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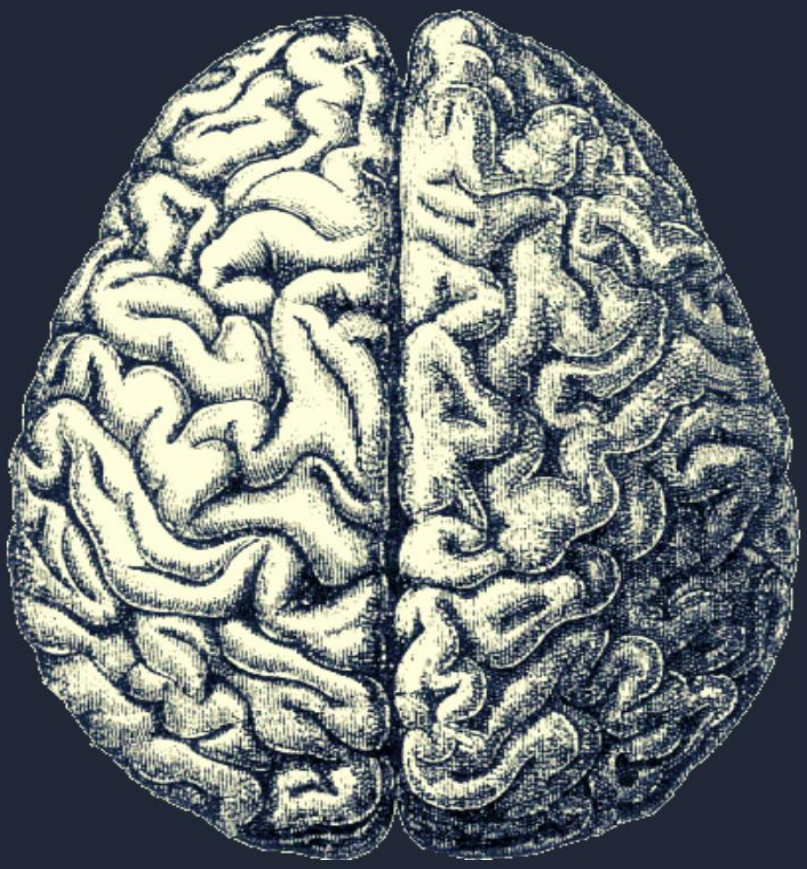

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On thin ice. Does season influence the risk of haemorrhagic stroke from brain vascular malformations?

Ioan Alexandru Florian[1,2], Teodora Larisa Timiș[3], Lehel Beni[1], Larisa Serban[1], Ioan Stefan Florian[1,2], Adrian Bălașa[4], Ioana Berindan-Neagoe[5]

[1] Clinic of Neurosurgery, Cluj County Emergency Clinical Hospital, Cluj-Napoca, ROMANIA
[2] Department of Neurosurgery, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, ROMANIA
[3] Department of Physiology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, ROMANIA
[4] Clinic of Neurosurgery, Tîrgu Mureș County Clinical Emergency Hospital and Department of Neurosurgery, Tîrgu Mureș University of Medicine, Pharmacy, Science and Technology, Tîrgu Mureș, ROMANIA
[5] Research Center for Functional Genomics, Biomedicine, and Translational Medicine, Institute of Doctoral Studies, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca and Department of Experimental Pathology "Prof. Ion Chiricuta", The Oncology Institute, Cluj-Napoca, ROMANIA

Keywords
arteriovenous malformation (avm), cavernous malformation (cm), rupture, haemorrhagic stroke, surgical removal, gender, season, meteorological conditions

✉
Corresponding author:
Ioan Alexandru Florian

Department of Neurosurgery, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

florian.ioan.alexandru@gmail.com

ABSTRACT

Introduction. Brain vascular malformations (BVMs) are congenital lesions with evolutive properties that possess a considerable chance of causing intracranial hemorrhage. The most common types are arteriovenous malformations (AVMs), aberrant entanglements of deformed vessels that shunt blood from the arteries directly into the veins, and cavernous malformations (CMs), being mulberry-shaped sinusoid spaces filled with blood. The rate of hemorrhagic stroke varies between these two types of lesions, being the most common form of symptomatic presentation for AVMs, but a much rarer occurrence for CMs. The purpose of our pilot study was to test whether the incidence of intracranial hemorrhage from BVMs varies between seasons, as well as examining a possible causality for this event.

Material and methods. We performed a retrospective analysis on the cases of ruptured BVMs of the brain operated by the senior surgeon in our department between January 2008 and December 2019. We then divided the patients according to type of lesion and gender, based on the month of the year when their pathologies caused hemorrhagic stroke. We performed Pearson's chi square test to verify the

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relationship between season and rate of rupture of AVMs and CMs, individual month and rate of rupture, season and gender, and individual month and gender.

Results. There were 87 ruptured vascular malformations, out of which 71 were AVMs and 16 were CMs. There were 51 males (40 AVMs, 11 CMs) and 36 females (31 AVMs, 5 CMs). The majority of hemorrhagic strokes occurred in the months of July (10 AVVMs, 2 CMs) and December (10 AVMs, 1 CM). We obtained a statistically significant correlation between the summer season and presentation with ruptured cavernous malformation, as well as the male sex and presentation with a ruptured AVM in December, whereas the female sex presented a correlation with ruptured AVMs in the month of March. We also obtained a correlation between the male sex and presenting with a ruptured vascular malformation of any kind in December, as well as the female gender and hemorrhagic stroke from any vascular malformation in the months January and August.

Conclusion. Despite promising statistical results, the relatively low number of cases may not be applicable to a larger patient population. It seems probable that meteorological conditions, especially extreme temperatures, might act as an additional risk factor for hemorrhagic stroke from vascular malformations, however these findings should be corroborated with supplementary case series from other centers, or a large prospective trial.

Introduction

Brain vascular malformations (BMVs) represent congenital aberrations of the cerebral blood vessels, having evolutive properties and a variable tendency to cause hemorrhagic stroke across its subtypes. The most common BMVs are arteriovenous malformations (AVMs), which consist of an entanglement of abnormal vessels that shunt blood from arterial feeders directly into one or more draining veins [4, 5, 10]. Hemorrhagic stroke stands as their most common form of symptomatic presentation, AVMs being also the leading cause of spontaneous intracranial hemorrhage in the young population. Cavernous malformations (CMs), also referred to as cavernomas, have a lower prevalence than AVMs, are mulberry-shaped sinusoid caverns filled with blood in various stages of hemolysis and are generally asymptomatic upon discovery [1, 2, 9]. Regarding symptoms, epilepsy is described as the most frequent for CMs, hemorrhagic stroke being slightly less common.

Spontaneous intracranial hemorrhage (ICH), or hemorrhagic stroke, is responsible for roughly 20% of all stroke types [15, 20]. Despite medical and surgical advancements, it remains a mortifying pathology with a mortality as high as 30%, as well as a strikingly elevated morbidity among survivors. The influence of seasonal change on the propensity of hemorrhagic stroke has been widely investigated across several areas of the world, although the results are inconsistent and continuously debated. The majority of such studies described a rise in the incidence of stroke throughout the colder months of the year and a decline in the warmer months [3, 11, 12, 22].

Since AVM and CM rupture depends on both acquired and environmental factors, it is reasonable to assume that meteorological factors may indeed contribute to this event. Nevertheless, our current comprehension of the individual environmental triggers is narrow at best. Aside from risk factors such as smoking, alcohol and drug consumption, and various comorbidities like arterial hypertension and diabetes mellitus, we believe it important to also tackle the added influence of seasonal variation in hemorrhagic stroke from these lesions. In the present study, we examine the seasonal rates of rupture from BVMs which were admitted in our hospital in a 12-year interval.

Materials and methods

We conducted a retrospective analysis on the cases of ruptured BVMs (AVMs and CMs) operated by the senior surgeon in our department (the third author) between January 2008 and December 2019. Patient data was gathered from the hospital internal electronic database (AtlasMed), patient observation forms, surgery registry and the clinical imaging study database. We then divided the patients according to gender, age, and the histological type of lesion, based on the month of the year when their pathologies caused ICH. Inclusion criteria were the imaging and pathological confirmation of the vascular malformation, the presence of intracranial hemorrhage upon admission, as well as the surgical removal of the lesion. Patients with BVMs that did not present with rupture, were not confirmed as either AVM or CM by the pathologist, did not have a visible BVM on imaging study, or that did not benefit from surgery in order to have a final diagnosis were excluded from the study. Using Microsoft® Excel for Mac, we made the appropriate value distribution graphs. We performed Pearson's chi square test to verify the relationship between season and rate of rupture of AVMs and CMs, individual month and rate

of rupture, season and gender, and individual month and gender.

RESULTS

From the total of 202 BVMs operated in the specified interval by our senior neurosurgeon, 87 had ruptured prior to admission, out of which 71 (81.61%) were AVMs and 16 (18.31%) were CMs. There were 51 males (58.62%, with 40 AVMs and 11 CMs, representing 45.98% and 12.64% respectively) and 36 females (41,38%, with 31 AVMs and 5 CMs, accounting for 35.63% and 5.75% of cases respectively). The majority of ICH occurred during the months of July – 12 BVMs or 13.79% (10 AVVMs or 11.49%; 2 CMs or 2.3%); followed by December – 11 BVMs or 12.64% (10 AVMs or 11.49%; 1 CM or 1.15%). The months of March and November both accumulated 10 BVMs each (11.49%), the former having a total of 9 AVMs (10.34%) and 1 CM (1.15%), whereas the latter amassed 7 AVMs (8.05%) and 3 CMs (3.45%). Figure 1 reveals the total number of cases presenting with ruptured AVMs and CMs across each month.

Using Pearson's Chi squared test, we first compared AVMs to CMs in respects to the season they were most likely to rupture and obtained obtained a statistically significant correlation between the summer season and presentation with ruptured CM (chi^2 value of 4.3291, $p<.05$). Moreover, when taking each month individually, we found a statistically significant correlation between August and ruptured CMs (chi^2 value of 4.2902, $p<.05$) No other associations were statistically significant for this step. Tables 1 and 2 show the all of the results emerging from this group of investigations.

Table 1. BVM Risk of Rupture According to Histological Type by Season and Period

season/ period	AVMs total/ month	CMs total/ month	chi^2 value	p value	Interpre-tation
Spring	19	1	1.9058	1.9058 >.05	Non-Significant
Summer	**17**	**8**	**4.3291**	**.037467 <.05**	**Significant**
Autumn	18	5	0.2336	.628903 >.05	Non-Significant
Winter	17	2	1.0018	.316884 >.05	Non-Significant
total	71	16			

AVMs, arteriovenous malformations; CMs, cavernous malformations

Table 2. BVM Risk of Rupture According to Histological Type by Month

month	AVMs total /month	CMs total /month	chi^2 value	P value	Interpre tation
January	5	1	0.0128	.910048 >.05	Non-Significant
February	2	0	Could not be calculated		
March	9	1	0.53	.081428 >.05	Non-Significant
April	6	0	Could not be calculated		
May	4	0	Could not be calculated		
June	4	3	3.0362	.096427 >.05	Non-significant
July	10	2	0.0276	.868123 >.05	Non-significant
August	**3**	**3**	**4.2902**	**.038334 <.05**	**Significant**
Sept.	6	1	0.0855	.770012 >.05	Non-significant
October	5	1	0.0128	.910048 >.05	Non-significant
Nov.	7	3	0.2564	.612595 >.05	Non-significant
Dec.	10	1	0.7256	.394304 >.05	Non-significant
total	71	16			

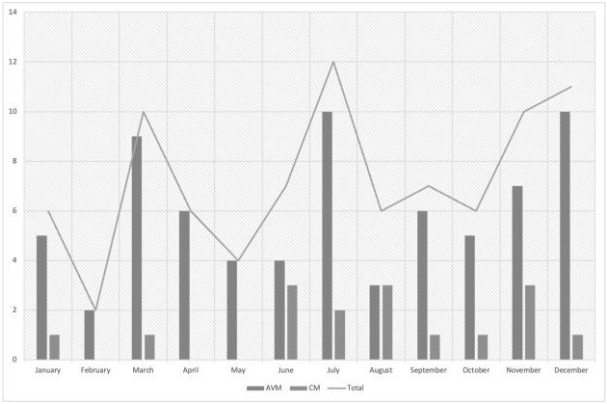

Figure 1. Diagram showing the cumulative incidence of ruptured brain vascular malformation based on type, according to calendar month. The ordinate shows the number of cases. AVM – arteriovenous malformation; CM – cavernous malformation.

Next, we took into account only the patients with ruptured AVMs and compared the two genders in respects to rupture risks during all the same months combined. Figure 2 shows the distribution of ruptured BVMs for both sexes across each month. We found a statistically significant correlation between the male sex and presentation with a ruptured AVM in the month of December (chi^2 value

of 5.3617, p<.05), whereas the female sex was significantly correlated with ruptured AVMs in the month of March (chi^2 value of 4.8766, p<.05). Table 3 illustrates the complete results for this set of tests.

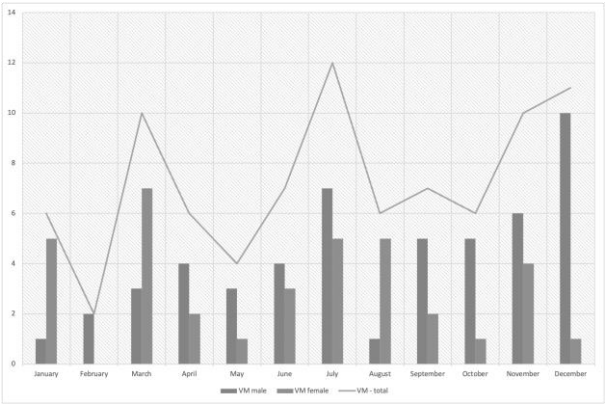

Figure 2. Diagram showing the cumulative incidence of ruptured brain vascular malformation based on patient gender, according to calendar month. The ordinate shows the number of cases. VM – vascular malformation.

Table 3. AVM Risk of Rupture According to Gender by Month

month	m. total /m.	f. total /m.	chi^2 value	P value	Interpre-tation
January	1	4	2.8874	.089277 >.05	Non-Significant
Feb.	2	0	Could not be calculated		
March	**2**	**7**	**4.8766**	**.027223 <.05**	**Significant**
April	4	2	0.2842	.593939 >.05	Non-significant
May	3	1	0.6001	.438524 >.05	Non-significant
June	1	3	1.6923	.193296 >.05	Non-significant
July	5	5	0.1901	.662852 >.05	Non-significant
August	1	2	0.6739	.411693 >.05	Non-Significant
Sept.	4	2	0.2842	.593939 >.05	Non-significant
Oct.	4	1	1.2243	.268522 >.05	Non-significant
Novem ber	4	3	0.002	963931 >.05	Non-significant
Dec.	**9**	**1**	**5.3617**	**.020584 <.05**	**Significant**
total	40	31			

AVMs, arteriovenous malformations; CMs, cavernous malformations

Last, we considered all BVMs, regardless of type, and again compared the hemorrhage risk for the two sexes along all of the same months. We discovered a statistically significant correlation between the male sex and a hemorrhage from a vascular malformation of any kind in December (chi^2 value of 5.412, p<.05), as well as the female gender and hemorrhagic stroke from any vascular malformation in the months January and August (chi^2 value of 4.6763 equally for each month, p<.05). No other significant associations could be established. The complete results of this step can be viewed in Table 4.

Table 4. Total BVM Risk of Rupture According to Gender by Month

month	m. total /m.	f. total /m.	chi^2 value	P value	Interpretation
Jan.	**1**	**5**	**4.6763**	**.030582 <.05**	**Significant**
Feb.	2	0	Could not be calculated		
March	3	7	3.8155	.05078 >.05	Non-significant
April	4	2	0.172	.678347 >.05	Non-significant
May	3	1	0.4637	.495889 >.05	Non-significant
June	4	3	0.0069	.934019 >.05	Non-significant
July	7	5	0.0005	.982633 >.05	Non-significant
Aug.	**1**	**5**	**4.6763**	**.030582 <.05**	**Significant**
Sept.	5	2	0.5148	.473064 >.05	Non-significant
Oct.	5	1	1.6225	.202741 >.05	Non-significant
Nov.	6	4	0.0089	.925001 >.05	Non-significant
Dec.	**10**	**1**	**5.412**	**.019999 <.05**	**Significant**
total	51	36			

DISCUSSIONS

Within seasons themselves, the differences regarding the total number of ruptured AVMs was minor, whereas CMs tended to bleed more frequently during summer. The month of August showed a significantly higher relative frequency of ICH from CMs when compared to AVMs. Males showed a clearer tendency of BVM rupture in the month of December, whereas female patients had a higher propensity for ICH strictly from AVMs in March and from BVMs in general in January and August.

Currently, there is a scarcity of studies dedicated to the effects of weather on the incidence of hemorrhagic stroke, especially those from preexisting vascular lesions such as aneurysms, AVMs or CMs. To the extent of our knowledge, a single other article addresses the influence of seasons on the risk of spontaneous hemorrhage from AVMs [6]. Hakan et al. discovered that the

highest incidence for AVM rupture in Istanbul ensued during winter, while its lowest occurred in summer, yet there were no proven statistical correlations to substantiate their results. With 78 ruptured malformations spread across 20 years, the difference between hemorrhagic stroke from AVMs was also higher for men during autumn and winter, although these were not as considerable the ones in our series. The authors concluded that aside from seasonal weather variations and individual risk factors such as alcohol consumption, the relative increase of the population during winter may also play a role in the upsurge of hemorrhagic stoke during winter. Regarding cavernomas, our literature search did not yield any articles discussing the effect of meteorological conditions on their rupture patterns.

Stroke mortality was proven to rise in holiday seasons, at least in certain regions such as in the Hiroshima Prefecture of Japan, or Taiwan [8, 14]. Yet the reason for this could not be accurately established due to a lack in more detailed clinical information like patient lifestyle, consumption of alcoholic beverages, smoking habits and so forth. In the Heilongjiang Province of China, the higher incidence of primary intracranial hemorrhage from hypertension within late spring and early autumn was attributed to the influence of daily mean ambient temperature, as well as its variation [22]. According to Zheng et al, unexpected changes in temperature, such as sudden drops during the hot weather or climbs during the cold, were met with an increase in the incidence of primary intracranial hemorrhage. Furthermore, in the same study, it was shown that the occurrence of SAH escalated throughout days with lower ambient temperature. On the other hand, in the Arab Peninsula, ischemic stroke was correlated with the higher amount of solar radiations specific for the summer season which could not be elucidated by physiological events indicative of either dehydration or hemoconcentration [19]. Therefore, the supposition that meteorological conditions influence the rates of stroke may not be far from true.

The peaks occurring at the months of March, July and December might suggest a propensity for BVMs to rupture whenever extreme temperatures are reached, or when there are large thermic variations. The more frequent hemorrhages could also be attributed to the stress related to the estival season or the festive holidays and their respective activities. The significant difference between genders within early winter remains intriguing and enigmatic, yet it cannot be entirely attributed to weather effects alone. One should also take into account the behavioral and socioeconomic aspects of the patients in the studied population. As such, there are clear trends of increasing alcohol consumption in the form of spirits and wine during late autumn and early winter in our country, possibly due to the lower temperatures occurring in this period, but also as a consequence of increased stress correlated with a progressively dynamic socioeconomic environment, as well as a widening poverty gap [16, 17]. Although probable interference from other seasonal exposures such as dietary changes, hypovitaminosis or viral infections cannot be excluded.

Studies have also tried to pinpoint specific individual meteorological factors which may influence the occurrence of spontaneous ICH. According to Neidert et al., relative humidity presented a strong fluctuation in the 2 days prior to ICH in patients with intracranial vascular lesions [15]. On the day of rupture relative humidity was significantly lower, suggesting that a low ambient humidity may promote hemodynamic and cardio-cerebrovascular conditions associated with ICH from these lesions. It has been shown that air humidity, along pollution and temperature, can influence the diameter of the brachial artery in patients with type 2 Diabetes mellitus, with higher temperature and humidity acting as vasodilators [21]. Conversely, it can be argued that a lower humidity may lead to vasoconstriction, although this might not suffice as a trigger for vascular malformation bleeds. Low humidity and air pressure cause an increase of blood viscosity via insensible water loss [7]. This in turn can also alter the autoregulation properties of arterial feeders in AVMs, as well as promote shear stress [13, 18]. Other reports revealed that low temperature is indeed a substantial risk factor for ICH, significantly correlated with the higher incidence of these occurrences during winter and early spring [11, 12]. Our findings are in line with these conjectures, showing that the increased incidence of ICH from vascular malformations during the colder months may not be coincidental. Nevertheless, it is as of yet unclear why so many our cases presented with rupture during summer and why the rate of rupture for CMs remains higher during the warmer months.

Nevertheless, these results should not be taken at face value. Statistical bias can occur from the relatively small number of cases from each individual month. We can, however, speculate that there is indeed a higher tendency for BVMs to rupture under certain environmental circumstances, such as high differences in temperature or atmospheric pressure. Yet determining these parameters retrospectively within a large timeframe can be difficult and more inaccurate than acquiring the same data upon hospital admission. Also, stress related to specific periods during the year may contribute to higher systemic blood pressure, ergo to an increase likelihood of these lesions to bleed. In order to resume and improve our research in the future, we intend to collect the meteorological data relevant to our patients on the same day in which they arrive. Another problem in our approach is that the total number of lesions is spread too thin across the twelve months, thus even a seemingly impressive frequency peak may actually denote a negligible difference. A larger case series, or a collaboration with other neurosurgical centers in this field, may solve this predicament in the future. Another limitation of this study is the lack of adequate meteorological data, particularly of the individual environmental factors such as temperature, relative humidity and air pressure in the days predating ICH. In a future continuation of this study, we propose a collaboration with the National Meteorological Association in order to obtain such relevant data. Despite this being a pilot study, we believe it could be further improved by enlarging the number of patients enrolled and by performing a multivariate analysis on the various individual meteorological, environmental, and geographical factors, as well as the individual characteristics of the patients and their BVMs.

Conclusions

According to our results, BVM rupture incidence is higher in the months of March, July and December. Moreover, CMs tend to rupture more frequently in the summer than AVMs. Males tend to present with rupture from AVMs during early winter, whereas females had ruptures in early spring. Despite the fact we achieved promising statistical results, due to the relatively low number of cases, our findings may not be applicable to a larger patient population. It may also be probable that our results are due to statistical bias, although we are optimistic regarding an actual relationship between meteorological conditions and an altered propensity of BVMs to rupture. This may also depend on geographical variations in risk factors. It seems likely that seasonal changes in the environment, especially extreme temperatures, might act as an additional risk factor for hemorrhagic stroke from vascular malformations, however these findings should be corroborated with supplementary case series from other centers, or a large prospective trial.

Conflicts of Interest

The authors have no conflicts of interest to report.

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Navigated transcranial magnetic stimulation mapping in patients with language-eloquent brain lesions

George E. D. Petrescu[1,2], Roxana Radu[1,2], Andrei Giovani[1], Cristina Gorgan[3], Felix M. Brehar[1,4], Radu M. Gorgan[1,4]

[1] Neurosurgery Department, "Bagdasar-Arseni" Emergency Hospital, Bucharest, ROMANIA
[2] PhD student, "Carol Davila" University of Medicine and Pharmacy, ROMANIA
[3] Neurology Department, "Bagdasar-Arseni" Emergency Hospital, Bucharest, ROMANIA
[4] Neurosurgery Department, "Carol Davila" University of Medicine and Pharmacy, ROMANIA

Keywords
navigated transcranial magnetic stimulation, language areas cortical mapping, brain tumours

ABSTRACT

Introduction: The surgical resection of brain lesions located in language-eloquent areas harbours a great risk for determining new functional deficits. Navigated transcranial magnetic stimulation represents a novel non-invasive cortical mapping method that can be used preoperative to determine language-eloquent areas.

Materials and methods: We retrospectively reviewed a prospectively maintained database of patients that underwent preoperative cortical mapping using nTMS between March 2017 and June 2020. Patients older than 18 years old with brain lesions situated in a presumed language eloquent area, that underwent surgical resection of the brain lesion were included in the study. Various parameters such as error rate, number of language-negative sites were assessed.

Results: Fourteen patients were included in the study. There were 10 males and 4 females in total. Most of the tumours were in the temporal and frontal lobes (five and four cases, respectively). The histopathological diagnosis was glioblastoma in seven cases, in one case there was an anaplastic astrocytoma and there were two cases of low-grade gliomas. There were three cases of brain metastasis and one cavernoma. The median (range) tumor volume was 25.01 cm3 (0.89 – 86.55 cm3). Gross-total resection (GTR) was achieved in seven cases. The error rate was significantly higher in patients that continued to have an impaired language function after surgical resection ($p = 0.016$), while the perilesional error rate was higher in patients with preoperative aphasia ($p = 0.019$).

Conclusion: Our findings suggest that a lower tumour volume to perilesional negative stimuli ratio is associated with an extended surgical resection of brain tumours located in language-eloquent areas and that patients that presented with aphasia and have a high error rate have a worse functional prognosis. Through nTMS preoperative cortical mapping of language-eloquent areas, the neurosurgeon has more insight regarding the cortical function and can maximize the surgical resection, while avoiding the onset of new functional deficits.

Corresponding author:
George E. D. Petrescu

"Carol Davila" University of Medicine and Pharmacy, Romania

gedpetrescu@gmail.com

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INTRODUCTION

The surgical resection of brain lesions located in language-eloquent areas harbors a great risk for determining new functional deficits. Since a complex network is involved in speech and language processing, and there is a high individual variability regarding the cortical representation of language areas, cortical mapping of eloquent areas should be performed in order to decrease this risk (1). Moreover, brain tumors can disrupt and reorganize the normal functional areas (2, 3). The" gold-standard" method for the mapping of language areas is direct cortical stimulation (DCS) under awake surgery (4). However, not all patients can tolerate or have contraindications for an awake craniotomy (5). Navigated transcranial magnetic stimulation (nTMS) represents a preoperative, non-invasive method used for cortical mapping of motor and language eloquent areas (6, 7). By using navigated repetitive TMS (nrTMS) pulses, language areas can be mapped in patients with brain tumors, as well as in healthy individuals, without adverse events (3).

In this study we present our experience with nTMS cortical mapping for language-eloquent brain lesions.

MATERIALS AND METHODS

Patient cohort

We retrospectively reviewed a prospectively maintained database of patients that underwent preoperative cortical mapping using nTMS between March 2017 and June 2020. The inclusion criteria were: (1) patients with brain lesions situated in a presumed language eloquent area; (2) patients that underwent surgical resection of the brain lesion; (3) age > 18 years old. Patients that had nTMS contraindications (e.g.: frequent generalized epileptic seizures, cranial implants) or did not undergo surgical resection or underwent only a stereotactic biopsy procedure were excluded from the study.

nTMS language mapping

Cortical mapping was performed by using the Nexstim Navigated Brain Stimulation System 5 (Nexstim Oy, Helsinki, Finland) according to the established protocol (8), as previously described (9). Briefly, the brain MRI and the patients' head were co-registered, and a motor mapping was performed to determine the resting motor threshold (RMT). Afterwards, using the NexSpeech Software (Nexstim Oy, Helsinki, Finland) the patients performed a baseline object-naming task without TMS stimuli, in order to evaluate each patients' vocabulary and misidentified pictures were removed. The baseline procedure was repeated twice. The remaining pictures were used for the object-naming task performed with nrTMS pulses. The following parameters were used for the language mapping: picture display time (PDT): 700 ms, interpicture interval (IPI): 2500 ms and picture-to-trigger (PTT) interval: 0 ms. The navigated repetitive TMS (nrTMS) pulses were applied in bursts of 5 pulses with 5 Hz frequency, with an intensity of 100% of the RMT. Individual adjustments were performed, when needed, based on the preexisting neurological deficits. Every site was stimulated three times. The results were analyzed blinded to the location of the TMS stimuli and compared with the baseline. The language errors were defined in the following categories: no response, performance error, semantic error and other. Errors due to muscle stimulation were discarded.

Surgical planning

The brain MRI scans with the annotated language errors were included in the intraoperative neuronavigation system (SonoWand Invite - SonoWand AS, Trondheim, Norway, or Medtronic Stealth S8 – Medtronic, Minneapolis, USA). The surgical planning took into account the results from the brain mapping, in order to select the optimal entry point and trajectory, with the goal of avoiding postoperative neurological deficits and maximizing the surgical resection.

Brain lesion evaluation

The brain MRI used for the mapping procedure was used the calculate to volume of the brain lesion with the aid of the 3D Slicer 4.10.0 Software (10, 11). Based on the histopathological diagnosis, the tumors were classified in two categories: (1) tumors with slow growth rate (low grade gliomas) and tumors with fast growth rate (high grade gliomas, metastases).

Language mapping analysis

In order to better evaluate the language function and the mapping results, a series of variables were assessed: number of language errors, number of no-response errors, number of language-negative sites,

error rate (ER) = language errors/total stimuli * 100, perilesional error rate (PER) = perilesional language errors/perilesional stimuli * 100. The tumor volume to language-negative sites ratio was calculated.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics, version 25 (IBM Corp., Armonk, N.Y., USA). The t-test was used for continuous variables with parametric distribution and the Mann-Whitney U test for the non-parametric ones. $p < 0.05$ was considered statistically significant.

Results

Patient cohort

Fourteen patients met the inclusion criteria with a mean (SD) age of 51.5 (13.9) years. There were 10 males and 4 females in total. All patients were right-handed, with the left hemisphere being considered the dominant one. Most of the tumors were located in the temporal and frontal lobes (five and four cases, respectively). Two tumors were in the fronto-temporal lobes and one in each of the following: parietal lobe, fronto-parietal and temporo-parietal. The histopathological diagnosis was glioblastoma in seven cases, in one case there was an anaplastic astrocytoma and there were two cases of low-grade gliomas. There were three cases of brain metastasis and one cavernoma. According to the growth rate classification, there were 11 fast-growing tumors and 2 slow-growing tumors (the cavernoma case was excluded from this classification). Gross-total resection (GTR) was achieved in seven cases, while in the others a subtotal resection (STR) was performed. The median (range) tumor volume was 25.01 cm3 (0.89 – 86.55 cm3). Cohort characteristics are summarized in Table 1.

Table 1. Cohort characteristics

	No.
Age – mean (SD)	51.5 (13.9)
Tumor location	
Temporal	5
Frontal	4
Fronto-temporal	2
Fronto-parietal	1
Parietal	1
Temporo-parietal	1
Histopathology	
High-grade glioma	8
Metastasis	3
Low-grade glioma	2
Cavernoma	1
Extent of resection	
GTR	7
STR	7

Table 1 summarizes the characteristics of the patient cohort. GTR = gross-total resection; STR = subtotal resection.

Language function analysis and cortical mapping results

Preoperatively, seven patients presented with aphasia. Short-term following the surgical resection, there was an improvement of function in four cases. None of the patients had new language functional deficits following surgery. No adverse events were encountered during the preoperative mapping procedure. Figure 1 illustrates the results of a language mapping procedure using nTMS.

The error rate was significantly higher in patients that continued to have an impaired language function after surgical resection ($p = 0.016$), while the perilesional error rate was higher in patients with preoperative aphasia ($p = 0.019$). Although, the perilesional error rate was increased in tumors with fast-growing rate compared to those with slow-growing rate, the result was not statistically significant ($p = 0.058$). The results of the language mapping analysis are depicted in Table 2 and Table 3.

Regarding the extent of resection, a lower ratio between tumor volume and number of perilesional negative stimuli (cm3/stimuli) was associated with an extended resection ($p = 0.004$).

Table 2. Patient characteristics and language mapping results

Pt. No.	Age	Sex	Tumor Location	Pathology	Preoperative aphasia	ER	Perilesional ER	EOR
1	65	Ma	TP	GBM	Yes	12%	25%	GTR
2	18	Ma	F	Cav.	No	8%	17%	GTR
3	70	Fe	P	Met.	No	8%	16%	GTR
4	62	Ma	T	GBM	Yes	8%	21%	STR

5	46	Ma	FP	GBM	No	13%	19%	GTR
6	54	Ma	F	GBM	Yes	26%	33%	STR
7	61	Fe	T	GBM	Yes	6%	16%	STR
8	59	Ma	T	Met.	Yes	17%	22%	GTR
9	43	Ma	T	LGG	No	4%	8%	STR
10	59	Ma	T	AA	No	9%	14%	GTR
11	32	Fe	FT	LGG	No	13%	12%	STR
12	45	Ma	F	Met.	No	8%	22%	GTR
13	58	Ma	FT	GBM	Yes	16%	22%	STR
14	49	Fe	F	GBM	Yes	37%	42%	STR

Table 2 presents the patients' characteristics and results of language mapping analysis. AA = anaplastic astrocytoma; Cav. = cavernoma; EOR = extent of resection; ER = error rate; F = frontal; Fe= female; FP = fronto-parietal; FT = fronto-temporal; GBM = glioblastoma; LGG = low-grade glioma; Ma = male; Met. = metastasis; P = parietal; T = temporal; TP = temporo-parietal.

Table 3. Language mapping analysis

	mean (SD) / median (range)	p value
Persistent aphasia	**Error rate**	
Yes	23.39% (11.82)	0.016
No	10.55% (5.92)	
Preoperative aphasia	**Perilesional error rate**	
Yes	25.72% (8.63)	0.019
No	15.40% (4.64)	
Tumor type (n = 13)	**Perilesional error rate**	
Fast growth rate	22.75% (8.12)	0.058
Slow growth rate	10.10% (2.68)	
Extent of resection	**Vol/ Perilesional Neg. Stim.**	0.004
GTR	0.97 (0.22-5.28)	
STR	10.10 (2.39-28.85)	

Table 3 depicts the results of the language mapping analysis. GTR = gross-total resection; STR = subtotal resection; Vol/ Perilesional Neg. Stim. = ratio between tumor volume and number of perilesional negative stimuli (cm3/stimuli).

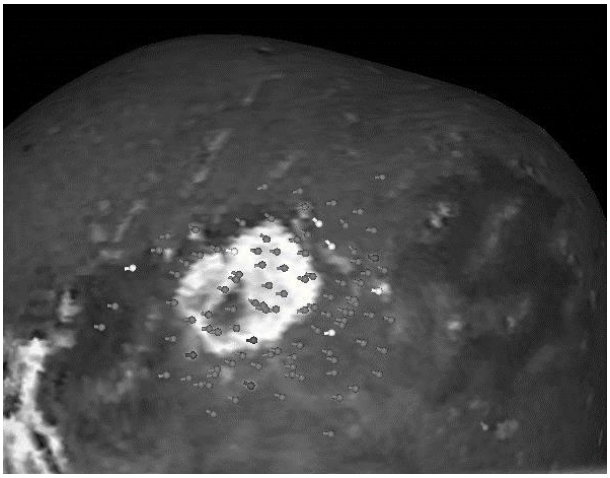

Figure 1 illustrates the results of the nTMS language mapping in a patient with a left temporal glioblastoma. white dots – no response error, blue dots – semantic error, green dots – performance error, orange dots – muscle stimulation, gray dots – negative stimuli. Color figure available only online.

Discussion

Numerous objections have been addressed to the classical localizationist theory of speech and language processing, that relies on modular, static structures (such as Broca's and Wernicke's areas) and instead a dynamic model consisting of networks between cortical and subcortical structures has been proposed (12-14). This concept supports the idea that brain has the ability to reorganize following brain injury, if the connection between axons is spared (13).

Although DCS remains the current "gold-standard" for language mapping, nrTMS can aid the surgeon in the preoperative surgical planning and has similar results to DCS regarding language-negative sites (5, 15-17). In our study, although the GTR group had a higher number of negative stimuli than the STR group, the difference was not statistically significant (p = 0.21). Therefore, we took into account the tumor volume and the negative stimuli that were situated perilesional. The tumor volume to perilesional negative stimuli ratio (cm3/ stimuli) was significantly lower in the GTR group, meaning that a higher number of negative stimuli were attributed per tumor volume, and thus creating a clearer and more reliable map of the language-negative areas, which consequently lead to a greater extent of resection. Even though nTMS is not as reliable as DCS, compared to functional MRI (fMRI) it has a greater sensitivity, but it is less specific (15, 16, 18). One of the advantages of nTMS over fMRI in language mapping is represented by the fact that

fMRI relies on task-induced metabolic changes and it well known that brain tumors, and especially high-grade gliomas, have the tendency to alter the local metabolic activity and vasculature (15, 19, 20).

In our cohort, even though there was no statistically significant difference, the error rate and the perilesional error rate were higher in patients with fast-growing brain tumors. The lack of significance might be due to the fact, that in our study there were few patients with lesions with slow growth rate. In their study, Schwarzer et al. had an increased ER in fast-growing lesions but, again, there was no statistically significant difference (1). However, the authors found a statistically significant difference regarding the baseline error rate between patients with lesions with fast growth rate and patients with vascular malformations (1). This could be explained through the plasticity of the brain, in reaction to the displacement caused by the brain lesion (2). Nevertheless, contradictory data regarding which lesion type (slow or fast-growing) induces an extensive reorganization exist (1, 21).

The perilesional error rate was significantly higher in patients that presented with aphasia (25.72% vs. 15.40%, p = 0.019) and the ER was increased in patients that had mild or no improvement of aphasia following surgery (23.39% vs. 10.55%, p = 0.016). Schwarzer et al. also reported an increased error rate in patients with severe aphasia and altered cognition and proposed a baseline error rate lower than 28% as more probable to correctly determine the true language-positive sites (1).

The current study is limited by a relatively small cohort size and the histological heterogeneity of the lesions included in the study.

Conclusions

Our findings suggest that a lower tumor volume to perilesional negative stimuli ratio is associated with an extended surgical resection of brain tumors located in language-eloquent areas and that patients that presented with aphasia and have a high error rate have a worse functional prognosis. Through nTMS preoperative cortical mapping of language-eloquent areas the neurosurgeon has more insight regarding the cortical function and is able to maximize the surgical resection, while avoiding the onset of new functional deficits.

Conflicts of Interest

The authors declare no potential conflict of interest.

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Odontogen frontoparial epidural and subdural empyema complicated with frontal intracerebral abscess and Covid. Case report

D. Balasa, A. Tunas, A.V. Stan

Department of Neurosurgery, Clinical Emergency Hospital "Sfantul Andrei", Constanta, ROMANIA

ABSTRACT

Introduction: Cerebral infections (frontoparietal extradural and subdural empyema) following a dental abscess and multiple sinusitis is a rare and potentially devastating entity even in the era of modern diagnosis and treatment.

Case presentation: We present a patient with parietal epidural and subdural empyema and intracerebral frontal abscess, sinusitis and dental abscess, chronic consumer of alcohol and with neglected diabetes mellitus. He was initially diagnosed with encapsulated hematoma and sinusitis. The pus obtained at the intervention was certified by our laboratory as sterile with the consequent difficulty in antibiotic treatment and who induced a longer antibiotic treatment, a second surgical intervention for an encapsulated frontal abscess, a longer hospitalisation and favoured contamination with Covid 19. Despite these, the patient had a finally good evolution.

Conclusions: A frontoparietal extradural and subdural empyema and an intracerebral frontal abscess produced by a dental abscess and sinusitis is a rare and potentially lethal complication. The multidisciplinary approach between radiologist, neurosurgeon, otolaryngologist, dentist, microbiologists is mandatory for a proper diagnosis and treatment of these pathologies.

Keywords
subdural empyema, intracerebral abscess, sinusitis

Corresponding author:
Daniel Balasa

Clinical Emergency Hospital "Sfantul Andrei", Constanta, Romania

balasadaniel100@yahoo.com

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INTRODUCTION

Sinusitis is an important and underrated source of intracranial infection (41% to 67%) . Even with modern improvements of diagnosys and treatment mortality from intracranial sinusitis-associated infection in the pre-CT era was 66%[9]but have decreased in the post-CT scan era to 5-40%.

CASE REPORT

A 42 years old patient was admitted in our hospital for diffuse headache,vertigo, nausea, vomiting, ethanolic halene, amnesia. No signs of head trauma. Anamnesis: chronic ethanolic consumer, glicemia 270 mg/dl in 2018 uncontrolled from diabetologist. Emergent CT Scan of the head revealed right parietal encapsulated subdural hematoma

(7 mm initially), right frontal contusion, right maxilar, right frontal, sfenoidal sinusitis, superior right premolar abscess. The patient was initially treated conservative with analgetics, neurotrophics, B vitamines, antibiotics for sinusitis.

The ENT specialist and the dentist apreciated that they will treat the sinusitis and the dental abscess after the neurosurgical colection will be healed. Despite the medical treatment the neurological status worsened within a few days with grand mal seizures, left hemiparesis, meningismus, photophobia . A new CT Scan was performed and revealed the increasing of subdural colection with a maximum diameter of 14 mm in parietal area.

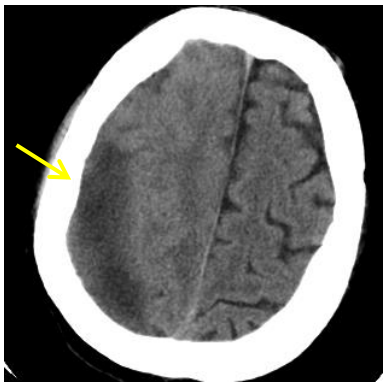
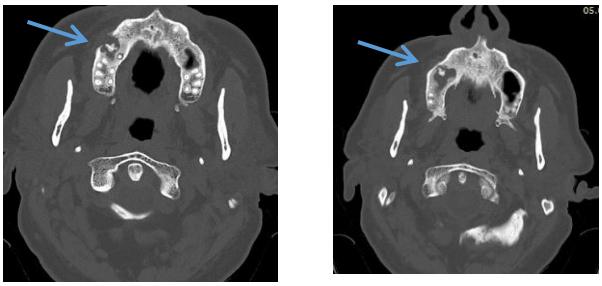


Figure 1. Hypodense subdural right parietal collection (yellow arrow)

He underwent evacuation of an epidural and subdural parietal empyema (mainly subdural) by right parietal craniectomy because of osteomielitis of cranial bone . Frank pus (sterile-because of initial antibiotic treatment for acute sinusitis) was drained and cortical suface was proper washed with diluted betadine. Post-operative, he was treated with intravenous antibiotics (Meropenem, Vancomycin and Metronidazol.) Despite of a favorable imediate postoperative evolution, the patient had multiple left motor jacksonian epilepsias.

The CT Scan with and without contrast revealed Right dental abscess with lysis of right maxilar floor and medial maxilar wall, maxilar sinusitis, right frontal sinus and right frontal bone osteolysis, right frontal sinusitis, right frontal cerebral abscess.



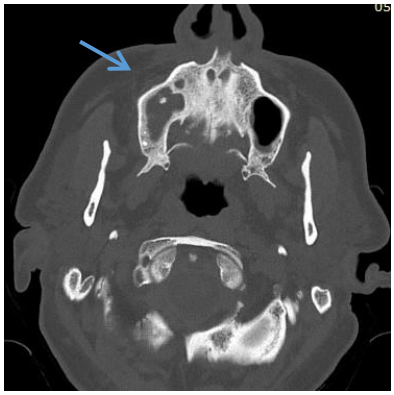


Figure 2. Axial CT Scan. Bone window. 1 5 right dental abscesses with lisis of the right maxilar floor and acute maxilar sinusitis (blue arrow).

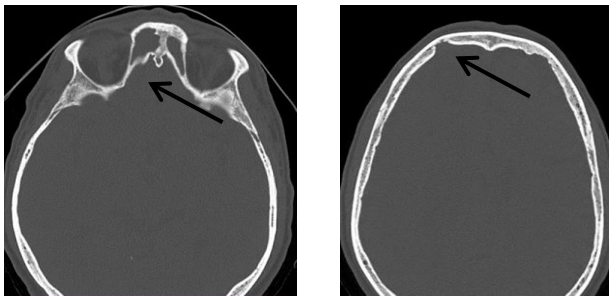


Figure 3. Axial CT Scan. Bone window. Right frontal sinus and right frontal bone osteolysis (black arrow).

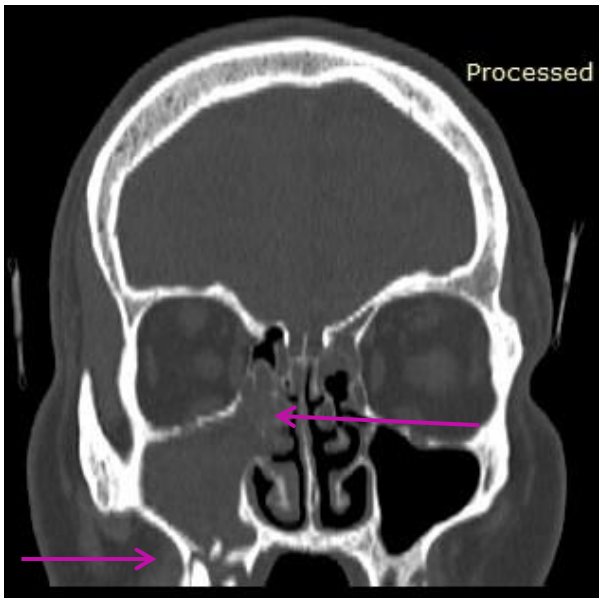


Figure 4. Coronal CT Scan. Bone window Ostyeolysis of the floor and medial wall of the right maxilar sinus, acute maxilar sinusitis (pink arrow).

The MRI Scan of the head revealed encapsulated right cerebral frontal abscess compressive on the ventricular median structures.

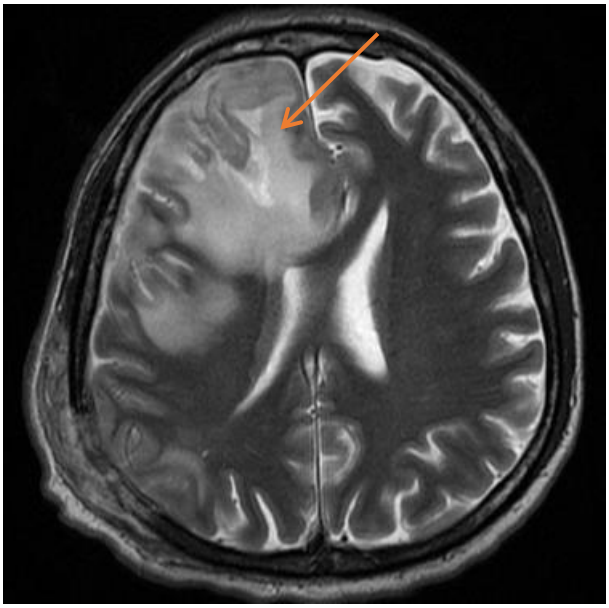


Figure 5. MRI Axial T2. Encapsulated right frontal abscess (red arrow) compressive on the frontal ventricular horns.

A new surgical intervention was performed with cerebral frontal abscess microsurgical exeresis and frontoparietal craniectomy. His neurological condition improved gradually and the follow up CT showed improvement of mass effect and cerebral edema.

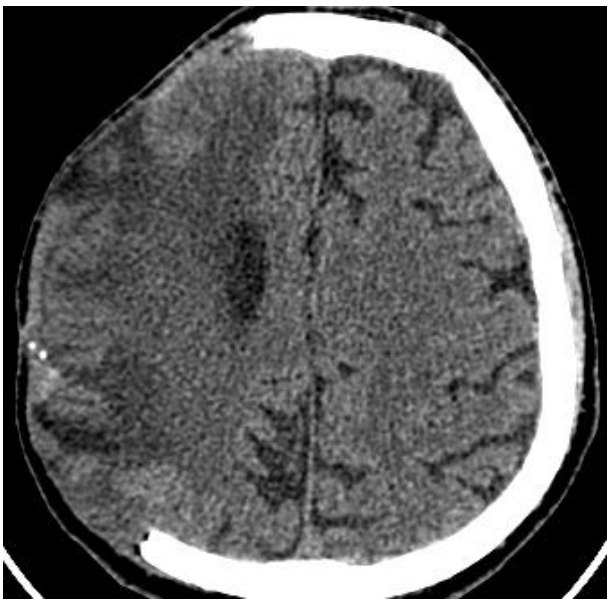


Figure 6. Postoperative Axial CT Scan -exeresis of empiema and frontal abscess. There is some residual edema. Acute fronto-etmoidal sinusitis and dental abscess are not cured yet.

After 8 weeks of treatment the patient developed cough, expectoration and hypoventilation (SPO2 93%). CT Scan of the chest revealed veiling areas "in matte glass" in the left upper lobe, subpleural with infectious substrate. The Covid Test was positive. The patient was transferred and treated 21 days in a Covid hospital. The neurological status at the transfer moment was: residual left pyramidal syndrome, left brachial paresis (ASIA 4/5) in progressive recovery. After 21 days of treatment the patient was healed of COVID and the brachial paresis disappeared.

Follow up: 3 months period

We hope good result of ENT and dental treatment to finally eradicate the infection and we scheduled a cranioplasty with titan mesh after one-year period.

Discussion

ENT brain abscess has a 3.2-to-I male predominance[1]. Although there are many causes of infections of the head and neck, odontogenic are the most common type, with over 53% being found as the main source of deep neck infections[2].

Sinusitis is an important and underrated source of intracranial infection (41% to 67%)[3] . Even with modern improvements of diagnosys and treatment mortality from intracranial sinusitis-associated infection in the pre-CT era was 66%[4] but have decreased in the post-CT scan era to 5-40%[5].

In our case the patient has had amnesia, so we (neurosurgeons and radiologists) didn't excluded a traumatic etiology, despite the absence of signs of cranial trauma and the presence of sinusitis.

The rarely encountered complications of bacterial sinusitis are subdivided into local manifestations (like mucocele, pyocele and recurrence) and extension of sepsis to the adjacent orbital or intracranial structures. Orbital complications include orbital cellulitis,subperiosteal abscess, intra-orbital abscess and osteomyelitis[6,7]. The intracranial complications comprise of meningitis, encephalitis,epidural or subdural empyema, cerebral abscess and cavernous or other dural venous sinuses thrombosis[4]. Subdural empyema, however, is much strongly associated with underlying sinusitis and is also the most common sinusitis-associated intracranial infection[6,7].

From the sinonasal region the infection can spread through direct or indirect routes. The direct spread occurs following the erosion of sinus wall or through preformed pathways like congenital or acquired skull defects (as seen in ISE associated with

trauma and neurosurgical procedures[8]) and the natural skull foramina[9]. The more commonly implicated mechanism however is the indirect spread via retrograde septic thrombophlebitis of valveless emissary veins or endolymphatic channels[10]. Compared with other causes of intracranial suppuration, a greater proportion of subdural empyemas (41% to 67%) result from sinusitis.[3] Brain abscesses and epidural abscesses typically have a more indolent presentation[9]. The anatomical considerations mentioned above are important determinants of the clinical course. For example, purulence in the epidural space is constrained by the dura, which is adherent to the calvarium. Therefore, clinical presentation of epidural abscess is insidious with fever and headache evolving over weeks. By contrast, seeding of the subdural space leads to rapid spread of purulence because of lack of anatomical constraints[4]. The most common symptoms in patients presenting with intracranial complications are fever and headache[4]. Altered mental status and focal neurological deficits are frequent. Seizures occur in 8–20% of cases[11]. Other symptoms include meningismus, decreased visual acuity or other ocular complaints including photophobia[4]. Most intracranial complications result from frontal, ethmoid, or sphenoid[3]sinusitis; sinusitis is often bilateral[11].

Long term sequelae of SDE include hydrocephalus, residual hemiparesis and epilepsy. CT is the imaging modality of choice[9]. Initial CT may be negative or nonspecific[10].

Medical management of subdural empyema includes early initiation of antibiotic therapy, anti-oedema measures and treatment of associated seizures. In most cases the medical management alone is insufficient and associated with high mortality[8,14].

Early surgical intervention by burr hole or craniotomy evacuation is the key to early recovery and salvage of maximal neurological function.[4]. In addition to drainage of intracranial purulence, definitive management of the infected sinuses should be done, preferably at the same time as empyema drainage[4]. Odontogen abscess must be prevented by a rapid diagnosys and combined treatment surgical and medical of dental absess and sinusitis[11]

In our patient, the ENT experts and dentists decided to treat (surgically) the sinusitis and dental infection after the healing of cerebral infection.

The combination of improvement of investigations and management strategies have decreased mortality of intracranial infection to 4-9%[12,13].

The intracerebral frontal abscess formation was determined by the result of pus culture: sterile and in consequence the difficulty of finding an adequate antibiotic[9,5] and the lack surgical treatment of synodental infections. Prolonged spitalisation of this patient increased the risc of Covid contamination.

Conclusions

If the cranial CT Scan reveals a sinusitis and a subdural/extradural hipodensity don't forget the probability of empiema

Odontogen cerebral epidural and subdural empiema and cerebral abscess must be prevented by a rapid diagnosis and treated by combined concomitent treatment medical and surgical of empiema, dental absess and sinusitis as a gold standard. This should be realised by a mutidisciplinary approach between radiologist, neurosurgeon, otolaryngologist, dentist, microbiologist.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Abbreviations

CT Scan - Computed tomography
MRI - Magnetic resonance imaging
SDE - Subdural Empiema

Author's contributions

BD was the major contributor to writing the manuscript;TAH: manuscript preparation, analysis, SAV contributor of the manuscript preparation. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare no potential conflict of interest.

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Management of a double basilar tip aneurysm

A. Chiriac[1], N. Dobrin[2], Georgiana Ion[2], I. Poeata[1]

[1] "Gr. T. Popa" University of Medicine and Pharmacy, Iasi, ROMANIA
[2] "N. Oblu" Emergency Clinical Hospital, Iasi, ROMANIA

ABSTRACT
Complex basilar tip aneurysms are still challenging to secure with coils or stent-assisted coiling. Double aneurysms at the basilar bifurcation and the basilar artery-superior cerebellar artery are a rare particular situation that usually requires more appropriate treatment. This case reports details of our experience with a double basilar tip aneurysm treated in two steps by coiling repair and stent-assisted coiling.

Keywords
double basilar tip aneurysm, stent-assisted coiling

Corresponding author:
A. Chiriac

"N. Oblu" Emergency Clinical Hospital, Iasi, Romania

chiriac_a@hotmail.com

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INTRODUCTION

The basilar tip aneurysm (BTA) is still represents a real challenge for a microsurgical approach due to the deep location and proximity to delicate neuro-vascular anatomical structures. Thus, endovascular techniques remain the most commonly used option for the treatment of these lesions.

A double basilar tip aneurysm is a very complex lesion usually characterized by a wide neck that often involves the origins of more vascular branches. This special vascular pathological condition makes even endovascular treatment a major challenge for most interventionists. In such cases, usually preservation techniques using a stent(s) or balloon can be attempted for a one or two steps intervention. Therefore, a proper diagnosis of these double aneurysms and an optimal technique selection are the most important facts in achieving complete obliteration of these lesions. In this paper we intended to report our experience with such rare case of double basilar tip aneurysm successfully treated while reviewing the literature to improve the understanding of this particular clinical situation.

CASE PRESENTATION

A 38-year-old man was addressed to our emergency room from a service in another hospital on 31 December 2020. A head CT examination at the local hospital suggested Fisher grade 3 subarachnoid haemorrhages and the contrast administration revealed a complex basilar artery aneurysm. The patient was transferred to our hospital for further diagnosis and treatment. At admission patient presented severe headache accompanied by episodes of nausea and

vomiting. The patient had a ten-year history of multiple sclerosis and hypertension with regular treatment. A ruptured large basilar tip aneurysm was confirmed on brain CT angiography, and subsequent subtraction catheter cerebral angiography confirmed a double basilar tip aneurysm at the basilar bifurcation and the basilar artery-superior cerebellar artery junction. A two steps aneurysms embolization treatment was decided. Based on predominant haemorrhage location and aneurysms characteristics the basilar artery-superior cerebellar artery junction aneurysm was considered the ruptured one.

Under general anaesthesia, 6F Merit Medical introducer sheath was placed into the right femoral artery. Using biplane roadmap fluoroscopy a 6F Chaperon guiding catheters (Microvention) were advanced over 0.035 glidewire up to the mid-V2 portion of the left vertebral artery. Based on 3D CT images analysis a working angle roadmap for the target aneurysm was obtained. A Prowler 10 microcatheter was then advanced over a 0.014 Transed microwire (Boston Scientific) into the basilar artery-superior cerebellar artery junction aneurysm to allow placement of coils inside the aneurysm dome. Five GALAXY G3 XSFT microcoils (Cerenovus Johnson&Johnson) were then sequentially inserted and detached into aneurysm. On final angiography, both PCAs were fully saved and the aneurysm was completely packed. The patient was placed into intensive care and received 75mg clopidogrel and 100mg aspirin daily.

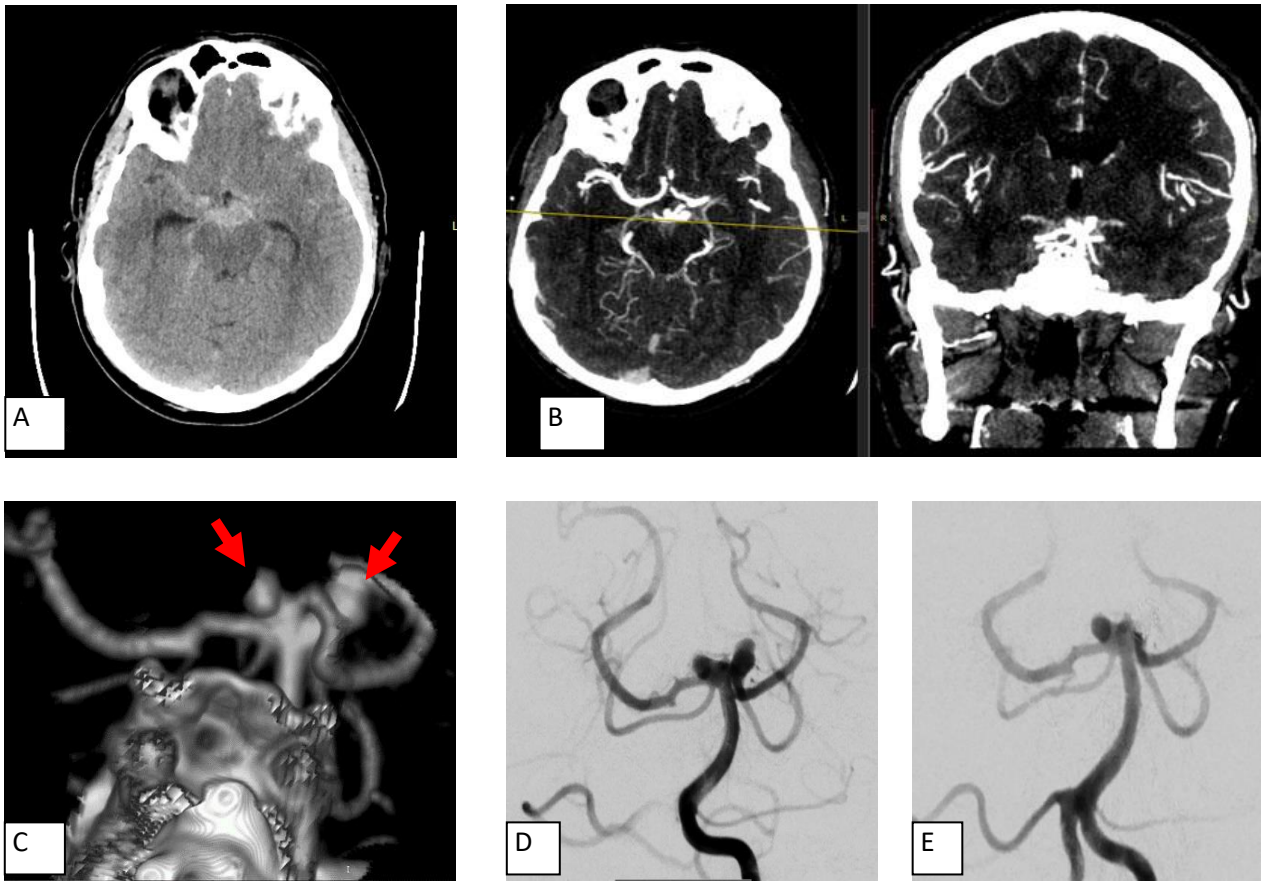

Figure 1. A - First head CT examination at the local hospital showing a SAH; B - brain CT angiography revealing a double basilar tip aneurysm; C – CTA 3D reconstruction; D – DSA in working projection; E – DSA control after basilar artery-superior cerebellar artery junction aneurysm coil occlusion.

After 7 days a second endovascular intervention was decided for associated unrupted basilar bifurcation aneurysm occlusion. A Chaperon guiding catheters (Microvention) was passed to the right femoral artery and securely advanced up to the half-V2 segment of the left vertebral artery. To pass an Enterprise 2 stent

(4/23mm), a Prowler Select Plus microcatheter (Codman &Shurtlett, Inc.) was carefully inserted into the right PCA under the guidance of a 0.014 Transed microwire. The stent was deployed over the P-com/PCA junction point and both aneurysms necks. The Prowler Select Plus microcatheter is than retracted and a Prowler 10 microcatheter is advanced into the basilar tip aneurysm through the stent using a 0.014 Transed microwire. Three GALAXY G3 XSFT microcoils were used for complete angiographic occlusion of the aneurysm. The patient was safely returned to intensive care and anti-hypertensive therapy, antiplatelet therapy, volume expansion therapy, and medication for the prevention of vasospasm were continued. The patient recovered without any complications, and was discarded home 10 days later. He is currently under follow-up as an outpatient.

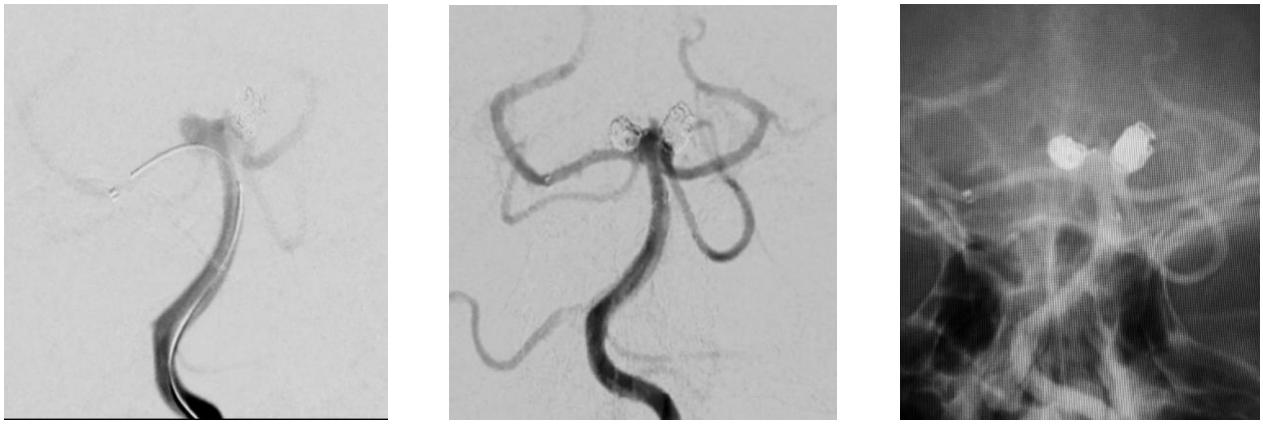

Figure 2. A – Microcatheterization of right PCA for stent placement; B,C – DSA control after stent detachment and trans-stent coil embolization of basilar bifurcation aneurysm.

Discussion

The basilar tip aneurysm is most commonly associated with a complex anatomical configuration. The main pitfall in the treatment of a basilar tip aneurysm consists in the presence of thalamoperforating arteries and numerous vascular branches in relation with a wide-neck or polylobated aneurysmal dome. Presence of a double basilar tip aneurysm at the basilar bifurcation and the basilar artery-superior cerebellar artery junction is a more complex treatment condition. Tanaka et al reported in 2001 the incidence of double basilar tip aneurysm as 5.3% and concluded that they were not extremely rare if accurately diagnosed by the use of modern techniques[4]. At the same time, Hernisniemi in an analysis of the article on double basilar aneurysms reported a much lower incidence of them (3 cases of double basilar aneurysms from a total of 112 patients)[2,3,4].

Due to a high reported morbidity of surgical clipping for basilar tip aneurysm, endovascular interventional therapy became commonly used for majority of these clinical situations. For complex basilar tip aneurysm several endovascular techniques such as stent assisted coiling, waffle cone technique and balloon remodelling can be used to increase aneurysm packing during aneurysm coiling [1].

The technique of balloon-assisted coil embolization, firstly introduced by Moret et al., even if it initially showed a high rate of aneurysmal occlusion, many delayed coil compaction and aneurysm recurrence were reported in time.[4,5] The emergence of various stent assisted coiling has offered a safe and effective clinical solution for this type of complex wide-necked bifurcation aneurysm[1,2,3]. These techniques provide scaffolding for stable and dense coil embolization and blood flow diversion effect away from aneurysm. The most representative stent remodelling techniques in coil embolization of basilar apex aneurysms include classical curvilinear stenting technique, double Y-stenting technique, and waffle cone technique. The waffle-cone technique first reported by Horowitz et al has proved in time a satisfactory protection of the parent arteries origins but not an optimal blockage of the aneurysmal neck. Y-stent assisted coiling technique firstly proposed by Chow et al. in 2004, showed a good clinical prognosis for the treatment of basilar tip aneurysm by

effectively reduction of the aneurysmal neck, protection of the parent arteries and by changing the angle of the blood vessels at the bifurcation. Even if the Y stent configuration has many advantages, it also has several important disadvantages represented by potential thrombus formation and the need for long-term application of double antiplatelet agents. The thrombotic complications associated with this procedure were reported in literature to be approximately 2-21.4%[4,6].

Given the above, there is clear evidence that the single stenting technique associated to basilar tip aneurysms coil occlusion is much easier and with much lower morbidity rates than the double stenting technique. Representative unique stent remodelling techniques of the basilar apex include a curvilinear or horizontal implant positioning.

Treatment of basilar tip aneurysms by horizontally stenting was firstly described by Cross and colab. They used a unique retrograde approach with horizontally stent deployment to both P1 segments perpendicular to the aneurysm, using the ICA-PCom route[2,3,4]. This approach is completely dependent on the tortuosity and size of the posterior communicating artery. In case of the double basilar apex aneurysms that implicate also the basilar artery-superior cerebellar artery junction, the horizontal stent deployment must start from artery-superior cerebellar artery to cover the both aneurysms neck.

Our experience as well as the few data reported in the literature has shown that single curvilinear stenting is the most optimal technique in the treatment of double basilar apex aneurysms. This consists of positioning a stent from the P1 segment opposite the junction aneurysm (BA-PCA) over the necks of both aneurysms to the distal segment of the basilar trunk. However, the stent placement strategy is also determined by a precisely differentiation of a double basilar aneurysm from a bilocular aneurysm at the basilar apex pre-intervenionally.

Conclusion

Double wide-neck basilar tip aneurysms are a challenge to repair, but the unique stent assisted coiling technique is proved to be quite effective whether performed in one or two separate sessions.

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The impact and causes of negative cortical mapping in primary motor area tumours

Mihaela Coșman[1], Bogdan Florin Iliescu[2,3], Anca Sava[4], Gabriela Florența Dumitrecu[4], Ion Poeata[3]

[1] Emergency County Hospital, Department of Neurosurgery, Braila, ROMANIA
[2] Department of Neurosurgery, "N. Oblu" Emergency Clinical Hospital, Iași, ROMANIA
[3] "Gr. T. Popa" University of Medicine and Pharmacy, Department of Neurosurgery, Iași, ROMANIA
[4] Department of Anatomopathology, "N. Oblu" Emergency Clinical Hospital, Iaşi, ROMANIA

Keywords
negative mapping,
positive mapping,
direct cortical stimulation,
primary motor area,
brain tumour

ABSTRACT

Introduction: Intraoperative neurophysiological monitoring is the golden standard for lesions located in eloquent areas of the brain. On the one hand, positive mapping offers a view of the relationship between the anatomo-functional cortical organisation of the patient and the lesion, facilitating the choice of the cerebrotomy entry point and the resection until the functional borders are found. On the other hand, negative mapping does not offer certainty that the absence of the motor response, from the operative field, is the real feedback or is the result of the false-negative response. In such a situation, a differentiation between those two must be done.

Materials and methods: We evaluated the results of direct cortical stimulation of lesion located in or near the primary motor area, which were diagnosticated with contrast-enhancement head MRI and admitted to the Third Department of Neurosurgery, "Prof. Dr N. Oblu" Emergency Clinical Hospital, Iasi, Romania, between January 2014 and July 2018. Special attention was given especially to the negative mapping cases, regarding the histological type, imagistic localisation, symptoms and neurological outcome immediate postoperative, at 6 months and one-year follow-up.

Results: From all 66 patients meeting the inclusion and exclusion criteria in 9,09% (6 cases) we did not obtain any motor response after direct cortical stimulation. The imagistic localisations of those cases were: 3 – Rolandic, 2 – pre-Rolandic and one retro-Rolandic. Tumors histological types were: glioblastoma, anaplastic astrocytoma, oligoastrocytoma and oligodendroglioma each one case and two cases of fibrillary astrocytoma. The intensity range was between 6 – 18mA, the mode – 12mA and the median – 10mA. Postoperatively the neurological condition of 3 patients worsened (4,54% from all the cases), while 3 had a favourable evolution with symptom remission. At 6monts and one-year follow-up in one case (1,51%), we observed no improvement in contrast with the other two, where dysfunction remission was highlighted.

Conclusion: The possible technical, surgical and anesthesiologic causes of false-negative motor response must be eliminated to be able to differentiate from the real

Corresponding author:
Mihaela Coșman

Emergency County Hospital,
Department of Neurosurgery,
Braila, Romania

mihaelacosman@yahoo.com

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absence of the functional area from the operative field. In the first scenario, the resection may be associated with permanent postoperative neurologic deficit and major life quality alteration while in the second one the patient presents no motor dysfunction after surgery and the resection may be extensive with multiple oncological benefits.

Introduction

Intraoperative neurophysiological monitoring (IOM) remains across time in the first line and have gotten the title of the golden standard procedure for lesion located in functional areas, even though we are witnessing a high development of functional imaging techniques especially 3D diffusion tractography and functional magnetic resonance imaging [1,9, 11].

A young age of presentation, paucisymptomatic cases, lesions with good survival rate make the life quality of the patients one of the main medical priorities and so an intraoperative real time feedback it is mandatory for a maximal surgical resection with a minimal neurological dysfunction. The presence of the tumour with its perilesional oedema modifies the normal functional cortical organisation and the topography of the eloquent areas is distorted. Brain mapping with direct cortical stimulation helps identify the functional tissue and differentiate the false-eloquent lesion from the real-eloquent ones, with a considerable impact over the degree of resection [4,5].

Positive mapping is recommended because reveals the anatomical-functional patients brain organisation, which has an interindividual degree of variability helping in choosing the best approach for the tumour resection considering the functional borders [31]. A negative mapping which means the absence of identification of the functional sites in the operative fields has the advantages of o smaller craniotomy, less time in performing the cortical stimulation and decrease the intervention time. A disadvantage of this technique is represented by the fact that negative is not equal with a shore absence of the functional tissue because of the possibility of occurrence of false negative response. The latter is associated with new, eventually permanent motor deficit. Hence the importance of clearing the false negative recordings and the real absence of functional cortex from the operative filed [27,33].

In the following article we present and discuss the poststimulation response after direct cortical stimulation performed on patients with tumors located in central area. The cases in which we did not obtain any response, even though radiologically the primary motor area was located in the operating field were study from clinical, histological and imagistic point of view.

Materials and methods

We present a study group which included patients with surgical lesions in primary motor area or in its vicinity, diagnosed using contrast-enhancement magnetic resonance imaging (MRI), who underwent surgery in the 3rd neurosurgery department of *Prof. Dr. N. Oblu* Clinical Emergency Hospital of Iasi, between 1 January 2015 and 1 July 2018. 76 patients were initially enrolled in the group, but 6 of them were excluded because they did not come to the 6-month and one-year follow-up examination after surgery, and 4 were excluded because they had a pacemaker. In the end, the group included 66 patients.

Inclusion criteria in the study group: tumor located in the primary motor area radiological diagnosed; age over 18 years; intraoperative use of IOM; presentation at the 6 months and one-year follow-up; consent to be included in the study.

Exclusion criteria in the study group: tumor located in the motor area, but inoperable; cases in which only stereotactic biopsy was performed; patients with pacemaker; incomplete patient data.

Intraoperative neurophysiological monitoring was performed using the Nim Eclipse device from Medtronic. Direct cortical stimulation was achieved by means of the short-train technique or train of five. The values of the parameters used in all patients were the following: frequency = 3 Hz, number of pulses = 5, duration = 500μsec, inter-stimuli interval = 4 msec, intensity interval: 6-18mA.The recording muscles were: abductor pollicis brevis, biceps brachii, deltoid, abductor hallucis and tibialis anterior muscle.

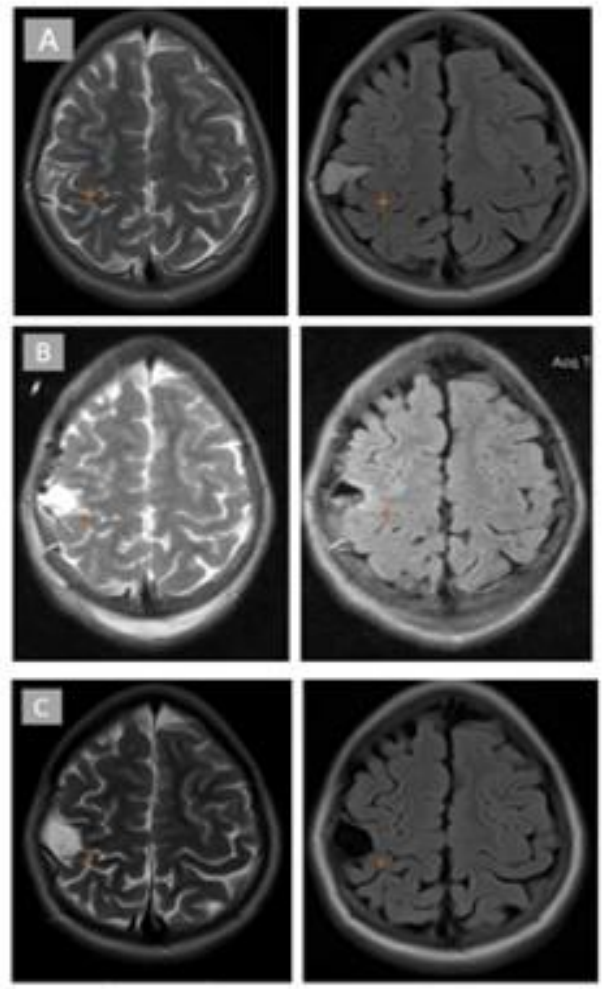
Results

76 patients were initially diagnosticated with a lesion in primary motor area, but after applying the inclusion and the exclusion criteria the study group included 66 patients. The age group distribution was 18 – 79 years and the male/female ratio: 32 (48.48%) / 34 (51.51%). As far as the clinical manifestation is concerned, Jacksonian seizures ranked first. The anatomopathological findings revealed a

glioblastoma (GB) predominance – 21 cases (31.81%), followed by meningioma (Mg) – 19 patients (28.78%), metastases (MTS) – 12 patients (18.18%), anaplastic astrocytoma (AA) – 4 cases (6.06%), fibrillary astrocytoma (AF) – 4 cases, oligoastrocytoma (OA) – 4 cases and oligodendroglioma (ODG) – 2 cases (3.03%).

The most frequent stimulation value that generated motor response was 12mA, then 8mA, followed by 10 mA and 9 mA; 13mA, 14mA, 15mA and 16mA, respectively, were necessary in a smaller number of cases. The peak value 18mA was used only when the stimulation produced no motor response at inferior values. The intensity range was between 6 – 18mA, the mode – 12mA and the median – 10mA.

No direct cortical stimulation response was received in 6 of all patients (9.09%). Preoperative lesions localization revealed by head MRI were: 3 – Rolandic, 2 – pre-Rolandic and one retro-Rolandic. From the anatomopathological point of view, there were 2 patients with AF and one case each following histological type: glioblastoma, anaplastic astrocytoma, oligoastrocytoma and oligodendroglioma. After surgery, the neurological condition of 3 patients worsened (4,54% from all the cases), while 3 had a favourable evolution with symptom remission. The functional status and extent of resection overlapped. Thus, 3 cases who underwent GTR showed motor deficit, while in the other 3 cases, where the resection was subtotal, the clinical manifestation improved. Overall, favourable outcome was achieved in 65,15% of the patients from the study group and new deficits or worsening of the pre-existent one was observed in 15,15% cases. At 6-months and one-year follow up, one case (1,51%) from those with no intraoperative motor response was stationary from the neurological point of view and the other two shown some functional improvement. An illustrative case is presented in **Figure 1**.



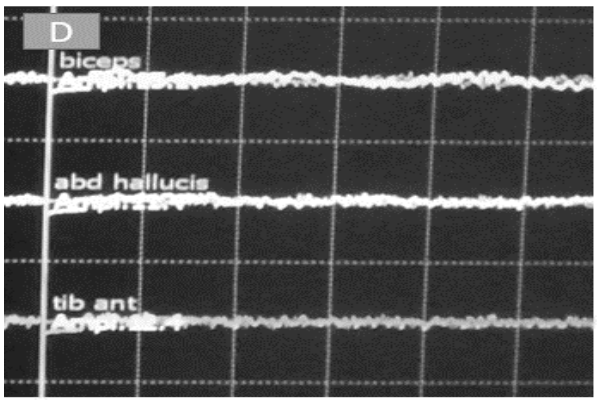


Figure 1. 28 years old female with right prerolandic oligodendroglioma (A-C) has presented with Jacksonian seizures which became drug resistant 2 years after the onset. She was operated using and IOM. Postoperatively she installed left brachial paresis even though intraoperative no cortical motor response was found at direct cortical stimulation (D). She slightly recovered the motor deficit at one year follow up. (A) preoperative head MRI: T2 and FLAIR weighted-images, the star – Rolandic area. (B) postoperative MRI hypersignal in hand area. (C) one year follow up images, oedema remission. (D) no motor response (intensity-18mA), standard baseline muscular recordings (biceps brachii, abductor hallucis, tibialis anterior muscle).

Discussion

For lesion with imagistic location in or near eloquent areas of the brain is extremely important to determine the precise relationship between the tumour and the functional cortex. In comparison with negative, positive cortical sites bring a higher confidence in choosing the cortectomy entry zone and in performing the maximal degree of resection with the aim of minimal postoperative neurological deficits. When in the operative field we do not have the presumed eloquent area is sometimes more stressful because we do not know its location and we are not sure of the postoperative neurologic status for cases with extensive resection [6, 36].

In our study group we had 6 cases in which we did not obtain the motor response. The percentage of 9,09% overlaps over the literature findings (Magill et al., reported 91% of positive mapping) [24].

The absence of the expected motor response or negative mapping creates uncertainty because we must differentiate form the false negative response over real absences of the functional cortex. The former is associated with new postoperative motor dysfunction and has technical, anaesthesiologic and surgical causes. The latter is often the result of neuroplasticity process and the patient remains neurological intact after tumour resection. Chang et al., revealed that 36% of his presumed eloquent cases, based on the radiological images, where in fact false-eloquent. This characterisation is associated with good outcome, because allows to perform an extended degree of resection. The impact of lesion location is considered especially in low grade glioma patients regarding the tumour ablation and progression free survival [5,8].

So et al., published an article in 2018 in which he showed that the motor response is not restricted only to the primary motor area, in 7% of the patient's motor response was observed and posterior to the central sulcus. In one-fourth of them positive sites were discovered anterior to the central sulcus. Tumours growth may be associated with displacement of the normal anatomy and of course of the functional areas, like in two-third of the tested patients [36]. Our results shown that only 3 lesions from those with negative mapping were situated strictly Rolandic and the other three were pre- and retro-Rolandic.

Regarding *technical causes*, those can be prevented by preoperative evaluation of the equipment quality, necessary for the procedure, e.g., the electrodes, the stimulation probe. Verification of the precise placement of the electrodes is particularly important for a correct recording with real assessment of the eloquent area, especially after the patient was positioned, looking for detachments. Another significative step is represented by performing the technique correctly intraoperatively, direct stimulating the cortex, avoiding other structures like blood vessels or through a high amount of cerebrospinal fluid [20, 21,25].

Other causes of negative mapping may be: stimulation with an intensity below the threshold value, shorter pulse duration, electric current transmission through the cerebrospinal fluid and stimulation during the refractory period (Pallud et al., 2017, Eseonu et al., 2018) [10, 27]. Therefor the parameters settings of the stimulation current are important and it's good to know de differences form the two methods of motor network assessment. The traditional technique – Penfield method uses a low frequency (LF) 50 – 60 Hz, a stimulus train of 1 – 4s of biphasic pulse, while short train technique or train of five (TOF, HF) uses a high frequency 250 – 500Hz, a stimulus train of 10 – 18milliseconds of monophasic pulse [3, 30, 32]. Those parameters are usually selected before the surgery and remain the same, the only variable being the value of the stimulus intensity. For our cases we chose the train of five technique and the intensity range was between 6 – 18mA, the mode – 12mA and the median – 10mA, for direct cortical stimulation.

In the speciality literature we usually find papers regarding one technique, but a comparison was made between the LF and HF used on the same patients, in an article from 2020 presented by Bander et al., and the results showed that bipolar HF technique allowed to identify the primary motor cortex in a proportion of 100% (13 cases) vs. 31% obtained using the bipolar LF stimulation [2].

Beside choosing from the two methods of performing IOM, we used, for brain mapping, the technique of stimulating the entire exposed cortex with a constant current value starting from an intensity of 6 mA, which was subsequently progressively increased with 1 mA until the motor response was generated or at a peak value of 18 mA. Another brain mapping technique consist in stimulating every single site with progressive higher current until the response is generated. This is based

on the interindividual and intraindividual threshold variability [6, 22, 29].

Pourtain et all, in 2004 observed significative differences between frontal motor response, parietal/temporal language response and frontal language mapping, the mean stimulation threshold was: 8,4± 2,8mA, 12,3 ±2,9 mA, 9,3 ±3,6mA. This type of mapping has the disadvantage of an increased risk of producing the afterdischarge potentials which may induce intraoperative seizures. Maximizing the current intensity may be associated with less specific cortical eloquent sites identification due to adjacent and subcortical functional stimulation. Another drawback may be represented by the fact that is not time efficient. Both approaches are able to determine the functional sites and the absence of the response is not dependent of which method we use but on knowing the advantages and disadvantages of both of them. In general, if the current intensity is used in order to prevent the appearance of afterdischarge potentials and the threshold is less than the minimum necessary to identify the functional sites, then false negative response will be generated [12, 14].

The bias generated by false negative response may be due to the *learning curve* of the team including the surgeon, the anesthesiologist and the neurophysiologist. The knowledge and the ability of response interpretation has a great impact on the postoperative neurological status and on the degree of tumor resection. In a paper from 2020 Pan et al., reveal that the run-in period for his team was around two years and the unexpected postoperative new motor deficit happened in the first three year from the technique application [28]. In our study all the patients had been operated by the same members of the team and the technical aspects were under the responsibility of the same person.

Discussing the *surgical aspects* one cause for the absence of a response after stimulation may also be due to a smaller craniotomy with more limited cortex exposure. The literature study showed that intraoperative eloquent sites were identified in a proportion of 30% to 100% of the cases: e.g., positive mapping (PM) 58% (Eseonu et al., 2018), 65% (Kim et al., 2009), 91% (Magil et al., 2018) The new postoperative deficit was 51,5% in PM patients vs. 12,5% negative mapping (NM) patients (Eseonu et al., 2018), 12% PM vs. 9% NM (Kim et al., 2009), 60% - new / worsen deficit, not specified regarding the PM nor NM (Magil et al.,2018) [10, 19, 24]. In our study group positive mapping was achieved in 90,91% of the patients. The postoperative outcome was represented by new dysfunction in 15,15% of the cases, 4,54% being from those how did not respond after stimulation. At one-year follow-up in just one case, from the study group, the motor deficit persisted.

It is clear that small craniotomy may limit the identification of the eloquent sites but as showed before the new postoperative motor deficit was higher in positive mapping patients, this suggesting that is not mandatory to perform a large bone flap just for cortical stimulation. Tailored craniotomy which includes the tumor and the adjacent cortex may be enough [24, 33]. In literature it is mentioned that in some limited number of cases, not the dimension of the bone flap is the cause of the negative mapping or of the new installed motor deficit but rather omission or not including a group of muscle from recording setup. Most often it is citated transient orofacial paresis [25].

Other surgical manoeuvres like dissection in the proximity of the corticospinal tract, vascular occlusion of the Rolandic artery or vein may create inadvertence in recording motor evocated potentials. For centres where the subdural grid /stipe electrode is used more attention must be offered to the possible device displacement [37].

The third possible reason for negative mapping is represented by *anaesthesia*, which has an important role in obtaining the proper result after stimulation. Special protocols have been used in order to avoid the medication that causes muscle relaxation which is associated with false negative recordings [16, 18, 26]. Those agents (Lystenon®) were used by our anaesthesia team, in general, at the induction step of the orotracheal intubation, just to facilitate the procedure. The drug's effects are over until the beginning of the operation.

Because a large spectrum of drugs decreases the synaptic activity, the effect being dose dependent, other criteria for the anaesthetic agents to be included in the protocol are represented by the impact on the latency and the response amplitude. Currently there are two directions represented by total intravenous anaesthesia (TIVA) and the use of volatile agents [23, 38]. The latter determines an increase of response latency and a decrease of amplitude, inducing pyramidal inhibition, dose

dependent. A concentration at the alveolar level of 0,5-1 have been found to be safe. The impact of TIVA is also dose dependent but in a smaller extent. Hence, due to their pharmacokinetic properties influence on motor response recordings, synthetic opioids such as Fentanyl and sedative-hypnotic agents represented by Propofol are preferred when IOM is used [13, 17]. These were included in the protocol used on the patients from our study.

From a histological point of view, even though our cases have a large category of tumor type, they have a common feature, namely slow development. This tumor characteristic allows for the neuroplasticity process to start. A consequence of this is function preservation, the main symptom of presentation of our patients being the Jacksonian seizures and not motor deficit.

Studying the neuroplasticity and searching for the reasons of paucisymptomatic cases it is important to understand the functional organisation of the primary motor area which depends on the strict equilibrium from inhibitory and excitatory intrinsic local mechanism. The main system involved in reorganization is represented by the horizontal connections. The redundant motor sites within this map may be reviled using GABAergic inhibition [34, 35]. Usually just this type of reshaping is not sufficient to maintain the function intact so other regions are recruited. First ipsilateral areas are involved e.g., premotor area, supplementary motor area and posterior parietal cortex. As a last resort contralateral "mirror" area participate to this process. In those situations, negative mapping may be found and the tumour resection is not associated with motor deficits [7, 15].

Conclusion

In cases where we do not have a motor response after direct cortical stimulation is applied, for lesion located in or near primary motor area is necessary to consider the step of the intervention to delineate the false negative recordings from real absence of the feedback. The three categories of causes must be eliminated starting with technical problems, anaesthesia and surgical issues. The differentiation from real absence of the motor response has an impact over the degree of resection and this in turn affects the survival rate and the progression free survival.

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Single-session treatment of bilateral, tandem, internal carotid artery aneurysms with pipeline flex with shield technology

Rares Cristian Filep[1], Lucian Marginean[1], Andrei Florin Bloj[1], Istvan Szikora[2]

[1] University of Medicine, Pharmacy, Sciences and Technology "George Emil Palade", PhD School of Medicine, Targu Mures, ROMANIA
[2] National Institute of Clinical Neurosciences, Department of Neurointerventions, Budapest, HUNGARY

Keywords
multiple intracranial aneurysms, flow-diversion, surface modification

ABSTRACT

The treatment of intracranial aneurysms (IA) has been transformed by the development of flow-diversion (FD) devices. Initially, these revolutionary devices were conceived for giant and fusiform aneurysms located on the internal carotid artery (ICA). Technological improvements have expanded their indications. Distal middle cerebral, anterior cerebral artery aneurysms, or even posterior fossa aneurysms can now benefit from this technology. One other category of aneurysms that can be treated is multiple IA's.

Multiple IA's are encountered in approximately one-quarter of patients presenting with subarachnoid haemorrhage. Endovascular management of such cases is complex, requiring different devices and treatment strategies to secure all lesions. FD's can be successfully employed to reconstruct vessels, which harbour more than one aneurysm, especially multiple ICA lesions. Multiple aneurysms located on both ICA's are generically known as tandem aneurysms.

We present the case of a patient with tandem aneurysms located on both intracranial internal carotid arteries that we treated simultaneously with the Pipeline Flex with Shield Technology in one single session. To the best of our knowledge, this is the first case reported in the literature so far.

Corresponding author:
Lucian Marginean

University of Medicine, Pharmacy, Sciences and Technology "George Emil Palade",
PhD School of Medicine,
Targu Mures, Romania

go2lucian@yahoo.com

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INTRODUCTION

Multiple intracranial aneurysms (IA) are found in up to 30% of patients with subarachnoid haemorrhage.[1] Endovascular cure of multiple IA's by simple coiling with or without balloon or stent assistance, performed in one single session, has been assessed in previous studies, as having high procedural success rates and a low number of complications. [2,3] Alternatively, only small patient series have explored the safety and efficacy of flow-diverters for multiple IA, especially as a one-stage treatment.[4]

Our case highlights the treatment of three intracranial aneurysms located on both internal carotid arteries (ICA), with two Pipeline Flex with Shield Technology devices implanted bilaterally in one single session. This is, to the best of our knowledge, the first case reported in the literature pertaining to the use of this device in bilateral, tandem intracranial aneurysms.

CASE REPORT

A 53-year-old female was brought in the emergency department with acute onset headache, dizziness, and nausea. Neurological examination revealed a conscious patient, GCS 15, with 1 point on the Hunt&Hess scale. CT showed mFisher 2 subarachnoid hemorrhage and multiple intracranial aneurysms (not shown). Catheter angiography was performed the next day demonstrating 5 aneurysms, one on the anterior communicating artery (ACA), one on the basilar tip, and 3 on both ICA's, in the ophthalmic segments. Based on the morphologic characteristics and the distribution of the blood on CT, a decision was made to coil the basilar tip and the ACA aneurysms, while the ICA lesions remained to be treated with flow-diversion in a further session. Simple coiling was performed under general anaesthesia for the two aneurysms mentioned above, without clinical complications and a good neurological outcome (Fig. 1 B, C).

Due to the lack of flow-diverter devices in our department at that time, the patient was scheduled nine months later for endovascular treatment of the remaining 3 ICA aneurysms in one single session. The patient received 75mg aspirin, and 75mg clopidogrel for 2 weeks before the intervention. No platelet function test was used before the intervention. Under general anaesthesia, a 7F Destination long sheath (Terumo, Tokyo, Japan) was placed consecutively in the left and right common carotid arteries, and a 6F Navien intracranial support catheter (Medtronic, California, USA) was navigated in the intracranial ICA. Phenom 27 microcatheters with 0,014" Avigo guidewires (Medtronic, California, USA) were used for distal navigation and flow-diverter implantation. Based on the vessel measurements, two Pipeline Flex with Shield technology devices (Medtronic, California, USA), 4x20mm on the left and 4x25 mm on the right, were successfully deployed in both ICA's without periprocedural complications (Fig. 1, 2 B, C). The patient was discharged two days later without neurological deficits, mRS 0. Dual antiplatelet therapy was continued for 6 months, and a control angiogram was performed. It showed complete obliteration of all aneurysms. (Figures 1, 2 D). Afterwards, clopidogrel was discontinued, while aspirin remained as a life-long treatment.

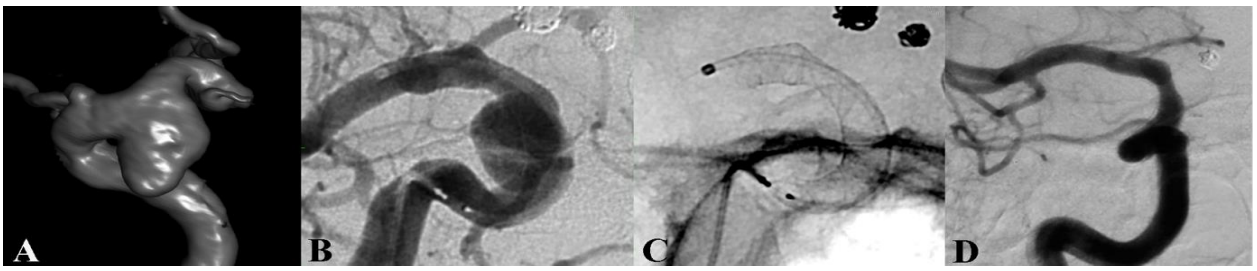

Figure 1. A. Volume rendered depiction of the right ICA shows the broad-neck aneurysm located in the ophthalmic segment. **B, C.** DSA and unsubtracted image in the "working" projection. Note the two coil masses at the top of the images, representing the previously coiled anterior communicating and basilar tip aneurysms. **D.** At 6-months the aneurysm is completely occluded. ICA=internal carotid artery; DSA=digital subtraction angiogram.

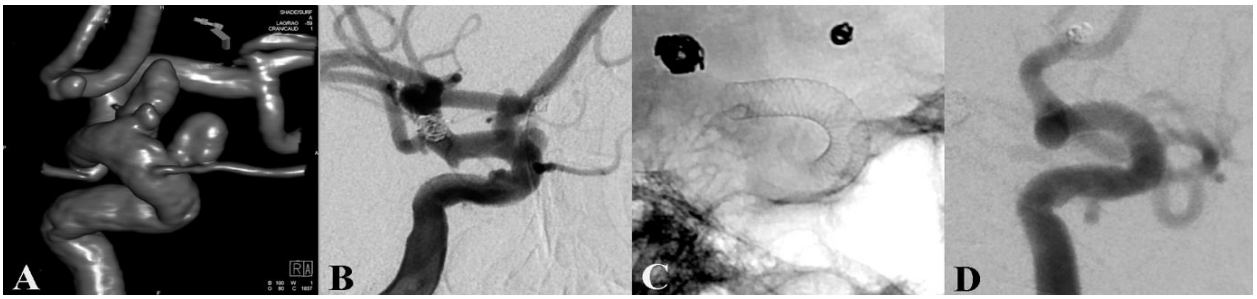

Figure 2. A. Virtual rendered angiogram of the left ICA denoting the two elongated aneurysms located in the ophthalmic segment. **B, C.** DSA and unsubtracted view in the "working" projection showing the position of the device. **D.** 6-months control angiogram highlighting the complete obliteration of the two aneurysms.
ICA=internal carotid artery; DSA=digital subtraction angiogram

Discussions

Flow-diverter devices have revolutionised the treatment of intracranial aneurysms. Large, wide-necked, even fusiform, or dissecting, can benefit from the concept of flow-diversion, progressive intra-aneurysmal thrombosis, endothelialisation of the aneurysm neck and subsequent vessel reconstruction[5,6]. One of the first devices to implement these notions was the Pipeline Embolization Device (PED) (Medtronic, California, USA). Currently at its third generation, the Pipeline Flex with Shield Technology, incorporates a phosphorylcholine surface modification, that acts to reduce the risk of platelet aggregation and thrombosis[7]. The use of this device for the cure of ICA aneurysms is safe and efficacious, with low complication rates, as reported in a recent study[8]. However, its employment, as a solution for multiple IA, especially in both ICA's, in one single treatment session, has not been reported before.

We based our decision to implant two devices for all five aneurysms as a one-shot therapy, based on a number of arguments: one single procedure implies the use of general anaesthesia and femoral artery puncture once, consequently avoiding their inherent risks; furthermore, only one set of devices for access and flow-diverter deployment during the same hospital admission would be more cost-effective.

On the other hand, bilateral flow-diverter implantation can expose the patient to a higher risk of specific complications. In-stent thrombosis and distal thromboembolic events were encountered in 4.7% of cases in the IntrePED study,[9] although older generation PED's, without surface modification, were used. The phosphorylcholine surface theoretically ensures a smaller rate of thromboembolic complications, confirmed in a more recent prospective trial.[8] The more dreaded haemorrhagic complications of flow-diverter treatment, delayed aneurysm rupture and delayed intraparenchymal bleeding, can be a reason for concern if a single-session, bilateral implantation is contemplated. Spontaneous aneurysm rupture can occur in up to 1% of cases,[9] especially if large or giant aneurysms are treated, which was not the case in our patient, the largest aneurysm having a maximal diameter less than 10 mm. Intraparenchymal haemorrhage and its pathophysiological mechanisms are still a matter of debate. If haemorrhagic transformation of small infarcts generated by microemboli are the main cause, the surface modification of the device, can potentially, reduce the likelyhood of such events. Otherwise, the "windkessel" effect is another mechanism incriminated. It relates mainly to the aneurysm size and its capacitance role, which in our case would not be a matter of concern due to their small to medium size.[10]

Conclusion

Flow-diversion can be a safe and effective therapeutic alternative for multiple intracranial aneurysms, with low periprocedural complication rates. Bilateral, multiple internal carotid artery aneurysms can benefit from this technique, even in one single treatment session.

In this regard, the Pipeline Flex with Shield Technology offers a potential advantage due to its phosphorylcholine surface modification. Nonetheless, further studies are mandatory to confirm the safety and efficacy of bilateral, single-session internal carotid artery flow-diverter vessel reconstruction.

Ethical requirements

No personal data of the patient is available for identification.

Conflicts of Interest

Szikora I. offered professional guidance on behalf of Medtronic for this case.

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The evolution of eloquent located low-grade gliomas surgical approaches, their natural history and molecular classification

Mihaela Coșman[1], Andrei Ionuț Cucu[2], Alin Constantin Iordache[2,3], Bogdan Florin Iliescu[2,3], Gabriela Florența Dumitrecu[4], Dana Mihaela Turliuc[2,3]

[1] Department of Neurosurgery, Emergency County Hospital, Braila, ROMANIA
[2] Department of Neurosurgery, "N. Oblu" Emergency Clinical Hospital, Iași, ROMANIA
[3] "Gr. T. Popa University of Medicine and Pharmacy", Department of Neurosurgery, Iași, ROMANIA
[4] Department of Anatomopathology. "N. Oblu" Emergency Clinical Hospital, Iaşi, ROMANIA

Keywords
low-grade glioma, LGG, molecular markers, functional area tumour, intraoperative neuropsychological monitoring

Corresponding author:
Andrei Ionuț Cucu

Department of Neurosurgery, "N. Oblu" Emergency Clinical Hospital, Iași, Romania

andreiucucu@yahoo.com

ABSTRACT

Low-grade glioma is characterized by slow growth, infiltrative pattern through white matter tracts and progression to a malignant tumour type. The traditional classification is newly replaced by molecular stratification. This reorganisation gathers glioma with similar prognosis and treatment protocols. The preferential location of that tumour in eloquent areas constituted, over time, a real challenge regarding the best surgical approach. Because of the high risk of postoperative neurological deficits initially a more conservative management was adopted. Once with the development of preoperative and intraoperative functional assessment techniques, a higher degree of resection was possible in the limits of cortico-subcortical eloquence, being well known that this is a statistically significant factor for survival. We present in this paper the natural evolution of low-grade glioma, their new molecular classification, prognostic factors and the various approach proposed for eloquent ones.

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NATURAL HISTORY AND THE NEW MOLECULAR CLASSIFICATION

Diffuse low-grade gliomas or World Health Organisation grade II gliomas (LGG) represents a group of tumours developed from oligodendrocyte and astrocytic precursors, with a slow and continuously growth pattern, infiltrative character, usually along white matter tracts and progression towards a malignant histological type. Traditionally this includes diffuse astrocytoma, oligodendroglioma and oligoastrocytoma [35,66].

In the new classification of central nervous system tumours from 2016, the phenotypical and genotypical manifestation are in the foreground. The molecular markers like isocitrate dehydrogenase (IDH) mutant / wild type, codeletion of chromosome 1p and 19q, α thalassemia mental retardation X-linked (ATRX) and tumour protein p53 (TP53) genes stratify patients in groups with the same prognostic and guides the cases to a specific therapeutic protocol [36,43]. According to those markers, nowadays, LGG grade II includes: oligodendroglioma IHD mutant and 1p / 19q codeleted, diffuse astrocytoma IDH mutant and diffuse astrocytoma IDH wild type. In patients to which these molecular markers cannot be evaluated the histological diagnosis will be oligodendroglioma not otherwise specified (NOS) or diffuse astrocytoma, NOS [16,35].

LGG occurs usually in young adult, 30-35 years old being the incidence peak [61]. Regarding the natural history of these lesions, it may be summarized in four steps. The first one consists in biological glioma tumoral cells transformation with no clinical manifestation and no routine head MRI detection [34]. The chronological order, from a molecular point of view is represented by IDH mutation, which is thought to be the first, next codeletion of chromosome 1 and 19 (1p/19q) occur and after telomerase reverse transcriptase (TERT) promotor mutation is produced. Some germ lines are associated with tumour grade, the former being found in low-grade glioma and the latter in high-grade glioma [3].

In the second step, the silent stage, the patient is asymptomatic but with imagistic alterations. In this period glioma may be incidentally diagnosed. In the literature, the percentage of incidental LGG (iLGG), from all LGGs, is approximatively similar between studies: 3-10% (Smits et al.,2019) – 3,8%-9,6% (Ius et al., 2020) [27,62]. They have a smaller volume and usually are within non-eloquent brain areas. Even though the diagnostic is obtained after imagistic head investigation for other reasons than a tumour, 36% of all the patient with LGG had the workload decreased for at list one year before lesion discovery [62]. In a study from 2013, Pallud et al., evaluated 148 iLGG cases and observed that the mean time duration until the next phase was 14 ± 7,8 years [46]. Concerning the growth rate of iLGG which was obtained after at list two MRI investigation evaluation at 3 months interval was found to be ranging from 2,93 mm/year (Opoku – Darko et al., 2019) to approximately 4mm/year (Pallud et al., 2013) [43,46].

In the third step, the symptomatic stage, the lesion generates clinical manifestation, most frequently epileptic seizures, which are a proof of somatotopic organization of the cortex where the tumor locates. For example, pericentral region induce Jacksonian motor or somatosensory seizures; temporal lobe – déjà vu phenomena, memory dysfunctions, auditory hallucinations; Wernicke area – sensitive aphasia; Broca area – speech arrest, mutism; insula – paraesthesia, dysarthria, abdominal and thoracic discomfort [47,62]. The average period of this stage is about 7 years and sometimes subtle cognitive impairment may be associated. In general, the cognitive performance is similar to that of healthy population, but specific neurophysiological assessment protocols may highlight memory, attention and executive function disturbance [14,15,49].

The fourth step, the malignant stage consists in tumor malignant progression to a higher histological grade. This happens over a period of 2-3 years and the clinical manifestations are more complex, with neurological degradation and in the final stage death occurs [16,19,34].

Survival and prognostic factors

The survival rate of LGG grade II it is variable, ranging from a few months to over 15 years. The possible factors which may influence the overall survival (OS) are represented by the neurosurgical and oncological management, the histological type or more precise by molecular markers and by clinical parameters [2,22]. Some of them are independent and cannot be changed, but on others we may act. Taking this into account, Zhao et al., proposed in 2019 a nomogram to predict individual 5- and 9-years OS, using 7 clinical and paraclinical parameters [67].

A meta-analysis published in 2019 by Brown et al., confirms that extent of resection has a statistically significant impact over survival rate and progression free survival at 2, 5, 10 years. This parameter constitutes an independent predictor, not being influenced by age or preoperative tumor volume [8,16]. The same results are confirmed and by Choi et al., in a paper from 2020 where he showed that for patients in whom gross total resection (GTR) could not be performed presented recurrence more

frequently after radiotherapy (IDH wild type: 57,9% and IDH mutant: 47,6%) [12].

Regarding the precise value of the extent of resection, there are no exact values, positive effects were observed even from a debulking of 40 % of the tumor and a residual volume <15cm³ (Roelz et al., 2016), but is well known the statistical significance of a higher resection [2,52]. This is confirmed in a paper of Ius et al., in which 190 cases of LGG located in functional areas were included. A resection less than 70% compared with one of more than 90% had a risk of death 19,7 times higher, tumour progression was found to be 13,6 times higher and malignant transformation 9,7 times higher [28].

The best prognostic is carried by oligodendroglioma IDH mutant and 1p/19q codeleted and the worse by astrocytoma IDH wild type [8,35]. The negative prognostic was associated with a tumor volume > 5 cm (Nitta et al., 2015), functional area location (Gousias et al., 2014), Karnofsky performance scale ≤ 80% (Gousias et al., 2014), age ≥ 40 years (Franceschi et al., 2018) and IDH wild-type genetics (Lombardi et al., 2020) [22,25,35,42].

Clinical manifestation with neurological deficits, the absence of seizures, tumour crossing the midline, short time of symptoms before diagnosis, rapid growth rate and the astrocytic type carry an unfavourable impact [16,19,24,30,44]. In **Table I** we have a schematic representation of the new classification of LGG grade II with their specific molecular markers, the impact over survival rate and some specific characteristics.

Table 1. Low grade glioma, the molecular diagnosis markers, and survival impact [1, 16,19, 32,36, 38, 40].

Tumor nomenclature	Molecular markers and prognosis	Notes
Oligodendroglioma, IDH mutant and 1p/19q codeleted	IDH mutant (70-80% of the tumors) – longer OS 1p/19q codeleted Tp53 (5% of the tumors)	-the best prognosis. -more sensitive to chemotherapy.
Oligodendroglioma, NOS	No molecular marker evaluated	
Diffuse astrocytoma, IDH mutant	IDH mutant – mandatory. Tp53 mutation –may be found, shorter OS. ATRX loss – may be found.	-the classical variants protoplasmic and fibrillary astrocytoma were deleted. - small difference in OS compared to anaplastic astrocytoma IDH mutant*.
Gemistocytic astrocytoma, IDH mutant	Tp53 mutation in >80% of cases	-the only type of astrocytoma recognized
Diffuse astrocytoma, IDH wild type	No mutation present of IDH1 codon 123 and or IDH2 codon 172	- usually, uncommon. - not all have poor prognosis. - some have similar manifestation as glioblastoma.
Diffuse astrocytoma, NOS	No molecular marker evaluated	
Oligoastrocytoma, NOS	Oligodendroglioma and astrocytic elements Only in the absence of molecular assessment Under previous entities	- "true" lesion with spatial distinct of both elements in the same tumor are reported.

* OS for diffuse astrocytoma IDH mutant was 10,9 years and for anaplastic astrocytoma IDH mutant 9,3 years in a large series similar regarding the age distribution (Reuss et al., 2015) [51].

SURGICAL APPROACH

The infiltrative feature of these lesions determined Duffau to describe them as" an infiltrating chronic disease that progressively invades the central nervous system", usually the subcortical pathways are affected, and so different neurological functions may be altered [19]. Regarding their location, usually are found in eloquent areas, especially in supplementary motor area and insula, followed by language centres. The preferential development may be explained by cytoarchitectonic (agranular – dysgranular – granular cortex) and functional

similarities between these brain regions [17]. As far their position, the surgical management remain a challenge for every neurosurgeon. Over time, the strategies changed aiming a higher degree of resection with minimal neurologic postsurgical deficits [6].

Because of the increased risk of postoperative neurologic dysfunction for gliomas located in eloquent areas, functional preoperative and intraoperative techniques use is mandatory. The evolution of surgical strategies for these lesions was corelated with the rapid and continuous development of imagistic diagnosis modalities and intraoperative functional assessment techniques. Even though the extent of resection is corelated with survival, nowadays the quality of patient's life is one of the main goals [21, 50, 53].

The surgical management of eloquent LGG suffered many changes over the time. Initially, the approach "wait and see" was applied, but nowadays we can talk even about supratotal resection. The conservative treatment was indicated for incidental glioma and for young patients with minor symptoms [9,21,54].

After a period, when "wait and see" policy was the only measure taken, biopsy become a part of the surgical management, especially for young patients with no neurological deficits, no mass effect and with minor symptoms. This type of treatment has one drawback: because of the tumors heterogeneity, even image-guided stereotactic samples may impair the histological diagnoses, undergrading the lesion. Muragaki et al., highlighted in an article from 2008 that tumors with low proliferative activity, MIB-1 less than 3% and mixt gliomas are more susceptible to this error. This situation may induce a wrong inclusion of the case in a protocol treatment and a misinterpretation of the prognosis. On the one hand, a way to lower this possibility is to perform multiple sampling from various parts of the tumor. On the other hand, for neoplasms located in functional areas this action may be associated with postoperative neurological dysfunctions [41].

Nowadays the bias, in histological interpretation induced by stereotactic biopsy sampling compared with the specimens obtained from a classical intervention is reduced because of molecular analysis and new classification of the gliomas [29].

Clinical studies concluded that early surgery may delay malignant transformation and increases overall survival in low grade glioma patients. Maximal resection in functional limits is indicated and for tumours located in functional areas of the brain. The development of intraoperative neurological functions assessment technologies e.g., neurophysiological monitoring (Magil et al., 2018; Bander et al., 2020), 3D tractography integrated in neuro-navigation system (Romero-Garcia et al., 2020), awake craniotomy (Saito et al., 2018; Wang et al., 2019), fluorescein-based surgery (Coburger et al., 2019), intraoperative MRI (Caras et al., 2020; Scherer et al., 2020) help in obtaining a maximal resection with minimal postoperative dysfunction [6, 10, 13, 31, 37, 53, 56, 59, 63].

Jackola et al., highlighted the important survival advantage when comparing wait and see approach with early tumor resection. For the first group the median of OS was 5,8 years and 14,4 years for the second group [29].

In a metanalysis performed by Yang et al., in 2018 a comparison was made between biopsy and surgical resection (GTR and subtotal resection – STR). OS was found to be 3,7 years in biopsy patients' group, 6,6 years for STR cases and 10,6 years for GTR cases. Statistical significance was obtained comparing biopsy with any degree of resection, in favour of surgical debulking [65]. Considering the ones above, only biopsy is performed in patients who have contraindication for an open surgery because of severe medical pathologies or when even subtotal resection is not feasible [19].

As mentioned before, the study of LGG literature considers eloquence as a negative prognostic factor. Chang et al., showed that this parameter induced over the 281 functional located diffuse glioma cases an increased hazard ratio with shorter OS and PFF [11]. A shift from image – guided surgery to functional – guided resection made possible to perform a higher degree of resection by delineating the preoperative presumed eloquent situated lesion form the ones truly eloquent. When cortical mapping was negative and the functional area was actually relocated and not in contact with the tumour, the survival of those cases was longer and similar to those in non-eloquent areas [4,11].

Even if the glioma is developing in eloquent area, the slow growth pattern, is considered as an advantage which allows the neuroplasticity process to act. This concept was at the base of the proposal of individualized multistage surgery. A better

understanding of brain plasticity, development of neurocognitive protocol assessment for cerebral tumours and personalized postsurgical cognitive and functional rehabilitation increased the chance for a better outcome. Duffau presented the steps of this approach. After the first operation, where a subtotal resection was performed, limited by the functional borders, the patient was evaluated periodically clinically and radiologically and a second surgery was scheduled, if needed, considering the tumor regrowth and cortical remapping. This allows to increase the extent of resection and to maintain the neurological integrity [18,19,21].

One of the first presentation of this technique performed over 19 cases of eloquent LGG was from 2009. The results of Martino et al. showed the safety of this strategy. The patients were operated two times with a median time of 4,1 years between intervention and intraoperative neurophysiological monitoring was used. The functional guided surgery resulted in allowing 94,7% of the cases to have a normal socio-professional life [39].

Another strategy proposed for eloquent LGGs was the safe margin technique resection. This policy was based on the development of perioperative assessment methods, especially functional magnetic resonance imaging (fMRI) and brain mapping. In the early 90s, using intraoperative neurophysiological monitoring, Ojemann recommended a 7-10 mm secure margin preservation around positive sites, after observing that this is associated with fewer postoperative neurological deficits. The results were based on the fact that for cortical mapping the electrodes from the subdural grid were placed at one-centimetre distance from each other [26, 57].

In the same surgical direction are presented the results of 54 motor area tumour resection using the fusion of preoperative f MRI with neuro-navigation, in an article of Krishnan et al. published in 2004. In 83,33% of the cases gross total resection was achieved and subtotal (80-95% of the tumour volume) was performed to the rest of the patients, the postoperative new deficits were recorded in 16,7% of the cases. The author observed and concluded that a distance less than 5 mm from the tumour to the active functional site is associated with high risk of motor dysfunction and a greater distance than 10 mm is safe for gross total resection [33].

New fMRI studies confirmed the relationship between the tumour borders and the location of the eloquent sites, regarding the postoperative new neurologic deficits. In 2011 Wood et al. observed some difference between the behaviour of the motor and primary language areas regarding the distance to the lesion. For motor strip when the distance was 1 - 2 cm compared to greater than 2 cm, the incidence of neurological dysfunction was 39%, a 34% increase was observed when less than 1cm was meet. As for language area a nonlinear manifestation was found. The prevalence of aphasia increased significatively when the distance was less than 1 cm. The difference of the functional and structural organization of the motor area and language areas may explain these results, beside the high grade of individual variability of the latter [64].

It is well known that not only the cortical functional sites are important and need to be preserved but also the subcortical motor and language pathways. In 2015 Bailey et al. evaluated if the lesion to distance activation (LAD) is a predictor factor for the perioperative language and motor deficits. He used fMRI and assessed the superior longitudinal fasciculus (SLF) and corticospinal tract (CST) with diffusion tensor imaging (DTI) on 76 cases of functional located tumours. Postoperative, the only significative difference was noted for motor LAD with a trend level effect. The involvement of CST was significantly statistically for pre and postoperative motor deficit, in comparation SLF involvement had a significance only between asymptomatic and symptomatic preoperative cases [5].

Sollman et al. presented in 2020 the results of evaluating the impact of the distance from the lesion to CST or arcuate fascicle (AF) of 250 functional located tumours which were assessed using navigated transcranial magnetic stimulation and DTI fibre tracking. The most statistically significative postoperative neurological impact observed for CST was for a distance less than 12mm, for AF less than 16mm and the value of 25 mm for any other language tract [61]. In an previews study from 2019, Sollman et al. found that a distance greater than 8 mm from the tumour to the AF and one greater than 11mm for the other fascicle involved in the language pathways were associated with permanent aphasia. These differences may be explained by the difference between the two studies regarding the cases numbers and the fact that the permanent deficit was not so high, hindering the statistical evaluation [60].

White matter dissection, development of 3D tractography helped in discovering and understanding the subcortical pathways anatomy. A functional atlas of white matter fibres was proposed after evaluating 130 eloquent tumours operated awake and with intraoperative neurophysiological monitoring [58]. The anatomo-functional structure of the brain is the bases of the next type of approach used for functional located gliomas: cortical subpial dissection. Duffau and Gil-Robles compared the results regarding the postoperative deficits of the patient with eloquent glioma operated with and no safe margins around the functional area. They did not find a significative difference between the two techniques when the permanent deficit was evaluated (1-2,5% vs. 1,7%), even though the transient deficit was higher for the latter technique, this suggesting that subpial dissection and intraoperative mapping is a safe strategy for eloquent LGG. The assessment of cortical areas along with the projection tracts, long distance association fibres and short association fibres (U-fibre) increase the degree of resection while preserving and minimizing the postoperative deficits [23]. A tailored intraoperative monitoring may improve the neurological outcome, but the survival rate was found to be the same (Pan et al., 2020) [48].

Even though it seems utopian, the question about the feasibility of supramarginal resection for presumed eloquent glioma was asked. This concept has at the basis the observation made after biopsy tissue, from beyond the abnormal FLAIR-MRI signal, was evaluated and tumor cells were found, even at a distance of 20 mm from the preoperative images lesion demarcation. The first study with a long follow-up period (132 months) showed no case of malignant transformation and no relapse at half of patients, highlighting the impact of supramarginal resection over tumor progression [7, 20, 45].

An extensive analyse was performed by Rossi et al., in an article from 2020 regarding this supposition. The study group included 449 glioma cases, 413 of them imagistic located in functional areas. The results showed that the most important and statistically significant factor associated with achieving this degree of resection was the duration of the symptoms longer than 6 months and was independent of age, sex and tumor volume. The safety of this procedure for lesion preoperatively presumed to be in eloquent area and a good neurological outcome is explained by the activation of neuroplasticity processes with a high reorganisation of the cortico-subcortical pathways and intraoperative identification of the functional sites outside the tumors margins. Smaller odd of obtaining this result was for parietal lesions compared with temporal and frontal location. From all four hundred forty-nine patient supratotal resection was obtained in 32,2% and total resection in 40,8% of the cases. Regarding the postoperative new deficits, the transient type remitted in 1-2 week and the permanent one was lower in comparison with those from the patient's group where subtotal or partial removal was performed (6,6% vs 0,55%; 6,6% vs 0.68%, p<.001) [55].

Conclusion

Considering the natural history, the continuous, slow growth and histological progression make the surgical treatment of low-grade gliomas to be the first choice in their management. The development of preoperative radiologic evaluation and intraoperative function assessment techniques, especially cortical and subcortical mapping helps in performing a higher degree of resection with minimal neurological dysfunction and for eloquent located LGG. We witness the evolution and the advance made regarding the surgical approach of these tumours from wait and see policy to even evaluation the feasibility of supramarginal resection.

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Spontaneous intracerebral haemorrhage as an initial presentation of a choriocarcinoma. A case report

Maher Khashea Mustafa[1], Wamedh E. Matti[2], Hussain J. Kadhum[2], Zahraa A. Alsubaihawi[3], Zahraa M. Kareem[3], Zahraa F. Al-Sharshahi[2], Samer S. Hoz[2]

[1] Department of Neurosurgery, Fallujah Teaching Hospital, Anbar, IRAQ
[2] Department of Neurosurgery, Neurosurgery Teaching Hospital, Baghdad, IRAQ
[3] Medical student, College of Medicine, Baghdad University, IRAQ

ABSTRACT

Introduction: Choriocarcinoma is a rare gestational trophoblastic neoplasm with a high risk of pulmonary, hepatic, and, rarely, cerebral metastasis. We report a rare case of intracerebral haemorrhage as an initial manifestation of metastatic choriocarcinoma.

Case presentation: A 33-year-old female with a history of multiple abortions, ectopic pregnancy, and complete hydatidiform mole presented with a disturbed level of consciousness. Emergency brain computed tomography (CT) scan revealed an intraventricular haemorrhage (IVH) and a left frontoparietal, non-traumatic intracerebral haemorrhage (ICH) with a significant midline shift. The patient underwent emergency evacuation of the hematoma and histological evaluation revealed choriocarcinoma. Later investigations revealed evidence of systemic metastasis. The patient underwent chemoradiotherapy and recovered well.

Conclusion: Metastatic choriocarcinoma should always be in the differential of non-traumatic intracerebral haemorrhage in a female child-bearing age. Also, the pathological diagnosis should always be performed in cases of ICH of an unknown source.

Keywords
ICH,
brain metastasis,
choriocarcinoma

Corresponding author:
Zahraa F. Al-Sharshahi

Neurosurgery Teaching Hospital, Baghdad, Iraq

Zahraaalsharshahi@rcsi.com

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INTRODUCTION

Choriocarcinoma is a gestational trophoblastic disease; it is a rare, malignant tumor of human chorionic tissue (1). Choriocarcinomas have an incidence ranging between 3 and 21.4% with a higher incidence in southeast Asia. Choriocarcinomas may complicate any type of pregnancy, with more than 50% of cases arising from hydatidiform moles (2, 3). Choriocarcinoma is an aggressive tumor that frequently metastasizes to the lung, liver, and to a lesser extent to the brain (4,5).

Cerebral choriocarcinoma typically presents as single or multiple lesions, manifesting as infarction, subarachnoid hemorrhage, oncotic,

or pseudoaneurysms (6, 7). Intracerebral hemorrhage (ICH) as the initial manifestation of choriocarcinoma is an exceptionally rare presentation and signifies poor prognosis (8). The Initial appearance of choriocarcinoma in patients with intracranial hemorrhage (ICH) is extremely rare and is considered a poor prognosis factor (8). In this paper, we detail the case of an adult female with ICH that later led to a diagnosis of metastatic choriocarcinoma.

CASE REPORT

A 33-year- old female presented with a disturbed level of consciousness and a history of repeated episodes of vaginal bleeding lasting 3 days on average. Upon neurological examination, her Glasgow coma scale was 5/15 with fixed dilation of the left pupil.

This lady is a gravida, with a history of recent ectopic pregnancy and two abortions, one of them being a complete hydatidiform mole (G4P1A2). Initial brain computed tomography (CT) scan revealed an intraventricular hemorrhage (IVH) and a left frontoparietal, non-traumatic intracerebral hemorrhage (ICH) with a significant midline shift (**Figure 1**).

The patient underwent surgery to evacuate the hematoma and resect the lesion (**Figure 2**). Histopathological examination showed the lesion to be metastatic choriocarcinoma. Postoperative GCS was 10/15, and the patient had persistent aphasia with a right-sided hemiparesis (Medical Research Council grade 3/5).

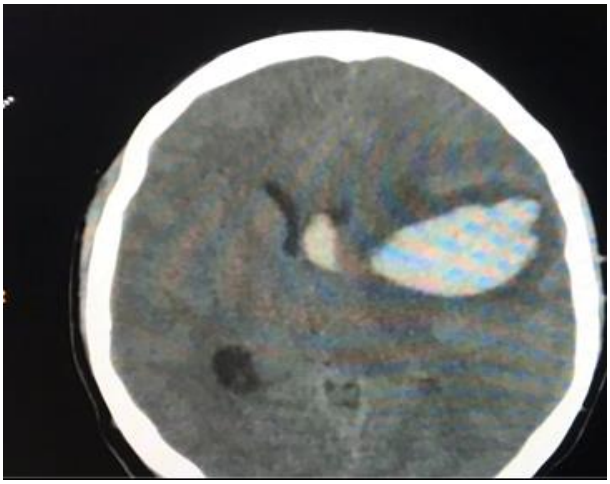

Figure 1. A non-contrast CT scan axial section showing a left lateral ventricular haemorrhage (IVH, left fronto-parietal intracranial hemorrhage (ICH), with significant midline shift and ventricular compression.

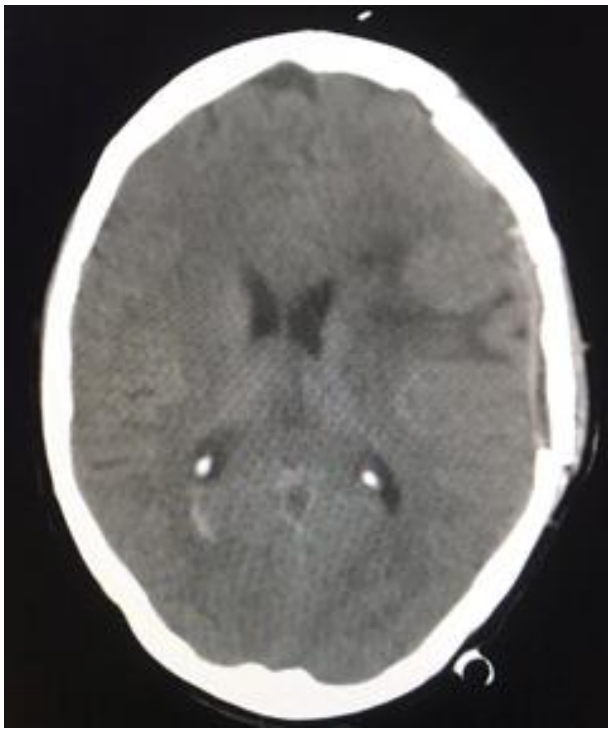

Figure 2. A non-contrast post-operative axial CT scan showing complete evacuation of the intracranial and intraventricular haemorrhages with a significant decrease in the midline shift.

The serum level of human chorionic gonadotropin hormone serotype Beta (B-HCG) was significantly elevated (78800 mIu/ml). Abdominal CT scan showed right, a pleural-based, well-defined lesion with a significant post-contrast enhancement. The CT also showed an ill-defined heterogeneously enhancing soft tissue lesion in the left kidney that suggesting a metastatic deposit. The uterus was normal in size. A well-defined mass was detected anterior to the uterus. Pelvic MRI showed a right ovarian mass that was complex, multiloculated, and had cystic components. The mass invaded the right posterolateral wall of the urinary bladder and uterus.

The patient was referred to oncology for further assessment and chemoradiotherapy. She later underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, radical left nephrectomy, and excision of the small intestinal metastasis.

On follow-up, her B-HCG levels started to normalize. Her subsequent follow-up head CTs revealed no residual or new lesions or recurrence.

Discussion

The clinical picture of tumoral ICH often overlaps that of cerebral vascular malformations, necessitating the exclusion of these more common pathologies (9, 10).

In neurosurgical practice, the primary presentation of non-traumatic ICH suggests a local cerebral cause, mostly vascular malformations, rather than tumor metastasis (11). However, Choriocarcinoma should be suspected in every female of reproductive age with an unexplained non-traumatic ICH and considerable perilesional edema and mass effect. Significant elevation of beta-HCG raises the suspicion of choriocarcinoma. Serum: CSF ratio of beta-HCG is usually used as a confirmatory test for diagnosis, as well as an important follow-up test to measure disease remission and detect recurrence (10-13).

The mechanism under which choriocarcinoma is disseminated explains its propensity to manifest as mass hemorrhage, vascular malformations, such as aneurysms or pseudoaneurysms. Choriocarcinoma progresses by blood-borne metastases at an early stage. Trophoblastic tumors are associated with fragile vessels, by their innate capacity to erode vessel wall after tumor embolization, causing weakening and destruction of the vessel wall, leading to the manifestation of intracranial hemorrhage, aneurysmal dilatation, or infraction if the emboli closed the vessel lumen (14,15).

Cerebral metastasis is most often seen in patients with advanced stages of choriocarcinoma and is considered to be a poor prognosis indicator. The treatment of choriocarcinoma with cerebral metastases includes chemoradiotherapy with or without surgery. Surgery is associated with a high risk of hemorrhagic complications and should thus only be performed in patients with life-threatening ICH or focal recurrent lesions resistant to chemo-irradiation (5,11,13,16)

Conclusion

Metastatic choriocarcinoma should always be in the differential of non-traumatic intracerebral haemorrhage in a female child-bearing age. Also, the pathological diagnosis should always be performed in cases of ICH of an unknown source.

Abbreviations

DLOC - Disturbed level of consciousness;
GCS - Glasgow coma scale;
ICH - Intracerebral hemorrhage;
IVH - Intraventricular hemorrhage;
AVM – Arteriovenous malformation.

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rCBV and ADC based grading of gliomas with glimpse into radiogenomics

Seema Rohilla[1], Ambresh R. Deodurg[1], Pritviraj S. Kanakavvanavar[1], Ishwar Singh[2], Veena Gupta[3], Dhara B. Dhaulakhandi[4]

[1] Department of Radiodiagnosis & Imaging. Post Graduate Institute of Medical Sciences, Pt. B.D. Sharma University of Health Sciences, Rohtak, INDIA
[2] Department of Neurosurgery. Post Graduate Institute of Medical Sciences, Pt. B.D. Sharma University of Health Sciences, Rohtak, INDIA
[3] Department of Pathology. Post Graduate Institute of Medical Sciences, Pt. B.D. Sharma University of Health Sciences, Rohtak, INDIA
[4] Department of Biotechnology & Molecular Medicine. Regional Cancer Centre. Post Graduate Institute of Medical Sciences, Pt. B.D. Sharma University of Health Sciences, Rohtak, INDIA

Keywords
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proteomics,
radiomic

ABSTRACT

Purpose. The present study was carried out to study the role of relative cerebral blood volume (rCBV), apparent diffusion coefficient (ADC) and MR spectroscopy in grading gliomas to help the surgeon plan the approach and extent of surgery as well as judge the need for any adjuvant radio/chemotherapy.

Methods. 65 patients with glioma were prospectively studied with MRI. Basic MR sequences (T1W, T2W, T2W/FLAIR) were followed by diffusion-weighted (DW) imaging with b value of 1000 (minimum ADC values used for analysis). Then the patients were administered Gadobenate Dimeglumine/ Meglumine Gadoterate in a dose of 0.1mmol/kg at a rate of 4ml/sec after which 20ml of saline was flushed at a rate of 4ml/sec and T2*W/FFE dynamic images were acquired; dynamics showing maximum fall in the intensity were used for creating rCBV and rCBF maps and calculating rCBV. Single voxel spectroscopy (SVC) was done using the PRESS sequence with intermediate TE of 144ms. NAA/Cr, Cho/Cr, Cho/NAA, Cho+Cr/NAA and NAA/Crn ratios (NAA from the tumour, Crn from the normal side) were calculated.

Results. Grade I gliomas showed minimum ADC>0.84x10^{-3}mm^2/s and maximum rCBV<1.9ml/100gm, grade II gliomas showed min ADC 0.75-0.84x10^{-3}mm^2/s and max rCBV of 1.9-2.6ml/100gm, grade III had min ADC of 0.70-0.75x10^{-3}mm^2/s and max rCBV of 2.7-3.0ml/100gm, while grade IV tumours showed min ADC<0.70x10^{-3}mm^2/s and max rCBV>3.0ml/100gm. rCBV values were better than ADC values in differentiating grade I from II and grade II from III. The ADC values were better than rCBV values in differentiating grade III from grade IV.

Conclusions. Both minimum ADC and maximum rCBV within the tumour were significant but these parameters within peritumoural oedema were not significant in grading gliomas. Though lipid and lactate (especially lipid) peaks were found more frequently in higher-grade tumours, various spectroscopy parameters were not significant in grading gliomas. Preoperative grading of gliomas with the help of

Corresponding author:
Seema Rohilla

Post Graduate Institute of Medical Sciences, Sharma University of Health Sciences, Rohtak, India

seemarohilla@yahoo.co.in

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advanced MR parameters like ADC and rCBV can help the surgeon plan the approach and extent of surgery as well as judge the need for any adjuvant radio/chemotherapy. Advancing radio-genomic and radiomic technologies can supplement the current radiologic methods of diagnosis and prognosis.

Introduction

The majority of primary brain tumours are gliomas which may be low (grade I and II) or high (grade III and IV) grade [1]. The inherent heterogeneity of gliomas makes it difficult to grade them with conventional MRI. However, advanced MRI techniques such as perfusion, diffusion, spectroscopy and largely experimental molecular imaging can aid in such grading.

Dynamic susceptibility contrast magnetic resonance (DSC-MR) imaging helps in assessing tumour vascularity and angiogenesis non-invasively by way of decrease in signal intensity with time during the first pass of a bolus of paramagnetic contrast agent. The maximum tumour rCBV tends to increase as the grade of astrocytoma increases. Increased cell density reduces Brownian motion leading to restricted diffusion and reduced ADC. Thus, higher the tumour grade, lower the ADC. In a tumour, the increase in cell turnover leads to an increase in choline concentration, along with a depression of the NAA peak due to loss of healthy glioneural structures. Lactate peak suggests hypoxia while lipid peak is suggestive of necrosis, an indicator of malignancy.

Preoperative grading of gliomas with the help of advanced MR parameters like ADC and rCBV (specially in hospital settings which lack stereotactic biopsy facility) can help surgeon plan the approach and extent of surgery as well as judge the need of any adjuvant radio/chemo therapy. Relationship between imaging features and genetic/molecular features of tumours can be addressed using radio-genomic methods. Continuously evolving “omics” procedures and modalities coupled with advances in basic tumour biology, histopathology, computational and molecular tools can complement imaging as well as genetic analysis. Integration of imaging markers derived from clinical images and genomic markers such as EGFR, MGMT, IDH1, 1p/19q codeletion can be explored in a non-invasive manner [2]. For example, a direct association is found in EGFR amplification and contrast enhancement in GBM; ill-defined tumour margins and tumour heterogeneity can potentially be used as imaging biomarkers for 1p/19q codeletion in gliomas [3]. Application of radiogenomic markers is particularly useful when taking biopsy is not possible. To have a deeper insight into tumour makeup, a wide array of quantitative and qualitative imaging features may be utilized to record distinct imaging phenotypes and link them to genomic profiles. Whereas staging signifies the tumour spread, grading signifies the general tumour aggressiveness. Hybrid of imaging and genomic techniques have not only led to improved tumour grading assessment by capturing heterogeneity more precisely but have also added refinement to staging. Various radiological features like location, lateralization, enhancement characteristics, perfusion parameters, ADC, etc. can help assess genetic/molecular make-up to some extent which further help in predicting prognosis and effectiveness of therapy. Current and evolving radio-genomic, proteomic and spectroscopic technologies can supplement the current radiologic methods and procedures to help clinicians better equip for making accurate diagnosis and precisely grade gliomas.

Material and methods

65 patients with glioma were evaluated. Basic MRI sequences i.e. T1W(TE-15 ms, TR-596 ms, field of view(FOV)-230 mm, matrix size-(186x256), flip angle-69o and NSA-1), T2W(TE-100 ms, TR-4431 ms, FOV-230 mm, matrix size-(236X512), flip angle-90o and NSA-2) and T2W/FLAIR(TE-120 ms, TR-6000 ms, FOV-230 mm, matrix size-(172x256), flip angle-100o TI(time to inversion)=2000 ms and NSA-1) were done in axial, sagittal and coronal plains as per requirement on Gyroscan Intera Nova gradient 1.5 Tesla Philips Imaging system, Best, Netherlands using a SENSE head coil (6 channel phased array coil). Informed consent was taken from the participants. Approval of the Dean, Faculty of Medicine and Allied Sciences was taken for the study which was conducted in accordance to provisions of Institutional Ethics Committee.

Diffusion weighted imaging (DWI) was carried out with a single shot echo planar imaging (EPI) sequence with a TE-89 ms, TR-2609 ms, FOV 230 mm, matrix size- 89x256, flip angle-90o and NSA-3, with a b value of 1000. ADC map was calculated by automated software on workstation (view forum version 5.1) and minimum ADC values used for analysis. The ADC

values were calculated in tumours in all 65 cases and in peritumoural edema 56 cases.

Perfusion weighted imaging (PWI). The patients were given gadobenate dimeglumine/ meglumine gadoterate in a dose of 0.1 mmol/kg at a rate of 4 ml/s followed by saline flush of 20 ml at a rate of 4 ml/s using pressure injector medrad spectrosolaris version 008.001-sa. T2*W/FFE dynamic sequence (TE-30 ms, TR-627 ms, FOV-230, matrix size-128x128, flip angle-40o and NSA -2) was acquired. rCBV and CBF maps were created on the dynamic showing maximum fall in signal intensity on first pass of contrast bolus. Maximum rCBV was calculated with the help of automated software on View Forum 5.1. The values were calculated in tumour in all 65 cases and in perirumoral edema in 35 cases.

Spectroscopy. Single voxel spectroscopy (SVC) was performed using PRESS sequence with intermediate TE of 144 ms. The voxel was placed at most dark area in ADC map/maximum enhancing area on contrast MRI (scalp and skull bones were excluded from the voxel). Two spectroscopy data sets were obtained - one from the most malignant appearing area of tumour and another from the corresponding normal white matter. NAA/Cr, Cho/Cr, Cho/NAA, Cho+Cr/NAA and NAA/Crn ratios- NAA from tumour, Crn from normal side were calculated.

Two sample Wilcoxon ranksum (Mann-whitney) test, Kruskal-Wallis equality-of-populations rank test and ROC analysis were the statistical tests applied with stata software version 11.2. Surgery/biopsy were used as gold standard for final diagnosis.

Results

65 patients with glioma (4-76 years old with mean age of 41 year) with 49 males and 16 females were studied. Basic MR sequences showed tumour appearance on T1W, T2W, FLAIR, and contrast enhanced T1W images (Figures 1-3). Most of the tumours were hypointense on T1W and hyperintense on T2W images. High grade tumours were more heterogeneous and showed contrast enhancement. Haemorrhage and necrosis were more common in grade IV tumours. They were seen less frequently in grade II and grade III tumours, were almost equally frequent in grade II and grade III tumours and were not seen in grade I tumour. Mild enhancement could be seen in some low-grade gliomas also.

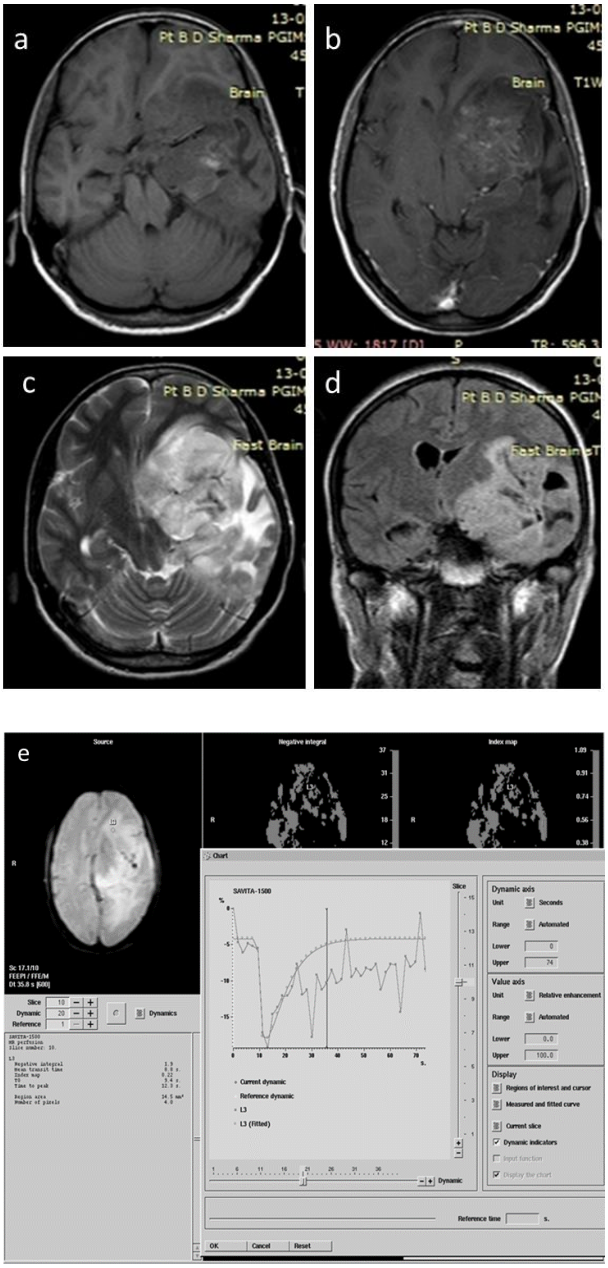


Figure 1. 40yr old female patient with oligodendroglioma in left frontotemporal region (Grade II):
(A) Axial T1W image showing illdefined hypointense lesion in left frontotemporal region showing area of hemorrhage as hyperintense signal and necrosis as hypointense signal.
(B) Axial T1W contrast image showing mild heterogenous contrast enhancement.
(C) Axial T2W image showing illdefined hyperintense lesion with minimal peitumoral edema.
(D) Coronal T2W/FLAIR image showing the lesion causing mass effect on surrounding parenchyma with midline shift towards right side.

(E) Axial T2*W first pass perfusion image showing color coded rCBV maps along with time-signal intensity curve and various parameters [rCBV (negative integral), rCBF (index map),MTT and TTP],rCBV being 1.9ml/100gm.

Even though the lesion appeared high grade on morphological features the parameters showed low grade and was proved to be grade II oligodendroglioma.

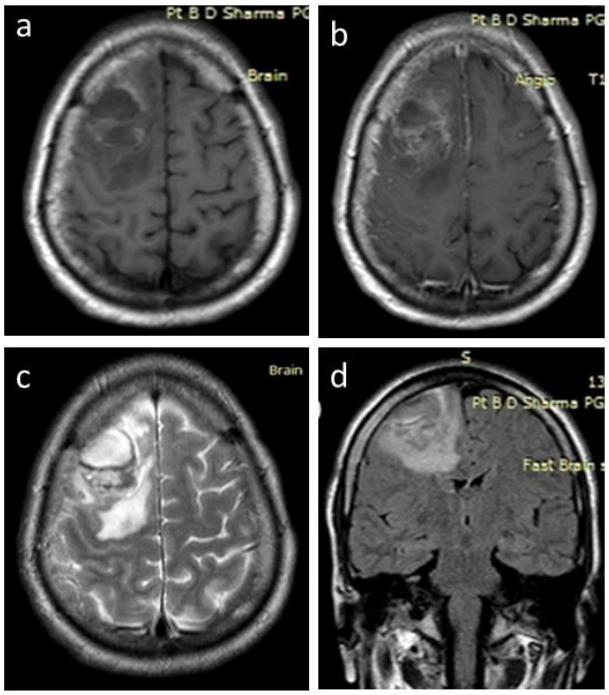


Figure 2. 52 yr old female patient with anaplastic astrocytoma in right frontal lobe (Grade III):

(A) Axial T1W image showingilldefinedhypointense lesion with hemorrhagic areas seen as hyperintense signal seen in right frontal lobe.

(B) Axial T1W contrast image showing mild heterogenous contrast enhancement.

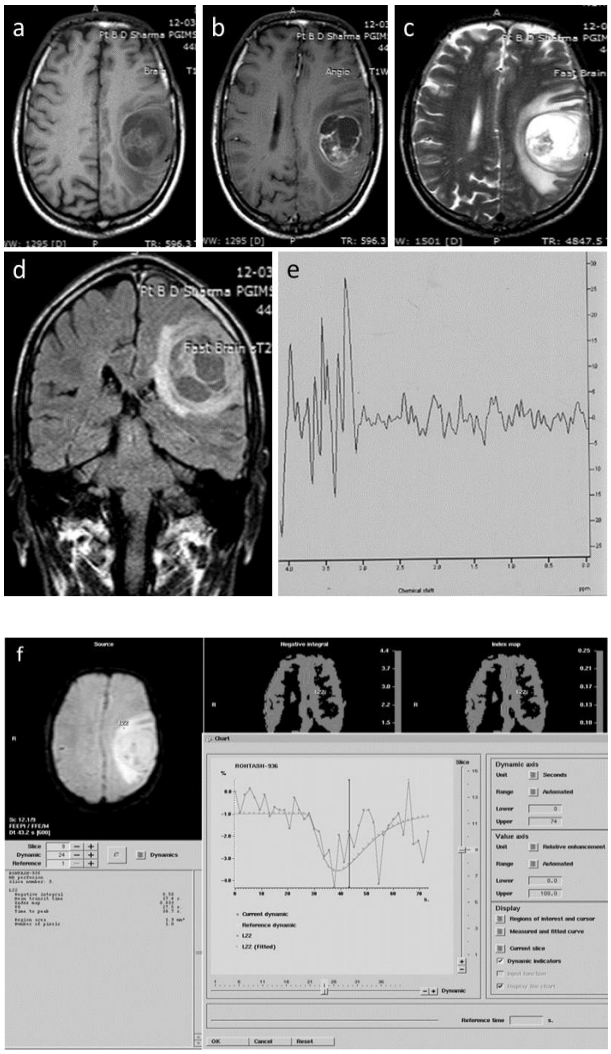
(C) Axial T2W image showing the lesion as heterogeneously hyperintense and peritumoral edema as hyperintense signal.

(D) Coronal T2W/FLAIR image showing the hyperintense mass in right frontal lobe no significantmass effect noted.

(E) Axial diffusion weighted image showing patchy areas of diffusion restriction seen as hyperintense signal, corresponding area is seen as hypointense signal in ADC map. Minimum ADC value calculated was 0.614x10-3mm2/ sec.

(F) DWI and ADC maps showing minimum ADC value calculated from the peritumoraledema which was 1.621x10-3mm2/sec.

(G) Axial T2*W first pass perfusion Image showing color coded rCBV maps along with timesignal intensity curve and various parameters [rCBV (negative integral), rCBF (index map),MTT and TTP],rCBV being 3.6ml/100gm.



DWI

Tumour areas which showed diffusion restriction appeared hyperintense on DW images and hypointense on ADC maps. The ADC values obtained for different tumour grades were analysed.

DWI in tumour

Population rank test for ADC values in tumour according to different grades showed a probability of 0.0001(highly significant). Box plot showing distribution of ADC values with respect to grades is shown in Figure 4(A). ROC curve analysis is shown in Figure 4(B-D). The summary statistics [sensitivity, specificity, accuracy, area under the curve (AUC), standard error and 95% confidence interval for differentiating various grades based on different cut off values of ADC] are shown in Table 1. The range of ADC values for different tumour grades is as shown in Table 2.

DWI in peritumoural edema

Population rank test for ADC values in edema according to different tumour grades showed a p value of 0.4386. Since p value is more than 0.05 this parameter is not significant in assessing tumour grades.

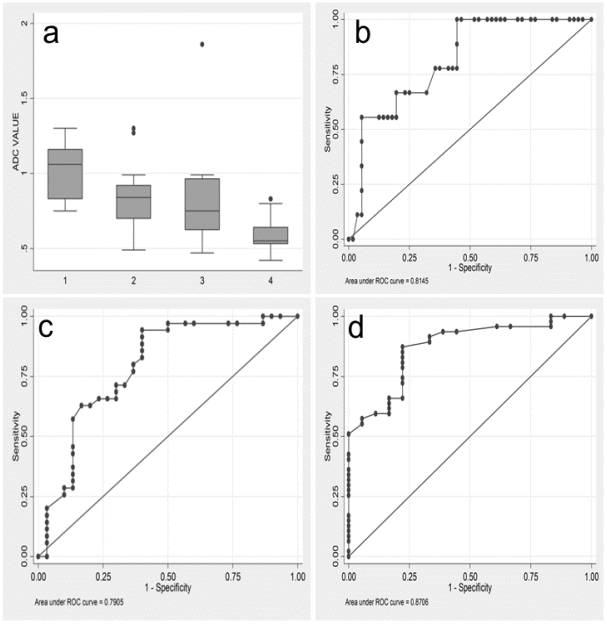


Figure 4.

a. Box plot showing distribution of ADC vaues;
b. ROC curves showing ADC values forgrade I v/s grade II;
c. ROC curves showing ADC values for grade II v/s grade III;
d. ROC curves showing ADC values for grade III v/s grade IV.

PWI

PWI in tumour

Population rank test for maximum rCBV values in tumour according to different grades showed a p value of 0.0002. Since p value is well below 0.05, the parameter was highly significant in grading tumours. Box plot showing distribution of maximum rCBV values in tumour with respect to various grades is shown in Figure 5(A). ROC curve analysis for this data is shown in Figure 5(B-D). The summary statistics [sensitivity, specificity, accuracy, AUC, standard error and 95% confidence interval for differentiating various grades based on different cut off values of rCBV] are shown in Table 1. The range of rCBV values in various grades is shown in Table 2.

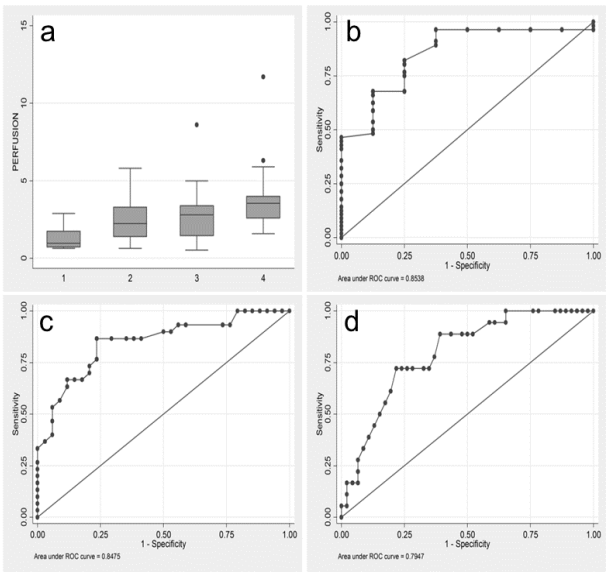


Figure 5.

a. Box plot showing distribution of rCBV values;
b. ROC curves showing rCBV values forgrade I v/s grade II;
c. ROC curves showing rCBV values forgrade for II v/s grade III;
d. ROC curve showing rCBV values for grade III v/s grade IV.

PWI in periumoural edema

Population rank test for maximum rCBV values in edema according to different grades showed a p value of 0.1362. Since the p value is well above 0.05, the parameter is not significant in grading tumours.

Percentage signal (%) drop in tumour

Another parameter obtained on perfusion studies is % drop in intensity. Kruskal-Wallis equality-of-populations rank test for %drop showed a p value of 0.0004. Since the p value is less than 0.05, %drop significantly co-related with tumour grade. Box plot

showing distribution of % drop values with respect to grades is shown in Figure 6(A). ROC curve analysis is shown in Figure 6(B-D). The summary statistics [sensitivity, specificity, accuracy, AUC, standard error and 95% confidence interval for differentiating various grades based on different cut off values of percentage drop] are shown in Table 1. The range of % drop values with respect to various grades is as shown in Table 2.

	Parameter	Cut Off Value	Sensitivity (%)	Specificity (%)	Accuracy (%)	Area Under the Curve	Standard Error	95% Confidence Interval
Grade I vs II	ADC Value	0.84x10^{-3} mm^2/s	66.67	67.86	67.69	0.8145	0.0684	0.68042-0.94855
	rCBV	1.9 ml/100 g	75	75	75	0.8538	0.0708	0.71500-0.99359
	Percentage Drop	9 %	88.24	100%	89.29	0.9255	0.0367	0.85354-0.99744
Grade II vs III	ADC Value (x10^{-3} mm^2/s	0.75x10^{-3} mm^2/s	71.43	70	70.77	0.7905	0.0593	0.67434-0.90667
	rCBV	2.6 ml/100 g	76.67	76.47	76.56	0.8475	0.0493	0.75094-0.94415
	Percentage Drop	18 %	70.37	68.97	69.64	0.7618	0.0651	0.63425-0.88938
Grade III vs IV	ADC Value	0.70x10^{-3} mm^2/s	78.72	77.78	78.46	0.8706	0.0470	0.77853-0.96260
	rCBV	3 ml/100 g	72.22	71.74	71.87	0.7947	0.0584	0.68026-0.90911
	Percentage Drop	22 %	75	75	75	0.7937	0.0700	0.65665-0.93085

Table 1. Table showing summary statistics for different values of ADC, rCBV and percentage drop in relation to tumor grades.

Tumor Grade	ADC value (x10^{-3} mm^2/s)	rCBV value (ml/100 g)	% Drop
Grade I	>0.84	<1.9	<9 %
Grade II	0.75-0.84	1.9-2.6	9-18 %
Grade III	0.70-0.75	2.7-3.0	19-22 %
Grade IV	<0.70	>3.0	>22 %

Table 2. Table showing range of ADC, rCBV and % drop values in various tumor grades

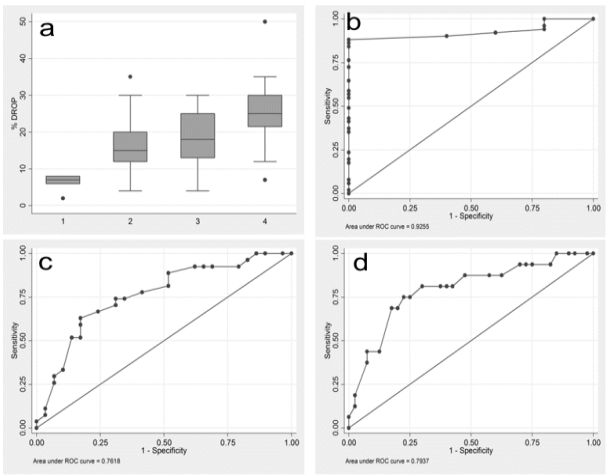


Figure 6.
a. Box plot showing distribution of percentage (%) drop values;
b. ROC curves showing % drop values for grade I v/s grade II;
c. ROC curves showing % drop values for grade II V/s grade III;
d. ROC curves showing % drop values for grade III V/s grade IV.

Comparision of ADC values and rCBV values for grading

The rCBV values were better than ADC values in differentiating grade I from grade II and grade II from grade III. The ADC values were better than rCBV values in differentiating grade III from grade IV as shown by comparison of AUC of ADC and maximum rCBV for different grades (Table 3).

Grades	AUC for ADC	AUC for rCBV
I vs II	0.8145	0.8538
II vs III	0.7905	0.8475
III vs IV	0.8706	0.7947

Table 3. Table showing AUC for ADC vs rCBV for different grades

Spectroscopy

Kruskal-Wallis equality-of-populations rank test showed a p value of 0.505 for NAA/Cr, 0.2058 for Cho/Cr, 0.6782 for Cho/NAA, 0.1275 for Cho+Cr/NAA and 0.5660 for NAA/Crn. Since the P value of all spectroscopy parameters were more than 0.05, these parameters were not significant in grading tumours. Hence the further statistical analysis was not done.

Discussion

Therapeutic strategies, prognosis, and monitoring response to therapy depend on accurate grading of gliomas [4]. Gliomas, specially GBM exhibit both spatial and temporal heterogeneity which allows them to adapt quickly. Spatial heterogeneity leads to inadequate sampling of tumour at biopsy which may lead to error in classification. In two of our patients, temporal heterogeneity was evident as radiologically they were grade III while pathologically, they were grade II. Both the patients deteriorated within six months of diagnosis, hence pointing towards higher grade. This may have been due to sampling error during biopsy. Temporal heterogeneity leads to treatment failure and disease progression. One of our patients had grade I tumour transformed to Grade III in which ADC dropped from 1.2 to 0.8 x10-3mm2/s and rCBV increased from 1.1 to 3.2ml/100g. Patient remained stable for 4 years, after which there was increased frequency of seizures, refractory to drugs at which stage, MRI showed it to be grade III. The patient died after 1 year.

MR imaging can be used to grade astrocytomas into low-grade astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme [5] and may help in management when the clinical course appears to be at odds with the neuropathologic diagnosis. Crossing midline, edema, signal heterogeneity, haemorrhage, border definition, cyst formation or necrosis and mass effect are some of the MRI features which can aid in predicting grade [6]. Necrosis was seen in 83.3% of glioblastoma multiforme (GBM) and 50% of anaplastic astrocytomas, irregular margins in 100% of GBM and anaplastic astrocytomas and haemorrhage in 55% of GBMs in our study. GBM most commonly showed edema (100%). Corpus callosum involvement was an indicator of higher grade. Conventional MR imaging, which depends on contrast enhancement, mass effect, edema, and necrosis for grading, is not always accurate for grading of gliomas. Contrast enhancement may be seen in some low grade gliomas while some high-grade tumours do not show enhancement. Advanced MR imaging techniques such as diffusion and perfusion imaging can help in such grading [5].

WHO formulated new guidelines in 2016 which emphasized integration of genetic make- up in classifying tumours. After conception of Radiogenomics Consortium in 2009, it is well known that distinct sub regions of tumours identifiable by MR imaging have distinct gene expression patterns [7,8]. Radiogenomics improved the diagnostic capability of even conventional MR imaging. Deep machine learning has increased the amount and accuracy of data by picking up subtle features that could not be picked up by even experienced radiologists. Age, gender, location, lateralization, signal intensity, enhancement pattern, surrounding edema and morphology of the tumour tell a lot about molecular subtypes and genetic profiling, based on which treatment selection, prognosis and follow-up can be decided. Ring like enhancement, large size with significant necrosis and temporal lobe (posterior subventricular, to be more precise) location suggest primary GBM, while frontal lobe location, homogeneous enhancement and young age suggest secondary GBM which has better prognosis [9]. The molecular subtypes of GBM are best predicted by edematous/tumour infiltrated volume and total tumour volume [10]. IDH-mutated gliomas can be differentiated from IDH wild type with 98% accuracy based on single lobe confinement, significant nonenhancing tumour, frontal lobe localization, large tumour size and presence of cysts and satellite lesions. MGMT methylated tumours show mixed nodular enhancement, small amount of edema, moderately elevated rCBV, and increased Ktrans [11]. Ring enhancement with necrosis suggest unmethylated MGMT-promoter region [12]. Frontal tumours are commoner in younger patients (<55 years) while elderly mostly have more posterior tumours [13]. This was clearly seen in our 40 year old patient with frontal tumour (Fig.1) and 58 year old patient with parietal tumour (Fig.3). Lower necrosis volume is seen in GBM in female patients. Higher necrosis volume in females predicted poor outcome [12]. GBMs in temporal lobe are likely to show EGFR amplification and EGFRv VIII mutation and show good effect of chemoradiation [12]. MGMT-methylated GBMs have predilection for left

hemisphere and MGMT- nonmethylated ones for right hemisphere [12]. In childhood brainstem gliomas, pontine involvement suggests high grade glioma (H3 K27 M mutant). Pilocytic astrocytoma, medulloblastoma {mainly sonic hedgehog (SHH) subtype or type 3} and atypical teratoid rhabdoid tumour (in less than 3 years of age) are the possibilities in posterolateral cerebellum [14]. Literature provides evidence that MGMT-methylated tumours show a lower volume of T2 abnormalities; a lower volume ratio of T2 abnormalities to contrast enhancement and central necrosis suggest a mesenchymal glioblastoma subtype and a sharp border makes a 1p19q-intact tumour more likely [11]. A multi institutional study of the cancer genome atlas (TCGA) GBM dataset by Gutman et al [15] demonstrated that proneural subtype showed low levels of contrast enhancement (reviewed in [9]).

Zinn et al [16] performed first comprehensive radiogenomic analysis using MRI volumetrics and gene and micro RNA expression profiling in GBM. They suggested that FLAIR is an imaging marker for edema and invasion and high FLAIR radiophenotypes may have a unique molecular tumour composition that leads to cellular migration and invasion [16]. By combining neuroimaging and DNA microarray analysis, multidimensional maps of gene-expression patterns in GBM were created. Diehn et al [17] hypothesized that underlying inter- and intratumoural gene-expression differences lead to phenotypic diversity of GBM which can be seen on neuroimaging. Unique imaging strategies could identify most of the gene expression signatures and hence radiophenotypes could be assessed more specifically by combining gene expression and MRI. There was significant complex and simple microvascular hyperplasia within contrast-enhancing regions which corresponded to a significant increase in rCBV and relative peak height (rPH) measurements. It was hypothesized that the enhancing and nonenhancing regions showed different gene expression patterns which was confirmed when 359 genes significantly overexpressed within contrast-enhancing samples were found to be associated with regulation of angiogenesis, proptosis and mitosis. Genes associated with cellular proliferative or infiltrative processes, hypoxia, and angiogenesis were upregulated in contrast enhancing tissues. Jain et al [18] showed that CBV and percentage signal (PS) estimates in GBMs correlate positively with proangiogenic genes and inversely with anti angiogenic genes. Rao et al [19], combining transcriptional, post-transcriptional and signal transduction correlates of relative cerebral blood volume, revealed 326 genes, 76 miRNA and 8 proteins expressed between two phenotype classes-cell proliferation and angiogenesis associated pathways. Molecular examination of hemodynamic characteristics other than rCBV may shed further light on useful aspects and enhanced application of the technique for grading gliomas.

It would be interesting to investigate if there could be a way to find radioproteomic phenotypes functionally correlating with tumour imaging features in gliomas. Hobbs et al [20] studied correlation between gadolinium contrast-enhancement patterns on T1-weighted magnetic resonance (MR) images and spatial changes in protein expression profiles in GBM. Tissue samples from nonenhancing (NE) and contrast enhancing (CE) regions within a given tumour were compared. Proteins common to all individuals studied in both CE and NE regions were used as internal controls. The CE regions were extremely heterogeneous not only across the patients, but also within same patient while NE regions were comparably homogeneous. CE regions also contained more protein species than the NE region. The extracellular matrix in contrast-enhancing regions was likely to contain factors that presented increased permeability or microvessel density in neoplastic disease state. This shows that CE-MRI can guide proteomic analysis with SELDI-TOF-MS in GBM.

DWI assesses cellularity of tumours and ADC gives quantitative information about the restriction of water movement. Brain neoplasms with higher cellularity or with a higher grade show significantly low ADC values [21]. In our study, difference in the minimum ADC values for different grades of tumour was significant (P<0 .001), finding similar to those of Lee et al [22] and Kono et al [23] that high-grade gliomas show significantly low ADC values and increased signal intensity on DWI. Hilario et al [24] found that at a cut off ADC value of 1.185x10-3 mm2/s high and low grade gliomas could be differentiated with a sensitivity of 97.6% and specificity of 53.1%. Comparison between Hilario et al and our study is shown in Table 4. A lower cut off

value in our study has reduced the sensitivity but improved the specificity.

Study	Cut off ADC value (for low v/s high grade)	Sensitivity	Specificity
Hilario et al (2012)	$1.185x10^{-3}$ mm^2/s	97.6 %	53.1 %
Our present study	$0.75x10^{-3}$ mm^2/s	71.43 %	70 %

Table 4. Table comparing ADC values in differentiation of high and low-grade gliomas in various studies.

Fan et al [25] have demonstrated that ADC values in peritumoural regions were decreased compared to the contralateral normal white matter, but no significant difference was found as p value was more than 0.05. In our study also p value was more than 0.05 and hence was not a significant parameter for grading gliomas. Moreover the edema surrounding the glioma is vasogenic edema [6] which normally does not show diffusion restriction this may also be the reason that ADC in peritumoural edema is not very reliable in grading the tumours. DTI, a method of visualizing the anisotropy of proton motion, may eliminate the partial volume effect of peritumoural edema, and may highlight the difference between high-grade and low-grade gliomas [26]. Zinn et al [27] described Diffusion Weighted magnetic resonance imaging radiophenotypes and associated molecular pathways in glioblastoma. Given that dMRI and ADC reflect tumour cellularity and a high N:C ratio in niches of restricted diffusion, authors hypothesized that dMRI signal intensity beyond the region of enhancement could identify GBMs that were highly infiltrative within nonenhancing peritumoural FLAIR area. Gene expression profiles associated with restricted diffusion in the peritumoural dMRI-FLAIR niche in GBM was examined which showed consistent upregulation of BMI1, a known regulator of stemlike states in cancer cells and is associated with migration, invasion and poor prognosis. Likewise, significant negative correlation has been shown between ADC and 2-hydroxyglutarate (2-HG) levels, a metabolite found in IDH mutated tumours [9], which suggests that ADC may be decreased in IDH-mutated tumours. Methylated tumours display features of lower cellularity (high minimum ADC ratio and low minimum FA ratio) [11]. Heiland et al [28] found that in enhancing tumour region, FA directly correlated with activation of epithelial-to-mesenchymal transition pathway. Hence high FA predicted worse prognosis in GBM, while higher MD predicted good prognosis.

Tumour growth depends largely on new blood vessel growth. Simple diffusion of oxygen, nutrients and other essential materials can support tumour growth only upto a size of 1-2mm3 beyond which neoangiogenesis is necessary. Metastasis also cannot occur without growth of new blood vessels [29]. Contrast enhancement occurs due to leakage of contrast and thus CE-MRI highlights only the blood brain barrier (BBB) disruption. On the other hand, perfusion study is based upon blood flow at capillary level. It tells about the capillary network and hence shows the degree of neoangiogenesis [30]. As the tumour growth and hence its grade depends on neoangiogenesis rather than on leakage of BBB, perfusion MRI is an earlier and better predictor of grade than contrast enhancement. Moreover, due to its ability to pick up areas of angiogenesis, PWI imaging has capacity to direct stereotactic biopsy to such areas (which have a higher grade) in an otherwise heterogeneous tumour, thus avoiding understaging of the tumour, specially in cases of non-enhancing gliomas which have comparatively intact BBB [31]. The drawback is that in cases of high grade enhancing gliomas, there is significant BBB breakdown leading to leakage of contrast in extravascular space during first pass of contrast and reduced susceptibility effects between intra and extravascular compartments in this area leading to underestimation of tumour vascularity and hence grade [32]. Peritumoural areas in anaplastic tumours show altered capillary morphology as well as tumour cells along newly formed or preexisting dilated vessels while low grade gliomas have less infiltrating tumour cells. This is reflected in elevated blood volume before enhancement. Vascularity related heterogeneity of peritumoural region as shown on PWI can be helpful in better estimation of true brain tumour size pre-operatively [33].

Although preoperative grading of gliomas is mainly done by DWI and PWI, there are only few studies validating the usefulness of diffusion and perfusion MRI solely in non-enhancing gliomas. Fan et al [25] hypothesized that DWI/PWI could provide additional useful information in the assessment and tumour grading of supratentorial glial neoplasms,

which lacked contrast enhancement on pre-operative neuroimaging and therefore evaluated the usefulness of diffusion/perfusion-weighted MRI in patients with non-enhancing supratentorial brain gliomas. Both solid portions as well as peritumoural regions of anaplastic gliomas showed high rCBV ratios but low grade gliomas did not [25]. So it was concluded that higher rCBV ratios in both solid portions and peritumoural regions correlate significantly with anaplasia. In our study rCBV in peritumoural edema was not significant (p = 0.13). Comparison of cut off rCBV values within the tumour between various studies is shown in Table 5. Spampinato et al [32] demonstrated best sensitivity and specificity for differentiating low and high grades, at a cut off of 2.14 ml/100 g. We also found best sensitivity and specificity at a cut off of 2.6 ml/100 g which is quite close to 2.1 ml/100 g though our sensitivity and specificity were less than that of Spampinato. This difference may be explained on the basis of different number of cases in two studies and because our study contained mix of astrocytoma and oligodendroglioma while Spampinato's study had only oligodendroglioma. Sensitivity of all the studies is comparable. The difference in specificity arises due to different cut off values of rCBV for low v/s high grade tumours. Near cut off of 1.75 ml/100 g, both Law et al [34] and Hilario et al [24] had a specifity of 50-60%. At a cut off of 3.3 ml/100 g, Roy et al [35] showed specificity of 88%. At a cut off of 2.6ml/100mg our specificity was 76.47% which is in between the above values (cut off is also in between the two) and hence in sync with previous studies.

Study	Cut off rCBVvalue (ml/100 g)	Sensitivity (%)	Specificity (%)
Law et al(2003)	1.75	95.0	57.5
Weber et al(2006)	1.6	94	78
Aprile et al(2012)	3.5	79.4	95.8
Hilario et al(2012)	1.74	94.4	50.0
Roy et al(2013)	3.34	100	88
Spampinato et al(2007)	2.14	100	86
Shin et al	3.57	72.7	100
Our present study	2.6	76.67	76.47

Table 5. Table comparing rCBV values within the tumor in differentiation of high and low grade gliomas in various studies.

Ellingson [13] based on his decades of work examined association between radiological and histological features in Glioblastoma. He comprehensively reviewed anatomical imaging pathology associations, association between tumour size, location and molecular characteristics, diffusion and perfusion MRI pathology correlation and quantification of intuitive radiographic features. Maximum rCBV is considered to be a significant predictor of mean vessel diameter. Smits and Bent [11] found that methylated tumours show less perfusion and increased volume transfer constant (Ktrans) than unmethylated tumours. Though pseudoprogression is seen commonly, but progression time is significantly longer in patients with MGMT-promoter methylation compared with the unmethylated group, both of which may be due to increased Ktrans, i.e., permeability in methylated group which leads to contrast leakage (seen as pseudoprogression) and better drug delivery (prolonging progression) [10]. Thus increase in enhancement within three months after completion of radiotherapy in patients with MGMT methylated tumours should be suspected as pseudoprogression rather than progressive disease. This shows how amalgamation of imaging and genomics can reinforce each other. Imaging can help in predicting tumour genetics, while genetic profile helps in cautious interpretation of post-treatment enhancement in terms of progression vs pseudoprogression. Oligodendroglioma have comparatively higher rCBV regardless of grade on histology [13]. PWI can differentiate pilocytic astrocytoma (rCBVmax = 1.19±0.71)from hemangioblastoma (rCBVmax = 9.37±2.37) [14]. Vajepeyam et al have shown that ADC histogram metrics combined with permeability metrics differentiate low and high-grade pedistric brain tumours with high accuracy [14].

Bulakbasi et al [33, 36] studied usefulness of MR spectroscopy and ADC calculation for tumour grading. They found that though MR spectroscopy could not be of much help in grading malignant tumours, it could help to differentiate benign from malignant tumours [36]. In our study also spectroscopy was not helpful in grading of gliomas. Hsu et al [37] correlated metabolite ratios with histopathologic grading in 27 patients with cerebral gliomas. They concluded that there was no significant metabolite difference between grade III and grade IV tumours (p>0.1), or significant difference in lactate occurrence rates among

different grades (p = 0.26). Though the metabolite ratios in our study were not helpful quantitatively in grading of gliomas, presence of some peaks like lipid and lactate did help in grading. Poptani et al [38] and Hsu et al [37] stated that lactate peak can be found in all grades of tumours. In our study also lactate peak was found in almost all the grades though with more frequency in higher grades.

Radiogenomics focused on spectroscopic parameters may also aid in predicting molecular profiling of tumours. GBM harboring IDH1 mutation show 2-hydroxyglutarate (2-HG) on MR spectroscppy [9]. So 2-HG level can be a predictor of IDH1 mutation, but is not universally available in standard MR equipments at present, but is definitely a way forward. Likewise, oligodendrocytic tumours correlated with N-acetylaspartate metabolite, high creatine metabolite (nCr) was seen in proneural GBM subtype, and low nCr predicted mesenchymal subtype; low nGlx predicted neural subtype, and its high value suggested classical subtype [10]. A high peak of choline can help differentiate atypical laminated medulloblastoma from Lhermitte-Duclos disease which are difficult to differentiate on morphology alone [14].

Brain shift during surgery often leads to incongruence in tumour borders assessed by pre-operative and operative MRI. Some tumours show false-positive contrast enhancement and small molecule Gd-agents may also spread from the initial area of tumour enhancement into the peritumoural zone of edema over time. This leads to inaccuracies in assessment of tumour extent. Multimodality approach has been suggested to overcome this shortcoming and to assess true tumour extent. The focus in recent past has been on exploring optical methods which may be based on either intrinsic tissue properties or by using exogenous contrast agents. Nevertheless, small field of view, decreased specificity due to auto fluorescence, and rapid photobleaching pose challenges in using these optical procedures. Some other useful methods for defining tumour margins include fluorescence-guided resection of malignant gliomas using 5-aminolevulinic acid (body's own metabolite in heme biosynthesis pathway and metabolic marker of malignant cells which is converted into fluorescent porphyrins in cells) as marker [39] and Desorption Electrospray Ionization Mass Spectrometry (DESI-MS) imaging based on lipid patterns for intra operative molecular characterization of brain tumours [40]. Using mouse model of Glioblastoma, Huang et al have reported integrin –targeted SERRS nanoparticles to depict the true tumour extent. Method bears fairly high potential for clinical translation for glioma grading in humans [41].

Various radiological parameters can also predict prognosis with fair degree of accuracy. While performing an integrative network-based analysis of magnetic resonance spectroscopy and genome wide expression in glioblastoma multiforme, Heiland et al [42] found that patients with higher nNAA (N-Acetyl Aspartate) showed longer progression free survival (reviewed in [10]). Patients with highly perfused low grade tumours fared worse than patients with lowly perfused high grade tumours. IDH-mutated tumours fare much better than IDH wild type of same grade. Limited peritumoural edema predicted better prognosis in patients with methylated glioblastoma specifically [11]. Mutations in the promoter for telomerase reverse transcriptase (TERT), an enzyme that elongates telomeres, have been associated with a worse prognosis in both IDH mutant and IDH wild-type GBMs. Increased amounts of Ki-67, a cellular protein associated with proliferation and present in many tumours, is also associated with a worse prognosis [43].

Even choice of chemotherapy can be improved with radiogenomics approach. GBM with proneural signature had better outcome when bevacizumab was given from initiation of therapy. Mesenchymal phenotype responded better when bevacizumab was given at recurrence, but not when given as first line along with radiation and temozolomide [13]. The MGMT unmethylated group responded only to radiotherapy [10]. siRNA can transduce previously TMZ-resistant glioma-initiating cells, enhancing their chemosensitivity against TMZ [12]. Co-deletion of chromosomal arms 1p and 19q predict favorable outcome and sensitivity to chemotherapy respectively.

There are some major issues with universal application of conventional radiogenomics at present. These are overlap of MRI features between different mutations, several mutations like IDH, MGMT, and TP53, occuring in tandem, intratumoural heterogeneity with different portions of the tumour having different genetic and imaging features. Machine learning is better as it does objective quantitative evaluation and can detect subtle voxel-

level patterns [43]. So a combination of conventional and machine learning based radiogenomics has huge potential towards accurate diagnosis, classification, grading, prognosticating, selecting adequate therapy, monitoring therapy, identifying early therapy failure and modifying therapy accordingly in cases of glioma, i.e., it is the way forward in theranostics and has the potential to replace invasive and non-representative biopsies as it gives the total overview of the tumour.

Our study has some limitations. Stereotactic biopsies were not targeted according to rCBV or ADC maps. So there is possibility of histopathologic misdiagnosis attributable to sampling error in the pathologic examination because of the histologic heterogeneity of tumour tissues. Only elementary radiogenomics based approach could be followed as the facility for MR based stereotactic biopsies and advanced machine learning facilities do not exist at our place. Ongoing radiological, molecular profiling and proteomic studies in our laboratories are focused on providing additional translational tools to decipher MR, genomic and proteomic characteristics of gliomas to better grade them.

Conclusion

Both maximum rCBV and minimum ADC values within the tumour were useful in grading gliomas, but both these values in peritumoural edema were not significant in grading gliomas. rCBV values were better than ADC values in differentiating grade I from II and grade II from III. The ADC values were better than rCBV values in differentiating grade III from grade IV. The metabolite ratios were not helpful in grading of gliomas, but presence of some peaks like lipid and lactate did help in grading. Lactate peak was found in almost all the grades (except grade I) though with more frequency in higher grades. Presence of lipids suggested a higher grade of malignancy. Radiogenomics coupled with multimodality radiomic procedures can further improve the accuracy of grading.

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Ethical Considerations

The study was carried out in accordance to standards of the institutional ethics committee and with the 1964 Helsinki declaration.

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Volumetric threshold of pituitary macroadenoma as a predictor to visual impairment. Clinical correlation

Mohamed Elsherbini, Mahmoud Saad, Mohamed Deniwar

Mansoura University Hospital, Elgomhoreya St., Mansoura, EGYPT

ABSTRACT

Purpose: In this study, we aimed at correlating the curve of visual impairment against pituitary macroadenoma size.

Method: In this study, we retrospectively analyzed the visual correlation between the volume and dimensions of pituitary adenoma and the degree of visual impairment on patients' examination. 35 patients with no history of eye or refraction disorder were included in the study. Spearman correlation test was used to validate the correlation.

Results: 57 % of pituitary macroadenoma patients suffer from visual impairment, even if not the primary presentation. Macroadenomas greater than 5 cm^3 in volume and/or 2 cm height are more likely to cause various degrees of visual impairment, this correlation is not linear beyond these values.

Conclusion: Visual impairment due to pituitary adenomas is more frequent than the presentation, the threshold volume is 5 cm^3 and height is 2 cm, bigger adenomas behaviour is more multifactorial than the only size.

Keywords
visual impairment,
optic compression,
pituitary,
macroadenoma

Corresponding author:
Mohamed Elsherbini

Mansoura University Hospital,
Elgomhoreya St.,
Mansoura, Egypt

m_elsherbiny@mans.edu.eg

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INTRODUCTION

Pituitary gland lesions are commonly associated with visual manifestations at different levels, either as the primary presentation, or as a finding during neurological examination. These manifestations are explained by the intimate relationship between the pituitary gland and the visual pathway.

The pituitary gland is covered superiorly by the diaphragma sellae; a fibrous dural layer with a small opening called the diaphragmatic hiatus through which the infundibulum courses. The suprasellar cistern is located above the diaphragma sellae and separates it from the optic chiasm. The suprasellar cistern is first compressed by pituitary tumors before their growth proceeds to compress the optic chiasm. The size of the pituitary gland varies along life and differs from male to female; at birth it weights around 100 mg, while in adulthood it reaches up to 500 mg with tendency to be bigger in females especially during puberty, pregnancy and lactation. In adults it measures around 8-10 mm and reaches 12 mm in females during lactation. (Cox and Elster 1991).

Pituitary adenomas, when increase in size, may lead to visual impairment via direct optic pathway compression which leads to neuronal injury via blocking axonal conduction, blocking axoplasmic flow or/and demyelination. (Munoz Negrete and Rebolleda 2002) Chronic optic pathway compression leads to optic atrophy which is irreversible, this is more noted in non-functioning pituitary adenoma patients since secretory lesions tend to present earlier by hormonal imbalance. (Jagannathan, Dumont et al. 2005).

Direct optic pathway compression, though a primitive explanation, is not the only mechanism for visual impairment in patients with pituitary macroadenoma. The course of visual deterioration in relation to volume and height of the tumor is an important key to understanding the pathological process since the size of the tumor is the best predictor for visual recovery. (Monteiro, Zambon et al. 2010).

PATIENTS AND METHODS

Patients data

Data of patients admitted to Mansoura University Hospital with sellar lesion between 2017 and 2019 were reviewed and analyzed. Only patients with lesions larger than 10 mm in at least one dimension were included, patients with incomplete medical reports were excluded.

Visual acuity

Visual acuity is recorded in decimal method where values are obtained on snellen's chart, while severe visual impairment values are given according to Grover et (Grover, Fishman et al. 1999) al ; 0.0025 for CF "counting fingers", 0.002 for HM "hand movement", 0.0016 for "light perception" (LP), and 0.0013 for NLP "no perception of light". Values from both eyes are summed giving each patient a single value representing visual acuity in both eyes. Patients with history of eye surgeries and/or other local eye pathologies were excluded.

Measurement

Dimensions of the lesions are measured on MRI T1 with contrast axial, coronal and sagittal to obtain largest horizontal, vertical and AP diameters respectively. The volume of the tumor was calculated using the traditional geometric formula; ½ (length X width X height), patients with recurrent lesions were excluded since according to Chi-Cheng Chuanf (Chuang, Lin et al. 2017) the traditional formula is not applicable for recurrent cases while it proves high degree of accuracy for primary lesions.

Pathology

Lesions were classified into functioning and non-functioning according to patients' pre-operative serum hormonal levels. Histopathological examination reports were reviewed, patients with lesions other than pituitary adenomas were excluded.

Statistical analysis

Spearman correlation test was used to compare visual acuity values to adenoma volume and each dimension individually. Prism GraphPad version 5 software was used to perform statistical analysis.

RESULTS

35 patients were included in the study, 18 of them were males (51 %), mean age was 46.3 years which ranged from 23 to 75 years. Most common primary presentation is hormonal related symptoms, collectively, in 15 patients, followed headache in 13 patients, while visual impairment was the primary presentation for only 7 patients (20 %). (Table 1).

	Number, %
Gender:	
- Male	18 (51.4 %)
- Female	17
Clinical presentation:	
- Endocrinal	15 (42.9 %)
- Headache	13 (37.1 %)
- Visual	7 (20 %)
Visual acuity:	
- Intact	7 (20 %)
- Mean visual acuity	0.77
Tumor size:	
- Min	0.6 cm^3
- Max	40 cm^3
- Mean	12.3 cm^3
Pathology:	
- Non-secretory	16 (45.7 %)
- GH secreting	7 (20 %)
Acromegaly	6
Impotence	1
- Prolactin secreting	10 (28.6 %)
Amenorrhea	4
Accidentally discovered	4

Galactorrhea	
Impotence	1
- ACTH secreting	1
(Cushing)	2

Visual impairment was the secondary complaint in 13 patients (37 %) and on examination only 7 patients (20%) showed intact visual acuity (2/2).

19 adenomas were secretory, 15 of these patients' primary presentation was hormonal related symptoms and 4 were accidentally discovered during pre-operative lab assessment. Acromegaly was the most common hormonal presentation in 6 patients (31.5 %), amenorrhea in 4, Cushing in 2, male sexual dysfunction in 2 and galactorrhea in one patient. Pathologically, among the 19 secretory adenomas prolactin secreting was of the highest incidence in 10 patients, GH secreting in 7 and ACTH secreting in 2 patients. Male sexual dysfunction was the primary presentation for both Prolactin and GH secreting adenomas, one patient each.

Visual acuity mean is 0.77 for the sum of both eyes, ranged from No PL in one eye to intact vision (2). Mean tumor volume was 13.3 cm^3, ranged from 0.6 to 40 cm^3. Mean AP diameter, width and height were 2.57, 2.65 and 2.86 cm respectively.

According to spearman correlation test, visual acuity impairment is negatively correlated to lesions greater than 5 cc in volume (r – 0.67, $P < 0.001$, Fig 1) and greater than 2 cm in height (r – 0.6, $P < 0.001$, Fig 2), beyond these values visual acuity impairment was not in a linear relationship neither to tumor volume nor height.

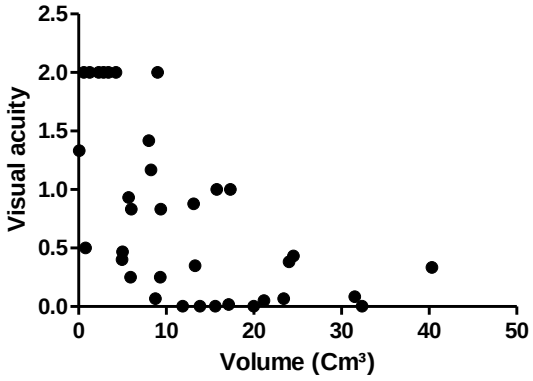

Figure 1. Representing visual acuity to tumor volume (Cm^3) correlation, showing just 2 patients with visual impairment with lesions less than 5 cm^3, while strong negative correlation right to the 5 cm^3 value (r – 0.67), but not linear.

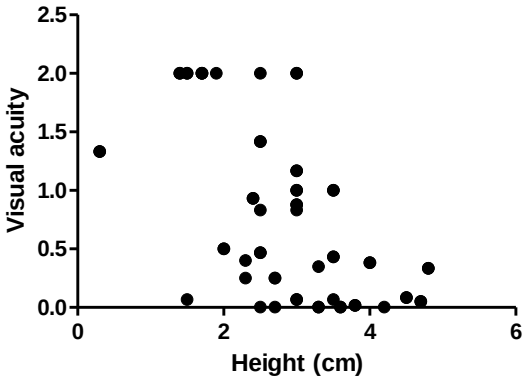

Figure 2. Representing visual acuity to tumor height (Cm) correlation, showing just 2 patients with visual impairment with lesions less than 2 cm, while strong negative correlation right to the 2 cm value (r – 0.6), but not linear.

Illustrative cases

Case 1

41 years old male presented with acromegalic features and sexual dysfunction. Hormonal assay showed elevated serum growth hormone level. Radiologically detected 3 X 3.5 X 3 cm lesion with severe chiasm displacement and stretch, Fig 3. Visual acuity was 0.67 and 0.33 for right and left eyes respectively.

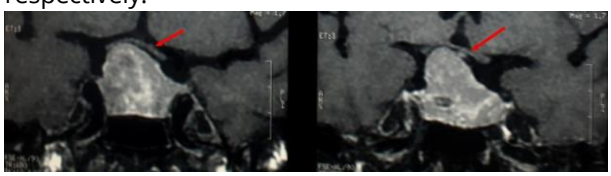

Figure 3. Case 1, Coronal MRI with contrast showing 3 X 3.5 X 3 cm lesion with severe chiasm displacement and stretch (Red arrow).

Case 2

33 years old female lady presented with typical Cushing syndrome, elevated serum cortisol, no significant visual affection, MRI with contrast showed pituitary lesion 1.1 X 0.5 X 0.3 cm with no chiasm compression, Fig 4. Typical hormonal presentation prior optic compression.

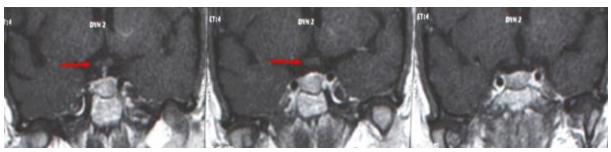

Figure 4. Case 2, Coronal MRI with contrast showing lesion 1.1 X 0.5 X 0.3 cm with no chiasm compression (Red arrow).

Case 3

55 years old post-menopausal lady presented with visual impairment; hormonal assay showed elevated serum prolactin which was not the primary presentation as the patient was postmenopausal; amenorrhea. Lesion dimensions were 2.5 X 3.8 X 2.5 cm with severe chiasmatic compression and corresponding visual acuity NPL and HM in right and left eye respectively, Fig 5.

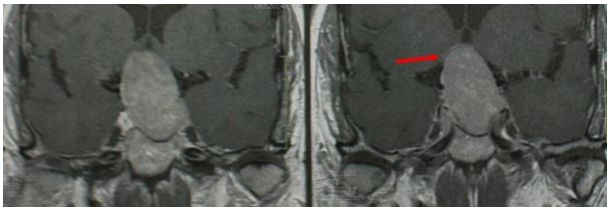

Figure 5. Case 3, Coronal MRI with contrast showing lesion 2.5 X 3.8 X 2.5 cm with severe chiasmatic compression and stretch.

Case 4

40 years old lady presented with visual impairment, examination showed visual acuity of HM and CF in right and left eye respectively. Dimensions of the lesion in MRI were 2X2.2X2.7 cm with severe optic compression, Fig 6.

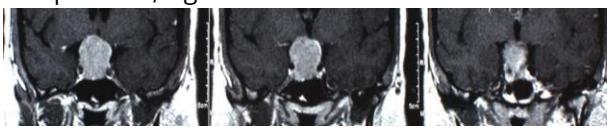

Figure 6. Case 4, Coronal MRI with contrast showing a 2X2.2X2.7 cm lesion.

Discussion

Pituitary adenomas are the most common tumor of the sellar region representing 10-15% of all intracranial neoplasm, they are classified according to size into microadenomas and macroadenomas; greater than 10 mm(Asa and Ezzat 2009). Macroadenomas start confined to the sella, the earliest extra-sellar extension is the upward growth into suprasellar cistern, this is anatomically explained by the hard-bony relationship in other directions. Less commonly macroadenomas are seen extending into the sphenoid sinus downwards, or laterally encasing the ICA within the cavernous sinus. (Ouyang, Rothfus et al. 2011)

Headache is the most common presentation of pituitary adenoma (Kim, Jin et al. 2019), in this study headache was the first primary presentation if hormonal presentations are separately listed, while hormonal presentation, in total, are of higher incidence. It's noted that patients with secretory adenomas seek medical advice in early stages due to hormonal related symptoms prior to visual pathway compression, except when amenorrhea is masked by menopause, Case 3.

Though it's not the most common presentation, optic pathway compression is eventual when the tumor volume exceeds certain limit, functioning adenomas tend to present early with hormonal manifestations prior to visual presentation, this was also concluded by Brada et al (Brada, Rajan et al. 1993) who reported visual compression in 73 % of non-functioning adenoma patients, while only in 44.7 % in functioning ones. In the current study, examination showed 28 patients (80%) of patients were found to have various degrees of visual impairment, taking in consideration that patients with history of errors of refraction and/or eye pathology were excluded, the incidence of visual impairment due to pituitary macroadenoma is higher than presentation which in this study was (20 patients, 57 %); with either main or secondary complaint.

Visual acuity deficits due to optic pathway compression by pituitary tumors are studied in several publications (Kim, Jin et al. 2019) (Kasputyte, Slatkeviciene et al. 2013) (Wang, Sun et al. 2008), as well as explained by the anatomical relationship of the pituitary gland to the optic pathway. In this study, the threshold of optic compression regarding volume and height of the tumor is identified.

Various anatomical factors may affect the degree of optic pathway compression including site of the chiasm and the capacity of suprasellar cistern which anatomically ranges from 8 – 13 mm (Rhoton 2002), this may explain the discrepancy between case 1 where the adenoma is greater in size and height than case 3 and yet shows radiologically less optic compression and clinically less visual impairment.

The volume of the pituitary tumor can be accurately measured via the traditional equation ½ (length x width x height). This method was validated by Chi-Cheng Chuang et al (Chuang, Lin et al. 2017) , where the equation was proven to be accurate for pre-operative assessment, but not valid for residual and hence recurrence, recurrent cases where excluded in this study based on that conclusion.

Similar to our results, H Wang et al (Wang, Sun et al. 2008) reported significant visual impairment in

patients with Hardy's grade above B, with no significant difference between the groups B, C and D. These results raise the debate regarding various factors affecting chiasm compression course, as for 2 cm height i.e Hardy grade B is the threshold for optic manifestations, lack of significant difference among greater sizes may be attributed to other factors including tumor consistency, growth rate and vascular interruption to the optic pathway. Anatomical reserve capacity and individual variation of cistern size should be taken in consideration. Visual field deficits, though not included in this study, are strongly associated with visual impairment in the majority (76 %) of cases. (Wang, Sun et al. 2008)

Unlike previous studies, in this study, visual acuity of both patients' eyes were summed giving each patient a single value representing visual acuity, authors believe this is a more accurate assessment of overall visual impairment than listing each eye individually, since decussation of optic fibers takes place in optic chiasm which is the most common site of compression.

Visual acuity impairment is seldomly significant in pituitary microadeoma patients (less than 1 cm) which are usually contained within the sella, while significant visual impairment starts beyond 2 cm height which can be explained by the growth into the supra-sellar cistern i.e transformation to Hardy grade B(Rilliet, Mohr et al. 1981).

According to Monteiro et al (Monteiro, Zambon et al. 2010), tumor size was the best predictor for post-operative visual recovery, the author reported that visual acuity is serviceable before optic atrophy develops hence the importance of correlating tumor volume to clinical visual impairment.

Conclusion

Pituitary macroadenomas with height greater than 2 cm and/or volume greater than 5 cc are significantly associated with visual acuity impairment, behavior beyond these values (Hardy groups B,C and D) is not linear and its course can neither be predicted nor explained by tumor size solely, to predict visual impairment due to pituitary macroadenomas, further multi-factorial studies are encouraged.

Declarations

Ethical approval: N/A, retrospective analysis of archive.

Consent for Publication: N/A.

Availability of data and materials: please contact the author for data requests.

Competing interests: the authors declare that they have no competing interests.

Funding: No fund was received for this study.

Authors' contribution:

ME: principle investigator, data collection, statistics and contribution to writing.

MS: data collection, revision.

MD: data collection, contribution to writing, revision and amendments.

Authors' information: all authors are staff members of neurosurgery department in Mansoura faculty of medicine and its affiliated hospital; Mansoura University Hospital.

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Primary multiple cerebral hydatid disease in a young patient with surgically-treated intracerebral haemorrhage. A case report

Anwar N. Hafedh[1], Awfa A. Aktham[1], Zahraa F. Al-Sharshahi[1], Ahmed Ibrahim Al-Jorani[2], Sama Albairamani[3], Zahraa A. Alsubaihawi[4], Aktham O. Al-Khafaji[4], Samer S. Hoz[1]

[1] Department of Neurosurgery, Neurosurgery Teaching Hospital, Baghdad, IRAQ
[2] Medical student, Alkindy College of Medicine, University of Baghdad, IRAQ
[3] Medical student, College of Medicine, Al-Iraqia University, IRAQ
[4] Medical student, College of Medicine, University of Baghdad, IRAQ

Keywords
cerebral hydatid disease, multiple, primary, intracerebral hemorrhage

Corresponding author:
Zahraa F. Al-Sharshahi

Neurosurgery Teaching Hospital, Baghdad, Iraq

Zahraaalsharshahi@rcsi.com

ABSTRACT

Introduction: Cerebral hydatid disease (CHD) is rare and the multiple-cystic variety is even rarer. In this paper, we report a case of multiple CHD and explore a possible link with a preceding spontaneous intracerebral haemorrhage (ICH).

Case presentation: A 27-year old gentleman with a history of surgically-evacuated, spontaneous ICH presented with severe headache, left-sided weakness - Medical Research Council (MRC) grade II - and recurrent tonic-clonic seizures, while on a full dose of anti-epileptic medication. Brain magnetic resonance imaging (MRI) scans showed multiple intra-axial cystic lesions in the right hemisphere. The cysts were removed intact using Dowling's technique through a large temporoparietal craniotomy. The surgery went uneventful and the patient recovered as expected. Post-operatively, a prophylactic course of albendazole (200 mg) was prescribed. On his one-year follow-up visit, the patient was symptom-free and his weakness had improved (left upper limb: MRC grade IV and full power of the left lower limb). The computed tomography (CT) scan showed no new findings.

Conclusion: Primary cerebral hydatid disease is rare and the multiple-cyst variety is even rare. In this case, a peculiar association with a surgically-treated ICH was explored with possible theories to suggest future research directions.

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INTRODUCTION

Hydatid disease is a parasitic infection caused by an endemic parasite, Echinococcus Granulosis, mostly present in sheep-raising countries (1, 2). Tapeworm larvae develop in the intestinal tract then pass through the bloodstream to reach the liver, lungs, kidney, and brain (3).

Cerebral hydatid disease (CHD) comprises only 2% of all hydatid-cyst cases and is classified as "primary" or "secondary" (4). "Primary" CHD

presents is rare and presents as a solitary single cyst surrounded by a broad capsule while the "secondary" type is characterized by multiple cerebral cysts that result from the rupture of a single cyst (1,5).

Preoperative diagnosis is necessary to avoid intra-operative cyst rupture. Cerebral hydatid cysts typically present with signs and symptoms related to raised intracranial pressure with or without focal neurological deficits depending on cyst size and location (5,6).

The authors report a case of a young patient with primary multiple cerebral hydatid disease and question its theoretical link with a prior, surgically-treated spontaneous ICH presenting at the age of 24.

Case report

A 27-years-old male presented with a single incidence of a generalized tonic-clonic seizure, headache, and vomiting. The patient had no history of head trauma. On examination, he had a left-sided weakness (MRC grade III) of both upper and lower limbs. Initial cranial CT scan (figure 1A) revealed an acute intracerebral hemorrhage (ICH) in the right parietal lobe. The hematoma was evacuated through the right parietal parasagittal approach. The postoperative CT scan revealed complete evacuation of the hematoma (figure 1B) and the post-operative course went uneventful. One month later, the patient's symptoms had resolved and the CT scan revealed no new findings (figure 1C).

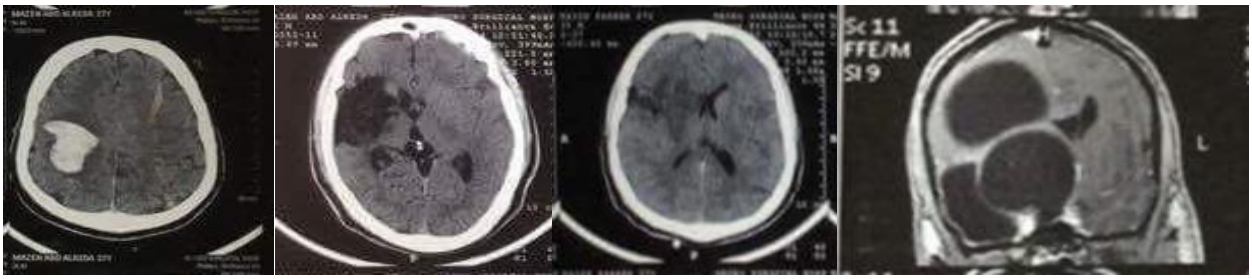

Figure 1. (A) Pre-operative CT scan (axial section), showing a well-defined, intracerebral hyperdensity representing intracerebral hemorrhage (ICH). (B) Post-operative cerebral CT scan (axial section) (C) Follow-up cerebral CT scan axial section shows no intracranial abnormalities. (D) FLAIR MRI coronal section showing a cystic lesion with a thin, hypointense marginal membrane with a marked mass effect causing contralateral displacement of midline structures.

Three years later, the patient presented with severe headache, left-sided weakness (MRC grade II), and recurrent tonic-clonic seizures, not responding to a full dose of anti-epileptic medication (carbamazepine 400mg bid). Cerebral CT and MRI scans (figure 1D) showed multiple intra-axial cystic lesions in the right hemisphere (figure 1). The cysts were removed intact using Dowling's technique through a large temporoparietal craniotomy. The surgery went uneventful. Post-operatively, the patient was started on a prophylactic course of albendazole (200 mg). His left-sided weakness remained the same (MRC grade 2). During his one-year follow-up visit, the patient was symptom-free and his weakness had improved (left upper limb: MRC grade IV and full power of the left lower limb). The CT scan showed no new intracranial pathology.

Discussion

Echinococcosis is an endemic infection in Mediterranean countries and Middle Eastern including Iraq. CHD is rare in comparison to other organ involvement, particularly the liver and lungs (7). Cerebral hydatid disease accounts for 0.05% of all cerebral mass lesions and is 2-3 times more common in children (3,8,9).

CHD can be primary or secondary. Primary CHD is the product of direct larval infestation in the brain without evidence of extracerebral disease. Secondary CHD occurs when the larvae exit the capillary beds of the lungs or liver to systemic circulation until they settle in the brain (10, 11). Primary CHD is uncommon, accounting for 1-2 percent of all Echinococcus granulosus infections, and multiple primary CHDs are even rarer (11-13).

Cerebral hydatid cysts are benign, slowly growing lesions with an annual growth rate of 1.5 to 10 cm and they can reach a considerable size before manifesting clinically. Headache, vomiting, symptoms of elevated intracranial pressure (ICP) are

some of the common presentations of cerebral hydatidosis (14). Other presentations are dictated by cyst size and location and may include hemiparesis, seizures, visual field disturbances, and gait disorders. Symptoms of raised ICP tend to predominate in the pediatric populations, while adults are more likely to present with focal neurological deficits and seizures (15,16). Cerebral hydatid cysts are most frequently located in the territory of the middle cerebral artery, commonly in the parietal lobe. The cysts are often found in the supratentorial regions and only rarely in the posterior cranial fossa, ventricles, or orbit (17).

Surgical excision of cysts without disruption of the capsule remains the standard management of CHD. A variety of surgical techniques have been developed to prevent cystic rupture. The most widely accepted method is Dowling's technique, in which the cyst is removed intact by injecting saline between the cyst wall-brain interface. This is made possible by the minimal adhesions that surround the cyst wall (18). Other techniques include cyst puncture and aspiration before removal or using cortical incision over the cyst, and ejection of the cyst by air insufflation of the contralateral ventricle (19). Possible postoperative complications include subdural effusions, obstructive hydrocephalus, and cortical collapse. In our case, the large spaces left behind after removing the three cysts were filled with isotonic saline prior to dural closure, in an attempt to reduce the risk of cortical collapse which carries a mortality of 7% (1,15). The follow-up CT scan showed a decrease in cavity size and an increase in brain tissue.

Medical treatment of hydatid cyst is required in cases of cyst rupture, recurrence, or systemic hydatid disease. It may also be used pre or post-operatively to shrink the cysts and prevent a recurrence, respectively (19-22). Our patient presented with three large cysts of different sizes and thus albendazole was prescribed post-operatively.

Whether this patient's past history of surgically evacuated ICH is related to CHD deserves further analysis. Although the sequence of events may be coincidental, the presence of spontaneous ICH in an otherwise healthy gentleman hints to a potential underlying connection. One theory is that surgical leukomalacia encouraged cystic development, particularly that the two pathologies are located in the same hemisphere. One other hypothesis is that the ICH provided an earlier manifestation of an occult CHD. Hemorrhagic CHD is, however, an uncommon occurrence. Another explanation is that this patient is a case of iatrogenic hydatidosis, which warrants institutional inquiry. In either case, we felt that documenting this case and discussing the possibility of association could direct further research efforts to better understand the etiology and presentation spectrum of CHD.

Conclusion

Primary cerebral hydatid disease is rare and the multiple-cyst variety is even rare. In this case, a peculiar association with a surgically-treated ICH was explored with possible theories to suggest future research directions.

Abbreviations

CHD: Cerebral Hydatid disease; ICH; intracerebral hemorrhage; MRC:

Medical Research Council; MRI: Magnetic Resonance Imaging; CT: Computed tomography;

ICP: Intracranial pressure.

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Radiological features of the intracranial extra-skeletal mesenchymal chondrosarcoma. A report of two cases insight in the literature review

Anas Abdallah, İrfan Çınar[1]

Department of Neurosurgery, Private Aile Hospital, Istanbul, TURKEY

ABSTRACT

Background: Mesenchymal chondrosarcomas are the most malignant form of chondrosarcomas. They have mostly affected bones. Rarely, these tumors can be intracranial extraskeletal (IEMC) that originates from the meninges or parenchyma.

Methods and Materials: We presented two IEMC patients who were treated at our institutions and followed up for the long-term. To understand the radiological features of IEMC, we conducted a systematic literature review for previously reported series and cases of IEMCs.

Results: We surgically treated two young males with IEMC initially diagnosed at their age of 18 and 20 years. The patients initially treated with gross total resection (GTR) and GTR followed by radiotherapy, and followed-up for 218 and 73 months, respectively. With both patients, we obtained 83 reported IEMC patients from the literature. Among them, only 30 cases were reported with their radiological MRI details. The mean age of the reported cases was 24.5±16.0 years (2 months–71 years). Female predominance was 54.2%. The mean progression-free and overall survivals were 27.9 and 39.0 months, respectively. Most IEMCs showed a partially calcified mass on roentgenography and a highly vascular mass on angiography. On T1WIs, IEMCs almost show hypo- to isointensity and intense heterogeneous enhancement after administering a contrast substance. On T2WIs, IEMCs show iso- to hyperintensity.

Conclusions: IEMCs usually show dural attachment without a net dural tail sign and a well-identified brimmed vascular nodule on TOF-MRA. This nodule appears as a prominent blooming on SWI. TOF-MRA and SWI images can help in the radiological diagnosis of IEMCs.

Keywords
intracranial extraskeletal mesenchymal chondrosarcoma, TOF-MRA, SWI, vasogenic edema, diagnosis

✉
Corresponding author:
Anas Abdallah

Department of Neurosurgery, Private Aile Hospital, Istanbul, Turkey

dr.anasabdallah@gmail.com

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1. BACKGROUND

Intracranial extraskeletal mesenchymal chondrosarcomas (IEMCs) are rare malignant neoplasms. They almost occurred among pediatric and young people. Primary intracranial chondrosarcomas constitute about 0.15% of all brain tumors.[1] After including our two patients and an exhaustive literature review, we find only 83 reported patients with IEMCs.

Microscopically, IEMC characterizes by two distinct components with a frequently abrupt transition between these two components.

The first component is comprised of highly cellular and undifferentiated mesenchymal cells. The second component is comprised of islands of well-differentiated and benign-appearing cartilage.[1,2]

The recommended appropriate management is gross total resection (GTR) followed by radiotherapy; however, IEMCs have a high propensity for neural axis dissemination.[1-4] IEMCs are reported to be aggressive, quick-growing tumors with high mitotic index properties.[1,2] Therefore, preoperative radiological distinguishing the subtype of chondrosarcoma is essential in managing these patients. In this study, we discuss the diagnostic radiological features that can help in distinguishing these rare malignant lesions by evaluation of the data from our two patients and followed with a brief review.

2. Methods and materials

We presented two IEMC patients who were treated at our institutions and followed up for the long-term. Both patients gave written consent to applied surgeries and for publications. To understand the radiological features of IEMC, we conducted a systematic literature review for previously reported series and cases of IEMCs.

To understand the radiological features of IEMCs, we identified the publications reported series or cases of IEMC. The selection criteria were; full-text published in English and accessed by MEDLINE, GOOGLE SCHOLAR, and PUBMED databases irrespective of the setting, study design, or details. Then, we analyzed the pooled sample after adding our two patients (n = 83). The search in the mentioned databases was up to Oct 1, 2020. We excluded the cases reported bone destructions, epidural location, tumors originate from skull bones, or reports did not identify non-skeletal situations.

Statistical analysis

Since the cases reported with sufficient data were less than 50 (cases with MRI and CT details 30 and 25 cases, respectively), most reported cases were case reports, and the early reported IEMC cases miss the important details regarding radiological examinations, we could not achieve meta-analysis.

3. Results

Our Illustrative Cases

Case 1: An 18-year-old boy presented to our outpatient clinic with a one-month history of headaches. A contrast-enhanced MRI revealed a well-capsulated heterogeneously enhanced tumoral mass measuring 4.9x4.5x4.2 cm. It was located in the right temporoparietal region. The intense contrast well-enhanced tumor was iso-hyperintense on T2WIs and iso-hypointense on T1WIs (Fig. 1). Presumptive diagnosis indicated that it is an atypical meningioma. At the time of surgery, we observed that the tumor had attached to the dura. GTR was applied to the mass. Histopathologically, the tumor was confirmed to be an MC. We discharged him on POD3 with no neurological deficits. No adjuvant treatment was applied. The postoperative metastatic work-up (PET-CT) demonstrated no extracranial involvement. Up to the POM22, his postoperative course was uneventful. At his yearly control visit, he had no symptoms. A contrast-enhanced MRI revealed a lobulated heterogeneously enhanced tumoral mass measuring 5.2x3.8x3.2 cm. It was located in the same first operation field. The tumor was resected completely. The tumor was confirmed histopathologically to be a recurrence of the first tumor. The patient received RT. On his POM72, he had been free of tumor recurrence or extracranial metastatic lesions. The patient had done his attended school. He works as an accountant for more than two years.

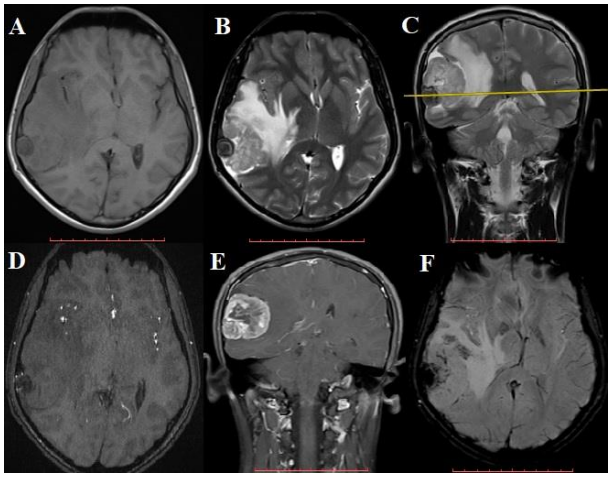

Figure 1. An 18-year-old boy presented to our outpatient clinic with a one-month history of headaches. His neurological examination was intact except for increases in DTRs. A contrast-enhanced MRI revealed a well-capsulated heterogeneously enhancing tumor measuring 4.9x4.5x4.2 cm. The mass was located in the right temporoparietal region and surrounded by diffuse edema. The lesion made a 7-8 mm shift to the left side and extending into the underlying brain

parenchyma. **[A]:** T1WIs demonstrated the lesion with two compartments. The lateral (small) one was hypointense and surrounded by the larger medial compartment. The medial compartment showed slight hypointensity compared to grey matter. **[B]:** T2WI-axial images demonstrated the lesion with separate two components. A small hypointense one was surrounded by the larger one that was hyperintense. **[C]:** T2WI-coronal images showed diffuse edema. **[D]:** TOF-MRA images showed a lateral hypointense nodule resembles the same as those that are seen in high vascularized lesions. The medial component was a slight inhomogeneous iso-hypointense. **[E]:** Contrast-enhanced T1WIs showed intense heterogeneously enhanced mas with two compartments. **[F]:** Brimmed prominent blooming nodule surrounded by the larger mild hyperintense component.

Case 2: A 38-year-old man referred to us with three days' duration of difficulties in speech, changes in consciousness, and severe headaches. A contrast-enhanced MRI revealed a multilobulated and well-capsulated mass. It was a heterogeneously enhanced tumor and measuring 8.2x6.2x5.6 cm. The tumor was located in the left frontotemporal region and surrounded by diffuse vasogenic edema. It was hyperintense on T2WIs and hypointense on T1WIs (Fig. 2). The tumor was diagnosed as intra-axial metastasis of MC. The patient received gross total resection followed by RT for right parietal IEMC 18 years ago. Over 18 years, he had received multiple mandibular and maxilla surgeries and twice adjuvant RT for several metastases. In his last presentation, he was lethargic and had not full responses to alters. NTR was achieved. After the surgical intervention, the patient required ICU care and died of disease on POD93.

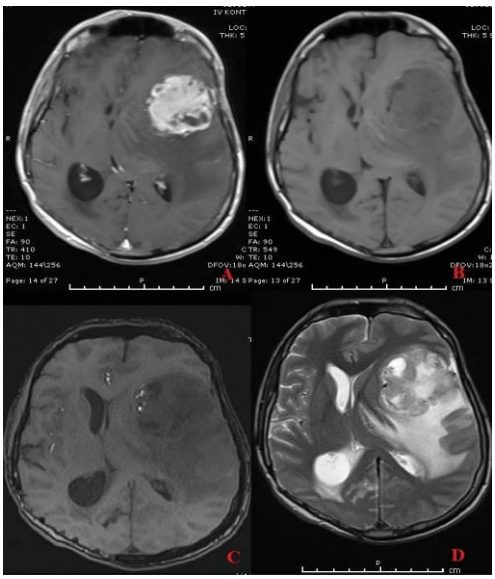

Figure 2. A 38-year-old man referred to us with three days' duration of difficulties in speech, changes in consciousness, and severe headaches. A contrast-enhanced MRI revealed a multilobulated heterogeneously intense enhanced tumor measuring 8.2x6.2x5.6 cm. The mass was located in the left frontotemporal region and surrounded by diffuse edema. The patient received gross total resection followed by RT for right parietal IEMC 18 years ago. Over 18 years, he had received multiple mandibular and maxilla surgeries and twice adjuvant RT for several metastases. **[A]:** Contrast-enhanced T1WIs revealed a multilobulated, heterogeneous, and intense enhanced tumor with distributed hypointense areas. **[B]:** T1WIs showed a mild hypointense lesion with a brimmed hypointense nodule. **[C]:** TOF-MRA images showed a hypointense lateral compartment. It resembles the nodule is seen in a high vascularized lesion. The medial component was a slight inhomogeneous iso-hypointense. **[D]:** T2WI showed heterogeneous hyperintense surrounded by diffuse vasogenic edema while the medial nodule was hyperintense.

Literature Review

We surgically treated two young males with IEMC initially diagnosed at their age of 18 and 20 years. The patients initially treated with gross total resection (GTR) and GTR followed by radiotherapy, and followed-up for 218 and 73 months, respectively. With both patients, we obtained 83 reported IEMC patients from the literature. Among them, only 30 cases were reported with their radiological MRI details. Thirty-three patients were reported without any radiological details. The mean age of the reported cases was 24.5±16.0 years (2 months–71 years). Female predominance was 54.2%. The mean progression-free and overall survivals were 27.9 and 39.0 months, respectively. The most commonly affected intracranial region was frontal that was seen in 22 patients (26.5%). The mean preoperative maximal diameter of 31 reported tumors was 6.0±2.3 cm (1.8–11.0 cm). The parenchymal origin was reported in 13 cases while falcine and tentorial originate were reported in 15 and 8 cases, respectively.

The early reported cases were reported with details regarding roentgenography and angiography. Early reports mentioned that IEMCs demonstrate several intracerebral flecks of calcification, destructive lesions, mottled calcification, or dense flocculent calcification on roentgenography. Some IEMCs showed a highly vascular mass on angiography. Twenty-five cases were reported with CT details. Most IEMCs showed a lesion with two compartments; one compartment had density higher than calcium and the other had

density lower than calcium on CT scan. Sometimes they show bone destructions. On T1WIs, IEMCs almost show hypo- to isointensity and intense heterogeneous enhancement after administering a contrast substance. On T2WIs, IEMCs show iso- to hyperintensity.

4. Discussion

Histopathologically, IEMC is a biomorphic tumor that comprises of undifferentiated cell mesenchymal mixed with differentiated cartilaginous tissue. Therefore, the tumor in most cases showed heterogeneous intensity in most sequences. Contrast-enhanced MRI remains the gold standard to demonstrate these lesions. However, the radiological findings are not pathognomonic for IEMCs. Calcifications that may appear incidentally on CT could be aware of the radiologist regarding IEMC. ICMEs almost are extra-axial, well-capsulated, and lobulated in shape. However, 13 cases were reported to be intra-axial (parenchymal in origin) lesions.[5]

TOF-MRA and SWI techniques help in the radiological diagnosis of IEMCs. The apparent dural tail is one of the most characteristic radiological features of meningioma. In our two cases, the dural tail sign wasn't net while we identified the brimmed vascular nodule without vessel dilatations on TOF-MRA. This nodule appears as a prominent blooming on SWI. This nodule is the same as those seen in vascular lesions. Although it is not pathognomonic, vasogenic peritumoral edema on FLAIR and T2WIs usually is prominent. The same features are seen in angiomatous meningiomas too. However, calcification can be distinguishable features for IEMCs. Additionally, we can recognize vascular lesions such as AVM and aneurysms by TOF-MRA.

Up-to-date, no study could differentiate IEMC from meningioma by radiological scanning studies. IEMCs are misdiagnosed as atypical meningioma,[1,2] hemangiopericytoma,[3] schwannomas,[4] dural-based metastasis,[5] gliomas, or oligodendroglioma.[6] IEMCs vary from hypo- to isointense on T1-WIs with intense heterogeneous enhancement after administering a contrast substance. On T2WIs, IEMCs demonstrate iso- to hyperintensity. These lesions show an iso- to hyperintensity on MRA images that mimic arteriovenous malformations. Sometimes IEMCs demonstrate extremely hypervascular on angiographic images.[3,4] Included in our two cases, the radiological features were mentioned in 30 patients. Six among them were reported to have cystic components, four were highly vascular, and three were hemorrhagic.

TOF-MRA can guide the surgeon in understanding the vascularity of the tumor, as TOF-MRA demonstrates the main vessels that passing through the tumors and is useful to identify tumor involvement with the cavernous sinus and main vascular structures. SWI technique is beneficial for detecting smaller vascular lesions that otherwise are missed by other sequences.

The craniospinal meninges are the most commonly seen location of IEMCs in CNS.[1,3-6] We can divide IEMCs into dural or parenchymal. The most commonly affected region was the frontal with a dural attachment that was seen in 23 patients. Most of the reported lesions with a dural or meningeal attachment are usually supratentorial (71 patients); 49 were reported to be lateral lesions while 22 were midline lesions. Parenchymal origin was reported in 13 tumors. One of the most challenging in diagnosis the lesion is taken small biopsy or specimens from one component without pieces from the second one when obtained pieces without the cartilaginous elements.[1,3-6] The lesion is generally demonstrated well-circumscribed, the rubbery firm solid, multilobulated, gray or reddish-brown colored, and almost invasive. Prominent vascularity and focal calcification are the main features of the lesion's cut surface.

The present study suffered from a few limitations, most of the early reported IEMC cases miss the important details needed to define the natural history and applied treatment, the recently reported cases miss sufficient data regarding the radiological examinations, and the pooled data were not sufficient to achieve meta-analysis review.

5. Conclusions

In our patients, we utilized TOF-MRA and SWI images to distinguish these malignant lesions from other benign lesions. Most reported IEMCs show hypo- to isointense and iso- to hyperintensity on T1-WIs and T2-WIs, respectively. They showed intense heterogeneous enhancement with contrast. On T2WIs, IEMCs show iso- to hyperintensity. Although we can't emphasize this due to their rarity, a brimmed vascular nodule on TOF-MRA and a prominent blooming (nodule) sign on SWI may distinguish these highly vascularized solid firm

lesions. They uncommonly have cystic, highly vascular, or hemorrhagic components.

Declarations

Consent for publication:
Informed written consent was obtained from both patients and their relatives for publication.

Competing interests:
None

Funding:
None

Authors' contributions:
AA: Conceptualization, Methodology, Software, Supervision, Formal analysis, Statistical analysis, Literature review, Visualization, Investigation, Writing – Original draft, Writing – Review, and Validation. **İÇ:** Validation, Writing, Reviewing, Literature Review, and Supervision.
Both authors deserve the first name.

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Authors' information:
Both authors work at the Department of Neurosurgery, Private Aile Hospital, 34590 Istanbul, Turkey.

Abbreviations

CNS = Central nervous system, DTRs = Deep tendon reflexes, ER = Emergency department, GTR = Gross-total resection, IEMC = Intracranial extraskeletal mesenchymal chondrosarcoma, MC = Mesenchymal chondrosarcoma, NTR = Near-total resection, POD = Postoperative day, POM = Postoperative month, RT = Radiotherapy, T1WIs = T1-weighted MR images, T2WIs = T2-weighted MR images, TOF-MRA = Time-of-Flight magnetic resonance angiography.

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Outcomes of surgical treatment for pituitary metastasis

Dmytro S. Teslenko[1], Mykola O. Guk[2], Olga Yu. Chuvashova[3]

[1] Department of Neuroendoscopy and Craniofacial Surgery, SI "Romodanov Neurosurgery Institute" NAMS of Ukraine, Kyiv, UKRAINE
[2] Department of Transsphenoidal Neurosurgery, SI "Romodanov Neurosurgery Institute" NAMS of Ukraine, Kyiv, UKRAINE
[3] Department of Neuroradiology and Radioneurosurgery, SI "Romodanov Neurosurgery Institute" NAMS of Ukraine, Kyiv, UKRAINE

Keywords
pituitary metastasis,
pituitary carcinoma,
surgical treatment,
outcomes,
survival,
skull base,
surgery

ABSTRACT

We analyzed the outcomes of surgical treatment for pituitary metastasis (PM) based on 35 observations. We registered the best estimates of resection radicalism in patients with minor PM, its inconsiderable spread ascending and descending from the diaphragm of the sella turcica, slightly bleeding metastasis, and no invading to the cavernous sinus. Positive changes in the PM patients' quality of life are chiefly associated with regressed visual impairment, local pain syndrome, and, to a lesser degree, oculomotor disorders. No post-operative regress or intensifying of hormonal impairments, such as diabetes insipidus and hypopituitarism, were seen. The age of patients, the time interval between the cancer diagnosis and the PM occurrence, control of the underlying disease, size of the tumour are the factors determining the life expectancy in PM patients.

Corresponding author:
Dmytro S. Teslenko

, SI "Romodanov Neurosurgery Institute" NAMS of Ukraine, Kyiv, Ukraine

tesldim@gmail.com

INTRODUCTION

Metastatic pituitary lesion (hereinafter as PM - pituitary metastasis) is a very rare condition of the central nervous system (CNS), with its frequency reported by various authors ranging from 0.14 to 20% among all metastatic invasions to the brain. [1-3; 5;8-14]. No way all PM cases require surgical intervention, as the majority of PM diagnosed at autopsy [2;4;6-8;] This evidence is associated with the commonly asymptomatic course: symptomatic PM incidence reaches only 7%. The largest actual studies concerning PM demonstrate heterogeneous and ambiguous treatment outcomes for the patients with this disease. [1-3;6; 8-14] Authors, though, state impossible to prolong the overall survival due to surgical intervention, concluding this based on the results of treatment of a significant number of patients having undergone surgery for PM. The number of observed patients operated on in these series ranges from 36 to 88 cases. [1;5;8] In this study, we attempted to clarify what post-operative outcomes are expected for PM surgery.

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The purpose of the study is to improve the surgical tactics in PM via analyzing surgical treatment outcomes for the patients with this condition.

Material and method

The work is based on the analysis of surgical outcomes of 35 PM patients treated and monitored at the SI «Romodanov Neurosurgery Institute» NAMS of Ukraine, Kyiv, Ukraine from 2005 to 2015. The PM diagnosis was confirmed histologically in all 35 patients.

The study included 17 males (47.9%) and 18 females (52.1%). The mean age of the enrolled individuals was 56.4 ± 10.4 years: 60.8 ± 2.4 years for men, 52.2 ± 2.1 years for women. All 35 patients evidenced the symptomatic course of the disease. Among these 35 patients, the most common primary tumor was lung cancer (34.3%), then in descending order, breast cancer (22.9%), renal (8.6%), rectal, prostate (all of 5.7%). Diagnostic patterns for PM included clinical and laboratory, neuroimaging evaluations, and examinations of the related specialists (oncologist, ophthalmologist, endocrinologist, therapist).

27 of 35 patients (77.2%) underwent microscopic PM removal. The observations were classified by type of approach, specifically, 7 (20.0%) patients were performed PM transcranial removal, and 20 (57.2%) transsphenoidal surgery. All cases of PM transcranial removal were performed from the subfrontal approach. In 8 patients (22.8%) the removal was carried out by the endoscopic technique.

While the statistical analysis of the obtained material, the Mann-Whitney U test was applied to independent samples, and the Wilcoxon signed-rank test to dependent samples to evaluate the probability of differences. Statistical correlation of parameters was estimated by the Spearman rank correlation test. The Kaplan–Meier method was applied to patient survival estimation. The Cox proportional hazard regression analysis was used to assess the prognosis.

Results and discussion

According to intraoperative findings and the results of post-operative tomographic control, total removal of PM took place in 7 patients (20.0%), subtotal in 17 (48.6%), partial in 9 (25.7%), a biopsy was done in 2 patients (5.7%). The most surgical radicalism was achieved in the patients who were operated on by transnasal endoscopic approach (4 cases). The lowest rates of total resection were registered in the group of patients who underwent microscopic transsphenoidal removal (2 observations). The distribution of PM patients by type and radicalism of the performed surgery is presented in Figure 1.

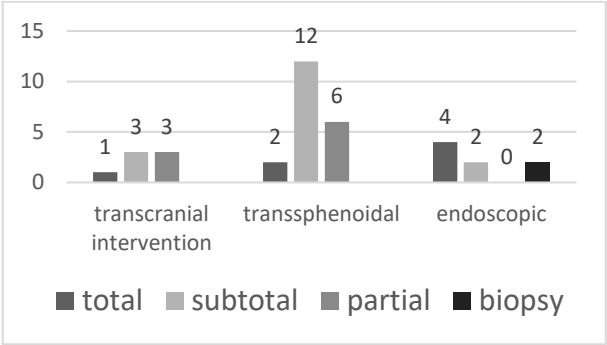


Figure 1. Observations distributed by the intervention radicalism and resection technique.

The Pairwise Correlation Method used for assessment of correlation between different factors and radicalism of operative intervention for PM showed an impact of the size of the metastasis, its spread, bleeding of tumor tissue, cavernous sinus lesions (all correlations significant at $p < 0.05$). The best levels of radicalism were seen in smaller sizes, inconsiderable ascending and descending spread from the diaphragm of the sella turcica, slightly bleeding metastasis, and no invading to the cavernous sinus. The significance of these factors impact model in the ordinal regression analysis was $p = 0.001$ ($\chi 2 = 82.9$). Visual disorders of varying severity were registered in 29 of 35 patients (82.9%). In most patients, visual disorders were the main, and often the only, manifestation of the disease. The request to improve vision or at least stabilize current visual impairments was the main goal of surgical treatment for a considerable number of patients. Among 6 (17.1%) of our patients with normal visual acuity and field of vision, no negative post-operative changes of visual functions were detected in any case. If the visual disorders were present primarily, the vision improvement was achieved in 79.3% cases (23 patients). Deterioration of vision was registered in 2 patients (6.9%), no changes were observed in 33 patients (13.8%). The Paired T-Test performed for comparison of two dependent samples (pre- and post-operative patients) showed the statistical significance of improvement of the visual disorders

in our patients undergone operation T = 5.2 at p = 0.000.

Among 18 patients with initial oculomotor disorders, post-operative improvement occurred in 9 cases (50.0%); no dynamics was seen in 6 patients (33.3%), deterioration occurred in 3 cases (16.7%). In 4 (23.5%) of 17 patients with no pre-operative oculomotor problems, post-operative oculomotor disorders appeared. Among 7 patients who developed or augmented oculomotor disorders after surgery, 2 cases of an isolated failure of sixth cranial nerves, 4 cases of third cranial nerves failure, and 1 case of combined lesions of third and sixth cranial nerves were observed.

Occurrence/deterioration of oculomotor functions in the study group after the endoscopic approach was equal to 14.7% of the total number of patients, and after microsurgical transsphenoidal and transcranial removal, these complications were registered more commonly, in 57.1% and 28.6% of cases, respectively. The obtained results are statistically significant (p = 0.041). Among those 4 patients who evidenced pre-operative dysfunction of trigeminal nerve branch, 2 individuals showed improvement (50%) due to decreased numbness in the area of the nerve innervation, 2 patients (50%) demonstrated no changes after surgery. In the post-operative period, trigeminal nerve failure appeared in 2 patients on the side of the tumor invasion into the cavernous sinus cavity.

Postoperatively, 14 patients with pre-operative hypopituitary disorders demonstrated no change in the severity of the pituitary failure. Deterioration of endocrine status, which was associated with the appeared hypothyroidism and hypocorticism, was observed in 3 patients. In the post-operative period, diabetes insipidus occurred in 4 patients who were not affected previously. In 20 patients with pre-operative evidence of diabetes insipidus, no changes of this symptom were seen. The results which we obtained prove that endoscopic PM removal leads to a statistically significantly lower rate of endocrine disorders, including the development of diabetes insipidus, compared to microsurgical techniques (p <0.05). Onset or increase of hypopituitary disorders was also statistically significantly more common at microsurgical removal of PM (p <0.05). Among 6 patients operated on for PM, with the Karnofsky Performance Scale Index of the quality of life > 80 in the early post-operative period, no worsening was registered in 5 patients, and in 1 individual the quality of life deteriorated. Among 19 patients with the Karnofsky Performance Scale Index of the quality of life equal to 70-80 in the early post-operative period, the condition did not worsen in 12 patients, in 7 the quality of life improved. Among the 10 patients with the Karnofsky Performance Scale Index of the quality of life <70 in the early post-operative period, the condition did not change in 7 patients, in 3 the quality of life improved. The Paired T-Test comparison of two dependent samples (pre- and post-operative patients) showed the statistical significance of improving the quality of life of our operated patients (T = -3.01 at p = 0.005).

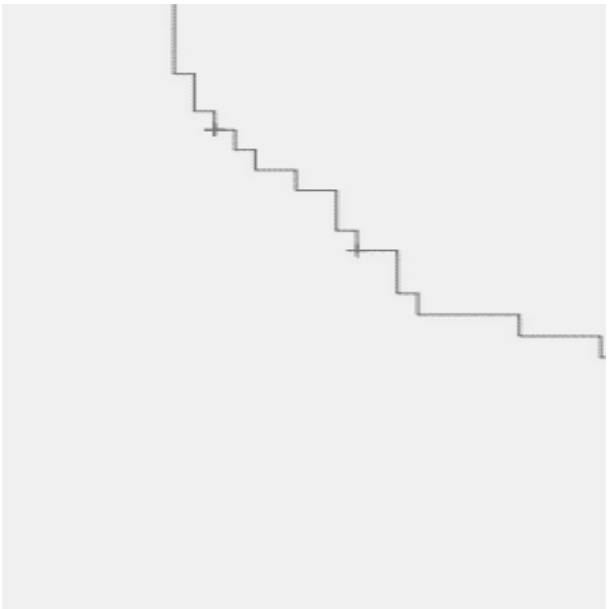
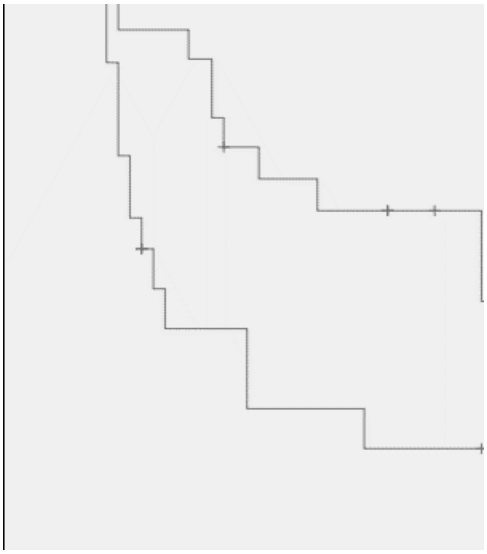


Figure 2. Overall survival of the patients operated on for PM (Kaplan-Meier).

All 35 observations were assessed with the Cox proportional hazards model regression analysis considering the available information on age, sex, the interval between diagnosis of the primary tumor and PM occurrence, the status of the primary lesion, PM maximum diameter, presence of other intracranial lesions, chemotherapy and/or radiation therapy. Our mathematical model was significant, p = 0.003 ($\chi 2$ = 15.9). The following independent factors were associated with a better prognosis in PM patients (relative risk <1, p <0.05): younger age; female sex; late-onset pituitary metastasis; the smaller size of PM; radiation therapy underwent; control of the primary site condition. Sex of patients and the clinical group of medical examination

considered as the factors with the most pronounced predictive properties in our patients. The average survival time in females was much longer than in males (31.6 ± 3.4 months compared to 15.8 ± 3.0 months, respectively). The average survival time in the patients of the cancer clinical group IV was statistically significantly shorter than in patients of groups II and III (7.3 ± 0.5 months compared to 27.3 ± 3.8 and 32.3 ± 4.3 months, respectively) (Figure 3B).

A.



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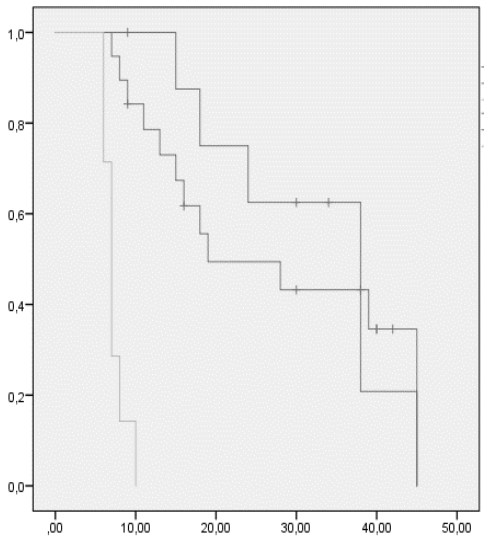

Figure 3. Survival curves of patients with PM (Kaplan-Meier): A. General survival curves obtained for different gender (male – blue line/female – green line) groups of patients; B. General survival curves obtained for patients of different clinical groups (1st clinical group - blue line, 2d clinical group - green line, 3rd clinical group – yellow line).

Thus, the analyzed treatment results of PM patients showed that the attempt to achieve an increased overall survival in PM patients compared to the available literature data failed. [ ] This result of the study indicates that the life expectancy in cancer patients with PM is primarily determined by the control of the underlying disease. In general, the life expectancy of PM patients was determined by the age of patients, the interval between the time of diagnosis of cancer and the occurrence of PM, control of the underlying disease, size of the tumor.

The individual tailoring principle should be followed when determining the indications to the surgical intervention for PM. If the tactics, technique of the surgical intervention, and the volume of removal are relevant, the quality of life in PM patients can be improved significantly. The dynamics of clinical manifestations in PM patients is more demonstrative in the long-term post-operative observations, that is associated either with a protracted recovery of neural structures of the sellar area after surgery, or the results of rehabilitation measures, as well.

Positive dynamics of the quality of life in PM patients is first and foremost associated with the regression of visual disturbances, local pain, and to a lesser extent oculomotor disorders. There is no post-operative regress or intensification of hormonal disorders, such as diabetes insipidus and hypopituitarism.

The prognosis for PM patients is poor, but it not attributable to the location, but due to the developing subsequent stages of primary cancer. We know that only 4 patients died of progressing pituitary lesions.

The short but definite survival time of PM cancer patients requires a change in the management strategy for these patients at all stages: from diagnosing to terminal care to ensure the long-term quality of life. In this context, we justify rationally in certain situations surgery and pituitary dysfunction treatment, including administration of gonadotropin, cortisol, thyroxine, which is rarely carried out in the complex management of patients with this condition.

Conclusions

1. The main indications for surgery for PM are present visual disorders, oculomotor impairments, pain syndrome caused by affected optic nerves and

cavernous sinus, and no verified cancer diagnosis in the presence of clinical manifestations of the disease. These factors influence the choice of approach and methods of PM removal.

2. The radicalism of PM removal is determined by the size of the tumor, bleeding tumor tissue, metastatic invasion to the cavernous sinus, use of endoscopic technologies.

3. The best results of surgical treatment for PM can be achieved in younger patients, individuals with the controlled underlying oncological condition, with good pre-operative neurological status and quality of life, in those undergone radical removals of the tumor.

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Intracranial hydatid disease. Our experience at peripheral tertiary care centre in India and review of literature

S.N. Gautam, Jigmisha Acharya, Banesh Jain, Piyush Kumar Panchariya

Government Medical College, Kota, Rajasthan, INDIA

ABSTRACT

Background: Echinococcosis also known as hydatid disease is an endemic zoonotic disease with growing public health concern with an estimated financial burden of US Dollars 193,539,740 annually. Its definitive host being carnivores and man being an accidental intermediate host. The most common organ affected is the liver, the brain is involved in about 2% of cases. Intracranial hydatid carries high morbidity owing to pressure effect and a slow-growing hence the diagnosis is often delayed. Surgery is the mainstay of treatment; medical management being reserved for selected cases.

Materials and method*:* A retrospective analysis of all the cases of intracranial hydatid disease managed at our department was done from 2013 to 2020 and data were analysed.

Results*:* A total of 6 cases were found with an incidence of 1.33% of all intracranial space-occupying lesions during the study period with male to female ratio of 5:1, mean age at presentation 21.2 years, 4 out of 6 patient in the pediatric age group, cyst localised mainly in middle cerebral artery territory, mostly solitary but multiple in one case, all cases managed surgically with preoperative rupture in one case, recurrence noted in another one, Albendazole was given to cases only with rupture or recurrence.

Conclusions: Intracranial hydatid disease should be suspected in all non-enhancing cystic brain lesions especially in endemic regions and all patients should have preferably surgical excision using the "Dowling technique" with medical management reserved for inaccessible lesions, patients unfit for surgery, rupture and recurrent cases. Its high time when public health strategies should also be focussed on prevention and control of disease with appropriate measure at the community level.

Keywords
intracranial hydatid, echinococcosis, zoonosis, Dowling's technique, Albendazole

Corresponding author:
Piyush Kumar Panchariya

Government Medical College, Kota, Rajasthan, India

drpiyushpanchariya@gmail.com

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INTRODUCTION

Hydatid is a Greek word meaning "a drop of water" [23]. Hydatid disease also known as echinococcosis is an endemic zoonotic disease, with studies showing it to be an increasing public health concern and can be regarded as emerging or re-emerging disease [22] with an estimated annual financial loss of US Dollars 193,539,740 [4]. It is known to occur in all continents and in at least 100 countries with much more frequency in South America, Australia, Middle East, and parts of North Africa than in Europe and North America [31]. The highest prevalence

of human hydatid disease in India has been reported from Andhra Pradesh, Saurashtra, and Tamil Nadu [25]. About 60-75% of affected patients are from paediatric age group [31]. Echinococcosis is caused by infestation of larvae of taenia echinococcus. The definite host in the life cycle are carnivores commonly dog and humans being the accidental intermediate hosts who are infected by the feco oral route or by direct contact. Liver is most commonly affected organ followed by lungs. The brain is involved in less than 2% of cases [20], and incidence of hydatic among all intracranial space occupying lesions is 1-2% only [29]. Intracranial echinococcosis is treated primarily by surgery using "Dowling technique" with proctoscolicidal drugs used to sterilize the cyst, decrease the chances of anaphylaxis, decrease the tension in the cyst wall, reducing the risk of spillage during surgery and the recurrence rate, recurrent cysts, multiple inaccessible cysts [12]. We present here a case series of 6 consecutive case of intracranial hydatid disease successfully treated at our institute and literature about intracranial echinococcosis is reviewed.

Materials and methods

We retrospectively analysed six cases of intracranial echinococcosis managed at Department of Neurosurgery, Government Medical College, Kota from 2013 to 2020. A detailed recording of demographic profile of patients, presenting factors, risk factors, investigations, surgical procedure and its outcome, other treatment modalities and their follow up was made.

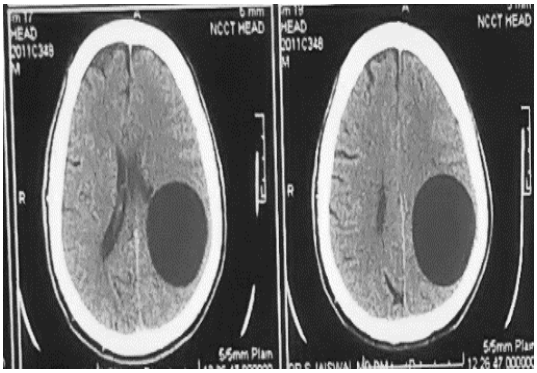
Observation and Results

An overall 6 cases of intracranial echinococcosis reported to our centre over the period and a total of 450 intracranial space occupying lesions operated during this period representing an incidence of 1.3% among all intracranial space occupying lesions. The details of patients recording are as given in Table 1.

Table 1. Case details of patients with intracranial hydatid cyst.

Age/ Sex	Presentation and duration of symptoms	Location and number	Manage-ment	Recur-rence	Intra operati-ve rupture	Albenda-Zole	Risk factor
12y/ F	Headache, seizures, Right hemiparesis; 6 Months	Left temporoparietal , single	Surgery	No	No	No	History of contact to pets.
14y/ M	Headache, Vomiting, Left hemiparesis; 3 Months	Right temporoparietal , single	Surgery	No	No	No	No documented risk factor.
8y/ M	Headache, vomiting, seizures ; 1 Month	Left temporop-arietal, Multiple	Surgery	Yes	No	Yes [After surgery for recur-ence]	History of contact to pets.
31y/ M	Headache, Vomiting Reduced vision in right eye; 3 Months	Right mastoid region, Single	Surgery	No	No	No	No documented risk factor
5y/ M	Headache, Vomiting, Left hemiparesis; 3 Months	Right lateral ventricle, Single	Surgery	No	No	No	No documented risk factor
60y/ M	Headache, Right hemiparesis; 5 Months	Left Parietal, Single	Surgery	No	No	No	No documented risk factor

The mean age of presentation was 21.2 years and a total of 4 out of 6 [66.6%] patients were below 16 years. The mean duration of symptoms was 3.5 Months. There was a male to female ratio of 5:1. Two of the patients had history of contact with pets. All patients came from rural area of Rajasthan. The commonest presentation was headache present in all cases [100%] followed by vomiting and hemiparesis being present in 4 out of 6 patients [66.66%], seizures in 2 out of 6 patients [33.33%] and reduced visual acuity in one patient [16.66%]. The commonest location of cysts were in temporoparietal region with single cases each of intraventricular and infratentorial locations [Figure 1].



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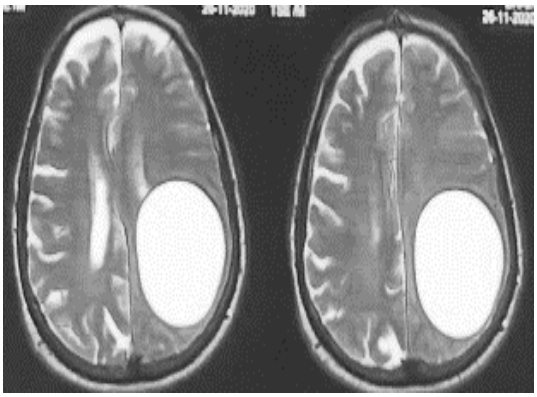

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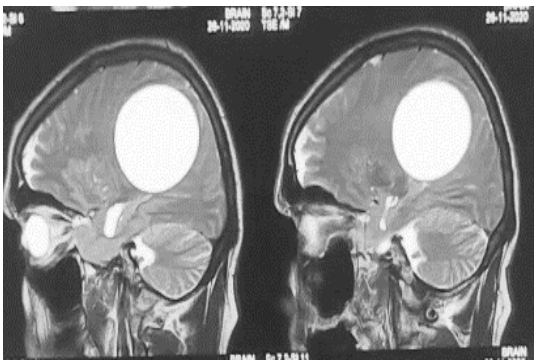

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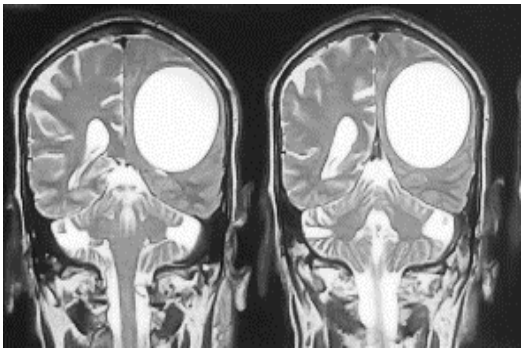

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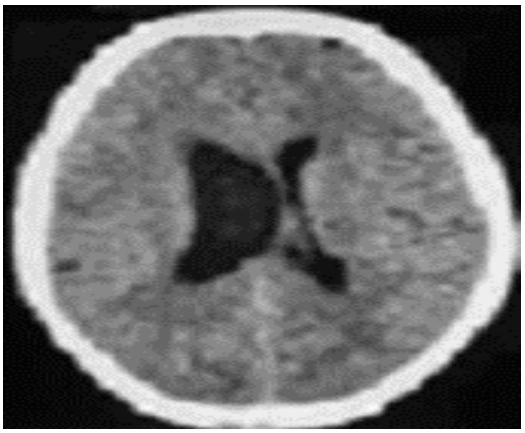

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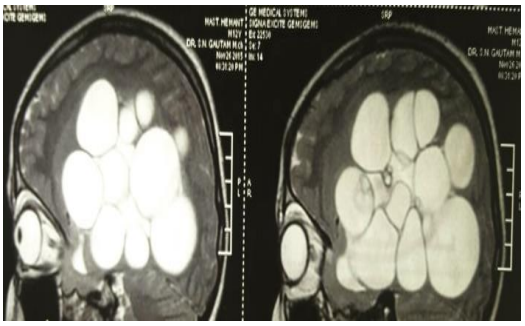


[f]

Figure 1. Pre-operative scans showing location of intracranial hydatid cyst [a] to [d] left temporoparietal, [e] Right intraventricular location, [f] Multiple intracranial hydatid cysts.

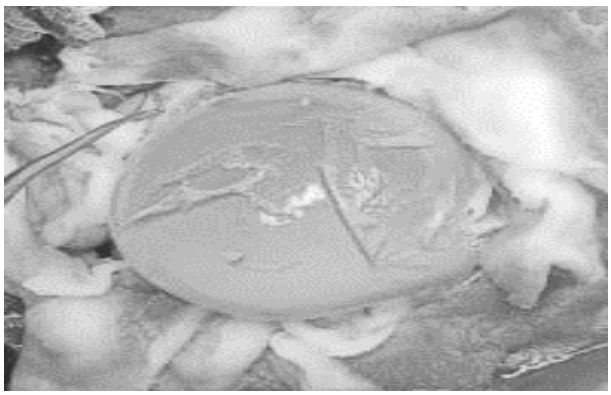
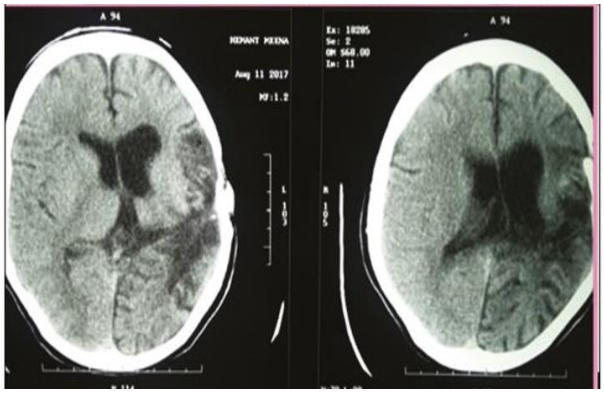


Figure 2. Delivery of intracranial hydatid cyst using Dowling's technique.



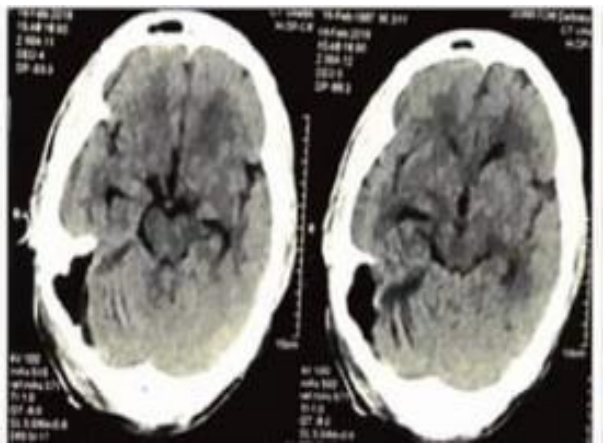


Figure 3. Post operated scans showing complete excision of cyst.

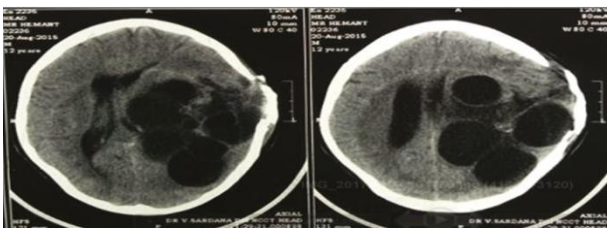


Figure 4. Recurrence in patient after 6 month of primary surgery.

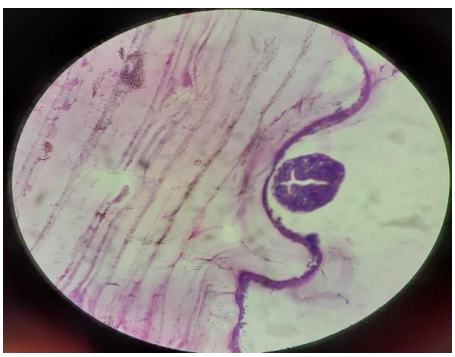


Figure 5. Histopathological microphotograph [40X] showing laminated ectocyst, scolex and inflammatory infiltrate.

Only one patient [16.66%] presented with multiple cysts [Figure 1f] . All patients were undergone a plain CT brain followed by an MRI brain to exactly localise the cyst, looking for consistency, number and status of surrounding brain parenchyma. The search of cyst located in other body organs using X ray chest and USG abdomen revealed no other associated cyst. All patient underwent craniotomy and cyst excision after routine investigations and anaesthesia clearance. We did not carry out serological investigations to test presence of antigen as it has less probability to be positive in intracranial hydatid disease and adds no significance to the management. All patients received a peri operative coverage of steroids for the risk of intraoperative rupture and dissemination . An adequate craniotomy was made as per the location of cyst, cyst was approached via corticectomy of size at least three fourth of size of cyst. The cyst was delivered through Dowling's technique dissecting peri cystic plane using hydro dissection and lowering the head end of table [Figure 2]. There was an intraoperative rupture of cyst in one case. Complete excision of cyst were achieved in all cases [Figure 3]. No intraoperative anaphylaxis was noted in any case. One patient developed extradural hematoma at craniotomy site in post operative period which was successfully managed conservatively. All excised cysts were subjected to histopathological confirmation which were consistent with hydatid cyst. There had been recurrence reported after 6 months of primary surgery in one case who was then operated at some other centre for recurrence but developed recurrence again after second surgery and later operated again at our centre only [Figure 4]. Cases who had rupture during surgery and recurrence following surgery were given tablet albendazole in divided doses of 10 mg/kg/day for a 28 days cycle followed by 14 days drug free interval upto 4 cycles. There has been a constant and good recovery of neurological symptoms in all cases. All the cases have been in follow up over a variable period of 6 months to seven years, we have a protocol of having post operated CT brain in immediate post operated period, an MRI brain at three months and one years of follow up.

DISCUSSION AND REVIEW OF LITERATURE

Hydatid disease is an emerging zoonotic parasitic disease, cases have been reported in all continents and across 50 countries around the globe. The countries with higher prevalence included Mediterranean countries, middle east countries, Russia, Australia, New Zealand, France, China, India [1]. The worldwide incidence of echinococcosis has been estimated to be 100,000 – 3,00,000 cases annually but only about 2-3% cases are of intracranial echinococcosis which actually may be higher but underreported [25, 12]. Guesnar reported first case of cerebral hydatid [9]. Intracranial hydatid forms about 1-2 % of all intracranial space occupying lesions [21], the ratio in our series reported to be 1.33% of all brain space occupying lesions operated during this period. The majority of cases about 65-80% found in paediatric age group possibly because of patent ductus arteriosus [9,14], in our series 4 out of 6 patients [66.66%] were under 15 years of age. No patent ductus arteriosus was found in any of our patient. There has been a male preponderance which was seen in present series also.

In Indian context, lot of single case reports are there on intracranial hydatid cyst, we found two case series of nine cases by Tanki etal [29] and five cases by Gupta etal [14] and compared the results with present series [Table 2].

Table 2. Comparison of results of case series by Tanki etal [29] , Gupta etal [14] and current Series

	Tanki etal [2009-2015]	**Gupta etal [1984-1997]**	**Current Series [2013-2020]**
Number of cases	9	5	6
Incidence in terms of Percentage of total intracranial space occupying lesion	0.06%	0.05%	1.13%
Mean Age of presentation	11.5 years	13.4 years	21.2 years
Paediatric patients	9/9 [100%]	4/5 [80%]	4/6 [66.66%]
Duration of symptoms	1 Month to 2 years	1 Month to 2 years	1 Months to 6 Months
Male : female ratio	5:4	3:2	5:1
Risk factors 1) Contact to pets 2) Rural location	 7/9 8/9	 2/5 3/5	 2/6 6/6
Symptoms	Seizures [Most common], Hemiparesis, Vomiting and Headache	Hemiparesis [Most common], Seizures	Headache [Most common], Hemiparesis, Vomiting, Seizures
Location of cyst	Four parietal solitary cysts, two frontal solitary, one parietooccipital solitary, two parietal multiple cysts	One patient each with frontal, lateral ventricle, parietal. Two patients with multiple cysts in parietal and temporoparietal region.	Two patients each with temporoparietal solitary cyst, one with lateral ventricle, one parietal, one mastoid, one with multiple temporoparietal cysts
Intraoperative Rupture	3 cases	2 cases	1 case

Anaphylaxis following rupture	Nil	Nil	Nil
Recurrence	Two cases; One year of surgery	Two cases; six month to one year after primary surgery	One case, 6 months following surgery
Albendazole	To all patients following surgery, 10 mg/kg for two months	To two patients following recurrence, 10 mg/kg for one month	Two patients, one with rupture another with recurrence, 10mg/kg upto 4 cycles
Follow up period	6 months to five years	Six months to eight years	Six months to seven years

Echinococcosis is caused by larvae [metacestode] of cestode species of the genus Echinococcus like E. granulosus [cystic echinococcosis], E. multilocularis [alveolar], E. vogeli or E. oligarthus [polycystic echinococcosis]. The two most common affecting humans are granulosus which has a limiting membrane and multilocularis with no limiting membrane and hence grow aggressively [23,25]. At least 7 of 9 strains of E. granulosus are found to be infective in humans with G5 strain responsible for most cases globally while G1 and G5 causes most infections in India [25].

Humans being the accidental intermediate host, get infected through the faeco oral route by ingestion of food or milk contaminated by dog faeces containing ova of the parasite or by direct contact with dogs. The eggs loose their enveloping layer in the stomach, releasing the embryos. The embryos pass through the wall of the gut into the portal system and are carried to the liver where most larvae get entrapped and encysted. Some may reach the lungs and occasionally, some may pass through the capillary filter of the liver and lungs and get entry into the systemic circulation. These may even reach the brain. Commonly affected organs include liver, lungs, brain, spleen, kidney, orbit, musculoskeletal system [23,11,13] . Contact to pets may or may not be always present, it was there in two of our patients. All the patients of our series were from rural area where there are large open areas and contamination of soil with stray dog's faeces is a common occurrence which is in accordance with the hypothesis of significant environmental contamination where in parasite eggs can survive longer in conditions of high humidity [32].

Intracranial hydatid cyst may be primary [single] with multiple scolices and broods capsule hence fertile with a risk of recurrence following rupture while secondary [multiple] thought to arise from multiple scolices released from left side of heart or cyst rupture in heart, lacks broods capsule hence non fertile with negligible risk of recurrence following rupture[12,1,14,26]. In cerebral tissue most common location of hydatid disease is in territory of middle cerebral artery which was also seen in our series where 4 out of 6 locations were in territory of terminal branches of middle cerebral artery [23,12,14]. Intraventricular location is now being reported in literature more and more as has been reported by Sharad et al [23], we had one patient with lateral ventricle hydatid cyst and contrary to common supratentorial locations [12,14] we had one patient with hydatid cyst located in right mastoid region. Other locations of intracranial echinococcosis reported in literature are orbit, skull bones, pons, basal ganglia [10,27].

The usual clinical presentation may be signs of raised intracranial pressure more common in paediatric population or focal neurological deficits common in adults [12,14]. Headache was commonest presentation in present series in all cases followed by vomiting, hemiparesis and seizures.

The diagnosis of intracranial hydatid relies on radiological investigations. On CT head, there is hypodense non contrast enhancing oval homogenous cystic mass lesion with thin walls and smooth margins usually in territory of middle cerebral artery with pressure effect on surrounding brain parenchyma as per the size of lesion with no surrounding edema [10,30]. Usually upon diagnosis the lesions are of considerable size before symptoms appear as intracranial hydatid cyst is a slow growing lesion although a variable growth rate of 1-10 cm/ year has been documented in literature [23,9,14,28].

On MRI brain, cyst wall has low signal intensity on both T1 and T2 imaging with no enhancement, daughter cysts or hydatid sand may be visible on MRI, no rim enhancement is a differentiating feature from cystic high grade tumours or abscess [10,30]. Infiltrating margin and surrounding edema may be a

feature of echinococcus multilocularis. MRS and diffusion weighted imaging has now being used to further aids to diagnosis. Chand et al [7] demonstrated mildly elevated choline, depressed creatine and NAA, and a large peak of lactate, pyruvate and acetate. Pyruvate has been considered a specific in vivo marker for cestodal, in particular hydatid cysts [7,19,17,35]. All patient underwent CT brain followed by MRI brain in current series and pre op diagnosis of Hydatid cyst was considered in all cases was considered based on consistent radiological findings. No patient in current series was subjected to MRS. The various differential diagnosis to be considered on radiology should include cystic tumours, porencephalic cysts, arachnoid cysts, epidermoid cysts, neurocysticercosis, toxoplasma [23,30,5].

Among serological tests immunoblot test is the test of choice targeting the specific arc 5 antigen present in hydatid fluid of E.granulosus. The sensitivity and specificity of test is 91% and 98% respectively. It may show cross reaction with Taenia cysticercosis. Casoni's test is of little significance in cerebral hydatid disease [23, 22]. No patient in current series was subjected to any laboratory investigation to ascertain hydatid disease pre operatively as radiological findings were typical of disease.

The treatment of choice for intracranial hydatid disease is surgical excision of cyst without rupture [16]. The preferred technique includes the Dowling technique later modified by Arana Iniguez and San Julian. The essential steps include creation of a large flap; careful handing during all operative steps to avoid monopolar coagulation; opening the atrophic cortex overlying the cyst over an area with a diameter no less than three quarters of the diameter of the cyst; and allowing the cyst to fall out by just lowering the head of the operating table and flushing warm saline between the cyst and surrounding brain [6,2]. In case of multiple cyst , largest one is targeted first. No technique can be applied to all the cases as a general rule and there should be an approach pre operatively identified for each case [16]. We got a complete resection of cyst in all the cases under microscopic guidance, although rupture was there in one case but no anaphylaxis was seen. There have been reports of irrigating the cavity with hypertonic saline to prevent recurrence specially after inadvertent intra operative cyst rupture [26,33].

There may be post operative cerebral edema, sub dural effusions, hydrocephalus, loss of autoregulatory mechanisms following cyst excision and decompression which should be suspected and diagnosed timely [23,15]. No such complication was seen in our series. Although an underlying EDH at craniotomy site was seen in one case which was successfully managed conservatively.

The pathological character of cyst consists of three layers the endocyst which has inner germinal layer, scolices, brood capsule which proliferate by internal budding. In E. multilocularis there is external budding and hence infiltrating margins are there. The ectocyst the outer laminated layer, the host inflammatory capsule Pericyst which has blood vessels to supply nutrition to the parasite[23,9,14]. All cases were subjected to histopathological confirmation in current series with confirmation of all the layers in the specimen. [Figure 5]

The medical management consists of protoscolicidal agent Albendazole in divided doses with a total dose of 10 mg/kg/day. It is parasiticidal and acts by blocking the uptake of glucose by larvae and adult parasites [18]. Albendazole results in disappearance of up to 48% of cysts and a substantial reduction in size of the cysts in another 28% [26]. Praziquantel increases the serum concentration of Albendazole four fold and hence a combination of drugs is more effective than either alone [23,26]. The use of drugs is limited to patient not fit for surgery, inaccessible cyst, history of intraoperative rupture, recurrence. The drugs are given over a 28 days cycle with 14 days drug free interval upto 4 to 6 cycles[12,15] . Although isolated case reports of medical management of intracranial echinococcosis are there in literature[24,8]. In the current series two patients one with recurrent disease and another with intraoperative rupture of cyst were put on albendazole upto 4 cycles after surgical excision and no recurrence has been documented till now in regular follow up.

Hydatid disease is an emerging and remerging public health problem where surgical and medical management of individual cases is just a palliation and a public heath strategy to control and prevent the disease is reasonable approach. Each country need to identify the prevalent strain, definitive and intermediate host in her geographical location and derive policies accordingly. As far as India is concerned, checking the population of stray dogs, surveillance of dogs, periodic stool testing and

accordingly treatment, preventing direct access to raw offal at slaughter house and farms should be implemented. Many countries such as New Zealand, Australia, and China have been successful in this regard and India is yet to catch up [31,34].

Despite a silent but constantly growing public health concern and growing number of intracranial hydatid disease, there has been a need of more and more literature to better manage the cases of intracranial echinococcosis and also to address this entity on community level also. Through this series we have shared our experience of successful management of intracranial echinococcosis and also adds on to a complete literature review over this under reported cerebral disease.

Conclusions

Hydatid disease should be suspected in all cystic non enhancing mass lesions specially in endemic regions and goal of treatment should be complete surgical excision with no rupture of cyst while reserving albendazole for selected cases, alongside addressing this condition on community level also with incorporation of carefully drafted public health policies.

Declarations

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Retrospective study on early outcomes of carotid stenting. Institutional experience

Saurabh Sharma[1], Prashant Raj Singh[2], Ram Kumar Goyal[3], Raghavendra Kumar Sharma[4], Yashuhiro Yamada[5], Yoko Kato[6]

[1] M.Ch. Neurosurgery. Associate consultant, Max Hospital, Delhi, India
[2] D.N.B. Neurosurgery. Assistant professor, A.I.I.M.S. Raipur, C.G. India
[3] M.Ch. Neurosurgery. Consultant, GNRC Hospital, Guwahati, Assam, India
[4] M.Ch. Neurosurgery. Assistant professor, A.I.I.M.S. Raipur, C.G. India
[5] MD. PhD. Consultant neurosurgeon, Department of Neurosurgery, Bantane Hospital, Fujita Health University, Nagoya, Japan
[6] Prof. Dr MD. PhD. Consultant Neurosurgeon, Department of Neurosurgery, Bantane Hospital, Fujita Health University, Nagoya, Japan

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Corresponding author:
Raghavendra Kumar Sharma

A.I.I.M.S. Raipur, C.G., India

sdr.raghavendra@gmail.com

Abstract

Objective: This study is conducted to evaluate the early events after Carotid artery stenting (CAS) among our patients in a single institute.

Methods: This study was conducted on 40 patients. These patients underwent stenting of extracranial carotid arteries. Stenting was performed on symptomatic patients with carotid artery stenosis of more than 50 per cent of asymptomatic patients with more than 70 per cent carotid artery stenosis on Doppler ultrasonography. Follow up period for this study was of one month.

Results: 40 patients who underwent CAS between August 2018 and June 2019 were included in the study. Self-expandable hybrid stents were implanted in all patients and pre or poststent-dilatation was performed if required after implantation. None of the patients suffered from a stroke, myocardial infarction or death due to CAS during their hospital stay. Only one patient had a minor stroke during follow up, which was managed conservatively. No transient ischemic attack (TIA), myocardial infarction or death during the follow-up period. Re-stenosis was not observed in the follow-up carotid Doppler ultrasonography; flow rates were within normal limits.

Conclusions: Carotid stenting is a safe alternative to CEA (carotid endarterectomy) in the treatment of carotid stenosis regardless of age. CAS with cerebral protection can be performed safely in patients who are at high surgical risk, with low perioperative morbidity and mortality. The durability of the procedure must be determined with a longer follow-up. Further high-quality RCTs are required to address other shortcomings and controversies.

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Introduction

In the industrialized world, the leading cause of death is stroke. [1]

Stroke is also the major culprit of disability in the affected individuals. About 6.5 million strokes occur per year. Atherosclerosis and embolization from stenosed carotid arteries are one of the most common causes of vascular stroke. Bifurcation of the common carotid artery is the common site of stenosis and the atherosclerotic plaques found in this stenosed area. It accounts for nearly 20 % of strokes. This embolization can lead to TIA, brain ischemia, and other neurological manifestations. [2,3] Carotid atherosclerosis is often asymptomatic until a disabling or fatal stroke occurs. Predisposing factors for carotid atherosclerosis are diabetes mellitus, hypertension, hyperlipidemia, and smoking. There is a strong association between the severity of stenosis and stroke risk exists. Medical treatment, interventional angioplasty, and carotid endarterectomy (CEA) are some treatment options for symptomatic carotid artery stenosis.[4] As compared to CEA, Carotid artery stenting (CAS) is a minimally invasive alternative for the treatment of carotid artery stenosis. However, the safety and efficacy of CAS have been approved by various randomized trials (RCTs). The incidence of restenosis after CAS is comparatively low but periprocedural stroke after CAS is a little concern.[4] In this article, we are sharing our institutional experience with CAS, its complication, and early outcome.

Material and methods

We conducted a retrospective study on patients who underwent carotid artery stenting from August 2017 to June 2019 to determine the various outcomes of the procedure and to find out the different outcomes in asymptomatic and symptomatic patients. The total number of patients undergone carotid stenting in our study was 40. As per our departmental protocol the patients who underwent CAS, required to have symptoms with more than 50% of carotid artery stenosis. Asymptomatic patients who had more than 70% carotid artery stenosis on Doppler ultrasonography were also selected for CAS. Patients who suffered transient ischemic attacks (defined as focal neurological dysfunction due to focal brain ischemia without cerebral infarct), minor non-disabling stroke, or amaurosis fugax, considered as symptomatic. Those patients, who have a history of severe stroke, were excluded from the study.

Before the procedure, detailed history and clinical and laboratory examinations were performed. Routinely electrocardiography (ECG) was done in all patients and detailed interpretation performed by the cardiology team.

All patients underwent carotid Doppler ultrasound, magnetic resonance angiography (MRA) of the carotid arteries, or computed tomography angiography (CTA) of the carotid arteries. Data were collected for both rights and left carotid arteries, regardless of which carotid artery was stented. The degree of stenosis was grouped into ranges using velocity criteria in Doppler ultrasound. The categories were: < 70% stenosis and >70% stenosis or occluded.

In this procedure, we used self-expandable stents and both proximal and distal embolic protection devices (Figure 1). In all patients, a stent with a distal or proximal protection device was placed after accessing a femoral artery. Predilatation before stent placement and post dilatation after stenting was performed depending upon the surgeon's choice and requirement. Every patient received standard medical care post-procedural, including the treatment of hypertension, hyperlipidemia, and diabetes. In our study, a detailed neurologic evaluation was performed at baseline, during the hospital stay. Any complications such as transient ischemic stroke, myocardial infarction, visual deterioration, and death were reported. Follow up period of our study was 30 days.

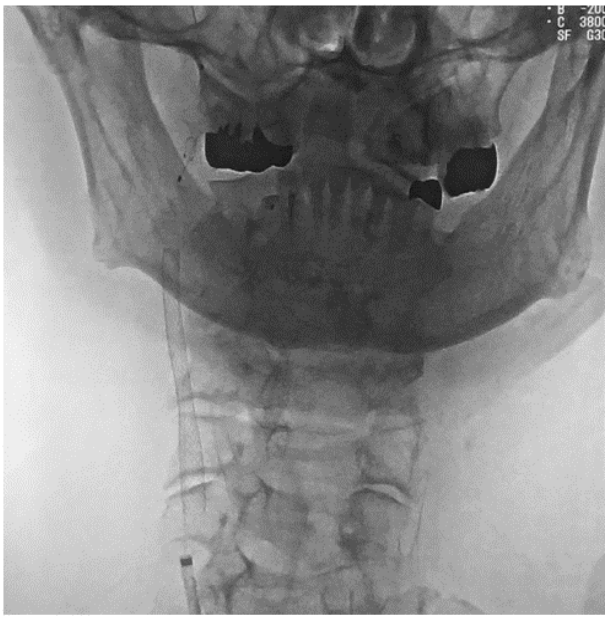

Figure 1. Showing self-expandable stent with diastal embolic protection device.

Results

Forty patients who underwent CAS between the study periods were included in the study conducted at Bantane hospital, Fujita health university, Nagoya, Japan. The mean age was 71.61 years (range: 48-89 years old) and the percentage of male participants was 90%. 40% of our patients were less than 70 years of age. 72.5% of patients were having a history of hypertension which was considered as the most common cardiac risk factor. 60 % of our patients had stenosis > 70 percent and among them 41.66 % were symptomatic. The most common neurologic sign was hemiparesis (stroke- 8 patients) followed by transient ischemic attack (TIA-5 patients) and amaurosis fugax (2 patients). The ratio of males and females in our study was 9:1. 38% patients were symptomatic and the rest was asymptomatic. Embolic protection devices (EPDs), as well as self-expandable hybrid stents, were used in all cases. Distal EPDs were used in 25% cases whereas, proximal EPDs in 75% cases. There was no stroke, MI, or death in our study population during the period of hospital stay. Patients were followed up and the mean follow-up period was 30 days after discharge. Only one patient had a minor stroke in the follow-up period, which was managed conservatively. No TIA, myocardial infarction, or death during the follow-up period. Doppler Ultrasonography was used to look for re-stenosis (observed by flow rate) of carotid vessels during the follow-up periods. No evidence of restenosis was noticed during this period.

Discussion

Before the introduction of embolic protection devices and hybrid self- expandable stents, the post-procedural complications used to be high but with the uses of these devices, morbidity and mortality were remarkably reduced. Setacci et al. observed in his prospective study that the combined stroke and death rate at 30 days for symptomatic patients who underwent CAS was about 10 percent.[5] Gray et al. analyze the data from 2 prospective multicentric studies. Analysis from these 2 post-market surveillance studies (EXACT, CAPTURE-2) on 6,320 high-risk patients, showed a 3.6 percent death and stroke rate over a period of 30 posts procedural days.[6] The mean age of patients in our study was 71.61 years. One patient in our study developed a minor no disabling stroke which was managed conservatively and successfully. No associated mortality in our cases as compared to other studies. 30 days stroke rate is also comparable to other studies on exclusive carotid stenting.[5]

The absolute perioperative risks we observed when considering CAS is that there is a lower absolute risk of stroke in asymptomatic patients than for symptomatic carotid stenosis. Previous studies have suggested that prophylactic revascularization for asymptomatic carotid stenosis may not have clear advantages over medical management when the procedural risk exceeds 3%.[7] In our center procedural risk is less than 3%.

According to a study, the 30-day stroke of 16% for symptomatic primary-CAS patients but no stroke in the asymptomatic group.[8] Their 16% stroke rate significantly exceeds the 2.5% rate reported in the current study.

In a study by Hobson et al, CAS was successful in all 17 cases and produced no periprocedural neurologic deficits or deaths.[9] Similar favorable results were reported by Yadav et al, with only one minor stroke in 25 CAS procedures in 22 symptomatic patients.[10]

Naggara et al showed that the use of an embolic protection device (EPD) lowers the risk of stroke at the time of CAS. In our study, we used distal or proximal embolic protection devices and self-expandable stents.[11] According to some studies, the use of closed-cell stent design decreases the operative and postoperative stroke rates.[12] Calvin et al stated that high volume operators had the lowest operative stroke and death rates.[13] In SAPPHIRE and CREST studies post-CAS myocardial infarction (MI) was associated with 2.4 and 1.1 % cases respectively.[14,15] Antiplatelet therapy when initiated early can reduce the recurrence of neurological events after non-cardioembolic TIA/stroke.[16] In our study, one patient developed minor strokes which was not disabling and there was no effect on hospital stay and all patients were discharged in stable conditions. As compared to other studies, there was no mortality or myocardial infarction in our groups. A 2012 Cochrane review of 7572 patients from 16 trials reported that endovascular treatment was associated with significantly lower risks of MI, cranial nerve palsy, and haematomas.[17]

Conclusion

Stroke is a major contributor to the global health

burden. CAS is a good alternative treatment for carotid artery stenosis. According to many studies, periprocedural stroke is more commonly associated with CAS but MI and other complications are far less in post-CAS patients. The present analysis emphasizes that CAS can be performed with high procedural success and reasonable procedural safety in a high-volume center with experienced interventionists, utilization of appropriate devices, and under embolic protection devices. However, an expert operator is needed to avoid cardiovascular complications in high-risk patients. Guidelines for performing CAS, use of instruments, embolic devices, dual or single antiplatelet therapy pre and post-procedure, and use of closed or open cell stents are variable and need to be defined. High-quality RCT is required so that CAS can be performed for specific reasons and with specific instruments. This procedure is less invasive and better tolerated, and is a better future treatment option for carotid stenosis. Moreover, in comparison with CEA, CAS is an effective as well as a safe treatment option for the high-risk patients with carotid artery stenosis, and hence it is expected that more institutes will opt for this intervention in upcoming years.

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The effect of long-term subgaleal drain retention (for 14 days) in preventing Cerebro-Spinal Fluid (CSF) fistula development in cases with an insufficiently closed dural defect after craniotomy or craniectomy

Umit Kocaman[1], Hakan Yilmaz[2]

[1] Izmir Cigli Region Education and Research Hospital, Department of Neurosurgery, Izmir, TURKEY
[2] University of Health Sciences, Izmir Bozyaka Education and Research Hospital, Department of Neurosurgery, Izmir, TURKEY

Keywords
subgaleal drain,
CSF fistula,
dural defect

ABSTRACT

Purpose: Our aim was to determine the effectiveness of long-term subgaleal drain retention in preventing CSF fistula development that may occur in the wound site when the dura cannot be completely closed after craniotomy or craniectomy.

Material and method: This study was planned to include the cases of craniotomy and craniectomy performed at Bakırcay University Cigli Training and Research Hospital during 2017-2021. The study has been made in a retrospective manner to include a subgaleal drain group and a control group. Both groups were selected from Bakırcay University Cigli Training and Research Hospital. A subgaleal drain was placed in 18 cases with a large or multiple defect after craniotomy or craniectomy where the defect could not be completely closed with grafts. It was planned to be kept in place for 14days with free drainage. Patients were administered antibiotics for three days after the surgery. Patients were monitored for CSF fistula and infection development. On the other hand, 12 patients having large dural defect were included in the control group. Patients in the control group were determined by a random selection method. Patients were followed for 2 days under subgaleal drainage. The Control group was also monitored for CSF fistula and infection development. Both groups statistically were compared with each other in terms of CSF fistula and infection development.

Results: There were 18 cases where the dura was closed insufficiently, long-term subgaleal drainage was performed. The mean age was 66.6 (34-82) years. The surgery performed was craniotomy/craniectomy for cerebellar hematoma drainage in 3 cases, acute subdural hematoma drainage in 5 cases, supratentorial tumour resection in 5 cases, large depression fracture in 4 cases and debridement of cerebral tissue damaged by firearm injury in 1 case. The drain was withdrawn at the end of the 14th day in all patients. A CSF fistula did not occur in any of 18 patients (%0) included in the study. In all patients (%100), the wounds were healed without any problems and no signs of local or systemic infection were found. In the control group, the mean age is 62.2 (48-88) years. CSF fistula developed in 4 (%33.3) of 12 patients

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Corresponding author:
Hakan Yilmaz

University of Health Sciences, Izmir Bozyaka Education and Research Hospital, Department of Neurosurgery, Izmir, Turkey

dr_hakanyilmaz@hotmail.com

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in the control group. We had to apply lumbal external drainage in 2(%50) of 4 patients with CSF fistula. Central nervous system infection developed in one (% 8.33) patient.

Conclusion: Long-term subgaleal drainage can be used as an alternative to lumbar external drainage.

Introduction

CSF leakage is an important risk factor in cranial surgeries where the dura is opened. This risk may increase even further in cases requiring dural patches, those with history of diabetes mellitus, during surgery for meningioma that has invaded the dura and bones, and according to craniotomy localization [1]. CSF leakage after craniotomy is directly related to intracranial infections [2].

Conventional methods are currently successfully used to minimize CSF fistula development. Primary tight closure of the dura and patching with galeal graft, lata graft or allograft when necessary and providing support to the dural repair site with biological tissue adhesives are certain precautions that can be taken during the surgery. The most important established method after the development of an CSF fistula is the resuturing of the wound area and simultaneous insertion of lumbar drainage [3,4,5]. External ventricular drainage can be used for CSF fistula treatment in selected cases and when lumbar drainage is contra-indicated.

We think that a subgaleal drain can be safely used as an alternative to lumbar drainage when the dura cannot be closed completely after craniotomy or when leak proof characteristics of the duraplasty are suspect. We share our results from the clinical experinces on this subject.

Material and method

We included cases of craniotomy and craniectomy performed at Bakırcay University Cigli Training and Research Hospital during 2017-2021 in this retrospective study. Cases in which the dura had a large defect and could not be closed were investigated in the study. Although duraplasty was performed with the aid of a galeal graft or dural patch, it had not been possible to ensure adequate closure. The subgaleal drain placed during surgery was therefore left for free drainage for 14 days. A 10 ch soft drain with a drainage bag was prefered as the subgaleal drain. The drain was always kept open and below the head level of the patient. Daily wound dressing and drain care was performed. Hemogram, sedimentation and CRP were monitored every 3 days; daily 2x1g cefazolin was administered intravenously during 3 days. On the other hand, 12 patients having large dural defect were include to the control group. Patients in control grup were determined by random selection method. The control group was followed for 2 days under subgaleal dranaige. Control group was also monitered for CSF fistula and infection development. The both groups statistically was compared with each other in terms of CSF fistula and infection development. Statistical analysis was performed with Pearson's chi-square test.

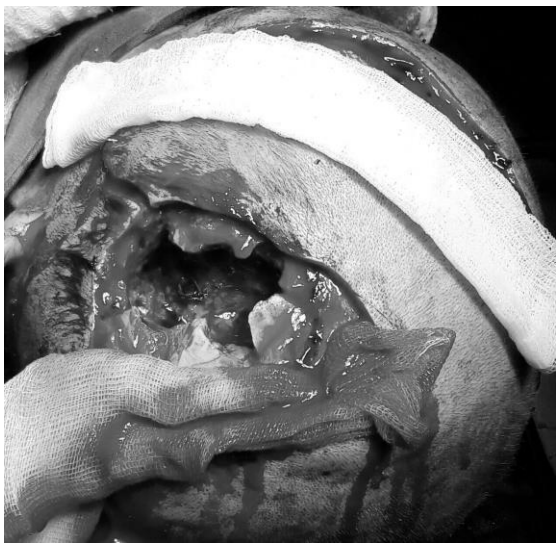

Figure 1. A case where the defect dural to firearm injury is too large that duraplasty cannot be made.

Figure 2. Closure of the case using frontal flap and soft subgaleal drainage with 10 ch drainage bag.

Results

There were 18 cases where the dura had a large defect and could not be closed and where subgaleal drainage was planned. The surgery performed was craniotomy/craniectomy for cerebellar hematoma drainage in 3 cases, acute subdural hematoma drainage in 5 cases, supratentorial tumor resection in 5 cases, large depression fracture in 4 cases and debridement of cerebral tissue damaged by firearm injury in 1 cases, The mean age of 18 patients included in the evaluation was 66.6 (34-82) years. There were 11 males and 7 females. Duraplasty with a galeal graft had been attempted first, followed by a dural patch if that was not possible. However, adequate dura closure could not be ensured due to reasons such as dural tissue loss, dura maceration, cerebral edema, and damaged dura structure in traumatic cases. Long-term subgaleal drainage was planned during operation in these patients. The subgaleal drain was withdrawn and closed with a single suture at the end of 14 days. A CSF fistula did notdevelop in any patient (%0). Suture removal was at the 7-10 days on average. Local or systemic infection were not found in any of the cases (%0). In the control group, mean age is 62.2 (48-88) years. There were 7 males, 5 females. CSF fistula developed in 4(%33.3) of 12 patients in control group. We had to apply lumbal external dranaige in 2(%50) of 4 patients with CSF fistula. Central nervous system infection developed in one (% 8.33) patient.

The development of CSF fistula is statistically significant in patients with long-term subgaleal drain use compared to the control group (according to Pearson's chi-square test; p:0.018).

Again, there is no statistically significant difference between the long-term subgaleal drain group and the control group in terms of preventing the development of central nervous system infection due to CSF fistula (according to Pearson's chi-square test; p:0.400).

Discussion

Long-term subgaleal drainage provides time for wound site healing in cases where duraplasty is not possible due to a large dural defect. The drainage bag was kept just below the head level. We used long-term subgaleal drainage in 18 patients with a dural defect in this study. The lack of a CSF fistula in the patients indicates that this is an effective and practical method.

A study similar to ours was conducted in patients who underwent spinal surgery and had an iatrogenic dural tear. A subfascial drain was inserted for the patients who had CSF leakage despite dura repair and wound healing was allowed. The drain was left for 15 days. None of the patients developed long-term drainage-related complications and no permanent CSF fistula was observed [4].

Another study evaluated 24 patients who had undergone posterior fossa surgery with a CSF fistula. The CSF fistula was treated with conservative treatment that required resuturing in only 2 of the patients and lumbar external drainage was used in 20 patients. Two patients required ventriculo-peritoneal shunt insertion due to hydrocephalus. The importance of lumbar external drainage with resuturing of the wound site in the treatment of a CSF fistula was emphasized in that study [5].

We believe that subgaleal drainage could provide an alternative to lumbar external drainage. Placing a subgaleal drain during surgery and conducting the follow-up with drainage from the beginning reduces the risk of CSF fistula development while we are trying to treat a CSF fistula that has already developed with lumbar external drainage. This may be an advantage of subgaleal drainage. There may also be a period of a few days when CSF leakage is followedup with sutures while the flow continues after the CSF fistula develops in patients with lumbar external drainage. The patient can also suffer from infections during this time. There is no such period with subgaleal drainage.

Another study compared infection rates in terms of meningoventriculitis development in patients who required lumbar external drainage (LED) and external ventricular drainage (EVD). The infection rates for EVD and LED were reported as 7.5 and 24.7 per 1000 EVD and LED days respectively. The meningoventriculitis rate was highest between the 4th and 9th days. They found EVD not to be an important meningoventriculitis risk factor while LED was among the major risk factors [3].Furthermore, subgaleal drainage may have a lower infection risk as it is less invasive than EVD. Since both lumbar external drainage and subgaleal drainage are placed under sterile conditions, a significant risk may not occur as long as drainage care is performed regularly. We did not find any significant findings in terms of infection. Some articles suggest replacement of external ventricular catheters every

10 days [6]. A similar study was also conducted in spinal durotomy cases. A subfascial epidural drain was placed after primary repair and left for a mean period of 5.3 days for draining in these patients. A CSF fistula did not develop in any patient and no excessive drainage occurred. It should be noted here that daily and careful monitoring of the drainage and wound dressing during long-term subfascial drainage follow-up is very important in terms of reducing the risk of infection. If signs of infection develop, the drain should be withdrawn, appropriate antibiotic treatment should be reviewed and repair with re-exploration considered.

Another study has reported that the prolonged subgaleal drainage and suture technique used to eliminate CSF leakage and wound problems after decompressive craniectomy significantly decreases wound problems [7].

We would like to emphasize that long-term subgaleal drainage may be less invasive and more practical than LED. LED has several disadvantages. It is contra-indicated in some cases. It cannot be performed following cranial surgery for tumor resection and if there is a residual mass that can cause tonsillar herniation. LED after surgery that may interrupt CSF flow creates a risk of tonsillar herniation [8]. These risks do not seem to be present with subgaleal drainage.

As the biggest disadvantage of the application is that we cannot know in advance whether a patient develops a CSF fistula. We decided to extend the subgaleal drainage period in patients with one criteria. This is large dural defect despite duraplasty.

Our experince has shown that complete dural closure is not possible in some cases. In these cases, prolonging the subgaleal drainage time can give us time for wound healing.

LED is an invasive procedure. Known complications that can develop during or after the procedure include spinal headache, spinal epidural hemorrhage, radiculopathy, epidermoid tumor formation, intracranial subdural hygroma or bleeding, vestibulo-cochlear dysfunction, ocular problems and dural sinus thrombosis [8]. These complications are not encountered with subgaleal drainage in practice. LED can also lead to problems during the follow-up. Too much drainage can result in serious morbidity and mortality. Experienced ancillary healthcare staff are therefore required to monitor the lumbar drainage.

The disadvantage of subgaleal drainage is the risk of CSF leakage from drain path after the drain itself is removed. We used a compressive dressing after the removal of the drain and no CSF fistula occurred in any of our cases. Biological tissue adhesive can be applied to the drain route as an alternative as mentioned in the Menovsky et al. study [9]. Another study has reported biological tissue adhesive applied to sutures after primary dura repair to reduce the risk of CSF fistula [1].

Our study can clarify the following issue: The development of CSF fistula is statistically significant in patients with long-term subgaleal drain use compared to the control group.

Conclusion

Long-term subgaleal drainage in preventing CSF fistula development in cases with dural defect is a less invasive and more effective alternative to LED with practical application and follow-up. There is no risk of infection if the drain is cared for properly.

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Safety of surgical management of accessory sinus pericranii in infants

Mohamed M. Elsherbini, Hatem Badr, Amr Farid Khalil

Mansoura University, EGYPT

ABSTRACT

Purpose: to better understand the pathological process of sinus pericranii and the safety of the surgical intervention.

Methods: patients' archive review of patients who underwent surgical management for sinus pericranii with a confirmed diagnosis and with follow up period greater than 6 months.

Results: 6 infants were included; all underwent disconnection surgically with good outcome in all cases.

Conclusion: disconnection surgery for sinus pericranii is a safe procedure with a good prognosis.

Keywords
sinus pericranii, scalp swelling, developmental venous anomaly

Corresponding author:
Mohamed M Elsherbini

Mansoura University, Egypt

m_elsherbiny@mans.edu.eg

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INTRODUCTION

Sinus pericranii (SP) is first described in 1850, definition evolved over time with better understanding of the pathology, firstly described by Stromeyer as a bag of blood [1], later it was described as an outpouch of the dural sinus till 1936 when Fevre and Modec outlined the communication between intracranial and extra-cranial venous systems.

Sinus pericranii is a rare extracranial developmental venous anomaly characterized by emissionary vein connecting dural venous sinus to a subgaleal venous varix which may cause skull erosion [2]. Though the exact pathogenesis is not well understood, a number of post- traumatic cases were reported even if the trauma passed unnoticed at the time [1,3]. On the other hand, SP has been associated with congenital conditions like esophygeal atresia, meningocele, craniosinostenosis and other intracranial venous anomalies [4,5,6].

Another theory adopted by Renier and Marche proposed SP is linked to increased intracranial pressure, based upon observing SP in patients with hydrocephalus, macrocephaly and craniosinostenosis [7]. SP is presented solely as "primary" pathology, or "secondary" to an intracranial vascular malformation.

The rarity of the pathology and paucity of observational studies make it challenging to plan for treatment and/or expect the course of the disease, however the natural course of the disease is benign, hemorrhage could be fatal in case of accidental injury.

In this study, we report our experience with six cases of SP who were managed surgically, all of them were of infantile group age.

Patients and methods

Patients' archive was reviewed to include patients who were admitted to neurosurgery ward for scalp lump during the years 2018 to 2020 and whose follow up continued for at least 6 months. Patients with other extracranial vascular malformations other than SP e.g scalp AVM were excluded as well as patients with non-vascular scalp lesions. Only patients younger than 2 years were included.

Medical records were searched for clinical presentation, radiology, associated pathology and management. Follow up records in outpatient clinic were obtained for the mentioned period.

Results

Study included 6 infants ,4 of them were males. Age ranged from 3 to 8 months, with average 4.3 months. Four families (67 %) gave history of head trauma, patients were followed up for at least 6 months with average 11.8 months follow up period (Table 1).

Case	Age (months)	Sex	Head Trauma	Radiology	Surgical maneuver	Follow up (months)
1	3	m	yes	CT, MRI, MRV	Disconnection, mass excision	6
2	4	m	yes	MRI, MRV	Disconnection	17
3	8	f	yes	MRI, MRV	Disconnection, mass excision	15
4	5	f	no	MRI, MRV	Disconnection, mass excision	13
5	3	m	no	CT, MRI, MRV	Disconnection	11
6	3	m	yes	CT, MRI, MRV	Disconnection	9

Table 1.

Five lesions were midline and one lesion was parasagittal, while all were related to Superior Sagittal Sinus with various patterns of venous drainage but no cases showed significant parenchymal drainage into the varix. Pathological examination showed endothelial lining of the varix in five cases, and one case's pathology report was irrelevant. One case was associated with esophageal atresia, otherwise neither associated pathologies nor intracranial vascular anomalies were reported.

Surgical technique: all surgeries were performed under general anesthesia, scalp incision directly over the lesion with surgical target to identify the emerging vein to disconnect and excise the subgaleal mass when applicable.

Outcome: All patients were discharged fully conscious with no neurological deficit either on discharge or during follow up visits. One patient showed superficial wound infection in the first follow up visit (one-week post-operative), which responded to conservative management.

Discussion

SP is presented early in life either with mild symptoms e.g pain and tenderness or severe symptoms related to hemodynamic disturbance e.g bradycardi[8], however the most common presentation is non-pulsatile soft scalp swelling (Fig 1) which becomes tense on crying and straining, scalp swelling causing cosmetic disfigurement was the main complaint for all the cases in this study, such cases should be clinically and radiologically differentiated from other scalp lumps before proceeding to treatment [8]. Parents seek medical advice with or without history of head trauma which could be missed as well, majority (67%) of patients in our study gave positive history of trauma.

Though some cases are strongly linked to head trauma, the frequent association with other cranial vascular anomalies especially developmental venous anomalies supports the congenital theory of the origin of SP such as failure of regression of interperiosteodural venous plexus or non-closure of skull sutures [5,6].

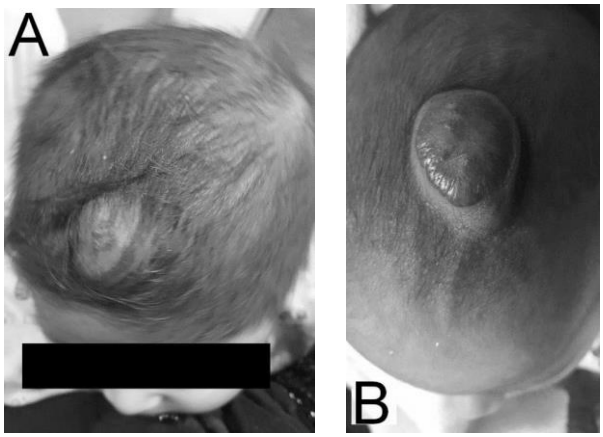

Figure 1. Main presentation of SP as a scalp swelling, usually

devoting hair on top when increases in size. Related to coronal suture (A), behind the coronal suture (B). Both infants with open fontanile.

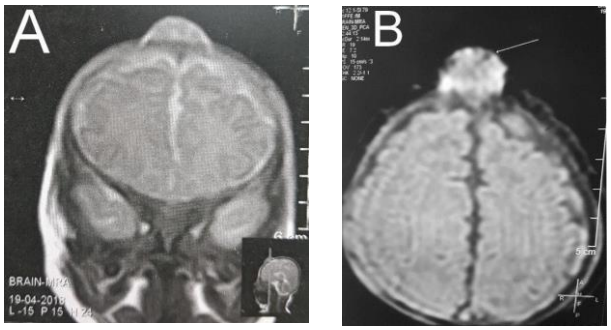

Figure 2. MRI T2 coronal (A), and axial T1 of two different cases showing midline SP related to SSS.

CT scan is required to identify skull erosion and enlarged diploic vein. MRI (Fig 2) is needed to exclude parenchymal lesions and AVM's [9], no cases of co-existing intracranial pathology were encountered in this study, while MRV we found beneficial to classify SP via a non-invasive tool.

The necessity of digital subtraction angiography (DSA), though concluded by Gandolfo is not indicated in all cases according to our experience. In our study, MRV was sufficient to classify SP into primary and accessory, no dominant cases were encountered in this study. MRV was not among the radiology options for Gandolf series [10]. We suggest that DSA could be reserved to cases with associated intracranial vascular anomaly or with suspected significant venous drainage into the varix.

Pathologically SP is categorized into two main groups, dominant where it represents a drainage to the cortex and accessory where part of the cortex or the dural sinus drains directly and solely into the varix 10. Another classification suggested by Brook et al 11 to categorize SP according to the feasibility of endovascular treatment, A, B, C. Where A stands for the dominant variant, B for the accessory variant and C variant in which no parenchymal venous drainage into the varix. Type C is the safest for endovascular embolization and type A is an absolute contraindication for.

Histological classification by Nakasu[12] listed three different types; a) fibrous architecture with cavernoma like structure, b) venous varix with endothelial lining and c) herniated dural venous sinus.

Though spontaneous regression of SP through thrombosis had been reported, cases underwent surgery in this series were large and parents decided to undergo surgery [4,13]. Surgical management includes disconnection of the emissary vein (Fig 3) with excision of the mass when applicable, which was performed for all our cases. For three patients in this study (50 %), disconnection of the vein was enough to collapse the mass completely with no actual mass to be excised, for these cases only biopsy of the potential cavity was performed, one of which showed irrelevant sample. Some authors reported closure of bone defect with bone wax or cranioplasty for larger defects which was not necessary in this series. Serious complication such dural sinus laceration and hemorrhage were reported [14], though not encountered in this study, we believe this complication is liable to happen with Nakasu type C which could be excluded preoperatively and intra-operatively with microsurgical microscope.

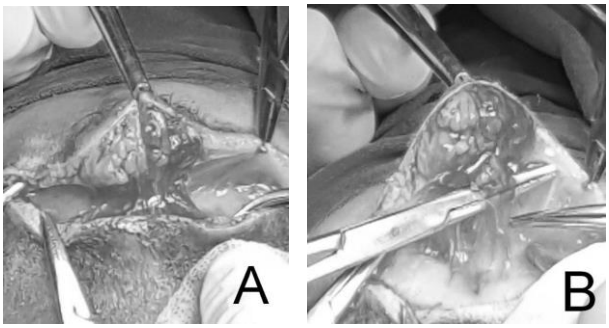

Figure 3. Surgical management, subcutaneous dissection to identify the connection vein thoroughly (A), identification of the connection vein, skeletonization and cauterization (B).

Endovascular therapy is a valid means for treatment of SP, it can be performed either via direct puncture, transvenous or combined. Endovascular therapy carries the risk of skin sloughing and thromboembolic events, also it is questionable to consider it less invasive than surgery in infantile age group included in this study. In a case report by Brook et al [11], nBCA was used to embolize the varix however cosmetic outcome is questionable as it initiates an inflammatory reaction which might lead to varix hardening. Another case report by Kessler et al[15] reported good cosmetic result using direct absolute alcohol injection after transvenous endovascular closure of the in/outflow point. The concerns about absolute alcohol leakage into circulation are serious, connection site to systemic

circulation should be confirmed to be sealed before proceeding to injection. Also, theoretical assumption that embolization might lead to development of new vascular anomalies in the region surrounding the occluded one is a reasonable concern.

Although most of cases of Pavanello et al series[8], the largest to our knowledge, were treated via endovascular techniques, it included only 7 infantile cases which were managed conservatively except for one which was treated surgically during the corrective surgery of the associated craniosynostosis. The same study reported spontaneous resolution of a number of accessory cases, an option was not accepted for all the parents in this study due to the disfigurement at time of presentation.

Another large study by Gandoflo et al [10] included 15 infants, six of which required surgical intervention, four of them were dominant variant, with good outcome for all cases including dominant cases which were managed surgically. These results make the necessity of DSA, which is an invasive maneuver, questionable since categorizing SP via DSA didn't change the role of surgery, also significant brain parenchymal drainage is diagnosed with MRV (Fig 4).

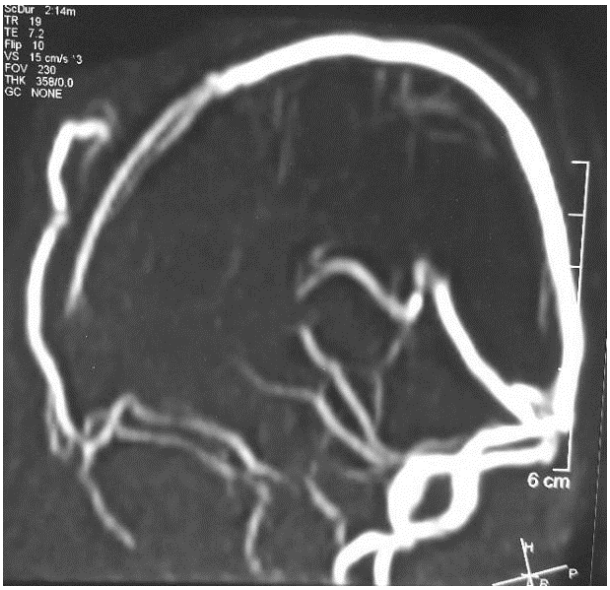

Figure 4. MRV showing accessory SP, related to SSS. With no significant brain parenchymal drainage into the varix.

In all means, the extent of treatment depends on the degree of normal brain parenchyma draining into the DVA, as a rule no normal parenchymal brain drainage should be compromised.

Conclusion

SP is a rare condition in infants characterized by a subgaleal venous varix connected to intracranial venous system via abnormally enlarged emissary vein(s), surgical management of sinus pericranii in infants is safe method for accessory cases with no significant parenchymal drainage into the varix.

Abbreviations

AVM: Arteriovenous Malformation;
CT: Computed Tomography;
DSA: Digital Subtraction Angiography;
DVA: Developmental Venous Anomaly;
MRI: Magnetic Resonance Imaging;
MRV: Magnetic Resonance Venogram;
nBCA: N-butyl cyanoacrylate;
SP: Sinus Pericranii.

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Endoscopic lumbar discectomy using side viewing conical working tube. An institutional experience

Mohammad Kaif, Kuldeep Yadav, Rakesh Kumar, Deepak Kumar Singh

Department of Neurosurgery. "Dr Ram Manohar Lohia" Institute of Medical Sciences, Lucknow, INDIA

ABSTRACT

Objective: The paradigm of surgical therapy for spinal disease especially for lumbar disc herniation has gradually shifted from traditional open surgeries to minimally invasive spinal surgeries. Endoscopic discectomy has been performed widely using various devices and techniques. In this study, we present our experience of endoscopic discectomy using a unique device with separate side viewing channel.

Methods: 26 patients of lumbar disc herniation treated between March 2015 to April 2018 using the unique conical working tube with separate side-viewing endoscopic channel have been retrospectively analysed. Their preoperative and postoperative Oswestry Disability Index (ODI) and Macnab scores were used to evaluate the outcome with a mean follow up of 37.04 months.

Results: There were 18 males and 08 females with age ranging from 19-72 years (mean-38.4 years). The follow up ranged from 25 months to 60 months with a mean of 37.04 months. The mean preoperative ODI score was 72.4 which decreased to a mean of 7.6 and the outcome evaluated by Macnab criteria was 65.3% excellent, 19.2 % good, 11.5% fair, 3.8% poor. 1 patient underwent a second surgery. None of the patients had to change their occupation postoperatively. Complications occurred were dural tear in 1 patient and transient foot paresis in 1 which improved spontaneously.

Conclusion: Endoscopic discectomy using conical working tube is a safe and effective technique for lumbar disc prolapse. The long-term results are comparable to conventional techniques.

Keywords
lumbar disc herniation, endoscopic discectomy, side viewing endoscopic device

Corresponding author:
Mohammad Kaif

"Dr Ram Manohar Lohia" Institute of Medical Sciences, Lucknow, India

dr_kaifmohd@yahoo.co.in

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INTRODUCTION

Endoscopic lumbar discectomy for lumbar disc herniation (LDH) has been an ever-evolving procedure since its inception, because of the benefits it caters over open surgery. Open surgical procedures for LDH are associated with greater muscle, nerve roots and dural sac retraction, lamina and facet joint resection, etc. This leads to more muscular injury, epidural scarring, postoperative pain, longer hospital stays and greater blood loss.

Endoscopic lumbar discectomy overcomes these associated drawbacks of open surgery for LDH but is associated with its own

difficulties and complications. Steep learning curve, endoscopic approach related anatomical limitations and vague tissue differences are few problems associated with endoscopic procedures. Various devices have been developed to increase the ease of procedure and reduce the learning curve along with associated complications. Kambin and Gellman first introduced endoscopic lumbar discectomy in 1973.[11] Later various devices were introduced like Yeung endoscopic spine system (YESS), transforaminal endoscopic spine system (TESSYS), Destandau system etc.[18,7,4] Similarly various authors have reported their experience of endoscopic discectomy using different devices , although many of these lack the literature on long term results of endoscopic surgery.[4,5,12,2] In this article we present our institutional experience of endoscopic discectomy using the conical working tube with separate viewing channel.

Methods

Study setting: This study was conducted in the Department of Neurosurgery Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India.

Study Design and Period: It is a retrospective study based on follow up of 26 patients of LDH treated using the conical working tube with side viewing endoscopic channel.[9] The hospital records of 38 patients who underwent endoscopic lumbar discectomy using this device between March 2015 to April 2018 were retrieved. Only those patients were included in this study who could be contacted on telephone and responded to the ODI (Oswestry Disability Index) and Macnab score formats.

Study Participants: Endoscopic surgery was conducted on patients who presented with low backache along with radicular pain in lower limbs with or without neurological deficit and failed conservative management. Patients with segmental instability, no clinico-radiological correlation or evidence of infection were excluded from this study. There were 18 males and 08 females with age ranging from 19 years-72 years (mean-38.4 years). The follow up ranged from 25 months to 60 months with mean of 37.04 months.

Instrument design: This device comprises of a conical working tube which is passed over coaxial dilators and secured in position by a holding device attached to the operating table. It has a separate side viewing channel for the telescope which is attached to a light source and camera. No special instruments are used for laminotomy and discectomy. **(Figure 1)**

Operative technique: Patient is positioned prone after general anaesthesia on a Wilson's frame or foam bolsters. Level is localised using fluoroscopy. Incision deep to fascia is given 1 cm lateral to midline. Firstly, a dilator is passed with a 5mm trocar up to the lamina and the trocar is removed. A gentle medial to lateral and cranial to caudal sweeping movements are done for the elevation of soft tissue. Serial dilators are passed over this first tube followed by the working tube over these dilators which is finally fixed to table after removal of serial dilators. Position of the working tube is confirmed under fluoroscopy. A cannula with trocar is passed from the separate side channel through a separate stab incision and locked in the working tube using the locking mechanism. A zero-degree telescope (4 mm diameter and 180 mm length) is passed through this separate channel. The tip of the telescope just reaches up to the inner part of the working tube. The light source and camera is attached to the cannula and the image orientation is done by rotating the camera on scope. **(Figure 1)**

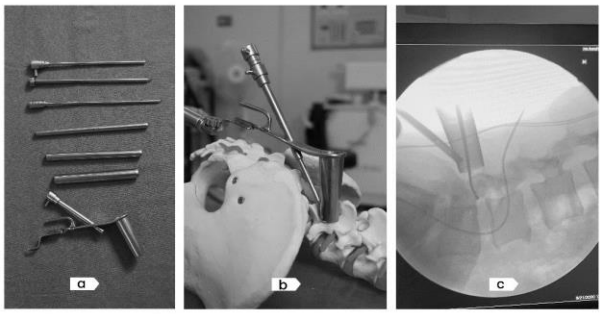

Figure 1. a - instrument design, b - Instrument setup with telescope and light source, c - fluoroscopic view with endoscopic device.

Medial part of the facet and contiguous lamina are identified. A small hemi-laminotomy and medial facetectomy were done using Kerrison rounger. The Ligamentum flavum is detached from the under surface of the lamina and removed. Traversing nerve root and thecal sac are identified using a ball probe.

The nerve root is retracted medially and the disc is removed by entering the disc space through the annular tear or an annulotomy. The disc space is irrigated with normal saline to wash out the loose

disc fragments. The nerve root is inspected to ensure adequate decompression. **(Figure 2)** The entire assembly is removed and the fascia is closed with absorbable suture. Skin is closed using subcuticular sutures.

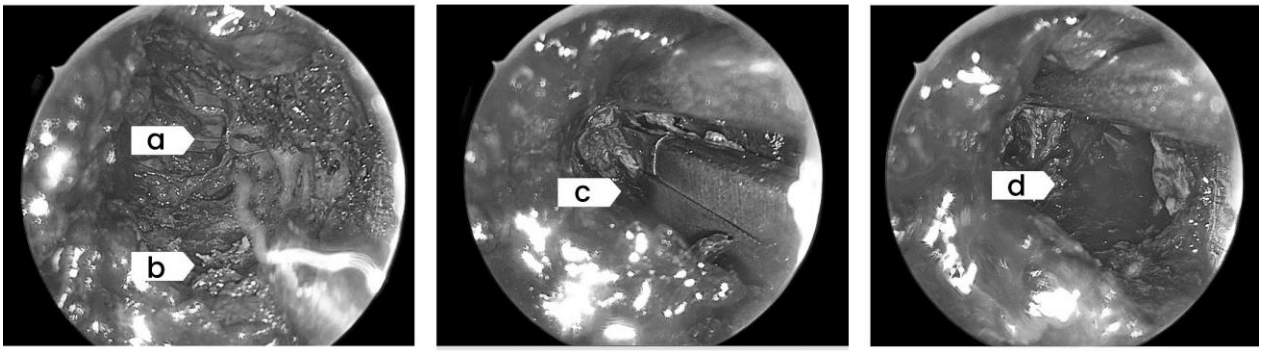

Figure 2. a - nerve root, b - medial of part facet joint, c - disc fragment being excised, d - disc space after discectomy.

Postoperative management: Patients were mobilized in the evening of the day of surgery and were discharged on the next postoperative day. In this study the mean hospital stay was 1.6 days.

Complications: An incidental dural tear was observed in 1 patient. This was managed by sealing the defect by fibrin glue. No postoperative CSF leak or pseudomeningocele or any long-term sequelae were observed. The other postoperative complication was transient foot paresis in 1 patient which improved spontaneously.

Results

Patients were evaluated using ODI score. The score was interpreted as 0% to 20% (minimal disability), 21% to 40% (moderate disability), 41%to 60% (severe disability), 61% to 80% (crippled) and 81% to 100% (bed bound/ exaggerating their symptoms). Both the preoperative and postoperative ODI were compared and its differences were calculated. The mean preoperative ODI score was 72.4 which decreased to a mean of 7.6 postoperatively. The final outcome was evaluated using Macnab criteria which was divided into excellent, good, fair and poor categories. As per Macnab criteria 65.3% (n=17) had excellent outcome, 19.2 % (n=05) had good, 11.5% (n=03) had fair, 3.8% (n=01) had poor outcome. One patient experienced persistent radicular pain of same intensity and was diagnosed to have a residual disc fragment which was removed later by microsurgery. None of the patients had to change their occupation due to their lumbar disc disease. **(Table 1)**

S. No	Procedural characteristics	Value
1	**Outcome (Mac Nab)**	
	Excellent	n=17 (65.3%)
	Good	n=5 (19.2%)
	Fair	n=3 (11.5%)
	Poor	n=1 (3.8%)
	Oswestry Disability Index (ODI)	
	Mean Preoperative score	72.4
	Mean Postoperative score	7.6
2	**Complications**	
	Dural tear	n=1 (3.8%)
	Transient foot paresis	n=1 (3.8%)
3	**Repeated Surgery**	n=1 (3.8%)

Table 1. Summary of procedure related data.

Discussion

Lumbar intervertebral disc herniation, leading to various symptoms have been catered through multiple operative modalities. The classic discectomy described by Mixter and Barr[14] has undergone a series of modifications to develop into the present day discectomy procedure.[15] The classic discectomy required a larger incision, separation and retraction of paraspinal muscles that led to an increase in postoperative morbidity such as increased pain, a delay in resuming activities and a lengthy hospital stay with significant financial burden on patients especially in a developing nation. Moreover, the extensive surgery could lead to the instability of spine with due course of time.

To overcome the disadvantages and problems

associated with classic discectomy, various minimal invasive techniques have been developed. In 1978, Williams[17] described micro discectomy which established as a guide to a lesser invasive approach to lumbar spine. This was the mini variant of conventional discectomy through a much smaller incision as compared to the previous technique. Howe and Frymoyer[8] reported a success rate of 60%–97% with the micro discectomy but it still required the separation of paraspinal muscles from the lamina and spinous process leading to the denervation of the paraspinal muscle complex and causing a delay for the patient in resuming daily activities.

Endoscopic spinal surgery began as percutaneous endoscopic discectomy. Kambin (1973) and Hijikata et al. (1975) had attempted the earliest endoscopic surgery in 1970's.[16] Since then this technique has got modifications through generations[10], in order to improve the patient outcome and increase the domain of indications for endoscopic spine surgery **(Table 2)**. Various authors have described their results of Micro endoscopic discectomy (MED) some of which are mentioned in **Table 3**. Jensdottir et al in their retrospective study reported a good/excellent outcome of micro discectomy[10]. Casal Moro et al in their prospective study reported that MED is a safe technique with lesser tissue trauma and comparable results to that of conventional techniques[3]. Bhansare et al reported their experience using the Destandau technique with excellent short and long term results[1].

First Generation	Second Generation	Third Generation	Newer Innovation
Yeung endoscopic spine system	Interlaminar uniportal endoscopic spine surgery	Endoscopic decompression	Endoscopic lumbar interbody fusion surgery
Percutaneous endoscopic lumbar discectomy	Interlaminar biportal endoscopic spine surgery	Endoscopic foraminotomy	
Transforaminal endoscopic lumbar discectomy			

Table 2. Generations of endoscopic spinal surgery.

Author/year	Number of patients	Outcome measures	Outcome	Recurrence	Complication
Kulkarni et al. 2014	188	VAS, ODI	Statistically significant pain relief	3 (1.5%)	11 (5%) dural tears, 1(0.5%)infection, 1(0.5%) wrong level
Hussein et al. 2014	185	NRS, Mcnab ODI	Statistically significant pain relief	2 converted to open	3 dural tears
Li et al. 2015	72	VAS, ODI, Mcnab	97% good to excellent	1	No complications
Kyung Chul Choi et al. 2016	20	VAS, ODI	91.3% good to excellent	1	1 transient neurological deficit
Sung Soo Eun et al. 2016	62	VAS, Mac Nab	Significant pain relief	06	2 dural tears
Kyung Chul Choi et al. 2017	149	VAS, ODI	90.6% good improvement	04	1 transient neurological deficit
Kaif et al 2017	66	VAS, ODI, Mac Nab	86.36% good to excellent	02	Discitis 1, dural tear 2, transient foot paresis 1
Hyung Sun Kim et al. 2018	98	VAS, ODI	96.1% good to excellent	03	2 Neurological deficit
Ziquan Li et al. 2019	21	VAS, ODI	Significant improvement	00	2 dural tear 1 dysesthesia
Chao Li et al. 2019	184	VAS, ODI, Mac Nab	89.3% good to excellent	14	4 dural tear 1 neurological deficit

***** VAS: Visual analogue scale, ODI: Oswestry disability index.

Table 2. Studies of endoscopic discectomy.

Our study also reveals the similar results regarding the excellent/good outcome of the patients using our specific side viewing conical working tube. The results with this device were excellent to good in 84.5% of cases after a mean follow up of 37.04 months which is comparable with other studies of all the minimally invasive lumbar discectomy techniques practiced worldwide. Casalmoro reported surgical complication rate of 3 to 10 % in various techniques whereas Destandau in his series reported 3.5% and 4 of his patients required reoperation[18]. In our series we experienced 7.7% (n=2) of such complications and 3.8% (n=1) required reoperation.

The popular device used for MED is the METRx system, which is a serial dilator system utilizing the interlaminar corridor. It has a telescope mounted at the top end edge of the working channel, but as experienced by the senior surgeons this technique causes clutter while working bimanually through the working tube. The other disadvantage is the high cost of the specialized hardware. The Destandau system is another popular device with excellent to good long-term results but it has the disadvantage that direct visualization using naked eye or microscope is not possible and also minimally invasive inter-body fusion cannot be performed through this device. The cost of these devices are very high which is one of the major hindrance in expansion of this technique. Our system is an indigenous innovation with a very low cost. The freedom of surgical maneuverability is the advantage[9]. The hardware cost is further reduced as it utilizes the conventional discectomy instruments and same telescope which is used in transcranial endoscopic surgeries.

Conclusions

Endoscopic discectomy using this conical working tube is a safe, effective and low cost technique for lumbar disc prolapse. It has the advantage for early mobilization, short hospital stays and lower financial burden. Overall outcome is comparable to the conventional techniques.

Limitation

Our study has limitations with the retrospective nature of the data collection. Small sample size is also a limitation of this study.

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Ossified longitudinal ligament causing same level cord contusion in a case of Klippel-Feil syndrome

Amit Agrawal

Professor of Neurosurgery, Department of Neurosurgery, Narayna Medical College Hospital, Nellore, (AP), INDIA

ABSTRACT

Klippel-Feil syndrome (KFS) is a congenital fusion of two or more cervical vertebrae due to faulty segmentation of the vertebral axis during gestation. (1-5) These patients present with a constellation of manifes-tations and are typically prone to cervical cord injury after a minor fall or a major traumatic episode. (2, 5-8) 34 years old gentlemen, a plumber by profession presented with a history of slipped and fall about two stairs height while he was working.

Keywords
Klippel-Feil,
cervical,
spinal cord,
cord contusion

LETTER TO THE EDITOR

Dear Sir,

Klippel-Feil syndrome (KFS) is a congenital fusion of two or more cervical vertebrae due to faulty segmentation of the vertebral axis during gestation. (1-5) These patients present with a constellation of manifestations and are typically prone to cervical cord injury after a minor fall or a major traumatic episode. (2, 5-8) 34 years old gentlemen, a plumber by profession presented with history of slipped and fall about two stairs height while he was working. Following that he had transient loss of consciousness when he regained the consciousness, he realized that he was not able to move his all four limbs. He also could not pass urine. There was no history of vomiting, ENT bleed or convulsion. At the time of admission, he was conscious, oriented to time place and person. His general examination was normal. He had breathing difficulty and the respiration was of diaphragmatic type. Chest wall expansion was absent. Single breath count was 5. Neurologically he was conscious, alert and oriented. Cranial nerves were normal. Motor system examination revealed quadriparesis with muscle power grade 3/5 in shoulders, 2/5 at elbow, 1/5 at wrist and absent grip in both upper limbs. All the deep tendon jerks were sluggish. The patient was catheterized as he was not able to pass urine. All the sensations were reduced below D8 level. Bilateral planters were extensor. The gag and palate reflexes were normal. X-ray films of the

Corresponding author:
Amit Agrawal

Department of Neurosurgery,
Narayna Medical College Hospital,
Nellore, (AP), India

dramitagrawal@gmail.com

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cervical spine showed fusion of the spinous processes of cervical vertebrae at C2 and C3 vertebrae with ossification of posterior longitudinal ligament at the same level (Figure-1). Magnetic resonance imaging (MRI) of the cervical spine showed congenital fusion of the same vertebral spinous processes and in addition there was ossified posterior longitudinal ligament with canal stenosis and cord contusion (Figure-2). The patient received injection Methylprednisolone as per the standard protocol and planned for surgical decompression at the earliest. The patient underwent posterior approach and C2 and C3 laminectomy to relive the compression of the cord. The patient made gradual recovery. At follow-up the power in all four limbs was improved to grade 4/5.

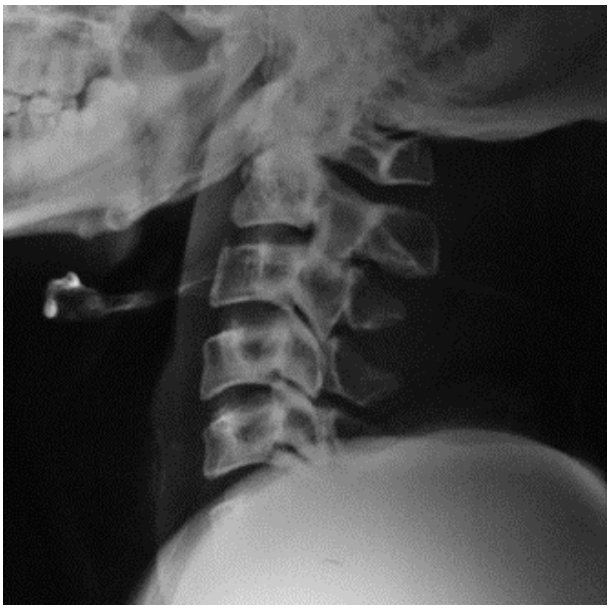

Figure 1. a - Lateral x-rays of the cervical spine showing fusion of the spinous processes of C2-3 vertebral body, also note the ossified posterior longitudinal ligament bridging the posterior border of the C2-3 vertebral bodies.

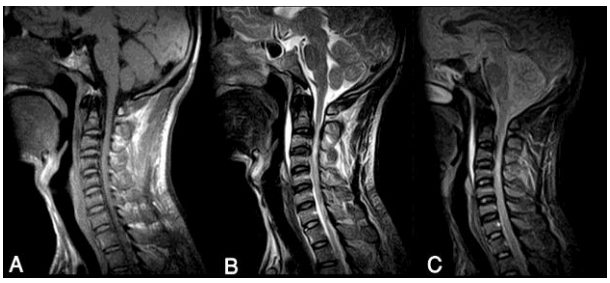

Figure 2. MRI cervical T1, T2 and FLAIR sagittal images showing calcified posterior longitudinal ligament behind C2-3-disc space with cord compression and cord signal changes.

In cases of Klippel-Feil syndrome fusion of one segment of the spinal column causes hypermobility of the non-fused adjoining segments thus cervical spine is unable to compensate for excessive flexion, extension, rotation and lateral bending and predisposing disc prolapse at adjacent levels and neurological deterioration following even minor trauma. (2, 4, 7-13) Central cord syndrome typically described in the elderly patients with preexisting cervical spine spondylosis, only few reports discuss in patients with Klippel-Feil syndrome with cord compression at adjacent level. (9, 11, 14, 15) In contrary to many other cases where the patients with Klippel-Feil anomaly presented with adjacent level disc prolapsed and instability, the present case was unique as he developed spinal cord injury due to canal compromise at the level of used segment because of ossified posterior longitudinal ligament leading to canal stenosis. X-ray cervical spine is useful to understand the bony anomalies, however as in present case the MRI will better delineate the normal as well pathological spinal cord anatomy including disc prolapsed and cord contusion. (6, 9) Treatment regimens depend on the severity of symptoms and the segmental instability or cord compression and vary from modification of activities to extensive spinal surgery including microsurgical removal of the herniated disc with instrumentation. (6, 10, 16-19) However, in presented case the extensive ossification in the posterior ligament was cause of canal compromise and cord compression and, as there was no instability, we opted for posterior decompression alone.

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