral angular dermoid with congenital sphenoid wing dysplasia, without any features of NF-1.

CASE REPORT

A 3 years old male child presented with CSF leak from wound near lateral canthus of right eye with suture breakdown and features of meningitis (Fig 1A). He had history of recurrent right orbital swelling on crying since birth, and fowl smelling discharge from the swelling before surgery. Excision biopsy of the swelling was reported to be a dermoid cyst. Three-dimensional CT scan with CT-cisternogram showed a bony defect in the right sphenoid wing forming lateral wall of orbit (Fig 1B) and CSF pooling at lateral angle of orbit (Fig 2A). MRI revealed evidence of soft tissue thickening and fluid collection in extraconal compartment,

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with orbital and para-orbital cellulitis. We performed a right pterional craniotomy, excision of infected residual dermoid, wound debridement and CSF fistula repair with the help of a rotated pedicled temporalis muscle graft and Tisseel (Fibrin) glue. In the immediate post-operative period, there was no CSF leak (Fig 2B).

Figure 1A. CSF leak from operative wounds with breakdown of stitches (white solid arrows)

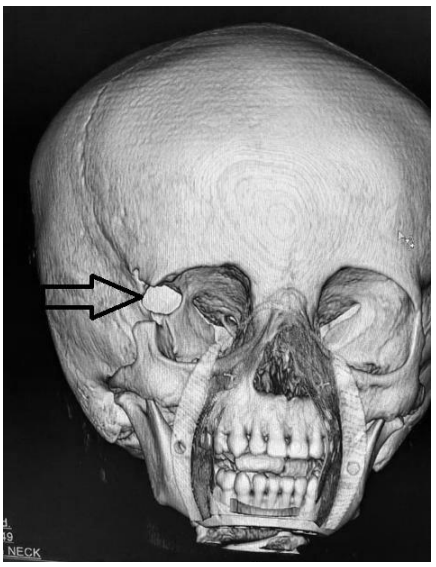

Figure 1B. 3D-CT of face showing a large bony defect in the greater sphenoid wing, involving the orbital rim and zygomatic arch on the right side (black arrow)

Figure 2A. CT-cisternogram showing pooling and leakage of contrast at the defect site

Figure 2B. Post-operative image

Discussion

Dermoid cysts are congenital benign tumours that originate from an embryonic ectodermal cell. These ectodermal cells are involved in neurulation during neural tube closure resulting in abnormal fusion. Common sites of dermoid cysts are periorbital (zygomatico-frontal suture), nasal (fronto-nasal suture and rhinion), intraoral (floor of mouth), scalp (anterior fontanelle and cranial sutures) and postauricular[2]. Angular dermoid occurs at the outer angle of eye, beneath or in close proximity to the eyebrows[3]. These tumours are ovoid, soft to firm, may be lobulated, containing a lipomatous element having a cystic nature.

SWD is a characteristic feature and one of the diagnostic criteria of NF-1. It occurs in 5-10% of the cases. Features of NF-1 are six or more café-au-lait macules, 2 or more cutaneous/ subcutaneous neurofibromas or plexiform neurofibromas, axillary or groin freckling, optic pathway glioma, two or more Lisch nodules in iris, bony dysplasia (SWD, bowing or long bone +/- pseudoarthrosis) and first degree relative of NF-11. SWD can be an isolated finding also, like in our case, which is extremely rare.

Zygomatico-frontal suture defect has a strong association with orbital dermoid cyst[4].

N. Sathananthan et.al reviewed CT scan of 70 patients (43 male and 27 female) who had a lesion palpable at outer canthus, and histologically proven dermoid cyst[5]. Mean age of patients was 29 years. The lesion was always unilateral and 34 were on the left. The bone of the lateral wall and supero-temporal angle of orbit showed following abnormalities, often in combination: pressure erosion in 61 cases, abnormal developmental shape

in 55, the dermoid cyst entering a tunnel or canal through the lateral wall in 24, a blind pit or crater in 15, and a cleft in 20.

There are reports of unusual and interesting presentations of angular dermoids[6,7,8]. Proptosis of eye with mastication was reported in a woman because of orbital mass communicating with the temporal fossa through a bony defect in lateral orbital wall; pressure by the temporalis muscle with mastication, on the dumb-bell shaped cyst caused the proptosis[6]. Frontal headache and chewing related oscillopsia is reported in 60 years old man[7]. Illusion of movement was due to mechanical displacement of retro-orbital cyst and eye by contraction of the temporalis muscle; removal of the cyst leads to complete remission of oscillopsia. History of blurring of vision of an eye with chewing is reported in a 29 years old lady with a dumb-bell dermoid cyst[8].

In this endoscopic era, direct surgical excision is an excellent approach, with a low complication rate and a very high aesthetic success rate, when performed through supra-eye brow or infra-eyebrow approach[9,10].

Proper anatomical delineation of the lesion and the bony defect with High resolution CT and MRI imaging is extremely important as many of the angular dermoid have intracranial extension. Involvement of a neurosurgeon in such cases is thus imperative and combined transcranial approach is done where indicated.

Conclusion

Lateral angular dermoid is associated with supero-lateral bony abnormality of orbital wall. Congenital sphenoid wing dysplasia is a spectrum of bony defect. We present a case of congenital sphenoid wing dysplasia in a case of lateral angular dermoid presenting in post-orbital surgery CSF leak. Proper anatomical delineation of angular dermoid is extremely important as there are high chances of intracranial extension of the angular dermoid, and transcranial approach for complete excision for possible intracranial extension have to be kept in mind while dealing with angular dermoid.

Conflicts of interest: None declared.
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Postoperative complications in endoscopic frontal transcortical surgery of lateral and third ventricle tumours. Speech disorders

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Keywords
endoscopic,
lateral ventricle,
mutism.
third ventricle,
transcortical approach

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Abstract

Neurosurgical approaches to lesions of the lateral and the third ventricles are divided into two fundamentally different groups: transcortical neurosurgical approaches, including - endoscopic and interhemispheric transcallosal microneurosurgical approaches. Complications in surgery of lateral and third ventricle tumours are often associated with the specific approach technique and could be transient. We analyzed postoperative neurological complications and the approach criteria on MRI or CT scans in postoperative period such as localization of corticotomy, distance from corticotomy to coronal suture, "angle of attack" after the frontal transcortical approach to the lateral and third ventricle based on 54 cases and presume transient nature of specific to approach complications and approaches' factors that have role in postoperative mutism.

Introduction

Neurosurgical approaches to the tumors of the lateral and the third ventricles are divided into two fundamentally different groups: transcortical neurosurgical approaches, including - endoscopic and interhemispheric transcallosal microneurosurgical approaches. Two different approaches to the ventricular system cause distinct brain injuries: tightly compressed commissural fibers of the corpus callosum are injured by the interhemispheric transcallosal approach, while the transcortical approach damages gray and white matter of the brain on its way [1,2].

Complications in surgery of lateral and third ventricle lesions are often associated with the specific approach technique and today is a widely discussed problem [3,4]. When applying the abovementioned approaches, the most common complications are aphasia, mutism, hemiparesis, seizure, memory impairment, apatheia/abulia, endocrinopathy, subdural hygroma, etc. [1,16].

Manifestations of mutism, which are currently little studied in the context of the use of these neurosurgical approaches, constitute a field of particular scientific interest. Mutism is a clinical state, in which a conscious patient is unwilling to or unable to speak, resulting in the absence or marked paucity of verbal output. The patients can be mute while their ability to write or comprehend spoken language is intact [1,11]. Mutism can occur as a result of damage to the Broca area, premotor cortex, and supplementary motor area of the dominant hemisphere, association fibers of white matter, the anterior part of the cingulate gyrus, commissural fibers of the corpus callosum, damage of the cortical-bulbar fibers bilaterally, bilateral thalamotomy and damage of reticular formation of the midbrain [7,5].

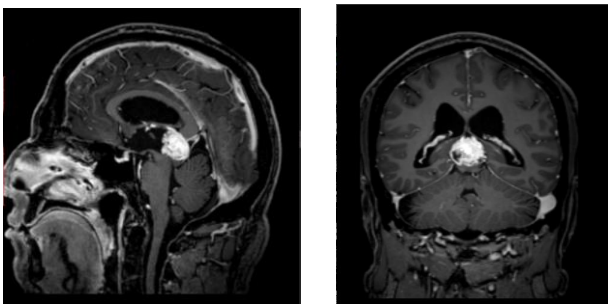
Materials and methods

A retrospective analysis of 54 patients with neoplasms and lesions of lateral (anterior horn, body, atrium) and third ventricles who underwent surgery in the period from October 2015 to May 2021. Male – 26 patients, the mean age was 44.5 years (range: 20-71 years), female – 28 patients, the mean age was 42.4 years. (range: 15-74 years). Mean preoperative Karnofsky Performance Statuse Score (KPS) was 76.37.

Localization of neoplasm: the third ventricle - 41 (75.9 %) patients; lateral ventricular tumors - 13 (24.1 %) patients. Histological distribution depending on the location is given in Table. No. 1. Histopathological evaluation of these 54 neoplasms and lesions indicated 15 distinct diagnostic entities including brain tumors of glial origin with invasion in the ventricular system (diffuse and anaplastic astrocytoma, glioblastoma, oligodendroglioma, and anaplastic oligoastrocytomas) accounted for 35,2% (Fig. 1), subependymoma and ependymomas varying degrees of malignancy – 14,8%, colloid cysts - 13%, central neurocytomas - 11.1%, craniopharyngiomas 11.1%, germinomas - 7.4%, others - 7.4%

Histopathology	**Lateral ventricles (n-13)**	**Third ventricle (n-41)**
Pilocytic astrocytoma, WHO Gr I	-	1
Diffuse astrocytoma, WHO Gr II	2	3
Anaplastic astrocytoma, WHO Gr III	-	3
Glioblastoma, WHO Gr IV	1	5
Oligodendroglioma, WHO Gr II	1	2
Anaplastic oligoastrocytomas WHO Gr III	1	-
Subependymoma, WHO Gr I	1	1
Typical and atypical meningiomas, WHO Gr I та II	2	-
central neurocytomas, WHO Gr II	4	2
Pineoblastoma, WHO Gr IV	-	1
Ependymoma, WHO Gr II, anaplastic ependymoma WHO Gr III	1	5
Craniopharyngioma, WHO Gr I	-	6
Colloid cysts	-	7
Germinomas	-	4
Mature teratoma	-	1

Table 1. Histopathology of intraventricular neoplasms.

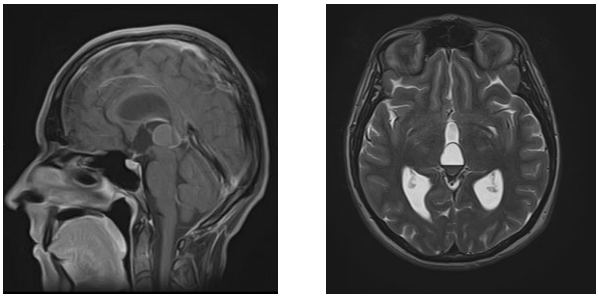


A. **B.**

Figure 1. A-B. Tumor in the posterior part of the third ventricle (Glioblastoma), preoperative contrast-enhanced, T1W images.

Preoperative symptoms include: cephalalgia - 49 (90.7 %) patients, sings of elevated ICP - 32 (59.25 %) patients, neurocognitive disorders and psychoorganic syndrome - 10 (18.5%) patients, oculomotor dysfunction - 10 (18.5%) patients, motor deficits - 9 (16.6%) patients, short term memory loss-8 (14.8%) paients, decreased visual acuity and loss of peripheral vision - 7 (12.9%) patients,

endocrinopathy - 4 (7.4%) patients, seizures - 2 (3.7%) patients.



A. **B.**

Figure 2. A-B. Tumor in the posterior part of the third ventricle (ependymoma), preoperative contrast-enhanced T1W images and T2W images.

Preoperative contrast-enhanced magnetic resonance imaging (MRI) (Fig.2) of the brain and computer tomography (CT) were also used for the preoperative planning of the approach side, optimal for the resection of the neoplasm and minimization of postoperative complications. We analyzed the localization of the neoplasms in the ventricular system, the side with greater distribution, signs of occlusive hydrocephalus, the side with the wider interventricular foramen of Monro, localization of estimated corticotomy ("entry point"), and the best "angle of attack ".

In surgery of neoplasms of the lateral (anterior horn, body, atrium) and third ventricle, we use endoscopic frontal (craniotomy over the frontal lobe) transcortical (corticotomy through the upper or middle frontal gyrus) approache. We perform an endoscopic frontal transcortical approach via parasagittal craniotomy over the non-dominant hemisphere of the brain (or over the priority hemisphere for approach) with the centration at the Kocher's point. Corticotomy up to 2.2 cm. is carried out through the top of the middle or upper frontal gyrus. The next stage is white matter fibers dissection to the front horn of the lateral ventricle and the subsequent introduction of intracerebral retractors.

Depending on the location of the tumor or lesion in the third ventricle, its size, and available hydrocephalus we used transventricular (through the cavity of the lateral ventricles) approach and further transforaminal (approach to the third ventricle through the interventricular foramen of Monro) or extended transforaminal transchoroidal approach (approach to the third ventricle through the interventricular foramen of Monro with the anterior choroidal dissection). Surgery was performed using an endoscopic stand based on the HD- endoscope "Image-1HD" (Karl Storz, Germany). Rigid endoscopes "Karl Storz" 4 mm in diameter with viewing angles of 0 and 35 degrees were used as the main tool for visualization of the operating field.

Approach through the right hemisphere has been performed in 38 (70.4 %) cases and through the left one in 16 (29, 6 %) cases. Endoscopic frontal transcortical approach to the lateral ventricles was used in 13 (24.1 %) cases; endoscopic frontal transcortical transentricular transforaminal approach to the third ventricle - 13 (24.1 %) cases, extended transforaminal transchoroidal approach - 28 (52%) cases. In all cases, a 100% endoscopic technique ("fully endoscopic resection") was performed.

In case of clinical and MR signs of occlusive hydrocephalus and with the purpose of preventing the progression of hydrocephalus in 22 (40.7%) cases with simultaneous resection of tumor we performed endoscopic third ventriculostomy.

In the early postoperative period, all patients underwent contrast-enhanced CT or MRI in order to detect residual component of the tumor, potential postoperative ischemia and bleeding, and evaluations of the ventricular system.

The follow-up ranged from 3 to 42 months, at average 12.5 months. During the follow-up examination of patients, which was performed approximately 2-4 months after the surgery, we assessed the overall health status, neurological status, contrast-enhanced MRI of the brain (Fig. 3). On MRI we evaluated the presence of residual component of the tumor or tumor growth, ventricular system (presence of hydrocephalus), expansion/narrowing of the transcortical channel in the matter of the frontal lobe.

RESULTS AND DISCUSSION

Extent of resection in our series: gross total resection/near total resection - 34 (63 %) patients, subtotal/partial resection - 15 (27.7 %) cases, biopsy - 5 (9.2 %) cases.

39 (72.2 %) patients had no postoperative complications, 15 (27.7 %) patients had at least one postoperative complication. Postoperative complications included:

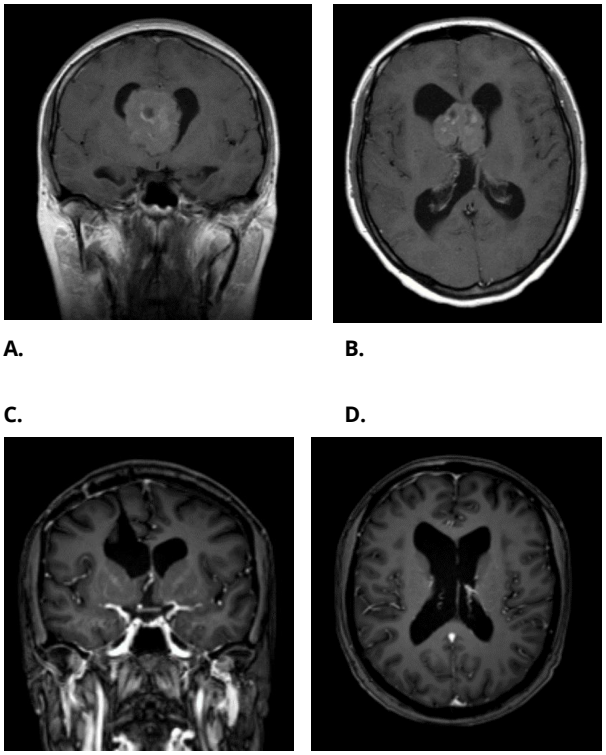


Figure 3. A-B. Tumor in the right lateral ventricle (ependymoma), preoperative T1W images.

C-D. 5-month postoperative contrast-enhanced T1W images depicted gross total resection of the tumor.

- speech disorders such as mutism - 6 (11.1 %) patients and apathia/abulia - 5 (9.2%) patients . We observed that 4 patients with postoperative manifestations of apathia/abulia also had concomitant mutism. In the postoperative period, at the follow-up examination 2-4 months after the surgery, a complete or partial regression of both mutism and apathia/abulia was observed in all 6 patients;
- short term, "fixation" memory loss - 5 (9.2 %) patients. In all 5 cases the endoscopic transcortical transventricular transforaminal or extended transforaminal transchoroidal approach to the third ventricle was applied. In the postoperative period, at the follow-up examinations during the next 2-6 months after the surgery, a complete or partial regression was observed in 3 patients;
- oculomotor dysfunction - 5 (9.2%) patients. Oculomotor dysfunction included paresis of n. oculomotorius and/or Parinaud syndrome and in all 5 cases have been associated with tumor resection of the posterior part of the third ventricle. In the postoperative period, complete or partial regression was observed in 1 patient;
- motor deficits - 4 (7, 4%) patients. In our series, we associate the occurrence of this complication either with resection of the glial tumor (originated in close proximity to corticospinal tracts) with the invasion in the third ventricle or with the premotor cortex and supplementary motor area injury. We observed the complete regression in 2 patients during the next 4 months after the surgery;
- neurocognitive disorders - 4 (7.4%) patients which regressed in 1 patient 4 months after the surgery;
- endocrinopathy - 3 (5.5%) patients. We associate this complication with the resection of tumors that have been tightly fused to the hypothalamic area of the bottom of the third ventricle. Regression was observed in 1 patient after 3 months.
- postoperative hemorrhage – 2 (3,7%) patients;
- postoperative wound infection occurred in 1 (1.85%) patient;
- postoperative meningitis - 1 (1.85%) patient.

In our series, seizures, as a postoperative complication, did not occur.

Postoperative mortality - 1 (1.9%) patients due to hypothalamic dysfunction, leading to acute electrolyte shifts, after the resection of craniopharyngioma with the significant spread in the third ventricle.

Compared with the series Brian D. Milligan at al in the group transcortical approach, short-term memory loss in the postoperative period was recorded in 6 (12 %) patients, that is 2.8% higher than in our series. Motor deficits were recorded in 18 (35%) patients, that is 27.6 % higher than in our series. Neurocognitive disorders were 4.6% higher than in our series, and the percentage of patients with endocrinopathy was the same as in the series Brian D. Milligan at al. [16]

The average KPS on the day of discharge was 83,35%.

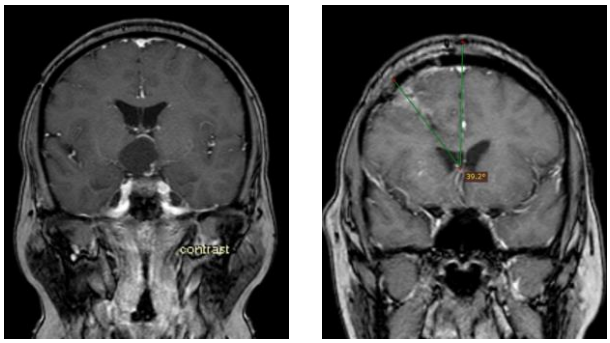
In the early postoperative period, all patients underwent contrast-enhanced CT or MRI of the brain and, among other things, we evaluated the following approach criteria (Table. 2) using RadiAnt DICOM Viewer software:

1) localization of corticotomy, "entry point" (upper/middle frontal gyrus (upper parts);

2) the distance from the coronal suture to the corticotomy in front;
3) "Angle of attack " (the angle between the sagittal plane and plain "entry point" - the point of entry into the frontal horn of the lateral ventricle). (Fig. 4).

Localization of corticotomy	Right hemisphere n-38 (70,4%)	Left hemisphere n -16 (29,6%)
Upper frontal gyrus	12 (31,5 %)	7 (43,7%)
Middle frontal gyrus, upper part	26 (68,5 %)	9 (56,3%)
Distance from the coronal suture to the corticotomy (mean, min-, max).	2,8 cm, min- 1,2, max- 3,6	2,8 cm, min- 0,5, max- 2,9
"Angle of attack" (mean, min-, max).	27,4°, min-17°, max- 35°	26,7°, min-21°, max- 34°

Table 2. Approach criteria



A. **B.**

Figure 4. A.Tumor of the third ventricle (craniopharyngioma), preoperative, contrast-enhanced T1W image.
B. 4-month postoperative contrast-enhanced T1W images, "angle of attack" calculation using using RadiAnt DICOM Viewer software.

In our series, mutism, as a manifestation of specific speech disorders caused by the frontal transcortical approach to the lateral and third ventricles, was observed in the postoperative period in 6 (11.1 %) patients (approach on the left - 6 patients). This clinical condition was transient and regressed within 4 months after the surgery. We indicate that corticotomy in patients who had postoperative mutism was performed in the upper frontal gyrus – 4 patients, in the middle frontal gyrus – 2 patients. We presume that postoperative mutism is related to the following features of the approach:

1) the approach side - dominant hemisphere.
2) corticotomy in the upper frontal gyrus and at a distance of less than 2 cm. from the coronal suture.
3) "angle of attack" less than 26.7○.

In their series, S. Asgari et al reported that when applying the transcortical approach, transient mutism occurred in 11% of patients, while via interhemispheric/transcallosal approach in 18% of patients, that equals and is 8.2% higher compared to our series respectively [7]. R. G. Ellenborg concluded that speech disorders are a fairly common complication when applying a transcortical approach through the dominant hemisphere and occur in 10-30% of patients [13]. In the article by Brian D. Milligan et, when comparing transcortical and interhemispheric approaches, mutism is not distinguished as a complication, instead this clinical condition is classified as a separate group of complications - aphasia/abulia, which occurs in 31% and 25% of cases, respectively, when applying transcortical and transcallosal approaches [16]. In our series of cases, aphatia/abulia manifested in the postoperative period in 5 (9.2%) patients, in all cases - together with mutism. It is uncertain whether there is a direct link between apathy, abulia and mutism. However, there is some evidence that the medial part of the frontal lobes, especially the cortex and fibers of the anterior cingulate gyrus, may play a role in manifestations of aphatia/abulia along with signs of mutism, as well as akinetic mutism [12]. The anterior part of the cingulate gyrus has a complex relationship with the limbic structures, other parts of the frontal cortex and periaqueductal gray matter of the midbrain. It is involved in interaction between the decision-making process and the "emotional" world of the limbic system, which is considered crucial for the start of speech and vocalization [6,19].

Functionally, the corpus callosum is closely related to speech function [9,20]. Mutism often occurs in the postoperative period after the interhemispheric approach with callosotomy [8,18]. Jin Hong et al suggested that damage to the corpus callosum can lead to speech disorders [15]. Ishizaki et al describe that transcallosal diaschisis is a possible mechanism of aphasia [14]. In our opinion, the commissural fibers of the corpus callosum and forceps minor fibers injury while applying the transcortical approach to the ventricular system, may play a role in the development of transient mutism.

Utilizing magnetic resonance diffusion-tensor tractography and comparing two different localizations of corticotomy (through the middle frontal gyrus and through the upper frontal gyrus) applying transfrontal transcortical access, T. Szmuda et al concluded that the application of access through the upper and middle frontal gyrus one way or another leads to trauma, including the upper longitudinal fascicles II, which is partially responsible for the relationship between the fields of Brock and Wernicke [21]. Although most of the fibers involved in the speech network and connecting the middle and lower frontal gyrus and posterior part of superior temporal gyrus are a part of the so-called upper longitudinal fasciculus III (anterior fibers of arcuate), they are located more caudally to the potential injury of the white matter via frontal transcortical approach in our cases [17].

Injury to the supplementary motor area and the premotor cortex, especially of the dominant hemisphere of the brain, can also cause mutism. Penfield and Welch used cortical stimulation to identify the boundaries and functions of this area. The connections of this cortex are quite branched and include the upper temporal gyrus, the intraparietal sulcus, the caudate nucleus, the thalamus, and other. [10]

Conclusion

The endoscopic frontal transcortical approach in surgery of neoplasm and lesions of the lateral and third ventricle is effective and minimally invasive approach. The transient nature of postoperative complications is due to the gentle manipulations of anatomical structures when applying this approach. Specific surgical approach complications such as mutism, apathia/abulia, motor deficits (due to the injury of the premotor cortex and supplementary motor area) were mostly transient and had a tendency to regress immediately in the postoperative period and most of them completely regressed from 2 to 4 months after the surgery.

The nature of mutism as a manifestation of speech complications when applying endoscopic frontal transcortical approach is multifactorial. The development of postoperative speech complications, namely of transient mutism when applying the endoscopic frontal transcortical approach is not a frequent complication and according to our observations regresses within 4 months. In our opinion, in order to reduce the risk of mutism in the postoperative period, endoscopic frontal transcortical approach should be performed via the non-dominant hemisphere (unless otherwise specified during preoperative planning) and in the upper part of the middle frontal gyrus at a distance more than 2 cm from the coronal suture. Corticotomy should be gentle and based on our series no more than 2.2 cm in length, "angle of attack" should be no less than 26.7○ which reduces cerebral cortex and white matter injury and the risk of postoperative complications associated with the application of this approach, including manifestations of mutism.

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Recent descriptions on physiological concepts of the pineal gland: what's new?

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ABSTRACT

The pineal gland is an endocrine organ located in the cranial vault. Its endocrine function has been extensively studied and has been found to be the cause of important regulatory functions in the physiology of the human body. Although the initial approaches to the suggestive action of this organ on the organism were of a philosophical and spiritual nature, in the last century technological advances have made it possible to clearly elucidate its effector function as an endocrine gland. In this order of ideas, the objective of this review is to address basic and recent descriptions of the physiology of the pineal gland.

Introduction

The pineal gland (PG) has been described as an organ that is capable of excreting a hormone called melatonin (MLT) that plays an important role in the circadian cycle (1). At the beginning of mankind's interest in anatomy and physiology (Renaissance era) this gland was still considered as part of the spiritual component of the body, as science evolved through later discoveries that the pineal gland exerted a regulating and synchronizing effect on the physiology of the organism, it was given physical functions (2). The scope of the hormone it excretes extends to important fields of human physiology such as the circadian cycle, sleep-wake cycle, mood states (its deficit causes depressive states), some topics that we will go into below, but not before addressing what was assumed about this gland throughout history.

History

The PG has been the subject of debate in philosophical circles. It was Ariens-Kappers who expressed that the oldest references with physiological-spiritual connotations regarding this gland were made by Herophilus, a philosopher who proposed that the PG had control over blood circulation by functioning as a sphincter that regulated the flow of *pneuma psychikon*, or the breath of life, from the central ventricle to the posterior ventricle in the brain (3). Galen proposed that the PG was nothing more than a pseudo-lymphatic gland that functioned as an anchor site to the intricate network of blood vessels that irrigate the brain mass belonging to the dorsal and posterior diencephalon regions, a somewhat more physical approach, however, still related to spiritual theories (4).

In the Middle Ages, different theories enriched the *theoretical corpus* regarding the duality between the soul and the body, assigning to the organs some probable spiritual functions, with new thoughts or improvement of the existing ones by important figures such as Thomas Aquinas, a famous monk influenced by the prevailing Christianity of the feudal age (5). In the Renaissance there was an explosion in anatomical explorations led by important figures such as Leonardo Da Vinci, who through his detailed drawings of human anatomy deepened the curiosity of the medical eminences of the time about the vital functions of different organs (6). The soul was located in the third ventricle of the brain, while the spinal cord was responsible for distributing the sensations generated in the soul to the body (6). Later Descartes proposed that the soul should have a physical residence or physical counterpart in the human body, the PG being the abode of the soul. According to him, the cerebral organs were duplicated except for the PG, which was curiously located in the center of the brain (7). Descartes' theories were later discredited by figures such as Antoine Jacques Louis Jourdan who argued that his ideas were nothing more than chimeras relegated to the realm of fiction (8).

Descartes' theories were later discredited by figures such as Antoine Jacques Louis Jourdan who argued that his ideas were nothing more than chimeras relegated to the realm of fiction (9). In addition, it was also hypothesized that the pineal is an endocrine gland. In 1958, it was determined that the pineal gland secretes melatonin, which regulates the circadian rhythm in the studies of Lerner et al (1,10). The history of the pineal gland is long and its functions were only elucidated in the 20th century. In previous centuries the gland's functions were based on superstition and a misunderstanding of its anatomy. However, even with our better understanding of the gland, all of its functions have yet to be determined (11).

Embryology and histology

The PG is formed from the neuroectoderm of the posterior portion of the roof of the diencephalon. It is initially recognized in the caudal portion of the diencephalon as a structure called the pineal body. This pineal body is nothing more than an epithelial thickening in the midline at the level of the diencephalon that from the seventh week begins to undergo a process of invagination that will culminate in the formation of the solid organ (12).

Histologically the PG is mainly composed of two types of parenchymal cells. Pinealocytes and interstitial cells (13). Pinealocytes are organized in lobules formed by connective tissue. They are mainly characterized by the production of MLT, a hormone important for metabolic regulation processes, as well as for the control of the sleep-wake cycle (14). Interstitial cells constitute approximately 5% of the cell types in this gland, established as supporting cells in the tissue (15).

Morphological structure

The PG has been described as a small, odd, endocrine organ located in the roof of the midbrain, above the superior colliculi and behind the third ventricle (16). It is joined to the habenular and posterior commissures by means of the pineal stalk, whose body is bathed by cerebrospinal fluid and covered by pia mater, the pia mater in turn becomes a capsule that provides the gland with partitions that in turn allow its irrigation (17). The so-called pineal region, however, contains the gland in a wider space, defined by the corpus callosum and the choroid plexus of the third ventricle above, by the lamina quadrigemina and the cerebellum below, and laterally by the thalamus and the cerebral hemispheres (18).

The weight of the gland can vary between 100 to 200 mg, and measure between 5 to 8 mm long and 3 to 5 mm wide (12). Its innervation is given mainly by the superior cervical ganglion of the paravertebral chain, of sympathetic and parasympathetic type (12,13).

On the other hand, its irrigation, unlike others in the body, is considered of a high flow considering that it is a small endocrine organ, in addition to the fact that the blood vessels that integrate it lack a blood-brain barrier (13,16). In addition, a study by Macchi & Bruce identified that the PG reached a blood flow that equaled the neurohypophysis in rats and was exceeded only by the flow from the kidneys (12,13). Cellularly, it has been described that pinealocytes, so called the cells that compose the PG, are equivalent to those found in the retina, more specifically to retinal cones, lower order neurons and glial cells; therefore, it was mainly catalogued as a visual organ (12).

Neurological pathways and tracts

Anatomically, the structures that make up the central nervous system comprise a series of complex interconnected pathways for the fulfillment of various functions (15). The PG communicates via the suprachiasmatic nucleus (SCN) and the retinohypothalamic tract (RHT), such that afferent fibers coming from the RHT are mainly located in the ventrolateral region of the CNS, while efferents depart to the dorsolateral region (15).

The most studied afferent pathway is part of the visual pathway, starting in the ganglion cells of the retina, which are conducted through the optic nerve and optic chiasm until they reach the hypothalamus, however, it is independently of the perception of images (12,15).

On the other hand, the efferent fibers that cross the suprachiasmatic nucleus form the so-called multisynaptic pathway of the PG, whose route guides it to the hypothalamus, specifically its paraventricular nucleus, from there its axons depart to preganglionic neurons in the lateral intermediate column of the sympathetic type in the spinal cord between the T1 and T3 segments, and to the superior cervical ganglion where they activate noradrenergic neurons (18). The latter form the *nervus conarii*, whose fibers reach both sides of the tentorium and unite in the midline to finally enter the PG in its posterior portion, taking the name of pineal nerve (13,18). The parasympathetic innervation is provided by the sphenopalatine nerve and the otic ganglia. And for its part, the trigeminal ganglion through some of its branches also provides innervation to the gland (14).

Neuroendocrine component

The main hormonal molecule secreted by the PG is MLT, which is able to exert many endocrine functions at the CNS level and throughout the body physiology, so it is not considered a pure neural hormone (19). MLT is an endogenous indolamine, with circadian regulation given by the suprachiasmatic nucleus; characteristically, it is a lipophilic hormone, which confers it the ability to rapidly cross the blood-brain barrier and target cells of its action (20).

MLT is released into the bloodstream, following the endogenous circadian cycle given by the hypothalamus, through the light-dark cycle, i.e. it is produced during the night as long as it is dark, in addition to the sympathetic stimulation given by the adrenergic nerves that make up the hypothalamic retino pathway (18,21). Because melanopsin decomposition is stimulated during the day in the retinal ganglion cells, it uses the hypothalamic retinal pathway to carry its signal to the hypothalamus and thus inhibit its synthesis. It is synthesized from an essential amino acid, tryptophan, which is biotransformed by the action of four enzymes (20).

Initially, tryptophan through the action of the enzyme tryptophan hydroxylase, which adds a hydroxyl group to the 5-position of the indole ring to form 5-hydroxytryptophan (5-HTP). Subsequently, 5-hydroxytryptophan forms serotonin via an aromatic

amino acid decarboxylase. Now, before finally being MLT, serotonin is transformed by the enzyme serotonin N-acetyltransferase. And finally, MLT is formed from N-acetyl serotonin as substrate and obligatory step for its synthesis by means of the enzyme hydroxyindole-O-methyltransferase (20-22).

After its synthesis, MLT travels through the bloodstream bound to albumin, and upon reaching the liver it is metabolized to 6-hydroxymelatonin by cytochrome P450, mainly in its CYP1A2 isoform, and the latter is conjugated to 6-sulfamethoxymelatonin for its subsequent urinary excretion (21).

Regulation and functions of the pineal gland

It has been difficult to determine all the physiological functions of PG because its main product (MLT) has a complex regulation in vivo, being controlled by various stimuli inside and outside the individual. Therefore, experimental studies have not found a way to reproduce the exact pattern of natural MLT production (22-24), but we know that the main regulation comes from the suprachiasmatic nucleus, which is the circadian pacemaker (20,23,24).

MLT peaks depend on light exposure and season (due to changes in day length). MLT production increases in the dark phases of the day in almost all animals. Light exposure in the retina stimulates the suprachiasmatic nucleus which sends signals that decrease MLT production. This regulation gives the body representation of external environmental conditions (28-31).

Other factors involved in MLT production are adrenergic stimuli and inflammatory products. Another important source of control is known to be the release of noradrenaline (NE) by the sympathetic fibers of the cervical sympathetic ganglia that stimulate its secretion mainly at night (24,30,31,32,33). Extra-pineal MLT production is also under the control of several neurotransmitters (glutamate, acetylcholine, vasoactive intestinal peptide, substance P and pituitary adenylate cyclase-activating peptide), but to a lesser extent than NE (27,30). Inflammatory products can increase or decrease MLT production. Pathogen- and hazard-associated molecular patterns (PAMP and DAMP) modulate nocturnal MLT synthesis during inflammatory processes (27,33). In addition, several cytokines and signaling pathways such as IFN, LPS, beta-amyloid peptide, NFκB, JAK/STAT have been observed to have complex effects on MLT production (33).

MLT has a wide range of effects in the body and acts through two G-paired protein receptors (MT1, MT2) and another of the quinone reductase family: MT3 (27). It is involved in important and basic processes in mammalian life, such as the timing of seasonal physiology, reproduction and sleep **(Table 1).**

Table 1. Summary of pineal gland functions (21,24,31).

- Negative regulation of thyroid activity
- Hypothermic
- Sleep inducer
- Hypotensive by increasing norepinephrine levels, regulating cardiac beta receptors and increasing mesenteric arterial dilation capacity
- Immunoregulatory through the use of transcription factor NFκB and binding to κB receptors, regulating glucocorticoid and MLT synthesis rates
- Antioxidant by inducing the Nrf2-ARE signaling pathway and scavenging free radicals
- Oncostatic
- Thymic modulator
- Neuroprotector

Reproduction

PG has several effects on reproduction and sexual maturation due to its effects on the regulation of hormone release at the pituitary level. It determines gametogenesis, sexual maturation, pregnancy and menopause (35). It is considered to have paradoxical effects at the reproductive level as its effect depends on peaks of secretion and the season in which it occurs. However, it is not yet clear how the duration of MLT exposure in the *pars tuberalis* may affect TSH and GnRH release and its effects on peripheral tissues to regulate reproduction (22,24).

Sleep

Park et al investigated the relationship between pineal gland volume (PGV) and symptoms of REM sleep behavior disorder (RBD) in a cohort of previously healthy individuals. They followed the cohort for two years and administered the REM Behavioral Sleep Disorder Screening Questionnaire (RBDSQ) and measured VMP by magnetic resonance imaging (MRI). The results showed that individuals with symptoms or at risk for RBD had a smaller PGV (37). This finding is supported by other studies, just

as PG calcification and cysts are also known to trigger sleep disturbances (27). MLT deficits due to weight gain and obesity have deleterious effects on sleep, circadian rhythm, and neuroendocrine functions (30,37). In addition, it has been shown in several studies that MLT administration greatly improves sleep disorders (34,37,38).

MLT improves sleep through several mechanisms by acting on muscle tone, controlling GABAergic function and improving sleep efficiency (33).

Circadian rhythm

In mammals, PG adjusts organisms to respond to the needs of each season and choose the best time of the year for reproduction, hibernation, etc. as it translates environmental changes depending on changes in light during the day. MLT acts on clock neurons and clock genes to generate a circadian rhythm (33,34).

It appears that gestational MLT synchronizes maternal and fetal circadian clocks and also regulates the timing of offspring puberty, as it also determines fetal adrenal development (23,30). Nowadays the circadian rhythm can be altered due to exposure to nocturnal light. This alteration may even increase the likelihood of tumor growth as the protective effect of MLT is lost (23).

Mood

PGV is associated with mood disorders (39). There have been reports of abnormal MLT secretion and increased expression of stress hormones at night that alter sleep and, consequently, mood. It has a relationship not only with mood disorders, but also with other mental illnesses such as schizophrenia (26).

In depression, MLT has been used as a treatment because its levels decrease during the crisis and increase immediately after recovery (25).

Pregnancy

During pregnancy, MLT is responsible for synchronizing maternal and fetal physiology and guiding fetal development through MLT receptors in the fetal pituitary gland. In addition, the circadian rhythm of maternal control by light exposure and transmitted to the fetus as an MLT signal determines the future behavior of the offspring in terms of growth and sexual maturation (28). On the other hand, MLT levels in lactation show no relationship with offspring behavior and circadian regulation (23).

Temperature

The relationship between MLT and core body temperature is still a matter of debate. Some research shows a decrease in MLT during the rise in temperature in the ovulatory phase of the menstrual cycle and a higher peak MLT concentration during the luteal phase than during the follicular phase (35).

Endocrine control

In a case-control study, the PGV was compared with MRI techniques. It showed that healthy controls had a larger PGV in contrast to obese people. And that PGV was inversely related to body mass index (BMI). Decreased LTM has also been related to insulin resistance and the presence of type II diabetes mellitus (37).

Pain

MLT has an effect on pain control through its effects on sleep, and control over neurotransmitters such as GABA and dopamine. It can decrease cyclic AMP production and activates the opioid receptor directly or indirectly. In addition, in animal models, a decrease in NMDA-induced currents in spinal cord gelatinous neurons has been observed (38).

Oxidative Stress

MLT protects the cell through its direct and indirect antioxidant and anti-inflammatory effects, as it is a neutralizer of oxygen free radicals, as well as regulating the activation of second messengers that activate pro-inflammatory pathways such as cAMP and cGMP. It has been shown that it can control transcription factors related to the retinoic acid receptor (ROR) (27,30). It has also been shown to have protective effects on X-ray exposure (24).

Neurogenesis

MLT also plays a neuroprotective role in many central nervous system disorders, especially in dementias. MLT is thought to exert anti-neurodegenerative properties through ROR receptors (30) and the disappearance of MLT receptors leads to neuropsychiatric disorders in the elderly (25).

In Alzheimer's disease (AD) it has been identified that MLT production is impaired and leads to

impaired neurogenesis due to reduced expression of brain-derived neurotrophic factor and glial cell-derived neurotrophic factor. MLT stimulates neural stem cell replication in the midbrain and hippocampus, depending on day length (27).

Other functions

The effects of MLT are not only central. In the gastrointestinal tract, MLT has protective effects on the gastric mucosa. In addition, it has regulatory effects on the immune response that controls leukocyte migration, inhibits the activation of inflammatory signaling, and regulates the proliferation and activation of immunocompetent cells (24). It also has regenerative effects on corneal lesions and regulation of intracranial pressure (24).

There is evidence that reduced levels of MLT contribute to cognitive impairment in AD patients. This not only affects cognition but also sleep and circadian rhythm (27). In addition, MLT appears to be involved in the pathogenesis of AD, as it is implicated in the inhibition of tau phosphorylation, attenuated levels of beta-amyloid protein precursor production and its deposition in the CNS (27).

Melatonin could be considered a cardioprotective agent, it is associated with a reduction of iatrogenic lipoproteins (40). In a murine model, hypercholesterolemia was induced in rats by a diet rich in lipids and carbohydrates, melatonin was administered orally at a dose of 10 mg/kg/day, presenting in the lipid profiles measured. Subsequently, these profiles were characteristically antiatherogenic: total cholesterol, very low-density lipoprotein (VLDL) and low density lipoprotein (LDL) concentrations decreased, while high density lipoprotein (HDL) cholesterol concentrations increased (41). Another product of PG (and other peripheral tissues), N-dimethyltryptamine, is responsible for perception, consciousness, vision, imagination and dreams, and has potential therapeutic targets for depression, anxiety and psychosis (24).

Future perspectives include the need to investigate whether there are chronic changes in the physiology of the pineal gland due to the new disease called COVID-19, specifically due to the neurotropism of SARS-Cov-2 and neuroinflammatory mechanisms caused by this virus (42-45). In addition, the development of robotic neurosurgery and other emerging techniques such as neurogenomics and neuroimaging genetics should also be encouraged in order to better understand the pathophysiology of pineal gland-associated diseases (46,47).

Conclusions

The pineal gland is an endocrine organ that fulfills multiple functions in the physiology of the body, so it is very important to understand and study it. Its main product is the hormone melatonin, in future research this hormone could play a major role in the therapy of multiple neurodegenerative pathologies, such as Alzheimer's disease, schizophrenia and major depressive state, as well as protector of heart and cerebrovascular diseases.

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Aneurysmal subarachnoid haemorrhage in the context of a patient with traumatic brain injury

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ABSTRACT

Introduction: Traumatic brain injury is a major public health problem worldwide, with higher incidence rates in low- and middle-income countries. In this context, the development of major complications has been evidenced, such as the formation of haemorrhages due to traumatic rupture of a cerebral aneurysm, which may threaten the patient's life and therefore require immediate medical and neurosurgical procedures.

Case: We present the case of a male patient in the fourth decade of life, who presented a closed head trauma with the consequent development of subarachnoid haemorrhage in the territory of the right middle cerebral artery secondary to traumatic aneurysmal rupture

Conclusion: One of the complications that can occur in the context of head trauma is the development of subarachnoid haemorrhage due to traumatic aneurysmal rupture. Despite therapeutic options, these scenarios continue to be a challenge in low- and middle-income countries due to the lack of specialized tools in neurosurgical and neurorehabilitation areas.

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INTRODUCTION

Traumatic brain injury (TBI) is a major public health problem worldwide [1], representing a significant cause of disability and mortality in the population of all ages along with a great socioeconomic impact, its main causes being falls and traffic accidents [2,3]. Globally, it is estimated that

between 60 and 70 million new cases of TBI occur each year, with high incidence rates that varies considerably between different parts of the world and have been increasing especially in low- and middle-income countries [4,5]. It has also been shown that a large number of these cases will develop complications that can threaten the patient's life and therefore require immediate medical and neurosurgical procedures [6]. Among these complications is an increased risk of rupture of pre-existing cerebral aneurysms with the consequent formation of hemorrhages, due to the altered hemodynamics of cerebral blood flow in the context of neurotrauma [7].

The aim of this manuscript is to present a case of traumatic subarachnoid hemorrhage secondary to silent aneurysmal rupture and discuss aspects related to the limitations in the diagnosis and approach in low- and middle-income countries such as Colombia.

Case description

A 34-year-old male patient was admitted to the emergency department of a low-level hospital presenting closed head trauma secondary to a traffic accident as a motorcyclist, with scalp injury, headache, loss of consciousness, without convulsions, nausea or vomiting, muscle weakness, loss of sensation or visual disturbances. No personal or family medical pathological history.

On physical examination on admission, the patient had a blood pressure of 100/70 mmHg, heart rate of 93 beats per minute, respiratory rate of 21 breaths per minute, oxygen saturation of 98% while breathing ambient oxygen, weight of 85 kilograms and height of 1.82 meters. In addition, he presented alcoholic breath. On neurological examination there was evidence of temporal and spatial disorientation, ocular opening when called, Glasgow scale of 13, normal pupillary response, fundus without papilledema, normal venous and arterial pulses, normoreflexia, no muscle weakness and preserved sensation. Initial paraclinical tests showed hemoglobin within normal limits.

He did not present neurological deterioration, however, due to a history of alcohol consumption, a simple cerebral computed tomography was requested, which showed subarachnoid hemorrhage in the right middle cerebral artery territory in segment M2, with the presence of blood in the interhemispheric cistern and in the perimesencephalic cisterns with intraparenchymal hematoma in the sylvian valley **(Figure 1)**. Due to the location of bleeding, aneurysmal hemorrhage is suspected. It was decided to refer to the neurosurgery department, who indicated cerebral angiography with endovascular management of aneurysm, where a ruptured aneurysm of M2 segment of 6 mm in diameter was found **(Figure 2)**. It is managed endovascularly with coils, no flow-diversifying stents were placed.

During his stay in the ICU, the patient showed no neurological deterioration, no evidence of rebleeding or vasospasm; however, he presented cough, deterioration of the ventilatory pattern with bilateral pulmonary rales and fever with a temperature of 39°C. Antibiotic management with ampicillin/sulbactam 3 grams intravenously every 8 hours is indicated. She presented positive RT-PCR for SARS-CoV-2. Patient died 3 days later due to COVID-19 pneumonia.

Figure 1. Computed axial tomography of the brain without contrast 2 hours after trauma.

Discussion

TBI is a major cause of morbidity and mortality worldwide [1]. Incidence rates vary significantly in different parts of the world, with a greater burden in low- and middle-income countries [2,4]. Likewise, the highest incidence occurs in adolescents and young

adults and in the population over 65 years of age, with the most frequent responsible events being traffic accidents and falls, respectively [3].

Figure 2. Angiography showing right middle cerebral artery aneurysm. A: Before endovascular management. B: Aneurysm with total occlusion (100%).

Most of the patients with TBI will develop serious complications that demand immediate medical and surgical measures in order to safeguard the patient's life [6]. Traumatic aneurysmal rupture is one of the complications to be taken into account since trauma can cause various cerebrovascular damages that can affect the integrity of a pre-existing cerebral aneurysm, leading to subsequent hemorrhage formation [7].

Aneurysmal subarachnoid hemorrhage, as described in our case, represents a serious and complex phenomenon in which there is extravasation of blood into the subarachnoid space as a consequence of an aneurysm rupture [8]. In this context, it is extremely important to provide an adequate and timely multidisciplinary approach in order to achieve satisfactory results [9].

Considering the above, early management, during the first 24 hours, of aneurysmal subarachnoid hemorrhage, will be directly related to a better prognosis, reduction of neurological involvement, and possible complications associated with this medical emergency, such as rebleeding, cerebral vasospasm, arrhythmias, pulmonary edema, among many others [10,11].

The initial approach to patient management should consist first of support and monitoring of vital signs, assessing the need for airway intervention to protect oxygen saturation [12] and then establishing the appropriate treatment to stop bleeding, through two options, either by placing clips at the neck of the aneurysm in a craniotomy or through endovascular treatment consisting of embolization of the lesion by means of platinum coils, as in our case [11].

Clipping surgery is indicated in patients with large intraparenchymal hematomas, middle cerebral artery aneurysms, wide neck aneurysms, and in patients who are unlikely to comply with long-term follow-up [13]. While endovascular treatment is preferred in patients older than 70 years, in severe aneurysmal subarachnoid hemorrhages and basilar artery aneurysms [14].

In order to establish the differences between endovascular treatment and clipping surgery, several studies have shown a lower percentage of mortality and disability at one-year follow-up in those patients managed with endovascular therapy compared to clipping surgery [15], while on the other hand, the latter has shown a slightly lower rebleeding rate. Because of this evidence, both procedures are considered valid and the choice of one or the other goes hand in hand with the individualization of each patient [16].

However, it should be noted that, although low- and middle-income countries, especially in Latin America, have the highest mortality and disability figures associated with trauma, it is in these countries where neurosurgical interventions, as well as scientific studies and advances in the areas of neurology and neurorehabilitation, continue to be a challenge for the future [17].

The prognosis of a patient suffering an aneurysmal subarachnoid hemorrhage depends on multiple factors such as the patient's comorbidities, age, bleeding volume, early management, and above all the state of consciousness, in fact 15-25% of patients are left with neurological sequelae [9]. The rehabilitation process is very dynamic, motor and psychomotor recovery often occurs after the first six months, but verbal memory and other cognitive aspects may require much more time, even after the first year [18]. According to the Pan American Health Organization, only 3% of people with neurological disabilities in Latin America have access to neurorehabilitation services, as a consequence of a significant lack of resources due to underfunding and poor infrastructure of the health systems in these countries [19,20].

Thus, based on this problem, it is of vital importance to establish support and funding strategies that allow the advancement of neuroeducation and neurorehabilitation in low- and

middle-income countries, in order to maintain and rehabilitate the patient's functionality and thereby reduce the high percentages of disability caused by neurotrauma [19,21,22]. As an example, it would be of great importance the implementation of robotic neurosurgery in these countries, being an innovative tool that has allowed a great advance in developed countries in the context of diagnostic and therapeutic approaches, providing great satisfactory neurosurgical results along with the consequent reduction of patients with disabilities due to greater ease in the course of neurorehabilitation [17].

Conclusions

Aneurysmal subarachnoid hemorrhage is one of the complications that can occur after traumatic brain injury. This entity leads to a rather late recovery process of psychomotor and cognitive abilities of patients, so early diagnosis and management are the fundamental basis for achieving more satisfactory results. However, despite the different therapeutic options currently available, high morbidity and mortality rates continue to occur, especially in low- and middle-income countries, as a consequence of deficits in access to adequate neurosurgical and neurorehabilitation tools.

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Multimodal neurological monitoring in neurotrauma. Theoretical considerations for a practical approach

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ABSTRACT

Multimodal neuromonitoring is used as an adjunct to clinical neurological examination, imaging and other diagnostic studies to obtain the most detailed information about the physiology of the brain. Neuromonitoring has been a standard of care for patients presenting with traumatic brain injury in most critical care centres for the past several years. Neuromonitoring is composed of multiple variables, which not only provides a better dynamic of the pathophysiology of the compromised brain but also how it might respond to the corresponding management procedures. Although the clinical neurological examination is the standard for monitoring the neurocritical patient, the results obtained in the latter may be insufficient or inconclusive to detect or prevent secondary brain injury. Therefore, multiple neuromonitoring tools have been developed to measure different physiological variables that can contribute to a better follow-up of patients with traumatic brain injury. These variables include cerebral blood flow, cerebral electrical activity, cerebral

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metabolism, cerebral oxygenation and cerebral pressure. Thanks to monitoring as an adjuvant in critical care, it has been possible to avoid, identify and manage secondary brain injuries that commonly aggravate patients. This review aims to illustrate the main advantages and most recent recommendations regarding neuromonitoring based on the most current evidence.

Introduction

The objective of patient management is the identification, prevention and treatment of secondary brain injuries that may aggravate the patient's outcome. Understanding the mechanisms of brain injury and its pathophysiology are necessary for an adequate and patient-oriented treatment. As the primary damage, which represents direct mechanical damage, cannot be influenced therapeutically, the goal of treatment is the limitation of secondary damage (delayed non-mechanical damage). It is influenced by changes in cerebral blood flow (hypo- and hyperperfusion), impaired cerebrovascular autoregulation, cerebral metabolic dysfunction and inadequate cerebral oxygenation. At this case, the neuromonitoring multimodal is useful to observe the alterations [1]. In this manuscript we describe the different tools used for multimodal neuromonitoring in traumatic brain injuries patients such as clinical examination, intracranial pressure, autoregulatory reserve, cerebral oxygenation, cerebral blood flow, cerebral microdialysis and electroencephalogram. ICP measurement, clinical neurological examination along with computed tomography have been the main methods for monitoring TBI patients [2]. Clinical examination is a key point of multimodal neuromonitoring; but despite its accuracy it can often be confounded by intravenous sedation or concomitant metabolic disturbances in the patient. In isolation, the clinical examination may be non-specific and deterioration occurs because of late manifestations of secondary brain injury that could have been avoided with a more complete management of the patient through all the tools that neuromonitoring provides [3]. This review aims to illustrate the main advantages and most recent recommendations regarding neuromonitoring based on the most current evidence.

Methods

A bibliographic search was carried out in the databases PubMed and Science Direct and in the Google Scholar search engine using the following terms: Intracranial pressure; Critical care, cranioencephalic trauma, multimodal monitoring, articles in English language were included, emphasizing the benefits obtained by performing neuromonitoring by means of the most determinant neurological variables that allow an adequate and complete analysis of brain functionality. The date of publication was not taken into account. A total of 245 articles were identified, including original articles, subject reviews, systematic reviews, letters to the editor, case reports and case series. 42 articles were selected that matched the goal of the article.

Results

Neurological assessment

Of all the modalities of neuromonitoring, the clinical examination of an awake and cooperative patient offers the most comprehensive assessment of the central nervous system (CNS) function. Despite the advances in neuroimaging and other diagnostic tools, the clinical examination performed by a trained staff is still the "Gold Standard" for the assessment of patients with TBI. This evaluation should include the examination of CNS structures at risk in a given patient and a general description such as the documentation of the level of consciousness, for example, through the Glasgow coma scale, motor responses to verbal stimuli and / or painful and the evaluation of brain stem reflexes [2].

Despite being a fundamental component in neuromonitoring, the neurological examination has limitations that may diminish its effectiveness: 1) Patients in the ICU frequently present with an altered state or with diseases that substantially limit the information obtained clinically [2]; 2) Neurological evaluations are often done at different times by different examiners resulting in different findings and relevant changes can go unnoticed; 3) the findings of the neurological examination are influenced by therapeutic interventions frequently done in the ICU such as endotracheal intubation, use of hypnotics / sedatives, analgesics or neuromuscular blockers, among others [3]; Therefore, clinical examination is insufficient to fully evaluate TBI patients and additional test is needed [4].

Multimodal monitoring

Multimodal neuromonitoring (MNM) is used as a

complement to clinical neurological evaluation, diagnostic imaging, among other diagnostic methods to obtain the most complete documentation of the brain physiological, particularly of changes [5]. MNM integrates several variables, not only providing a better overview of the physiopathology of the injured brain 'but also how it responds to interventions. Due to the vulnerability of neurocritical patients to suffer silent cerebral infarctions, MNM may timely diagnose deterioration and guiding the clinician to intervene before irreversible injuries take place. This is done by direct tissue monitoring, inserting probes into the cerebral parenchymal tissue through a trephine orifice and fixed by a cranial pin system. Although the ideal location of the probe is not available, it is considered essential for the interpretation of the data and it is suggested to monitor brain tissue with a higher risk of secondary injury [3,6].

The MNM integrates many devices such as intracranial pressure (ICP), cerebral oxygenation, cerebral blood flow, autoregulatory reserve, brain electrophysiology, cerebral oxygenation, cerebral microdialysis and electroencephalogram, and will be detailed below (Table 1).

Table 1. Procedures and variables of major importance in the neuromonitoring of patient with acute brain injury [1-7].

Technique	Advantages	Disadvantages
Intracranial pressure ventricular catheter	Gold Standard.	Technically difficult placement.
	Measures global pressure.	
	Therapeutic drainage of cerebrospinal fluid.	Risk of hemorrhage.
	In vivo calibration.	Risk of infection.
Microsensor	Intraparenchymatous subdural placement.	No in vivo calibration possible.
	Easy to place with low procedural complication rate.	Measures localized pressure.
	Low risk of infection.	Regular monitoring
Transcranial Doppler	Non-invasive real time with good temporal resolution.	Measures relative rather than absolute cerebral blood flow (FSC).
		Operator dependent.
		Failure rate of 5 to 10% (absence of acoustic window).
Jugular venous oximetry	Evaluates the balance between oxygen supply (blood flow) and demand (metabolism).	Global and insensitive to regional changes.
	Easy to perform.	Risk of venous thrombosis, hematoma, carotid puncture.
PO 2 of brain tissue	The bedside gold standard for cerebral oxygenation monitoring.	Invasive
	Assesses the balance between oxygen supply (FSC) and demand (metabolism).	Measures regional oxygen tension, so usefulness depends on the location of the probe.
	Continuum.	
Near infrared spectroscopy	Non-invasive real-time real-time of regional cerebral oxygenation in multiple regions of interest.	Depends on manufacturer's algorithms.
		Signals affected by extracerebral tissue.
Microdialysis	Measurement of local brain tissue biochemistry.	Focal measurement.
	Early detection of hypoxic / ischemic injury.	Uncertain anomaly thresholds.
Electro-encephalography	No invasive.	Expert interpretation required.
	At real time.	
	Correlates with ischemic and metabolic changes.	Affected by anesthetic/sedative agents.
	Non-convulsive seizure / status epilepticus evaluation.	

Intracranial pressure

Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) are the most commonly measured physiological brain parameters measured in the neurocritical care unit, and used in many treatment algorithms [7]. There is a large experience with ICP monitoring in TBI patients, aneurysmal subarachnoid hemorrhage, ischemic stroke and intracerebral hemorrhage in neurocritical care [1]. Normal ICP is 7-15mmHg in adults in the supine position, varying according to age, body position and clinical condition [2]. The term "intracranial hypertension" depends on the pathology, but levels above 15mmHg are considered abnormal [7]. An

increase in brain volume activates the regulatory mechanisms, but an alteration of these produces an elevation of the ICP, that is to say an increase of any component of the cranial vault demands a compensatory reduction of another to preserve a normal pressure [8]. The cerebrospinal fluid (CSF) is fundamental for the compensatory space mechanism because it can be distributed to the spinal cord reservoir [9].

ICP monitoring methods

ICP Monitoring provides information on the state of cerebral self-regulation and is essential for the treatment of severe TBI. ICP may be measured by parenchymal microtransducers or intraventricular catheters, the later considered the "Gold Standard" for ICP monitoring [9,10]. In addition, subarachnoid and epidural devices are also used, but they are less precise [2].

Intraventricular catheters are inserted into the lateral ventricles, and connected by fluid-filled tubing system to a pressure transducer [8,11]. This method allows to measure the global ICP and allows medication administration and therapeutic drainage of CSF. Risks associated with IV catheters are hemorrhages [12] and ventriculitis, often managed by exchanging to catheters impregnated with antibiotic [13]. Monitoring with intraparenchymal microtransducers the same precision as intraventricular catheters, lower infection rates, lower risk of hemorrhage, and can be easily placed providing continuous monitoring of the ICP. However, it is limited by its inability to be recalibrated [9]. Similar to clinical neuro examination, ICP monitorization alone is not sufficient to diagnose all relevant physiological brain derangements generated by the brain injury [14].

Other noninvasive ICP monitoring techniques have been proposed as alternatives to direct ICP measurement including transcranial Doppler, EEG, pupillometry and ultrasound measurement of the diameter of the optic nerve sheath (DONS) [15]. DONS is an ophthalmological technique used to measure ICP, because the optic nerve sheath is adjacent to the dura of the brain and contains CSF that communicates with the cerebral subarachnoid components, so it can be useful as a means to detect indirectly the increase in the CIP. The pupilometer measures ICP indirectly by quantitatively evaluating pupillary reflex. There is no evidence that non-invasive measures of the ICP has the same clinical utility as direct invasive monitors [15].

Cerebral perfusion pressure

CPP is a surrogate measurement of cerebral blood flow. CPP is the difference between mean arterial blood pressure and ICP measured by invasive methods [2,16]. When cerebral autoregulation is normal, any increase in CPP causes compensatory vasoconstriction, reducing cerebral blood volume and ICP [1]. However, when autoregulation is lost, elevated CPP (higher than 120mmHg) can cause an increase in brain flow causing cerebral hyperemia, edema and hypertensive encephalopathy [2]. Monitoring both the ICP and CPP is frequently done in patients with TBI, subarachnoid hemorrhage and intracranial hypertension [17].

Vascular self-regulation

Vascular self-regulation is a fundamental brain protective mechanism from variations in cerebral blood flow, CSF and blood pressure after TBI. This is evaluated using the index of reactivity to pressure (PRx) which is the coefficient between the mean arterial pressure (MAP) and the ICP. A negative PRx indicates a preservation of self-regulation. On the other hand, when there is an increase in the volume of the cerebral vascular compartment, the ICP is increased and we are talking about a positive PRx, this indicates a deterioration of the self-regulation [18]. Reactivity to cerebrovascular pressure is defined as the ability of vascular smooth muscle to respond to changes in transmural pressure and is determined by observing the response of ICP to changes in blood pressure [19]. This index allows us to calculate the cerebrovascular reactivity and give value to the cerebral autoregulatory reserves [9,20]. In addition, cerebrovascular reactivity can be evaluated with the oxygen reactivity index which is the mobile correlation between tissue oxygen pressure (PtiO2) and PPC. PRx is considered a global measure of self-regulatory status, while ORx represents regional self-regulation due to the focal nature of PtiO2 [13,20].

Cerebral blood flow

Maintaining adequate cerebral blood flow (CBF) is fundamental therapeutic target and is quantified by neuroimaging modalities including ultrasonography,

CT scan, positron emission tomography, and MRI [9]. The advantage of these techniques is their good spatial resolution. Limitation includes the need to transport the critically ill patient to the radiology department and are not continuous, providing information at a single point in time [21]. The ideal neuromonitoring demands continuous measurements that can be done at the bedside [3,11].

Continuous "real-time" CBF monitoring is relatively new in neurocritical care and the technology is still being developed and refined. However, another modality, transcranial Doppler (TCD) has been used to evaluate focal regions of the brain with thermal diffusion flowmetry [9].

Transcranial Doppler measures non-invasively the speed of blood flow by emitting and receiving high frequency energy in the form of waves. The change in frequency reflects the speed and direction of cerebral circulation [22]. It can be done at bedside but is limited for being operator dependent [9].

Fluxometry by thermal diffusion allows the measurement, through a catheter inserted in the white matter, of the local cerebral blood flow. The catheter consists of 2 thermistors. One measures brain temperature and the other rises slightly at a temperature higher than the first [3,18]. The energy required to maintain the temperature difference between the two thermistors is proportional to the conductive properties of heat of the white matter [23], which remain constant as long as the catheter is correctly positioned and does not move, and the convective cooling of the cerebral blood flow, which is reported in conventional units of ml/100 g/min [3].

Cerebral microdialysis: metabolic monitoring in real time

The cerebral microdialysis is a technique that consists of extracting and quantifying the substances of the cerebral interstitial space. It is a laboratory tool introduced in the 90s and its clinical use approved in Europe in 1995 and in the United States in 2002 [3]. The physiological premise to obtain tissue metabolites lies in the assumption that it is essential to know when the transition from an aerobic to an anaerobic metabolism occurs which results in an energy failure [24].

In practice, microdialysis focuses on markers of cerebral energy metabolism (glucose, lactate and pyruvate), neurotransmitters (glutamate) and cell damage markers (glycerol). Measurements of glucose, pyruvate and lactate provide information on the relative contributions of aerobic and anaerobic metabolism to bioenergetics [25]. As for glycerol, it is a lipid component of neurons and its elevation is commonly associated with death / irreversible cellular ischemia. The increase in glutamate concentrations has been associated with hypoxia, ischemia and reduced brain tissue oxygenation (PbtO2) or CPP [1,26].

Electroencephalography

Several studies have shown that seizures are relatively common in patients with severe TBI., and are frequently non-convulsive, which may go unrecognized. Prophylactic anti-seizure medication is indicated to all patients with severe TBI [27].

Seizure identification after TBI has important implications for the management and prognosis of the patient [11]. The electroencephalogram has long been used to study electrical activity of the brain and diagnose seizures [16].

Continuous electroencephalography (cEEG) is instrumental in diagnosing seizures [28]. Late detection and treatment result in a significant decrease in the efficacy of anticonvulsant drugs. Unrecognized seizures, particularly if prolonged (status epilepticus), may raise intracranial pressure, metabolic demand, excitotoxicity and worsen primary brain injury [29]. There are limitations for the use of cEEG in the ICU. These include: 1) The availability of trained personnel to place the electrodes, 2) artifacts, and 3) The lack of trained professionals able to interpret the EEG in a timely manner. Additionally, there is an inherent degree of variability between the different interpretations [30]. The invasive cEEG is also available to identify crises that are not visible using scalp electrodes. The use of this modality can provide greater sensitivity to detect crises and improve the signal-to-noise ratio when compared to surface electrical activity [31].

Measuring cerebral oxygenation

Oxygenation is vital to cellular homeostasis and neuronal integrity, and can be used as a marker for tissues at risk of secondary injury. Brain tissue oxygen (PbtO2) and jugular venous oxygen saturation (SjvO2) allow continuous real-time evaluation of cerebral oxygenation [32].

PbtO2 provides information on 2 contexts: 1) it can evaluate oxygenation when there are normal values of PPC, and 2) it can diagnose cerebral hypoxia secondary to low perfusion when the PPC is within normal limits.

The jugular venous oxygen saturation provides information on global cerebral oxygen. The catheter is placed in the dominant internal jugular vein and advanced to the upper part of the jugular bulb [33,34]. Normal values range between 55 and 75%. Lower values indicate increased oxygen extraction and risk of ischemia. The compensatory mechanisms for poor oxygen supply or an increase in demand is increased oxygen extraction [31]. In decompensated states, ischemia may occur while high SjvO2 indicates hyperemia, decreased metabolic demand or even cell death [3,35]. It is necessary to carry out a greater number of prospective multicenter studies, especially in low- and middle-income countries where there are still not enough specialized centers and high-quality mass training in neurological and neurosurgical monitoring, in order to improve the management of patients with neurotrauma and reduce the burden of neurological diseases [36-40]. In the same way, involve students and residents from early stages of their process, so that they are related to this type of recent techniques [41,42].

Conclusions

MNM integrates different equipments and measures that allow real-time monitoring of brain and identification of pathophysiological changes that occur after TBI. MNM allows early detection and compression of physiological changes caused by the injury, which will facilitate the determination of proper management of the neurocritical patient.

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Tumefactive multiple sclerosis. A rare but serious variable in multiple sclerosis

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ABSTRACT

Tumefactive multiple sclerosis is a rare variant of multiple sclerosis, characterized by the presence of brain lesions that may be solitary or multiple. Considering that these lesions have a pseudotumoral appearance, it is a challenge to differentiate them from central nervous system neoplasms through neuroimaging. Many cases are associated with the administration of monoclonal antibodies, and due to an increase in the incidence of cancer globally, it is expected that secondary to chemotherapeutic treatments, more and more cases may appear. Taking into account the above, the objective of this review is to review aspects of usefulness in clinical practice, on the diagnosis and approach of this pathological condition

Introduction

Tumefactive multiple sclerosis (TMS) is a rare variant of multiple sclerosis (MS) characterized by the presence of brain lesions that may be solitary or multiple with a diameter greater than or equal to 2 cm (1-5) These lesions are observed with a pseudotumoral appearance (6), larger than the typical MS plaques mimicking an intracranial neoplasm, infection or a non-demyelinating brain pathology (7). TMS accounts for approximately 2.8-7% of all MS cases (1,7). Magnetic resonance imaging (MRI) shows ring enhancement (4,5) and perifocal edema (2,3,5), in addition, the presence of decreased cerebral blood volume (3), hypervascularity, increased vascular permeability and mass effect, make it difficult to make a differential diagnosis with abscesses and brain tumors (2, 8). The brain lesions present in this entity are known as "tumefactive demyelinating lesions (TDL) (9), which are best described in MS (10) and are mainly located in the cerebral white matter, specifically in the frontal and parietal lobe, but can appear in any part of the central nervous system (CNS). Rare tumefactive variants of MS are Schilder's disease, acute Marburg MS and concentric Balo sclerosis (9).

TDLs in MS when presented as solitary lesions complicate the diagnosis due to their similarity to intracranial neoplasms, leading to misdiagnosis and therefore unnecessary intervention and treatments that put the patient's health at risk (5,10). To avoid misdiagnosis, better imaging techniques such as diffusion-weighted imaging (DWI), magnetic resonance spectroscopy (MRS), fluorodeoxyglucose positron emission tomography (FDGPET) (10), CSF examination (8) and brain biopsy have been sought, the latter being the one that establishes definitive diagnosis (10).

Epidemiology

The prevalence of TME is approximately 1 to 2 per 1000 cases diagnosed with MS (9-12) and a prevalence of tumor-type TDLs of 3 cases per 1,000,000 inhabitants, with the female sex being the most affected. The presentation of MS at older ages is rare with approximately 0.6-0.75 of cases diagnosed after the sixth decade of life, increasing the difficulty in distinguishing TDLs from brain tumors (11).

TDLs occur more frequently in Asian countries with an incidence between 6.3-11.76%, probably due to ethnic differences with heterogeneous immunological backgrounds (10). Kuan et al. in 2013 conducted a study in Taiwan with 190 patients with MS diagnoses between the years 1985 and 2010, of which 12 were confirmed with TMS, representing approximately 6.3% of MS patients, but this percentage does not represent the prevalence of the country because only patients who from a single medical center in Tapei City were included (13).

Aetiology

The causes that generate the appearance of TDL are not yet elucidated. However, a relationship has been found between the immature isoform of myelin basic protein (MBP) and the occurrence of extensive atypical demyelinating lesions in acute Marburg MS and probably the role of this protein in the development of TDL. Several isoforms may be involved in normal functioning and exposed to the process of protein degradation, leading to an increased likelihood of recurrence of TDLs (10).

Localization

TDLs occur most frequently in the cerebral hemispheres (especially in the frontal and parietal lobe) (5), but can be observed in different components of the CNS, such as segments of the cervical spine and the cervical spine (3). Kuan et al. reported that 80% of the lesions were found at the supratentorial level, mainly in the periventricular and juxtacortical area and 40% in the spinal cord (13,14).

Clinical manifestations

The clinical presentation of patients with TME can be polysymptomatic when the lesions are large and multiple (9). The symptoms originated by TDL can have an acute or subacute presentation (3) which depends on the location, size of the lesion and its mass effect (6,9). The clinical manifestations of TMS include headache, cognitive abnormalities, mental confusion, seizures, apraxia, aphasia (1,3,4), increased intracranial pressure, vomiting, behavioral disturbances, visual disturbances, optic neuritis and hemiparesis (3,15,16). TDL often causes memory dysfunction, Gerstmann's syndrome and in some patients, encephalopathies are observed (9). Visual and somatosensory potentials with abnormalities can be observed in 33-60% of cases diagnosed with TMS (1).

Generally, the signs and symptoms are not

associated with MS, which means that this entity is not considered in the differential diagnoses and a neoplasm or infection is suspected. However, even if there is a pre-existing diagnosis of MS, the probability of presenting a neoplasm or non-myelinating pathology is not ruled out, which leads to suggest a biopsy to diagnose the pathology (11,17,18).

Diagnosis

Histologically, TDLs show similarity to neoplasms by hypercellularity, gliosis, atypical reactive astrocytes, mitosis, permeabilized lymphocytes (6,11) necrosis, cystic changes (11) and Creutzfeldt cells (9). In addition, abundant foamy macrophages containing myelin debris and relative axonal preservation are observed (11,18,19).

Although the biopsy allows a definitive diagnosis to be made, it has been reported that the trauma produced by the intervention for taking the sample generates neurological deficit and even death (11). However, in patients with uncertain diagnosis and who present a complex clinical picture, a biopsy is justified in order to generate a definitive diagnosis. Misdiagnosis of TDL is estimated to be approximately 31% (9), leading to unnecessary interventions and treatment. It is important to distinguish LDT from a neoplasm in order not to expose the brain to inadvertent irradiation that aggravates TMS (11).

Hamed, in the published case report of a patient with TMS made the diagnosis based on: acute onset of the condition, cognitive impairment, multiple bilateral lesions on imaging studies, absence of cortical involvement, absence of mass effect, gadolinium enhancement, regression with corticosteroid, and lack of MRI evidence of new lesions on follow-up (1,18,19).

Differential diagnosis

The diagnosis of TDL in MS is a challenge due to its similarity with neoplasms, abscesses, acquired demyelinating disorders and vascular lesions (3). In order to achieve an adequate differentiation, imaging techniques have been used to avoid unnecessary biopsies that affect the patient's condition. MRS is a non-invasive imaging method that is useful for understanding biochemical alterations in various intracranial pathologies and according to studies is an important tool for the differential diagnosis of TMS with brain tumors. MRS focuses on the metabolites N-acetyl aspartate (NAA), choline, creatine, Lp and Lac; finding that when there is neuronal and axonal loss and impaired mitochondrial function, NAA levels are low. The detection of elevated levels of choline, Lp and Lac are related to myelin degradation or cell renewal processes. Kobayashi et al. found that in 2 of the 3 cases diagnosed with TMS, decreased NAA was observed and all 3 cases had in common that choline/creatine ratios were elevated in the peripheral areas associated with myelin degradation (2).

It is important to take into account that gliomas can develop in patients with MS, which makes it impossible to determine that the lesions that appear in this pathology are LDT without performing studies that support the diagnosis, because TMS can coexist with gliomas, which generates difficulties in making a differential diagnosis (9). Butteriss et al. in a study diagnosed TMS patients by using preoperative MRI, who after surgery were found to be oligodendroglioma (8). A positive response to steroids (6) and the reduction of the size of the lesions in serial neuroimaging allows distinguishing the demyelinating nature of a tumefactive lesion from an abscess or neoplasm (3). However, challenges have been reported in diagnosing TMS by MRS and PET, without biopsy and careful follow-up by serial MRI with or without steroid treatment is usually sufficient to establish a diagnosis (8,20,21).

On the other hand, although CSF analysis has not shown statistical significance as a support for the diagnosis of TMS, it has been observed that the presence of oligoclonal bands and elevated immunoglobulin G has allowed determining demyelinating processes (9,20,21).

Tumefactive variants of multiple sclerosis

Among the rare tumefactive variants of MS we find: Acute Marburg MS, Schilder's disease and concentric balloon sclerosis. Acute Marburg multiple sclerosis was described in 1906 by Otto Marburg as an idiopathic inflammatory demyelinating disease of the CNS characterized by large lesions of the CNS. Histologically, macrophage infiltration, generalized demyelination, axonal loss and areas of necrosis are observed. Mutations have been observed in MBP leading to structural instability of myelin (9). It is a pathology caused by severe axonal loss that leads to

rapid disability and can lead to death of the patient (1). Myelinoclastic sclerosis, also called Schilder's disease, was introduced in 1912 as a demyelinating disease with large lesions. However, this entity has not yet been fully elucidated and in some cases the term is used to refer to X-linked adrenoleukodystrophy. Finally, concentric Baló disease is an entity characterized by a pattern of concentric layers formed by damaged myelin tissue (1) and is known as an entity that presents rings of demyelination corresponding to areas of T2 hyperintensity on MRI alternating with rings of normal myelination or partial remyelination corresponding to areas of T2 isointensity. These lesions can be located in the basal ganglia, cerebellum and in some cases spinal cord and optic nerve (9).

Imaging

Among the imaging techniques proposed for the diagnosis of TME are: MRS, DWI, perfusion-weighted imaging (PWI), apparent diffusion coefficient (ADC) (6). TMS poses multiple challenges in imaging studies, since the mass effect and perilesional edema do not allow differentiation from a brain tumor or infection, but observing a ring enhancement after gadolinium administration suggests an TDL (7). Furthermore, it has been shown that when comparing MRI enhancement regions with the respective areas on CT, hypoattenuation was specific to make an adequate distinction of TDL from glioma or lymphoma, but this differentiation was only applicable for these two tumor subtypes. In relation to brain abscesses, lesions in TMS are centrally homogeneous on T2-w (6). Furthermore, relative to brain abscesses and tumors the mass effect along with edema in TMS are proportionally smaller relative to plaque size. It has been suggested that the lack of mass effect differentiates MS plaques from other space-occupying lesions (11,22,23).

Although there are no pathognomonic features for the diagnosis of LDT by imaging studies, features such as the presence of a hypointense ring in T2 around the lesion and the presence of white matter lesions typical of MS allow the diagnosis to be adequately directed (9). Some of the lesions on TMS are frequently enhanced on MRI, but cases have been found where this pattern is not observed, suggesting that a lack of enhancement does not rule out TDL (12). In addition, within the characteristics of the lesions on MRI are vascular structures crossing the center of the lesions in T2-w and marked reduction in blood flow perfusion compared to normal white matter (6,24,25).

DWI is an imaging method for the measurement of water molecules. Most lesions show variable ADC values on DWI as a result of the pathological heterogeneity of MS lesions (2). Most TDL demonstrate increased DWI and ADC signals on MRI, allowing differentiation of lymphomas with a water diffusivity restriction that makes them hyperintense on DWI and hypointense on ADC maps. Occasionally, acute demyelinating lesions may have areas of diffusion restriction with reduced ADC values at the periphery of the lesion (6,23,25).

MRS is an imaging method for the detection of biochemical alterations at the brain level, thus allowing improvements in the specificity of pathologies. When an increase in choline is observed due to elevated cell membrane turnover in MS during demyelination and inflammation processes, MRS is a method for the detection of biochemical alterations at the brain level, allowing for improved pathology specificity. NAA is an important brain marker because it is found only in neurons (4). A relationship of TDLs in MS and abnormal levels of choline, glutamate-glutamine and lactate has been found. In addition, an elevated choline/creatine ratio, increased lactate and an abnormal NAA/creatine ratio allow suspicion of inflammatory processes or demyelination (5,7). However, MRS is of limited utility, because TDLs present a similar pattern of increased choline/creatine and reduced NAA/creatine as in brain tumors. On the other hand, fluorodeoxyglucose positron emission tomography may provide diagnostic clues (9).

Treatment

There is still no standardized immunomodulatory treatment for TMS. Although within the pharmacological treatments we find methylprednisolone, beta interferons, plasma exchange, rituximab and natalizumab (1,9); the literature reports as first line treatment the use of high doses of steroids (9), due to the fact that in the majority of cases a positive response is obtained (6) and in some cases they are accompanied by surgical intervention (14). When patients do not respond to this, plasma exchange therapy is used. In cases

where an adequate response is not obtained, the use of rituximab or cyclosfamide is suggested (9).

On the other hand, some studies have recommended avoiding the use of fingolimod because of reports of cases of TDL occurring with the use of this drug (9).

Prognosis and neurosurgical education

The long-term prognosis depends largely on whether the patient has recurrent neurological disease. Most patients who relapse will have lesions typical of MS, with a minority recurring in a tumefactive form. Patients who develop MS after LDTs have similar long-term disability as those with prototypical MS (9). In low- and middle-income countries, where there are limitations with respect to the availability of high-cost technology and access to specialized health services, it is necessary to design strategies to facilitate the early diagnosis and management of these patients (26-28). The theoretical training of primary care physicians and medical students is a low-cost strategy that allows those who, due to policies and agreements, must go to provide health care in marginalized areas, to suspect this condition and refer the patient to high complexity hospitals (29,30). The implementation of robotic neurosurgery and translational research are other aspects that would improve patient prognosis (31). Neurosurgical education should be mainly focused on the physician, who is the one who should make the differential diagnosis.

Conclusions

Tumefactive multiple sclerosis is an infrequent disease, but it has a substantial negative impact on the functional capacity and quality of life of the affected person. It is necessary to have high quality imaging tools and suspicious clinical criteria to be able to suspect and differentiate this condition from other differential diagnoses, such as neoplasms of the central nervous system. More prospective multicenter studies are needed to more accurately characterize this condition.

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