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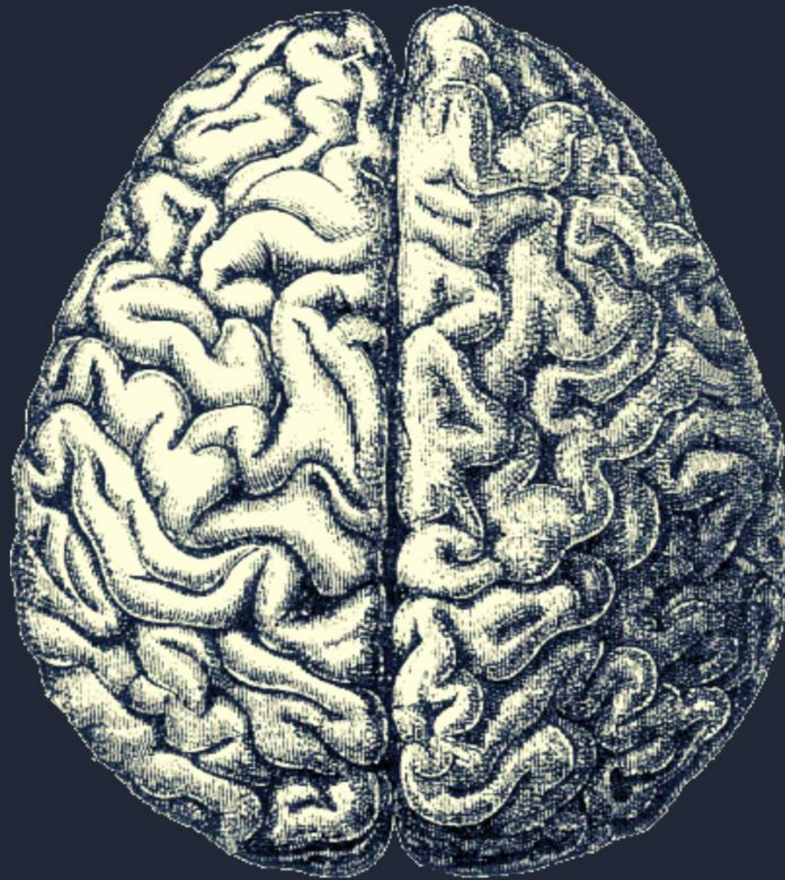

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Brain abcess with *Nocardia Farcinica*

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ABSTRACT
Introduction: Brain abscesses caused by *Nocardia farcinica* pathogen are rare and usually present as large abscesses with a thick and irregular wall. We present a case of a patient with signs and symptoms of central nervous system infection and had a fulminant evolution with malign cerebral oedema and death.
Case report: The 35-year-old patient presented with mild symptoms that appeared 2 weeks prior and became more aggressive in the last 48 hours. After the initial examination and blood tests, the patient was suspected of a systemic infection because of the high white cell count and high level of inflammatory markers. Antibiotic therapy was started with Ciprofloxacin and Amoxicillin/ Clavulanic Acid. The brain MRI showed a multinodular lesion in the right hemisphere, with contrast enhancement and central high diffusion restriction on T1, T2 and FLAIR. During the antibiotic treatment, the patient suddenly became comatose. Urgent brain CT scan showed malign cerebral oedema with brain shift.
Discussion: There are 58 documented cases of *Nocardia farcinica* in the literature, as shown in a recent systematic review. Most of the cases are with immunocompromised patients, either through disease or secondary to treatment after organ transplant. In our case, we suspected immunodeficiencies based on the anamnestic data offered by the patient's family. Mortality rates are between 19% and 36,7% in all reported cases, but in our presented case the patient had a rapid aggressive evolution with malign brain oedema that resulted in death.
Conclusions. The management of these cases requires urgent diagnostics and treatment. For our team, the first reported case of *Nocardia farcinica* and the fast aggressive evolution resulted in a negative outcome, even with antibiotics treatment and surgical evacuation of the abscess.

Keywords
brain abscess,
nocardia farcinica,
infection,
central nervous system

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INTRODUCTION

Nocardial brain abscesses are a serious and quite rare pathology caused by bacteria from the genus Nocardia, a group of gram-positive aerobic bacilli falling under the broader umbrella of aerobic actinomycetes (Loeffler et al., 2001; Prod'hom & Bille, 2017). Soil-based, these bacteria usually enter the body either by inhalation or local contamination of damaged skin (Corsini Campioli et al., 2021). Of these, *N. farcinica* is one of the more virulent species due to additional virulence factors (Prod'hom & Bille, 2017). The manifest infection usually presents as large abscesses with a thick, irregular wall with

multilocular abscesses not being uncommon. The preferred locations for these are the lungs and the brain (Beucler et al., 2022; Prod'hom & Bille, 2017). In the following report we will analyse the case of a patient who presented with a symptomatic nocardial abscess with *N. farcinica* leading to malign cerebral oedema and death.

CASE REPORT

We present the case of a 35-year-old patient that arrived at the Emergency Department complaining of an intense headache. The symptoms started two weeks prior to the presentation and intensified in the last 48hours. The patient presented one episode of vomiting which alleviated his symptoms.

On initial examination, the patient was alert, responsive but agitated with mild neck stiffness. We observed a generalized skin erythema and multiple tattoos. A cranial CT was performed (Figure 1) in which a nodular parenchymal lesion was observed in the right hemisphere. The lesion showed important perilesional digitiform oedema. Complementary tests were performed including serologies, HIV and QuantiFERON test. Blood test showed leucocytosis, thrombocytosis with high levels of fibrinogen and ESR. Tests for syphilis, tuberculosis and HIV were negative.

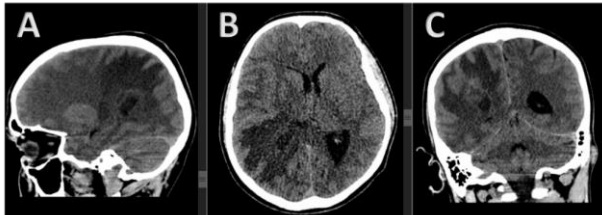

Figure 1. Initial Brain CT scan without contrast showing one nodular lesion in the right hemisphere on sagittal (A), axial (B) and coronal (C) planes. Perilesional digitiform oedema shown in the blue circle.

The family of the patient noted that he worked for 6 years in Barcelona, Spain, undocumented and is a frequent user of drugs and alcohol.

We performed a thoracic radiograph that showed multiple focal lesions bilaterally. We followed up with a thoracic CT scan that showed multiple cystic lesions with thin wall located in the superior lingula lobe and in the left Fowler segment with antero-posterior diameter of 24/15 mm and respectively 17/10mm. On the left inferior pulmonary lobe, it was found a cyst lesion with a 7,5 mm and 1,8 mm diameter (Figure 2).

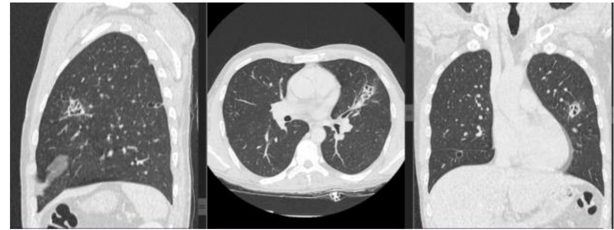

Figure 2. Thoracic CT scan showing multiple pulmonary cystic lesions (illustrated with the blue circle) with thin wall located in the superior lingula lobe and in the left Fowler segment with antero-posterior diameter of 24/15 mm and respectively 17/10mm. On the left inferior pulmonary lobe, it was found a cyst lesion with a 7,5 mm and 1,8 mm diameter.

Empirical antibiotic therapy was started with Ciprofloxacin 400mg per day + Amoxicillin/ Clavulanic Acid 6g per day.

In the following day he developed a high fever, a cough and became agitated and delirious. The symptoms did not respond to treatment.

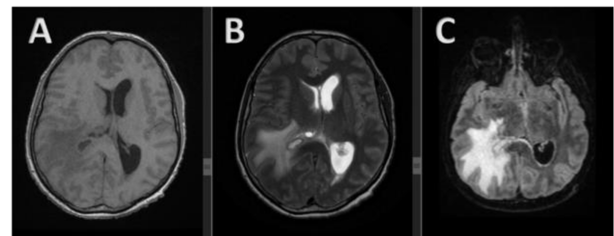

Figure 3. Brain MRI showing the heterogenous lesion in the right hemisphere, with extension in the right trigone of the lateral ventricle. The lesion shows central high diffusion restriction on T1 (A), T2 (B), FLAIR (C).

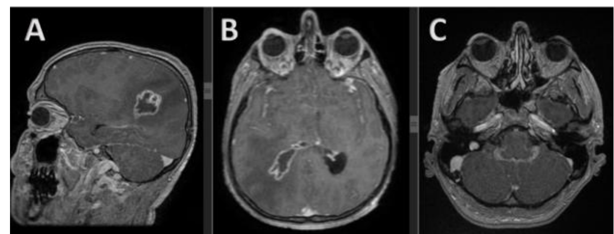

Figure 4. Brain MRI shows contrast ring enhancement on sagittal (A) and axial (B) plane. At the basal cisterns the contrast enhancement is suggestive for pachymeningitis (shown with blue arrows).

A brain MRI was performed showing an heterogenous lesion in the right hemisphere, located in the parietal lobe with extension in the right trigone

of the lateral ventricle without and evident delimitation. The lesion shows central high diffusion restriction on T1, T2 and FLAIR, with a low SWI signal (Figure 3). On T1 with contrast it presented ring and meningeal enhancement, especially at the basal cisterns. Furthermore, brain oedema was perilesional with digitiform aspect. All of these radiological features were suggestive of brain abscess and pachymeningitis (Figure 4).

On the 4th day of his stay, he suddenly became comatose and underwent urgent brain CT scan, that showed and important perilesional oedema with mass effect. A decompressive craniectomy was performed and the brain abscess was evacuated with ultrasonography guide for microbiological evaluation (Figure 5).

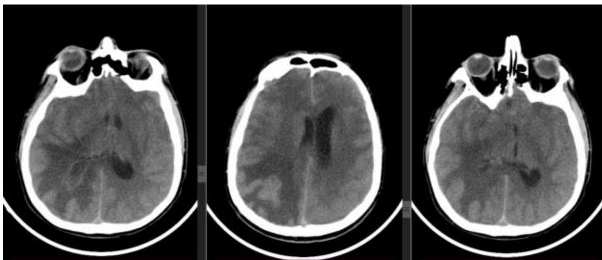

Figure 5. Brain CT scan performed on the 4th day of admission showing perilesional oedema with brain (illustrated with red circle in all images) with brain shift.

The brain abscess had multiple fibrin cells, PMN and macrophages, with negative bacterioscopy. Microbiological cultures revealed a gram-positive bacterium, Nocardia farcinica.

Postoperatively, the patient remained in comatose state, with fixed bilateral dilated pupils and the following day had a heart arrest that did not respond to resuscitation.

Discussion

Epidemiology

Brain abscesses with *N. farcinica* are a rare pathology, a recent systematic review describing only 58 completely documented cases in literature (Beucler et al., 2022). It seems that amongst nocardial infections, *N. farcinica* is a common pathogen involved in the formation of brain abscesses. There are differences in regions between The United States and Switzerland where it is the most common, and France and Italy where it was the second most common species.(Boiron et al., 1992; Corsini Campioli et al., 2021; Farina et al., 1995; Loeffler et al., 2001). In our case, this is the first documented instance of a nocardial brain abscess for our team.

The patients are generally immunocompromised. In his review, Beucler et al. reported that 74% of cases presented some form immunodeficiency whether through disease or secondary to treatment in case of organ transplant (Beucler et al., 2022). In other series immunodeficiencies were present in 83,3%, 70.5%, 90%, 62.5% and 82% of cases respectively (Anagnostou et al., 2014; Boiron et al., 1992; Corsini Campioli et al., 2021; Farina et al., 1995; Loeffler et al., 2001), one of them reporting cases of immunodeficiencies associated with drug abuse (Farina et al., 1995). In our case, no apparent immunocompromising factors were identified. The patient had white cell counts concurrent with normal response during infectious pathologies and the tests for syphilis, tuberculosis and HIV were all negative. The only reference we have is anamnestic data from the family about alleged drug abuse (unspecified) and chronic alcohol abuse which are both proven to induce a degree of immunodeficiency (Kaushik et al., 2011; Pasala et al., 2015), however only circumstantial evidence is available.

In our case the patient died 5 days after admission due to malign cerebral oedema combined with the systemic infection diagnosed. Mortality rates are high in all reported series ranging between 19% and 36.7% (Anagnostou et al., 2014; Beucler et al., 2022; Boiron et al., 1992; Corsini Campioli et al., 2021; Farina et al., 1995; Loeffler et al., 2001). Amongst these, higher mortality in nocardial infections with CNS determination was observed in immunocompromised patients: 57%, 55%, 64% (Corsini Campioli et al., 2021; Loeffler et al., 2001; Mamelak et al., 1994) rather than in immunocompetent hosts: 20%,42% (Loeffler et al., 2001; Mamelak et al., 1994). *N. farcinica* was by far the more aggressive species, representing a high proportion of the deaths: 57% (Boiron et al., 1992; Kumar et al., 2014). We cannot reflect on mortality rates in our area since this is the first documented case we encountered, but we will monitor and report any further cases.

Being such a rare entity, usually associated with other pathologies like immune deficiencies whether acquired or induced through medication, clinical and paraclinical presentations vary. The presentation in most series is intracranial hypertension (45%, 50%,

33% (Anagnostou et al., 2014; Beucler et al., 2022; Loeffler et al., 2001)), concurring with the findings for our patient. No neurological deficits were identified for our case although these are also very common (51%, 50% 50% (Anagnostou et al., 2014; Beucler et al., 2022; Loeffler et al., 2001). Meningismus is quite frequent, especially when abscesses are in contact with the ventricular walls (9%, 9%, 17% (Anagnostou et al., 2014; Beucler et al., 2022; Loeffler et al., 2001)). Fever was not present in our case, and despite the classic triad of fever, elevated ICP and focal deficit, is not seen in most cases, probably due to the immunodeficiencies related with this pathology. (Anagnostou et al., 2014; Beucler et al., 2022; Loeffler et al., 2001).

When it comes to paraclinical tests, an inflammatory syndrome marked by elevated WBC CRP, fibrinogen and platelets levels was present and is a possible, although quite inconsistent finding (Beucler et al., 2022). When it comes to intracerebral radiological findings, a single abscess is most common, 59%, 66%, 83% and 57% respectively (Beucler et al., 2022; Corsini Campioli et al., 2021; Loeffler et al., 2001; Mamelak et al., 1994), mostly supratentorial 52%, 91%, 83%, 57% (Beucler et al., 2022; Corsini Campioli et al., 2021; Loeffler et al., 2001; Mamelak et al., 1994). Described as looking as a grape bunch in most cases it is associated with intense vasogenic oedema (Beucler et al., 2022), which was certainly evident in our case since it evolved with malign cerebral oedema. The parietal lobe localisation seems to be the second most common (37.5% (Corsini Campioli et al., 2021)), and explains the lack of focal neurological deficits.

Management of these cases is complex and requires both surgical intervention and long-term antibiotic therapy. The surgical approach serves both to reduce the dimensions or completely excise the abscess and to produce pathological material for microbiological identification. However, when microbiological identification is possible from a secondary location, a more conservative approach can be considered. In general, between 45% and 77% of patients benefited from surgical intervention (Beucler et al., 2022; Corsini Campioli et al., 2021; Farina et al., 1995; Loeffler et al., 2001; Mamelak et al., 1994) and this led to a positive outcome for 93% 87% and 65% of them respectively (Anagnostou et al., 2014; Beucler et al., 2022; Mamelak et al., 1994). The preferred strategy was craniotomy an excision as opposed to aspiration and drainage since it led to better results 8% and 24% mortality versus 23% and 50% mortality respectively (Beucler et al., 2022; Mamelak et al., 1994), with a lower risk of surgical revision 8% vs 31% (Beucler et al., 2022), 22% vs 27% (Mamelak et al., 1994). Antibiotic treatment usually employed trimethoprim-sulfamethoxazole (TMP-SMX) in 45%, 41,6%, 90% (Beucler et al., 2022; Corsini Campioli et al., 2021; Mamelak et al., 1994) of cases usually associated with other antibiotics such as vancomycin, amikacin, metronidazole, ceftriaxone, minocycline and amoxicillin. (Corsini Campioli et al., 2021; Farina et al., 1995; Loeffler et al., 2001; Mamelak et al., 1994). In vitro studies showed the most susceptibility to TMP-SMX, linezolid, amikacin, imipenem and meropenem, minocycline (Beucler et al., 2022; Corsini Campioli et al., 2021; Mamelak et al., 1994). Other studies in Italy and France showed resistance to TMP-SMX, and high susceptibility to amikacin (Boiron et al., 1992; Farina et al., 1995), but these were not focused on *N. farcinica* only. Most found a high level of resistance to amoxicillin and clavulanic acid. (Beucler et al., 2022; Boiron et al., 1992; Corsini Campioli et al., 2021; Farina et al., 1995; Mamelak et al., 1994). Thus, it seems that the best empiric antibiotic treatment would combine amikacin with either TMP-SMX or imipenem, meropenem, minocycline depending on region related particularities.

Conclusions

This was the first reported case of a *N. farcinica* brain abscess in our region and represented a challenge through its particularities. The atypical presentation, the disseminated infection and the choice of treatment all contributed to the high degree of gravity of the case. Immunosuppression could not certainly be ruled out in our case. Management of these cases require prompt identification of the bacteria, aggressive surgical treatment, and the correct choice of antibiotic treatment. We aim to raise awareness about this pathology, seldom found in our geographical area and to further our standards of practice in these cases.

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Personal experience in intramedullary lesions, in adults

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ABSTRACT
Background: Intramedullary spinal cord lesions (IMSCL) although they are rare, it generates invasion and destruction of the spinal cord. Such lesions must be diagnosed as early as possible, some have histological and genetic aggressiveness, generating severe functional neurological damage.
Objective: To identify the optimal strategy for diagnosis and treatment in IMSC, to improve prognosis.
Methods: A retrospective clinical study from 2001 to 2021, was performed on 33 adult patients (18 women, 15 men), diagnosed with magnetic resonance imaging with IMSCT. The most common topography was: thoracic 27 cases disposed between T_2-T_{12}, cervical 6 cases disposed between C_2-C_6, lumbar 2 cases at L_1-L_2. The most frequent symptoms in my cases were: unilateral radicular pain related to the tumour topography or bilateral diffuse burning pain, especially during the night; back and neck stiffness; paresthesia, motor disturbances with an ASIA score of 2-4, and severe atrophy especially in cervical topography, ataxia, initial retention, impotence and later loss of bowel and bladder function with incontinence. All patients were operated by the same senior neurosurgeon with at least 6 months of follow-up postoperatively. For functional outcome, the most important predictors are the preoperative neurological grade, and the high-grade IMSCT generating recurrence and reoperations.
Results: The patients addressed the clinic for pain and neurological deficits; the topography of the intramedullary lesion was confirmed by MRI native / with contrast, ultrasonography, and spinal arteriography. Several histologic entities were recorded: ependymomas - 12 cases, astrocytomas - 8 cases, hemangioblastomas - 3 cases, cavernomas - 6 cases, metastases - 2 cases, germ cell tumour - 1 case, malignant peripheral nerve sheath tumour - 1 case. Gross total excision was performed in 25 cases, with no mortality. In eight cases recurrences were recorded requiring the resumption of surgical treatment. In all cases physiotherapy-rehabilitation approach was used, and the outcome was correlated with pre-operatory motor deficits severity, 3 patients with thoracic high-grade astrocytoma underwent stereotactic spine radiosurgery (SSR) with Cyberknife abroad, stopping tumour growth one year after.
Conclusions: Intramedullary spinal cord lesions (IMSCL) are rare conditions, and MRI development allows an early diagnosis of these tumours. To adequately counselled patients, with minor preoperative deficits, real expectations concerning the functional outcomes, in benign tumours, and even anatomical healing should be based still on refinements of radical surgical excision. Actual radiotherapy techniques should be used in aggressive tumours.

Keywords
intramedullary spinal cord lesions (IMSCL), radical excision, neurofibromatosis (NF), radiotherapy, stereotactic spine radiosurgery (SSR), chemotherapy, functional outcome

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INTRODUCTION

Intramedullary spinal cord lesions (IMSCL) are rare neoplasms, with various etiology (1-15). Spinal cord compression with mass effect in benign lesions or destruction and invasion of the gray and white matter in aggressive tumors may lead to a variable degree of neurological dysfunction, different symptomatology (2)(3). Spinal MRI is essential for early diagnosis due to its sensitivity, is the preferred modality to characterize IMSCL for preoperative planning and early detection of recurrent lesions, even if it does not allow for histological diagnosis (1)(2). The management of IMSCL is mainly surgical (3-10), despite surgical morbidity; provides the best outcome; adjuvant radiotherapy may be an available alternative in aggressive tumors subtotal excised with ill-defined margins; the role of chemotherapy is still questionable. I present my strategy, during 20 years, for diagnosis and treatment in IMSCL, to improve prognosis.

MATERIALS AND METHODS

A retrospective clinical study from 2001 to 2021, was performed on 33 adults patients (18 woman, 15 men), diagnosed on magnetic resonance imaging with IMSCL. The most common topography was: thoracic 27 cases disposed between T2-T12, cervical 6 cases disposed between C2-C6, lumbar 2 cases at L1-L2. Most frequent symptoms in my cases were: unilateral radicular pain related to the tumor topography or bilateral diffuse burning pain, especially during night; back and neck stiffness; paresthesia, motor disturbances with ASIA score of 2-4, severe atrophy especially in cervical topography, ataxia, initial retention, impotence and later loss of bowel and bladder function with incontinence. All patients where operated by the same senior neurosurgeon with at least 6 months follow up postoperatively. For functional outcome the most important predictor are the preoperative neurological grade, and the high grade IMSCT generating recurrence and reoperations.

RESULTS

The patients addressed the clinic for pain and neurological deficits; the topography of the intramedullary lesion being confirmed by MRI native with contrast, ultrasonography, spinal arteriography. Several histologic entities were recorded: ependymomas 12 cases, astrocytomas 8 cases, hemangioblastomas 3 cases, cavernomas 6 cases, metastases 2 cases, germ cell tumor 1 case, malignant peripheral nerve sheath tumor 1 case. Gross total excision was performed in 25 cases, with no mortality. In eight cases recurrence were recorded requiring the resumption of surgical treatment. In all cases physiotherapy-rehabilitation approach was used, outcome was correlated with pre-operatory motor deficits severity, 3 patients with high-grade thoracic astrocytoma underwent stereotactic spine radiosurgery (SSR) with Cyber-knife abroad, stopping tumor growth one year after.

DISCUSSION

Intramedullary spinal cord lesions (IMSCL) are rare tumors, located within the spinal cord, occur in both adult and pediatric population, predominantly in the middle decades of life (1-3). Their incidence is evaluated at: 4 cases per million inhabitants and per year (9), 2-6 % of all central nervous system tumors, found most frequently in the thoracic cord (1-3).

Most important historical data in intramedullary lesions (2)(3):

-first successful removal of an intramedullary tumor was realized by Elsberg in 1907

-Greenwald in 1963 has large series of successfully removed tumors published

-Kurze in 1964 has introduced operating microscope

IMSCL can be linked to genetic diseases (1-9) - more common in patients with neurofibromatosis: ependymomas occur more often in patients with an average of 40 years with NF_2, hemangioblastomas (associated with von Hippel Lindau syndrome); astrocytomas occur more often in young adults with an average age of 30 years with NF_1

Most common IMSCL (1-15) are:

- *glial neoplasms* - 90-95%

- *spinal ependymoma*: 60% of all glial spinal cord tumors, are found in adults in the third to sixth decades prevalence for the fourth-decade, with a slight male predominance, arise from the cells of the ependymal canal, are soft and encapsulated, grow slowly, their plane of cleavage from the surrounding medullary tissue is clear, are located centrally within the spinal cord leading to symmetric expansion, occupy the whole width of the cord. Histologically, ependymomas can be classified into 4

types: myxopapillary ependymoma (WHO Grade I), subependymoma (WHO Grade I), ependymoma (WHO Grade II), and anaplastic ependymoma (WHO Grade III). Myxopapillary ependymomas account for up to 50% of ependymoma cases, typically arise from the filum terminale, and are usually located in the cauda equina while the other 3 subtypes follow the normal distribution of IMSCTs and are most often found in the cervical or thoracic spinal cord (90%) extending on average in length across 3 to 5 medullary segments, but also lower cord, in the conus medullaris, and filum, where an exophytic component may be present, rarely metastasize. Lesions are characteristically hypo vascular, well circumscribed, and non-infiltrative of the surrounding cord. Intramedullary ependymomas are generally low-grade, symptoms are due to compression of the surrounding cord rather than infiltration, complete resection often results in prolonged survival; malignant variants having been reported only very exceptionally, also with intratumoral hemorrhage. In my series I have had 12 ependymomas, 4 cervical and 8 thoracic, from which in only 3 cases I identify aggressive malignant ependymomas, who should be reopererated. In one case of thoracic malignant IMSCT ependymoma the patient developed a secondary active hydrocephalus and shunt was placed

- *spinal astrocytoma*: 33% of all glial spinal cord tumors, are common in the third to fifth decades, are infiltrative, glossy, associated with microcysts or syrinxes. The pilocytic varieties are well differentiated and tend to be indolent, with a definable surgical plane. Spinal astrocytoma predominate at the cervical-thoracic level (80%) extending on average over 6 medullary segments, positioned more eccentrically, with a poorly defined surgical resection plane. Different histologic aspect could be seen: *low-grade astrocytomas* - papillary type, can degenerate into a malignant subtype and *high-grade astrocytomas* - more polymorphic, aggressive with nuclear abnormalities, areas of necrosis, new vessels, intra tumoral hemorrhage. (7%– 30% of astrocytomas are considered malignant). Grade III and IV astrocytomas carried a poor prognosis - the most aggressive and infiltrative, with a mean survival of 15.5 months In my series there were 8 cases in the thoracic level, 5 cases relapsed after 2 years, requiring reoperation.

- *spinal primary glioblastoma multiforme*: 7.5% of all intramedullary gliomas and only 1.5% of all spinal cord tumors, locally invasive, rapid growth, may seed the CSF, with very poorly defined surgical resection plane

- *spinal oligodendroglioma* (3%) unproved responses to chemotherapy as in intracranial type

- *spinal ganglioglioma*: 1% of all glial spinal cord tumors, they are very rare tumors from both neuronal and glial origins that are composed of glial and ganglion cells, usually located within the cervical level, larger than other types of IMSCTs and difficult to distinguish on MRI. They tend to mostly affect older children and young teenagers, are typically benign, slow-growing tumors (WHO Grade I or II), although malignant transformation has been shown and is presumed to involve the glial component of the tumor.

- *spinal hemangioblastoma*: are the third most common IMSCL, account for 2 to 15%, are rare, benign tumors of mesenchymal origin that originate from the vascular system within the spinal cord, more common in men, tend to develop in the dorsal portion of the spinal cord and thus present with progressive sensory deficits, particularly proprioceptive deficits; highly vascularized, with risk of hemorrhage: subarachnoid hemorrhage (73%) or intramedullary hemorrhage (27%). Tumor consist of small mural nodules with cysts, associated with syringomyelia (occurs in approximately 50% of all intramedullary tumors, but is most frequently associated with hemangioblastomas) rarely extend beyond one or two vertebral bodies. Some tumors have a tendency to occur in multiple areas, and imaging the entire neuroaxis may be indicated. Removal of the lesion is considered curative. Approximately 10%–30% of patients diagnosed with spinal cord hemangioblastoma is strongly associated with von Hippel-Lindau disease: multiple spinal tumors with abnormalities such as renal cell carcinoma, pheochromocytoma, pancreatic cysts; gene mutation results in the enhanced transcription of several genes, including vascular endothelial growth factor (VEGF). I have had 3 hemangioblastomas in thoracic area.

- *spinal cavernomas*, are unusual: solitary or multiple vascular malformation with abnormally dilated blood vessels, surrounded by gliotic tissue, often stained with hemosiderin, expression of previous hemorrhage. Account to woman in two thirds of cases, during the fourth decade of life, could

be concomitant discovered both in the brain and spinal cord, also skin, retina, associated with café au lait skin lesions. I have had only spinal cavernoma, disposed 2 cervical and 4 in thoracic areas.

- *developmental tumors* (3%) are slow-growing neoplasms with a thoraco-lumbar predominance: *teratoma, germ cell tumors* of the CNS are made up of cells similar to the germinal cells that develop in the gonads. There are 2 types of germ cell tumors: nongerminomatous and germinoma. Patients with primary intramedullary germinomas typically present with sensory and motor deficits of the lower extremities that can progress to include gait disturbance and urological dysfunction.

- *intramedullary spinal cord lymphoma* is a rare form of primary lymphoma and can occur anywhere in the CNS. It can originate in the spinal cord, accompany tumors in other locations throughout the CNS, or occur as a part of systemic lymphoma. It is usually an aggressive nonHodgkin lymphoma of B-cell origin.

- *spinal paraganglioma*

- *intramedullary metastasis* from a primary malignancy found in the lung (49%), breast (15%), and lymphoma (9%), are rare, they affect 0.4% of all patients with cancer and represent 1%–3% of intramedullary tumors, only two cases in my series from lung cancer

- *spinal primitive neuroectodermal tumor*

- *solitary fibrous tumor*

- *intramedullary schwannoma*, *neurofibroma*,

- *malignant peripheral nerve sheath tumor* 1 case in my series

- *primary intramedullary melanoma* are very rare, account for about 1% of all melanomas, develop with progression of symptoms more rapidly.

- *lipoma* (2%) may be associated with cutaneous abnormalities, difficult to perform complete excision due to fibrous adhesions to the spinal cord

- *spinal cysts* in 70% of intramedullary tumors:

lesional (*intratumoral*) *cysts*, contained within the tumor itself, may result from necrosis, fluid secretion, or degeneration of the neoplasm; with peripheral enhancement; need to be resected along with the solid portion of the tumor because there is a high likelihood of neoplastic cells within the cyst wall. Such cysts were described in: ganglioglioma - 46%, spinal ependymoma - 22%, spinal astrocytoma - 21%, spinal hemangioblastoma 2-4%

non-tumoral (*reactive*) *cysts* occur rostral or caudal to the solid portion of the tumor, due to dilatation of the central canal, do not enhance, present in 60% of all intramedullary spinal tumors, may resolve once the neoplasm is resected.

Clinical signs in IMSCT lesions (2-16) depends on lesion size and topography, evolve in general slowly; diagnosis is often made late - on average after 4 years of evolution. Symptoms are in general not specific to spinal cord lesions, may be present in any myelopathic process; vulnerable vascular areas for vascular insult are cervical, T_1-T_4 and L_1 areas. More rapid evolution it is found in intramedullary metastasis (12-14), which are diagnosed within one month of symptom, onset in up to 75% of cases.

-pain - more than 50% of cases, may be local or radiating; often is the earliest symptom, characteristically occurring at night when the patient is supine. Pain could be: *spinal type* - occurring at rest, increasing with exercise, typically dull, deep, tenacious, with stiffness, *radicular type* - cervical, brachial, thoracic, sciatic and *posterior cord pains* - with numbness, paresthesia, sensation of burning, stricture.

-cervical stiffness, weakness of an upper limb in particular clumsiness of one hand progressive weakness may occur in the arms or legs. Intramedullary thoracic tumors associate pain, motor deficit of the lower limbs with variable limitation of walking, spasticity, abolition of osteo-tendinous reflexes, paresthesia and localized suspended hypoesthesia, accompanied by sub-lesional signs - Brown-Sequard syndrome

-limping, instability, weakness in walking, poor or loss of balance

-sphincter disorders (dysuria, constipation, genital problems even impotence) – see conus medullary involvement.

In cavernomas there are 4 clinical patterns (10):

-acute headache due to subarachnoid hemorrhage, also complete paralysis due to hemorrhage extension into the spinal cord

-mild neurological symptoms with acute onset of gradual decline during weeks to months, events related to small hemorrhage or thrombosis within the lesion, with changes in the microcirculation surrounding the lesions

-chronic mild neurological deterioration from months to years with acute episodes lasting for

hours to days with possible neurological recovery between episodes during weeks to months

-gradual slow neurological deterioration over months to years, caused by small hemorrhages, changes in the blood flow surrounding the lesion or to changes in the size of the malformation.

IMSCL diagnosis is difficult, with discreet not specific neurological signs; it is sustained on MRI (1-9)(16-18):

-T1 weighted images sequences: spinal cord is increased in volume on one or more levels; hypo- or isointense signal for both ependymomas and astrocytomas span multiple vertebral segments, also cavities secondary to trauma, arachnoiditis, anomaly of the cranio-cervical hinge, rostral and caudal cysts, malformative syringomyelia. Hypointensity at the tumor margin (17) was found to be a relatively firm pseudocapsule and hypointensity within the tumor corresponded to intratumoral hematoma. When MR imaging shows an intramedullary tumor with hypointensity at the tumor margin, it is suggestive, but not pathognomonic, of an ependymoma (17)

-T2 weighted images sequences: hyper signal of the fleshy portion of the tumor both ependymomas and astrocytomas, by the cysts; hyposignals linked sometimes to chronic bleeding (deposits of hemosiderin, etc)

-after Gadolinium intravenous injection MRI exams highlights, a contrast enhancement in the majority of cases, in contrast to intracranial neoplasms, even low-grade intramedullary tumors enhance to some degree; however, the absence of enhancement does not exclude an intramedullary neoplasm in the presence of cord expansion

Ependymomas often are located centrally within the spinal cord leading to symmetric expansion, occupy the whole width of the cord, and enhance diffusely with a well-defined border.

Astrocytomas tend to be positioned more eccentrically, can be non-enhancing or have an enhancing nodule or large satellite cysts, usually do not have a well-defined border. Intratumoral hemorrhage can be seen in both types but are more common in ependymomas (17).

Hemangioblastomas have homogeneous contrast enhancement compared to the more heterogeneous pattern found in astrocytomas or ependymomas. They also have mural nodules, are associated with syringomyelia, and can have significant surrounding edema, also several topographies.

In cavernomas: MRI is the current study of choice both for diagnosis and for surgical planning, with high sensitivity blood oxygenation level. The typical manifestation is that of a webbed core, composed of blood and blood products in various states of evolution "popcorn appearance", of mixed spinal intensity on both T_1 and T_2-weighted images, with a moderate occasionally strong absorption of contrast medium after Gadolinium. For previous hemorrhage a proof is a black ring of low signal intensity around the cavernoma consistent with hemosiderin deposits both in T_1 and T_2 indicating disturbances of susceptibility caused by the iron in hemosiderin. If edema is present, the signal outside the hemosiderin rim is increased on the T_2-weighted images. Small cavernous malformations may appear only as petechial areas of decreased signal density "black dots". Depending the age of a hemorrhage blood products are isointense to slighty hypointense on T_1-weighted images and hypointense on T_2-weighted images – susceptibility effect. Few days later in the subacute hemorrhage stade, the lesion that contains methemoglobine are hyperintense on T_1-weighted images and hypointense on T_2-weighted images. After several weeks on the hemosiderin chronic stade old blood products are hypointense on both T_1 and T_2 weighted images. In cavernomas edema is usually absent in smaller cavernous malformations, different from hemorrhagic neoplasms, even when small, with characteristic surrounding edema.

In germinomas: MRI typically shows an expanding mass - often at the lower thoracic level, contrast enhancement with T_1 - and T_2 - weighted MRI can vary and focal spinal cord atrophy may be an important sign (one case in my series). These may have a dense capsule, precluding complete removal; although, this may be compatible with prolonged symptom-free survival. When complete removal is unobtainable, debris produced by the tumor may cause an early recurrence of symptoms

In lymphomas: T_1 - weighted MRI shows homogeneous contrast enhancement in an enlarged area of the spinal cord, while diffusion-weighted and T_2 - weighted MRI demonstrate hyperintensity

Melanomas typically display hyperintensity on T_1 - weighted images due to the presence of melanin, while T_2 - weighted images are generally hypo- or isointense.

Spinal arteriography is useful in hemangioblastoma (8), to characterize feeding

vessels and associated dilated pial veins, for pre-operative embolization.

The study of somatosensory evoked potentials (P.E.S.) and motor evoked potentials (P.E.M.) makes it possible to quantify the neurological impairment, to specify its topography at the medullary level and to monitor postoperative progress. Intraoperatively, it is possible to record the P.E.S. but this exploration is complicated and ultimately not very useful because it does not modify the surgical technique (19).

Surgery is the treatment of choice, It should be performed as soon as possible, observation can lead to further neurologic deficits, some of which are irreversible; outcome it correlate with the preoperative neurologic conditions (2-15) (20-21). In the perioperative period or in a rapid decline in neurologic function occurs, steroids are used. The goals of surgical treatment are:

1. to maximize tumor resection – good predictor of outcome, looking for a clear dissection plane, with preservation of neurologic function, in one stage operation, to avoid adhesions, using operating microscope, micro neurosurgical instrumentation, CUSA, electrophysiological monitoring to reduce the incidence of iatrogenic damage: intraoperative somatosensory, motor evoked potentials
2. to obtain a tissue diagnosis, after analysis of the surgical sample
3. to improve neurologic functions minimizing further neurologic deficits, avoiding pain
4. in case of clinical and/or radiological progression, especially in benign lesions
5. adjuvant therapy for those cases where the lesion cannot be completely excised
6. to be suited by physiotherapy-rehabilitation approach to provide better outcomes (21)(22)

Surgical technique (2-6). After general anesthesia induction, opioids, propofol and low levels of muscle relaxants are used to minimize spontaneous muscle activity, to enable EMG, motor evoked potentials. Halogenated volatile anesthetics are avoided because these interfere with sensory evoked potentials (SSEP). An arterial line is needed to ensure that dips in blood pressure are detected and corrected as quickly as possible because the spinal cord is sensitive to decreased perfusion. The patient is positioned prone on bolsters or a Wilson frame, freeing the abdomen and thorax from pressure and taking care to pad all pressure points. For cervical and high thoracic lesions, the head is immobilized using a Mayfield head holder or equivalent. The level is confirmed by with C- arm, O-arm, navigation. A standard dorsal midline approach is used, subperiosteal dissection of the paraspinal musculature expose the lamina and spinous processes A wide laminectomy or laminoplasty next to the fleshy portion of the tumour is performed. Meticulous hemostasis is obtained. A closed dura mater ultrasound is performed to confirm the correct exposure of the tumor, the satellite cysts being empty of echo. The dura is wide, bloodless exposed for 2 cm rostral and caudal to the upper and lower lesion margins. The dura is sharply incised on the midline, reflected to expose the lesion, the dural edges, without tension, are tacked to the soft tissues laterally using No. 4-0 silk sutures exposing the arachnoid overlying the swollen spinal cord. The tumor is localized visually with intraoperative ultrasound. Under operating microscope, the arachnoid is opened and tacked laterally to the dural edges, a midline longitudinal myelotomy between the dorsal columns, at the thinnest area between the tumor and spinal cord are performed, exposing the entire posterior face of the tumour, cysts adjacent to the tumor poles are open, the fine vascular network on the posterior face of the tumour is preserved also the white matter tracts; for eccentric lesions, incision through the dorsal root entry zone can be performed. The pia is sharply incised, the dorsal columns are dissected apart, traversing blood vessels are cauterized and divided, the tumor is encountered. The spinal cord parenchyma is dissected circumferentially off of the tumor capsule, looking for a clear plane between cord and tumor, sectioning and cauterizing thin vessels. the initial area of approach could be changed if the tumor has an exophytic component. A tumor specimen should be sent for frozen section early on in the dissection.

Intramedullary benign lesions (10) should optimally be removed en bloc, releasing the lesion poles and the anterior part of the lesion, disconnecting from its major blood supply off of the anterior spinal artery. If lesion are located more ventrally the margins of the myelotomy may be retracted with pial sutures. For very large lesions, for lesions with poor internal integrity and lesions with

an unclear surgical plane: a micro dissector, Cavitron ultrasonic surgical aspirator (CUSA) is often useful either to debulk internally to facilitate capsule dissection or to perform an inside-out resection, facilitating complete removal (20)

Intraoperative electrophysiology, such as somatosensory-evoked potentials and motor-evoked potentials may lead to improved outcomes, had a high sensitivity and specificity to prevent neurologic damage, but limited the extent of tumor resection (19) .

Dura is closed primary using a running stitch, or in case of subtotal resection dural grafting and sealants may be necessary to aid closure water-tight. Hemostasis should be careful performed, then the musculo-aponeurotic and cutaneous planes are closed, without drainage.

The outcomes of surgery (3)(4)(9)(10)(21-22) are related to:

-*early intervention*

-*younger age* (advancing age > 60 y is a negative prognostic factor)

-*the extent of preoperative neurologic deficit*: mild-to-moderate deficits often improve significantly following surgical removal, while those with advanced neurologic compromise generally have no worthwhile improvement

-*lesion topography*: patients with cervical tumors should be considered for continued mechanical ventilation in the immediate postoperative period with corticosteroid usage, upper thoracic and conus lesions induce higher morbidity, tumors spanning several levels requires extensive dissection of the spinal cord in order to expose the tumor.

-*extent of resection* - MRI the day after surgery gives the best estimate of completeness of resection, quality of surgery

-tumor histology:

-*for grade II WHO ependymomas* - gross total resection is reported in more than 90% of cases, with a distinct tumor and normal spinal cord interface. The rate of recurrence is dependent on the extent of tumor resection, avoiding scarring and cord atrophy

-*for low-grade astrocytoma*, if a plane can be developed between the non-encapsulated tumors tumor and spinal cord, gross total resection is an option

-*for low-grade astrocytoma with no definable plane of resection, high-grade astrocytoma*, biopsy plus limited resection or subtotal resection can be attempted, despite recurrence in 47.6% of patients (4). Postoperative radiotherapy can be used for *high-grade astrocytomas*, but with longer-term consequences - several adverse effects, including radiation myelopathy, radiation necrosis, vasculopathy, changes to the normal spine parenchyma and a 25% risk of secondary tumors in 30 years (6). For high-grade lesions, such as anaplastic astrocytoma and glioblastoma (15), the prognosis is clearly poor, aggressive surgical resection having a debatable role in prolonging survival.

- in *hemangioblastomas* preoperative emboli-zation can attenuate their rich vascular supply, such tumors exhibit a clear dissection plane, a complete resection is expected in 83% to 92% of patients with clinical improvements, especially for those disposed in the posterior half of the spinal cord. The presence of a syrinx suggests a noninfiltrative lesion and carries a better prognosis. Patients with von Hippel Lindau disease (8) are at risk of developing new lesions and must have their entire neuroaxis imaged periodically.

- in *spinal gangliogliomas*, resection is the primary treatment of choice, achieved at a much higher rate (83.3%) even in cervical spinal cord; spinal gangliogliomas have a higher relative risk of recurrence than both cerebral and brainstem topography and have a 10-year survival rate of 83%.

- In *aggressive intramedullary tumors* removal of tumor has not been shown to be of value, with survival of less than 2 years see anaplastic astrocytoma, a radical surgical removal can lead to severe neurologic impairment Recent studies, however, have shown that surgical intervention for the management of high-grade astrocytoma is associated with higher rates of long-term neurological complications with no derived benefit for patients (4). When a plane of dissection is absent (15), resection is often associated with poor outcomes (despite advances in microsurgical techniques, electrophysiological monitoring during the procedure). Fluorescence-guided resection of malignant cerebral gliomas utilizing 5-aminolevulinic acid (5-ALA) and protoporphyrin IX (PpIX) accumulation in tumors has not been determined in spinal intramedullary tumors (4)

- in *intramedullary lipomas* limits between lipoma and medullary tissue are imprecise, limiting surgical technique

- for *metastases, neuromas, teratomas, germ cell tumor, malignant peripheral nerve sheath tumor* the surgical technique remains unchanged, type of excision depending on the infiltrative nature of the lesion.

- in *cavernomas* surgical indication should be reserved to those with symptomatic lesion, causing objective neurological deficit, especially to those lesions that extend to the dorsal surface of the spinal cord with an exophytic component, subtotal removal can generate future hemorrhages.

- for *residual tumor growth or recurrence*, imaging the entire neuraxis is warranted to detect seeding. Therapeutic alternatives are: observation, repeat resection (reoperation is possible even in high grade lesions, but with high functional results), radiation therapy. For astrocytomas and ependymomas with no clear surgical resection planes, initial irradiation (20) improves neurological deficits.

- *closed follow-up*: increasing symptoms or new neurological deficits should lead to a search for tumor growth; *in general there is a transiently neurological worsening after surgery* - deep sensitivity disorders, balance, motor deficits; new-onset urinary retention may require prolonged bladder catheterization, either continual or intermittent, also a bowel stimulation regimen.

- *possible postoperatory complications*: spinal hematoma, deep vein thrombosis, pulmonary embolism, atelectasis, arachnoiditis, tumor dissemination, bedsores, infectious or chemical meningitis particularly from epidermoid and dermoid tumors, CSF fistula and meningocele, wound infection, sepsis, hydrocephalus.

- physical therapy, occupational therapy, rehabilitation should be instituted early in the postoperative course.

Radiotherapy in the management of IMSCL remains controversial (23-25):

- no lesion should undergo radiotherapy without a tissue diagnosis

- in spinal myxopapillary ependymomas more recent studies suggest that radiotherapy is not associated with lower overall recurrence regardless of the extent of resection (24)

- in radiosensitive germinomas 5-year survival rates of 65%–95% with irradiation alone is possible; for multiple spinal cord germinomas chemotherapy with cisplatin and etoposide might provide an alternate option in the treatment of intramedullary germinomas that could avoid the negative side effects associated with radiation treatment

- radiotherapy may be primary treatment for local control and survival in case of inoperable tumors and aggressive tumors such as: high grade ependymomas, anaplastic astrocytomas and glioblastomas with modestly improvement. Modern treatment planning and imaging allow more accurate target definition and respect for related normal tissue tolerances (23)

- in cases of residual or recurrent tumor viable options are watchful waiting, reoperation, radiation

- radiotherapy is responsible for acute and delayed myelopathy, increased difficulty with subsequent surgical tumor removal, diminished skeletal growth in young people.

- stereotactic spine radiosurgery (SSR)(25) is an alternative treatment option to conventional radiotherapy, effective and safe, using externally generated ionizing radiation to inactivate or eradicate defined targets in the spine, to reach local control by delivering large cumulative doses of RT in fewer fractions (less than 5). The most commonly utilized SSR machines include Elekta Synergy S, Novalis (Brainlab) and CyberKnife; all systems have excellent accuracy, targeting areas remain accurate to within 1mm. Prior reports of stereotactic spine radiosurgery for intramedullary metastases, arteriovenous malformations, ependymomas, and hemangioblastomas demonstrated favorable outcomes (25).

Chemotherapy (2-15) is considered experimental in the treatment of spinal cord tumors; is knowed the inability of large molecules to bypass the blood–spinal cord barrier (BSCB); unlike cerebral topography, intramedullary tumors do not respond to chemotherapy, also the rarity of these types of tumors make it very difficult to evaluate therapeutic options and potential at a statistically significant level

- *the topoisomerase-2 inhibitor, etoposide, temozolomide* had modest benefit and had a partial response in 2 of 10 treated patients (20%)(6) also with constipation, fatigue, neutropenia, lymphopenia and thrombocytopenia in several patients; 27% progression-free survival at 2 years with a median survival of 23 months

- *antiangiogenic therapy using the VEGF receptor-2 inhibitor SU5416* in patients with hemangioblastomas

and von Hippel Lindau disease (4)(8) shown to be somewhat effective; in contrast, the use of the monoclonal antibody bevacizumab to inhibit the VEGF receptor was shown to be ineffective, resulting in increased tumor invasiveness following antiangiogenic therapy, in conclusion some hemangioblastomas might show responsiveness to angiogenesis inhibitors, while others may not, depending on the level of upregulation of the VEGF gene

- *bevacizumab* may be beneficial for patients with significant tumor burden that is not amenable to resection - spinal cord ependymomas in neurofibromatosis type NF_2 (2)(3)(9)

- *epidermal growth factor receptor (EGFR) inhibitor gefitinib* following radiotherapy and other chemotherapeutic agents in intramedullary metastases from lung adenocarcinoma with mixed results of efficacy: 2 weeks improvements, even complete response; such response warrants continued investigation (13)

- *high-dose methotrexate-based therapy combined with alkylating agents such as temozolomide* has been shown to be effective in elderly patients suffering from primary CNS intramedullary lymphomas

- *in spinal melanomas* intrathecal injections of interferon-b, chemotherapy with dacarbazine following the resection of a primary spinal melanoma

While resection is the primary treatment option for intramedullary melanoma, gross total resection is difficult and most patients will require (20) postoperative radiotherapy (a combination of whole-brain and local radiation therapy), intrathecal injections of interferon-b and chemotherapy with dacarbazine following the resection of a primary spinal melanoma and demonstrated the control of progression and prolonged survival.

Therapeutic perspectives (22)(25) in intramedullary tumors are:

-development of neuroprotective agents to be use during surgery

-the development of drug delivery systems that allow the precise localization of chemotherapeutic drugs

Conclusions

Intramedullary spinal cord lesions (IMSCL) are rare condition. MRI even if it does not allow for histological diagnosis, still is the preferred method of diagnosis due to its sensitivity de detect lesion for preoperative planning: size, location, length, extent of surrounding edema, focal or diffuse spinal cord expansion, the cord - lesion interface, associated cysts, also to early detect recurrent lesions. To adequately counseled patients, with minor preoperative deficits, in benign lesion, real anatomical healing should be based on refinements of radical surgical excision. Actual radiotherapy techniques should be used in aggressive tumors anaplastic astrocytomas and high-grade ependymomas who are associated with a higher rate of recurrence, where radical excision is not achieved or in inoperable cases.

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Efficiency of 3d simulation models in emergency microsurgical clipping of intracranial aneurysms

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ABSTRACT
The latest developments in three-dimensional printing technology both in terms of equipment and materials offer a new opportunity in the microsurgical treatment of intracranial aneurysms. 3D printed model of the patient's aneurysms enables optimal anatomical visualization with personalized preoperative planning. This is a retrospective study of a series of 16 patients suffering from ruptured intracranial aneurysms, admitted and microsurgical treated based on rapid 3D printed models to our clinic from September 2016 to March 2018. We analyzed the dates concerning patient demographics, clinical, surgical technique and outcomes correlated with the data of the 3D-printed replica used for planning emergency surgeries.

Keywords
intracranial aneurysm,
3D printed models

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1. INTRODUCTION

Even if according to numerous international specialized studies, the endovascular treatment of intracranial aneurysms remains the first-line treatment, the microsurgical clipping technique is a necessary option, imposed by many particular anatomical-clinical situations. Also, an excellent trained vascular microneurosurgical team will definitely put the two intervention techniques on equal terms.

It is well known that extremely careful microsurgical planning is absolutely essential for achieving optimal postoperative results. Thus, by avoiding excessive manipulation of the parenchyma and intracranial vessels, with a significant reduction in the time of intervention, the main predisposing factors for intraoperative (aneurysmal rupture) and postoperative complications (vasospasm, infections, etc.) are eliminated. With the development of 3D printing technology, 3D simulation models have been adopted by the field of micro-neurosurgery [4.6]. The technology offers the advantage of 3-dimensional views of cerebral vessels and aneurysms from various angles, and of practicing the optimal clips construction for total aneurysm neck occlusion. Such 3D simulation models may improve our concepts of aneurysm configuration and approach and clipping

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technique selection. [2,3.8] Therefore, in this paper we aim to present our experience in the manufacture of aneurysmal simulation models by 3D printing technique and to investigate the possible effects of the application and utility of this printing system in emergency microsurgical clipping.

2. Materials and methods

2.1. Patients information

In this study 16 patients with intracranial aneurysms treated in our department from September 2016 to March 2018 were retrospectively selected. These were separated into two groups, 8 cases that benefited from microsurgical clipping after analysis and simulation of this technique on a preoperatively printed 3D model and 8 cases in which microsurgical clipping was performed only on the basis of 3D imaging analysis. A similarity in the location of aneurysms was followed in the selection of the two groups.

2.2. Image data generation and post-processing

Dynamic CTA imaging was obtained for all patients using a dynamic volume CT scanner with 32 detectors Toshiba Aquilion CT (Canon Medical Systems USA, Inc.). The scan parameters were as follows: scan interval, 16 cm; portal rotation time, 350 s; slice thickness, 0.5 mm; field of view (FOV), 240 mm; tube potential, 120 kV; and tube current, 218 mA. During the scanning process, the reconstruction with layer thickness (0.5 mm) and interval (0.5 mm) was obtained.

The images thus obtained were exported in standard digital imaging and medical communication (DICOM) format to a computerized unit for 3D image processing and reconstruction. They are imported into Mimics17.0 (Materialize, Leuven, Belgium) software. Mimics allow the automatic extraction of soft and cerebral tissue around the skull with the highlighting of cerebral vascularisation in 3D reconstruction. The image threshold should be carefully adjusted to display the image of the vessels as clearly as possible. The threshold segmentation method is combined with manual segmentation to obtain the most important region of interest (ROI). Also, interfering bone structures could be removed for better ROI (aneurysm region) exposure (Fig 1). The resulting 3D image is stored and sent as STL files. The procedure was performed together by a neurosurgeon and a software expert from our team.

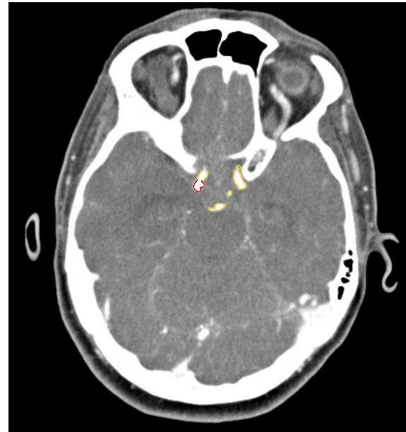
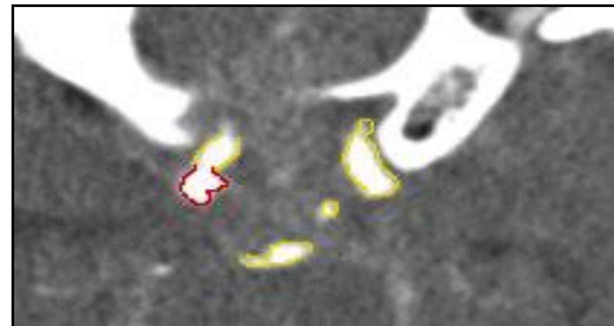


Figure 1. Vascular tree and aneurysmal lesion segmentation on 3D Angio CT acquisitions. images



2.3. 3D aneurysm model printing

The 3D aneurysm printed models were obtained using an Objet Connex 350 3D printer (Stratasys, Eden Prairie, MN, USA) or a Zortrax Inkspire printer (Zortrax S.A., Olsztyn, Poland). The manufacturing process of the 3D-printing machine is based on Fused Deposition Modeling (FDM) technologie. To make the prototype models, two types of semi-rigid and rigid materials were used as PLA (polylactic acid) and ABS (acrylonitrile–butadiene–styrene) filaments. Thus, to form the object, the printer heats the thermoplastic filament cable into liquid form and extrudes it layer by layer (Fig. 2).

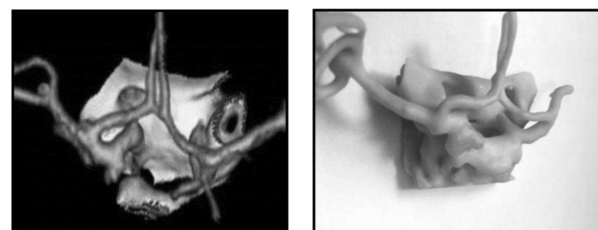
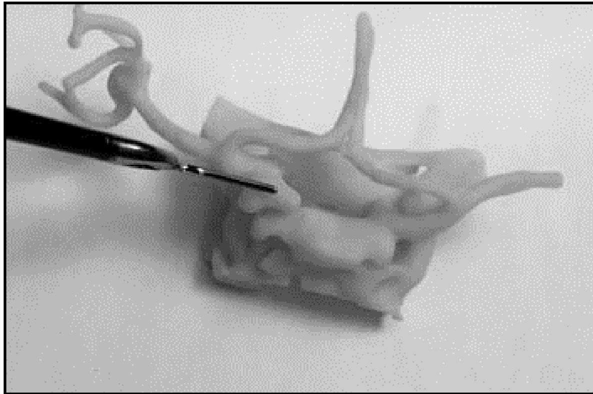
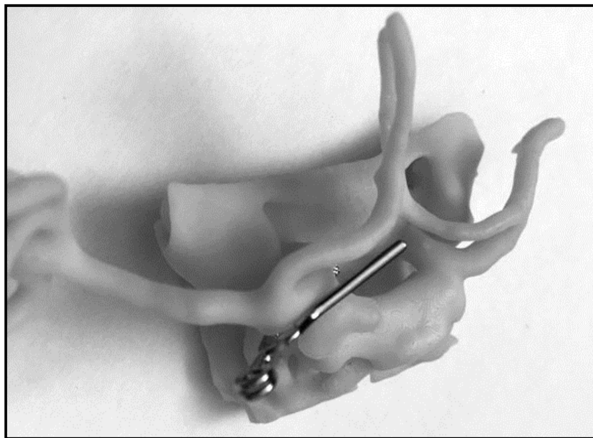


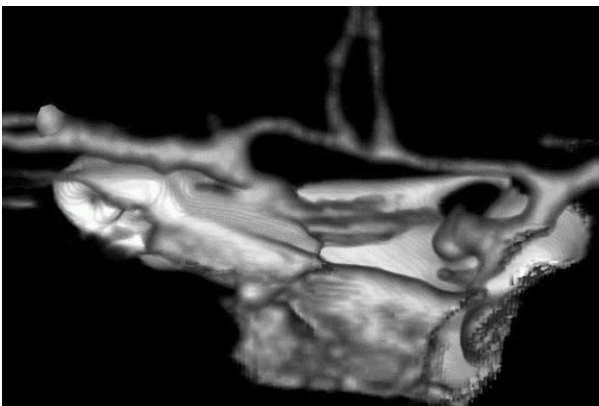
Figure 2. 3D Angio CT vascular tree and aneurysmal lesion and 3D printed models

2.4. Preoperative planning

All the models thus obtained were analysed by the vascular neurosurgery team in the preoperative period. Thus, 3D printed models were used to propose the most optimal approach to reach the target aneurysm. Also, a selection of clips regarding their size and shape as well as the configuration of their application on the aneurysmal neck was proposed and practiced. Model-based preoperative plans were correlated with CTA-based imaging to verify the value of the model in preoperative planning.







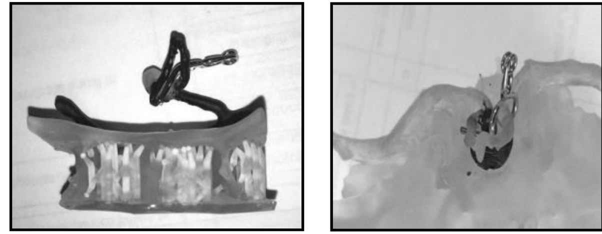


Figure 3. Preoperative clipping simulation on 3D printed models and postinterventional 3D Angio CT

3. Results

Our study included 16 patients with a total of 16 ruptured intracranial aneurysms. For all these patients, a 3D printed model was created and they benefited from microsurgical clipping of the aneurysm based on a preoperative planning simulated on these models. All surgeries were performed under general anesthesia by the same neurosurgical team. The mean age was 46 ± 7, with a median of 43.5 and a range of 35–65 years. About 62% (n = 10) of our patients were female with a female-to-male ratio of 1.6. Regarding the location of the aneurysms, there were 7 at the Acom level, 3 at the MCA bifurcation, 3 at the Posterior com and 2 at the terminal level of the internal carotid artery bifurcation and one at ophthalmic segment. The standard pterional approach for aneurysm clipping was followed in 11 of patients, whereas the other 5 of patients were treated through the fronto-pterional approach.

The conformation of the intraoperative clipping of the aneurysms, both in terms of arrangement and number of clips used, was similar in 13 of the cases to that practiced on the 3D printed models in the preoperative planning. In two cases, an additional clip had to be used for the complete and safe occlusion of the aneurysm. In one case, due to an atheromatous plaque at the level of the aneurysmal neck, which required the cutting of the aneurysmal sac and its extraction, and in the other case, as a result of the appearance of a rupture at the aneurysmal neck level during the microsurgical dissection. About 81% (n = 13) of the patients had a GOS of 5 and 19% (n = 3) had a GOS of 4. The median production time used for the models described in this manuscript was 4.25 h (range: 3.50–5.00 h). The average duration of microsurgical clipping interventions was 3h10, varying between 4 and 5 (Table1).

Patient	Age (years)	Sex	Lesion	Size mm	Clips configuration on model	Clips used in surgery	Residual neck	3D model production time	Surgical procedure time (h)
1	35	F	R MCA	7/6	Slightly curved	Same	No	3.50	3.00
2	65	F	AComA	6/5	Straight+ Slightly curved	Same	No	4.30	3.30
3	43	M	PComA	7//7	Angled laterally	Same	No	5.00	2.50
4	51	F	AComA	4/3	Bayonet+strait	Same	No	4.50	3.10
5	38	M	AComA	8/6	Straight x 2	Same	No	4	3.10
6	44	F	Oft ICA	11/ 9	Straight x2 +fenest.	Same	No	4.10	3.50
7	56	F	R MCA	5/6	Slightly curved + fenest.	Same	No	4.20	3.20
8	37	M	PComA	6/4	Straight	Same	No	4.55	2.30
9	40	F	AComA	4/3	Angled laterally	Same	No	4.40	3.00
10	55	M	Ter ICA	5/4	Angled laterally	Same	No	4.30	3.20
11	37	F	PComA	10/ 7	Straight x 2	Same	No	4.00	4.00
12	40	M	AComA	7/6	Straight x 2	Same	No	4.30	3.00
13	35	F	L MCA	8/7	Straight+fenest.	Same	No	4.10	5.00
14	41	M	Ter ICA	4/3	Straight	Same	No	4.50	3.15
15	53	F	AComA	5/4	Straight	Same	No	4	2.50
16	60	F	AComA	4/4	Slightly curved	Same	No	4	3.10

Table 1. Patients, aneurysms and interventions dates

Discussion

The technology of printing 3D models has become more and more popular in the field of medical applicability. This was mainly due to the increased availability, ease of use and affordability of 3D printers [1,4,6]. Numerous publications have described the increased applicability of 3D printing in intracranial aneurysm modeling and its benefits preoperatively [7,9].

One of the main difficulties during the microsurgical treatment of intracranial aneurysms is the selection of the appropriate clip(s) to be implanted according to anatomical variations. It is well known that surgical planning is essential [1,8], to avoid excessive manipulation of intracranial vessels and prolonged surgical time, which are predisposing factors of mechanical vasospasm and intraoperative aneurysmal rupture [9]. The results of this work describe a simplified and rapid method of manufacturing individualized 3D models and report the effects of its application to the choice and simulation of the pre-surgical approach. The total time used to create a 3D model experienced a spectacular evolution from a week, initially (Wurm et al) to 24 hours (Faraj et al) and later to 4-6 hours (Błaszczyk et all). The average total time required to make the 3D printed model in our study (from CTA acquisition to the finished model) was approximately 4.25 hours. This is registered in the direction of rapid protopiping in order to perform emergency surgical interventions.

Regarding the statistical comparison between the clipping configuration practiced preoperatively on the 3D printed model and the one performed during the microsurgical intervention for aneurysm occlusion, we note that this was not significant. Also, the analysis regarding the number, shape and dimensions of the clips used for each intervention compared to those proposed and practiced preoperatively on the 3D models showed a statistically no significant difference. All this demonstrated the relevance of using these 3D printed vascular models in preoperative interventional planning. These results are based on an observational analysis and objective evaluation of the diameter, length and thickness measurements of the aneurysm on the 3D printed model in relation to the computerized radiological image.

Although 3D printing technology has gained increased popularity in vascular neurosurgery due to its proven safety, feasibility, accuracy, efficacy, reproducibility, and cost-effectiveness, there are still several hurdles to overcome before the technology is fully incorporated into routine neurosurgical practice. As other reports have shown, an important limitation is determined by the lack of a standardized

production method that governs the assimilation of 3D models. This is due to a great variability in terms of the type of printers used, the 3D printing technology used and, perhaps most importantly, the characteristics of the resin materials used in the reconstruction process.

The use of 3D printed aneurysm models will also be a great success in the future, as they have proven to be an excellent tool in practical simulations, specialized educational training, as well as in educating patients and their families. [1,2,5]

Conclusions

The 3D printed model of the aneurysm is a precise, hands-on simulator, which allows neurosurgical specialists to plan and practice microsurgical intervention preoperatively even for emergency cases. They greatly improve their anatomical understanding of aneurysms, define surgical techniques and enhance their skills to choose of suitable clips and optimal clips arrangements.

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Notes on the history of Walter Edward Dandy - one of the outstanding fathers of neurosurgery

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ABSTRACT

Walter Dandy was born in 1886 in Missouri into an immigrant family. From an early age, he stood out as a good and curious student, which led him to study initially at the University of Missouri and later at the John Hopkins School of Medicine where he had the opportunity to develop his potential as a researcher in the Hunterian surgical laboratory, under the tutelage of the prestigious Dr Harvey Cushing. His contributions to medicine as a surgical resident and later neurosurgeon marked a before and after in the history of the modernization of neurosurgery and enriched the knowledge of the anatomical structures of the central nervous system, considering his discovery of ventriculography as "the greatest single contribution to brain surgery", also being the first to successfully perform various surgical procedures, such as the clipping of aneurysms and the resection of tumours of the cerebellopontine and hypophysial angle.

INTRODUCTION

Walter Edward Dandy was born on April 6, 1886 in Sedalia, Missouri as the only child of immigrants John and Rachel Dandy (1,2). Throughout his life he served as a neurosurgeon and scientist, being considered one

of the founders of neurosurgery and contributing innovative ideas in multiple fields of medicine, among which are ventriculography, the description of the circulation of cerebrospinal fluid, acoustic neurinomas, the function of the pituitary and pineal glands, pneumocephalus, Méniére's disease, glossopharyngeal neuralgia, intraventricular tumors, intracranial aneurysms, ruptured intervertebral discs and neuroradiology. He was also credited with the title of "father of neuroendoscopy", which made him the most famous and influential neurosurgeon in the world for 25 years (2-7).

Dandy was associated with the John Hopkins School of Medicine, as it was the place where he obtained his medical training, and later with the hospital of the same name, entering as an intern and remaining there throughout his career as a surgeon, and was associated with other great neurosurgeons even before his graduation as a physician, such as Harvey Cushing, with whom the differences in personalities and ideas that led to their separation and rivalry throughout their careers were very clearly highlighted (1,8,9,10,11). The importance of his contributions to neurosurgery and medicine in general have allowed the evolution of neurosurgery to what is known today, for this reason it is of great importance to remember and commemorate his work.

Early age and medical training

Born and raised in Sedalia, Missouri in 1886, Walter Dandy was the only child of the marriage between John and Rachel Dandy, who were immigrants from England and Ireland respectively, socialist supporters and ardent members of the religious sect called "Plymouth Brethren". John Dandy, his father, immigrated with his wife to the United States two years before Walter was born, in order to work in the railroad industry, where he worked initially as a fireman and later as a locomotive engineer on the Missouri-Kansas-Texas Railroad (1,2,12,13,14,15,16).

As an only child, Walter was instilled with competitiveness and excellence from a very early age, and established a strong and close relationship with his parents, who always supported his decisions and accompanied his greatest achievements, which is why Dandy considered family relationships to be "the best thing in life (7,14,15).

Dandy's childhood was no different from that of other children, he played with his classmates and frequently had disputes with children much older than him (1). He inherited from his father a taste for trains and from a very young age he showed his fascination for baseball, achieving a balance between his studies and baseball games, so much so that one of his roommates referred to him as a "tough student and a tough player" (12,14,17).

Dandy attended public school in Sedalia in a "1-room schoolhouse" along with other immigrant children, from which he graduated in 1903 as the valedictorian of his class and was awarded the title of Valedictorian, thus having the duty of giving the final valedictory address in which he spoke of the importance of education (1,2,7,14,15). Encouraged by his teachers, he entered the University of Missouri in 1903, where, motivated by his interest in learning biology and medicine, he did his laboratory work with Winterton C. Curtis, PhD of Johns Hopkins University, as an assistant in his zoology laboratory at the University of Missouri. This man motivated Dandy to continue his medical training at the Johns Hopkins School of Medicine (1,2,7,14,15).

In 1907 Dandy participated as a candidate for a Rhodes Scholarship to study at Oxford, passing the exams and winning the scholarship. However, he turned it down because in communication with Sir William Osler, professor of medicine in England, he suggested that he finish medicine at Hopkins and later do postgraduate studies abroad (1,2,7,14,16). In the same year, following the suggestions of Osler and Curtis, he entered the second year of medical school at Hopkins, because they recognized part of what he had studied at the University of Missouri, and it was not until 1910 that he received his degree from the John Hopkins School of Medicine (1,2,7,14,15,16).

Medical training

While studying at Johns Hopkins School of Medicine, Walter Dandy was strongly attracted to anatomy and went to work as a trainee in the laboratory of Franklin P. Mall, professor of anatomy at Johns Hopkins and founder of embryology, who upon seeing Dandy's skills in drawing and dissection, assigned him as his work the representation of the youngest human embryo he preserved, this work of Dandy was published shortly before finishing medical school and for which he was awarded a Master's degree, the embryo is still known as the "Dandy Embryo" (2,14).

After being awarded his medical degree in 1910, Dandy was assigned by the famous surgeon Dr. William Halsted to begin his surgical training by doing research work under Harvey Cushing at the Hunterian Surgical Laboratory, an experimental laboratory for surgical procedures on animals, because Halsted was impressed by Dandy's skills and relentless performance in his final year of medical school. A year after his assignment, Walter moved up to become Cushing's clinical assistant until 1916 (1,2,4,7,12,14,16,18).

At the time of Dandy's arrival at the Hunterian Laboratory, Cushing was conducting research on the function of the pituitary gland and it is at this time that, guided by Cushing, Dandy made studies on the irrigation and innervation of the pituitary glands of animals such as dogs and cats, such work earned him his second and third publications, in company with Emil Goetsch "The blood supply of the pituitary body" in 1911 and alone "The nervous supply of the pituitary body" in 1913 (1,2,7,14).

At the beginning of 1911, a great conflict began between the teacher Harvey Cushing and the trainee Walter Dandy, generated in the first instance by a controversy that was maintained in the results of a work that consisted in producing glucosuria by stimulation of the sympathetic nerves, in which Dandy affirmed that the stimulation produced a great glycosuria, something that made Cushing irritable, later Dandy corrected that by inhibiting the sympathetic stimulation the glycosuria continued to be produced, so Cushing commented "Dandy, nobody could think of something like that, except you" (1,2). Despite this altercation, Dandy was appointed months later as Cushing's clinical assistant, ensuring his tenure at the Laboratory and interested in investigating hydrocephalus using canines for his experiments, however, the conflict developed a tense and discordant atmosphere between the master and his apprentice, which lasted until the end of Cushing's life (1,12,14).

In 1912, an assistant resident in Pediatrics, Kenneth D. Blackfan, collaborated with Dandy in his research on hydrocephalus, this work led in 1914 to excellent results where they showed the physiology of cerebrospinal fluid and classified hydrocephalus into two types: obstructive and communicating (1,4,7).

In late 1912, Dr. Harvey Cushing leaves Johns Hopkins Hospital with the goal of going to Boston to give the Chair of Surgery at Harvard University. With this news, Walter assumed that, like all the other clinical assistants, Cushing would take him and he would have to move to Harvard, however, Cushing clearly stated that Dandy would not be going with him (1,2,7,12). Dandy was angered by Cushing's manner and, even more so, by the fact that he had previously turned down the position to join Dr. Halsted's surgical staff at Johns Hopkins, so he thought his career was totally over (1,4,7). However, Walter was rescued by the Hospital administrator at the time, Dr. Winford Smith, who provided him with a room to occupy while Dr. Halsted returned from a trip and could decide on his situation, who did not hesitate to reinstate Dandy in his position as Assistant Resident in General Surgery, after looking at his research on hydrocephalus (1,7).

After his reinstatement in 1914, Halstead encouraged him to investigate the pineal gland, and it was not until 1915 that he published the results of complete pinealectomies performed on dogs, with no effects on the physical well-being of the animals used (1). Dandy continued to work as an intern and assistant resident until 1916, when he finally adopted the title of surgical resident, which he held for approximately two years, until 1918, when he was appointed general surgeon. From that time on, all neurological patients at Johns Hopkins Hospital were attended by Dr. Dandy because of his great skill and surgical technique (1,2,7,14,18).

In 1921 he was appointed associate professor of surgery at Johns Hopkins Hospital and ten years later he was clinical professor of neurosurgery (14). Until the year of his death, he devoted himself to establishing a neurosurgical residency program at the hospital as a continuation of the strong neurosurgical department that Harvey Cushing had left behind (18).

CLINICAL AND SCIENTIFIC CONTRIBUTIONS

Ventriculography and neuroradiology

Among the many contributions made by Dandy, the procedure called ventriculography (2) is considered to be the most important. His studies in this area began in 1916, in which, together with his associate George Heuer MD, he showed the usefulness of x-rays for the diagnosis of pituitary tumors and calcified intracranial masses, such as aneurysms with calcification (4,7,18). However, this new finding was of no use to them because diagnosis of tumors by

this means was late, so they agreed that another method for early detection of these intracranial entities was going to be necessary, and this method was likely to be more than plain radiography because the neurological lesions had densities similar to those of normal brain (4,7,18).

Subsequently, they had 3 cases of patients with non-calcified tumors that were visualized with x-rays because they were located inside the paranasal sinuses, they then noticed that it was possible to visualize them because they were delineated with air, which contrasted with the tumor tissue (4,7). From this originated the idea that it was going to be possible to locate tumors by x-ray if the ventricles were filled with exogenously administered materials, so Dandy tested the injection of various radio-opaque dyes into animals, in his words "various solutions and suspensions used in pyelography: thorium, potassium, iodide, collargol, argirol, bismuth subnitrate and subcarbonate", finding that this gave excellent delineation. Unfortunately, however, he discovered that these substances were harmful to nerve tissue, as the animals that were injected always had fatal outcomes, producing "marked edema, serosanguinous exudate and petechial hemorrhages" (4,8,18,19,20). From this research Dandy concluded that it was unlikely to find a substance that would be so harmless as to warrant injection into the nervous system, and that ventriculography might therefore be possible using only "the substitution of a gas for cerebrospinal fluid" (7,19).

In 1917 Dandy, having already heard from Dr. Halsted about the ability of intestinal gas to detail abdominal X-rays, had the opportunity to be in contact with a patient with an intestinal perforation and consequent pneumoperitoneum, who had an abdominal X-ray in which the separation of the liver and diaphragm by a collection of air was seen in detail (4,7,8,18). This finding was surprising to Dandy, who published an article on this radiographic phenomenon ("pneumoperitoneum"), which had a major influence on his inventiveness and led him to suggest the injection of air into the ventricles, i.e., pneumoventriculography (18,21).

To perform the procedure, a small hole was made in the calvaria, subjecting the patient to local anesthesia, then a needle was inserted into the lateral ventricle and cerebrospinal fluid was extracted, replacing the same volume that was extracted with air. Once the air was injected, the patient was taken to the X-ray room and several frontal and lateral X-rays were taken (7,20).

By 1919, Dandy had already performed his innovative technique in several patients, being able to demonstrate not only intraventricular lesions, but also lesions of the cerebral subarachnoid spaces, as well as the localization of spinal tumors (7). Thus, Dandy was the first to perform pneumomyelography (22). Acceptance of radiographic studies of the nervous system was slow and there were many conservatives who were slow to accept this new technique, and Dr. Harvey Cushing disapproved of the procedure, commenting that he was reluctant to accept the new technique as he felt it might discourage neurosurgeons from training sufficiently and performing the thorough neurological examination, once again highlighting the rivalry between the two (7,18). However, Dandy's introduction of pneumoventriculography, fluroscopy of the ventricles, air encephalography and pneumomyelography revolutionized the radiological diagnosis of diseases of the nervous system (4,19,20,22,23).

Hydrocephalus and cerebrospinal fluid drainage

After graduating from John Hopkins School of Medicine in 1910, Dandy dedicated himself to researching hydrocephalus, in this process he associated with Dr. Kenneth Blackfan, pediatrician, who published in 1914 the first extensive study on the subject, from this and during the next 8 years approximately (1914-1922) published about 17 articles on this disease (1,24,25,26). In the initial study, he detailed for the first time the subtypes of hydrocephalus, classifying it as non-communicating (obstructive) and communicating, as well as proposed the surgical technique of removing the choroid plexus for the treatment of this type of hydrocephalus (24,27). Dandy emphasized the etiology, objecting that although it could be idiopathic in nature, they recognized that the condition could be the result of blockage at several sites and it was this that they documented in their paper (24).

As for the description of cerebrospinal fluid circulation, Dandy was the first to do so in his research on hydrocephalus. He developed a study that he published with his associate, Dr. Blackfan, in

December 1913, which was the first to describe the circulation and absorption of CSF in non-communicative hydrocephalus (24,27). This was achieved using canine models, to which he obstructed Silvio's aqueduct and subsequently evaluated their behavior and the possible symptoms that appeared, observing lethargy and vomiting as the first symptoms. Additionally, they observed the trajectory of the cerebrospinal fluid and its absorption when stained with phenolsulfonphthalein, a test used to verify whether the obstruction was in the aqueduct of Sylvius or in the foramina of Luschka and Magendie, He was able to visualize a suspension of granules injected into the subarachnoid space that did not pass freely into the blood, and with this Dandy became the first to observe that the problem was the lack of CSF absorption in the lateral ventricles (1,2,24,25,27,28,29).

As for treatment, Dandy worked on surgical procedures based on three principles: reducing CSF formation at its source, relieving the obstruction in the ventricular system and diverting the fluid to another location in the body where it can be absorbed or excreted. The first procedure for obstructive hydrocephalus was first observed on January 21, 1915, while for communicating hydrocephalus it was on February 6, 1918, three years later (2,24,25,27,29).

In 1918 Dandy published the technique of choroid plexectomy to communicate hydrocephalus, "Based on simple, fundamental, physiological and surgical principles", this procedure involved the removal of the choroid plexuses of the lateral ventricles, the main site of CSF formation (24,30). The surgery proposed by Dandy was performed through a frontal approach, cutting a window in the anterior wall of the third ventricle, thus releasing retained CSF directly into the ventricles while creating an opening for fluid into the chiasmatic cistern (25,26,30,31). By 1920, using ventriculography to determine the precise location of the obstruction, if found to be in the aqueduct of Sylvius, Dandy was forcing a small tube through the aqueduct to assist in reforming the canal, which would be removed two or three weeks later in a second operation (25,26,30,31). The striking feature of these early publications is the high mortality rate. There was more than 50% operative/immediate postoperative mortality, and few patients survived beyond a few months (24).

Neuroendoscopy

Another area of interest that Dandy researched was neuroendoscopy, and he was extremely curious about how things could be improved, which is why he strove to improve the instruments available to neurosurgeons (5). By the 1920s, he began to try to use cystoscopes in his operations to remove the choroid plexus, noting that he could visualize the lateral ventricles, the foramen of Monro, the choroid plexus and even vascular structures of the ventricle walls, results that greatly excited the researcher, giving rise to the concept of "ventriculoscopy" (5,32,33).

Then, in 1922, Dandy attempted to replace his routine dilator with a cystoscope and a small ventriculoscope; however, the results of these early interventions fell short of his expectations because he was unable to properly remove the choroid plexuses using these tools, so he had to return to the standard nasal dilator and forceps. In the face of this disappointment, he stated that "the instruments, in their relatively primitive construction, were not completely adaptable" for use in a neurointervention (5,32,33).

However, Dandy continued his research by consulting gynecologist Howard Kelly, the "father of cystoscopy," for assistance, who lent him one of his small cystoscopes for use in intraventricular surgery (5). This tool proved to be superior to any he had used before, so, making certain modifications to the original, in 1923 he asked the Wappler Electric Co. to help him design his reinvented version of the ventriculoscope (5,33). 10 years later, in 1932, the neurosurgeon had overcome the obstacles he had encountered in his first attempt with the ventriculoscope, and was able to perform choroid plexus resection surgeries with this instrument as routine procedures (5,33). Two years later, Tracy Putnam adapted a urethroscope for endoscopic electrocautery and successfully removed the choroid plexus without resection, so Dandy adopted Putnam's use of coagulation instead of clipping in his own endoscopic choroid plexectomies, using a probe similar to Putnam's that could pass through the endoscope (5).

Finally, Dandy felt that neuroendoscopic procedures were limited by instrumentation and illumination, noting in his book Surgery of the Brain, published in 1945, that their usefulness was restricted to young children and infants, as well as for

tumors found incidentally during plexectomies (5,33).

Aneurysms and neurovascular surgery

Dandy had a fascination with anomalies of the cerebral vascular tree, which is why this was one of his focuses (2). His research in this area began with his work with Dr. Heuer on the localization of intracranial tumors, as well as other research of the same era, such as frontotemporal craniotomy for optic chiasm lesions and pituitary tumors, which gave him the opportunity to visualize the cerebral vascular anatomy and provided him with the means he needed to approach and cut intracranial aneurysms (2,26,34). In 1928 he published an article dealing with venous anomalies and angiomas of the brain, and in the same year he recorded 8 cases of congenital arteriovenous aneurysms, and in 1929 he operated on middle cerebral aneurysms, but his first results were poor (2,35).

Dandy's first isolation of a carotid cavernous fistula resulted in 1934, proving a valuable treatment option for carotid ligation lesions and introducing his work on aneurysms of the circle of Willis (2). He maintained that the only hope for the patient with an aneurysm would be treatment that would clip or trap the neck of the anomaly, so 3 years later, on March 23, 1937, he succeeded in applying a silver clip to an internal carotid aneurysm, a procedure he successfully completed, marking a milestone in neurosurgery (2,34,35,36,37).

Dandy's work on aneurysms ended in 1944 when he published his book entitled "Intracranial Arterial Aneurysms" (34).

Other contributions

We cannot overlook Dandy's contributions to the physiology of the pituitary gland, as well as his research on the resection of its tumors. His research on animal models in which he resected the pituitary gland showed that these animals suffered from growth retardation and diabetes insipidus (2,14). Dandy performed his first pituitary surgery on July 13, 1912, still during his residency and in the absence of Dr. Cushing, his mentor, and in his lifetime he performed four times as many pituitary surgeries as Cushing, despite Cushing being his predecessor (14). He was also the first to use a transcranial approach to this gland, with better results than the traditional approach (2,14).

Similarly, his contribution to the resection of vestibular schwannomas, following his discovery of ventriculography, which he used as a diagnostic method for these tumors; Dandy thought to improve the technique described by Cushing in order to reduce the mortality rate, so in 1922 he published a preliminary report on his first successful operation in which he obtained a total resection margin for this tumor, the case had occurred 5 years earlier (38,39). In this report, he described his new method of approach, by means of a bilateral suboccipital flap, first removing the inner portion of the growth, as described by Cushing, but then meticulously cutting the veins and arteries surrounding the capsule, and finally separating the capsule carefully from the brainstem (38). However, Dandy did not cite Cushing's 1917 monograph on acoustic neurinomas, so the latter was offended and refused to accept the new technique (38,39). Finally, in 1934 Dandy described a more refined technique for the resection of tumors of the cerebellopontine angle with a less invasive unilateral unilateral suboccipital approach (38,40).

And as well as these we can mention the resection of pineal gland tumors and their physiology, the resection of tumors of the orbit, his intervention in brain trauma by devising a helmet for baseball players to protect them from blows to the head by balls, herniated discs, douloureux tic and trigeminal neuralgia, tumors of the third ventricle and Meniere's disease (1,2,11,17,28,41–46).

Personal life

Physically, Dandy used to be described as a man a little short in stature, with large hands, small feet, a high-pitched voice and somewhat stocky, but as time went by, the one characteristic that people who interacted with him never forgot was his piercing blue eyes (1). His classmates in medical school remember him as a guy with remarkable skill and determination when it came to work, also commenting that Dandy took very little time to spend with his friends on Saturday nights (2). While in residency, in the operating room he was described as bold with very confident hand movements, in addition, he liked to maintain a very strict protocol that consisted in that only the resident could talk to him, in case the resident assistant or the intern had any concerns they should communicate first with the resident, this behavior of Dandy could fluctuate

depending on the situation, if everything went well he was very easy to work with, in case something went wrong he would yell or throw the surgical instruments (1,13,15).

Most of the time Dandy appeared distant and cold, however, he was always kind to those doctors, residents, interns or patients who had financial problems, always with a great willingness to help them financially (1). Dandy's daughter, Kathleen Louise, related that her father's personality could be confusing for many people, however, the secret was in understanding the personalities of Walter Dandy's parents. Kathleen refers that he inherited the kindness and gentleness of his father, but at the same time the frankness and bad temper of his mother, therefore these opposite traits were in conflict and people usually ended up seeing only one side of the coin, but those who delved a little deeper could find the good side of his father (15).

That loving side of Walter Dandy can be seen in his interaction with his family. He always proved to be a loving father, a good husband and son (13). His relationship with his parents was very close. Throughout medical school and the years of his residency at Hopkins Hospital, he communicated weekly through letters, many of which recount Dandy's rivalry with Dr. Harvey Cushing (16). Dandy said that most of his neurosurgeon colleagues did not like him and apparently he was very suspicious of Harvey Cushing, because besides Cushing, Walter had controversies with different surgeons such as Charles Frazier, Temple Fay and Loyel Davis (1).

As a child, Dandy was a big baseball fan and player, during his years at the University of Missouri he would escape from his dorm to play night games, even while in residency with Dr. Cushing he managed to play three times a week, being so good that he became captain of the Johns Hopkins baseball team (17). Dandy wrote to his parents, giving merit to baseball, saying that thanks to this game he was able to refine his surgical technique and his skill with his hands became much greater (17). In addition to baseball, Dandy was attracted to trains, a taste instilled in him by his father since he was very young. In his spare time he would travel to New York by train to watch baseball games and on the way he would take advantage of the silence and comfort of the train to write his articles (15,17).

In Dandy's surgical career, one of his most significant early cases was related to the dangerous "beanballs", which consisted of a baseball player being hit in the head with a baseball, the patient suffering from a large cyst on the skull as a result of the traumatic impact, Therefore, when Dandy was asked thirty years later to work on a protective cover for baseball players' heads, he did not hesitate for a second to accept it, enthusiastic about his love of baseball and his professional attitude (15,17).

Marriage and family

In 1923, Walter was already known for his far-reaching research in the field of neurosurgery and his position at the hospital was that of associate professor of surgery; that same year, days before an academic trip to Europe to study with European doctors, Dandy met Sadie, a 22-year-old dietetic social worker from the same Johns Hopkins Hospital, at the entrance of an elevator (1,15).

Sadie and her friends had already seen the Hopkins surgeons play tennis on the hospital courts and considered Walter a "good catch." Some time later, Sadie and Walter began dating and meeting in places away from the hospital in order to avoid any kind of rumor (15). When Walter Dandy returned from his trip to Europe, he and Sadie were married and a year later they had their first child, Walter Jr.; later in 1927, a second child, Mary Ellen, was born; in 1928 Kathleen Louise and finally in 1935 the last daughter, Margaret, was born (15).

Dandy's stress at work was reduced when he played baseball, tennis or golf, and sometimes his great passion for trains meant that he could only relax by sitting and watching the cars go by on the tracks at Union Station or by riding them and writing articles in his Roomette, in order to be relaxed and away from the noise of the hospital (15,17).

Although he was a somewhat strict father, he never stopped being loving to his children, his home was a refuge in which he isolated himself from his busy work to live a home life with his children and wife (15). Dinnertime at Dandy's house consisted of the children being at the table by 6 p.m. to receive dinner promptly, properly cleaned and with good manners at mealtime. The topic of conversation was led by Dandy, talking excitedly about some tumor removed from one of his surgeries of the day or how stressful neurosurgery can be for the patient's family members (15). After being listened to at dinner, Walter always listened eagerly to his children's experiences throughout the day, which is why he was

always remembered as a warm and playful father. He often invented games to amuse the children, for example, on certain occasions they would sit on the sofa and try to spit plum seeds into the fireplace (15).

At the end of dinner, he would go into his room to change his clothes and the moment he would shake out his pants, coins would fall out of his pockets and the children would rush to pick them up and put them in their pockets. At other times he would simply lie down on the sofa and ask little Mary Ellen to lie in his arms for most of the night (15). In his home office, Walter kept a photo of himself and another man in tennis clothes, However, Sudie suggested to his children not to ask questions about the man in the photo and that they should only know that his name was Harvey Cushing (15). Dandy often took Walter Jr. to the hospital to see him operate, perhaps these acts influenced the boy to follow in his father's footsteps, as he later became a great anesthesiologist (15).

Hobbies and Pastimes

Dr. Walter Dandy spent his free time playing golf and bridge, most of the time with his family (47). Also from a very young age he was taken by his father to play baseball, so he became a fan of this sport, so that after his studies, Dr. Dandy, identified a natural association between baseball and medical practice for the reduction of brain injuries related to the incline. This history further supports the unique position of neurosurgeons to leverage clinical knowledge, inform innovation, and expand service to society (48). Many claim he was an expert in history and had a particular fascination with the American Civil War (47).

Death

In April 1946, Dandy was with his young daughter Margaret, in his backyard garden, when a pain in his chest caused him to stop the work he was doing, when Dandy's doctor was called, he diagnosed a "heart attack", he recovered, went home and 17 days later could not resist a second event and died on April 18, 1946 at Johns Hopkins Hospital (1,15).

Dandy Walter's story demonstrates that research in surgery and neurosurgery quickly changed the management and prognosis of certain diseases, which naturally have a chaotic course and are fatal. Today, these initiatives in the field of surgical sciences need to be highlighted in order to continue contributing to human development and the field of medicine (49-55). Above all, the fact that this author began his career in research from the beginning of his career in medicine, enhancing his skills as a physician and resident (52,53,55); skills that must be replicated today, to advance rapidly in the problems that afflict global health.

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Factors associated with success of trial spinal cord stimulation in patients with chronic pain. Preliminary data on the prognostic value of standardized health-related scales in a clinical practice setting

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ABSTRACT
Objective: Spinal cord stimulation (SCS) is a widely employed technique in treating chronic pain, however, it still fails in significantly reducing pain in one-out-of-three cases. Poor consensus exists on the most predictive factors of SCS outcomes. Although psychological criteria such as emotional stability are recommended for this treatment, it is not well understood if the perception of patients' own health may impact the SCS success. Therefore, we retrospectively examine factors associated with the patient's subjective conditions, to investigate their relationship with SCS success.
Methods: Before the implantation of an SCS trial per routine clinical decision-making, and independently from the implanted devices, patients treated in our clinical practice underwent an extensive evaluation of pain, disability, depression and the overall quality of life. In those patients with successful SCS trials, the pain level was also evaluated at the end of the trial period. Regression analyses were performed to investigate factors predicting successful trial stimulation.
Results: Successful trial stimulation was effective in 15 patients (75%). Perceived disability, pain and general health resulted as independent predictive factors on SCS trial outcome. Further investigation showed perceived disability (i.e. Oswestry Disability Index) as a crucial factor, and ROC curve analysis identifies a cut-off of 38 as a predictive score of success.
Conclusions: Although preliminary, these findings suggest that standardized scales examining the overall patients' perceived health status, particularly the disability index may help shed light on predicting SCS trial success. Thus, it is argued the potential application of self-administered scales in SCS patients' selection in routine clinical practice.

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Introduction

Chronic pain is a debilitating condition that has a significant impact on patients' quality of life (QoL). The treatment of chronic pain is still challenging, involving many disciplines, including physical and psychological therapies, as well as pharmacological and surgical treatments [1]. Since its introduction in the last half-century [2], spinal cord stimulation (SCS) has been a reliable treatment for chronic pain conditions, with no pharmacological assumption. Although SCS can reduce pain symptoms up to 70% with a significant improvement in QoL, some clinical features expose at the risk of SCS failure [3]. For example, psychiatric comorbidities, older age, longer pain duration prior to intervention, are all predictive of poorer outcome [4]. Interestingly, psychological factors are assumed to be essential for the efficacy of SCS. In the light of this consideration, it is worth noting that there is a strong association between pain and depression, and the latter has often been suggested as a possible impacting factor on SCS efficacy [5,6]. Moreover, pain catastrophizing has been described to adversely affect pain-coping behavior and the overall prognosis in susceptible individuals when challenging with painful conditions [7,8]. Those evidences have been confirmed in a research examining whether carefully screening patients could predict pain-related and functional outcomes, highlighting that presurgical psychological factors including somatization, depression, anxiety, and poor coping were most predictive of poor response to SCS [9].

In this scenario, it appears crucial to better understand those features that may lead to poor SCS outcomes. Often, the disease-specific scale might not reflect the patient's functional outcome [10], not capturing the patients' self-perception of disability, as well as more general aspect of wellbeing and mental health. At the same time, there is to date no "gold standard" in psychological or health-quality related tests for the assessment of SCS outcome.

Based on the aforementioned theoretical hypothesis, the study aim was to investigate the influence of patients' self-perception of pain and disability, health related QoL and depression on the success of SCS trial stimulation in a representative case series, to identify those factors that may be more prone to play a role in shaping negative outcomes after SCS trial and, therefore, to drive clinical decision-making on SCS permanent placement.

Methods

Participants

To investigate factors associated with successful trial stimulation, the medical records of 20 patients were reviewed. Each of the patients underwent to the implantation of SCS electrodes at our institution (From March 2017 to November 2019) to treat different chronic pain conditions. Review of clinical variables, duration of pain and the score of standardized, self-administered questionnaires were investigated. The entire sample gave informed consent at the time of the hospitalization, and the appraisal was managed in accordance with the clinical practice. Participation in the study is completely voluntary and patients could withdraw from the study at any moment, for any reason, without providing any justification. The whole procedures were conducted according to the principles expressed in the Helsinki Declaration.

The mean age of patients (14 F) was 60.00±15.0 (mean ± standard deviation). The sample's demographic data are summarized in Table 1.

Features	Total Trial Group n=20	Success Group n=15	Failure Group n=5
Gender F:M (%)	14 (70%): 6 (30%)	12 (80%): 3 (20%)	2 (40%): 3 (60%)
Age, years (Mean ± SD)	60 ±15	59±15	62±15
Years since diagnosis (Mean ± SD)	6.30 ±5.71	6.93 ±6.40	4.40 ± 2.30
FBSS/radiculopathy/foraminal stenosis	13	11	2
Lower limbs neuropathy	3	3	
Chronic pelvic pain	2	1	1
Herpetic neuralgia	1	1	
Ulnar neuropathy	1	1	
Baseline VAS, cm (Mean±SD)	8.3 ± 0.9	8.6 ± 0.8	7.7 ± 1.2

Table 1. Demographic and clinical data
Demographic and clinical data of patients who underwent SCS trial, including pain data etiology and VAS evaluation.

The inclusion criteria involved eligibility to SCS trial, independently from stimulation frequencies and surgical management. Patients must be refractory to previous medical treatments, including analgesics, opioid analgesics, physical therapy, and pain blocks. The exclusion criteria were to not complete the

questionnaires or reporting a VAS score measured at baseline lower than 6/10.

Patients were randomly assigned to four different stimulation paradigms during the trial period: i) traditional tonic stimulation, Intellis SCS trial (Medtronic Inc, Minneapolis, MN, USA); ii) burst stimulation, BurstDR, (Abbott, Texas, TX USA); iii) High-Density (HD) stimulation, the St. Jude Medical Invisible Trial System (Abbott, Texas, TX USA); iv) High Frequency (HF) Stimulation, Senza system (Nevro Corp., California, CA, USA).

Questionnaire

As part of the assessment, an extended preoperative evaluation of health related QoL was collected using self-administered, standardized questionnaires to investigate pain, disability, global QoL and depression. We acquired pain measures through VAS [11,12] before the surgery and at the end of the trial period on those patients who reached SCS trial success.

The test battery includes: Pain Catastrophizing Scale (PCS), an instrument derived from the definitions of catastrophizing described in the literature [13] and items from the catastrophizing subscale of the Coping Strategies Questionnaire (CSQ) [14]. It allows the evaluation of the patients' mentalization of pain through three subscales, helplessness, magnification and rumination; the Oswestry Disability Index (ODI) was included in the battery [15], it is a tool able to assess the level of pain interference with various activities of daily living. Indeed, it has been recommended to measure pain-related disability when considering areas other than and including low back pain [16,17]; a generic health-related QoL assessment, EuroQol five-dimensional questionnaire (EQ-5D-3L), was administered, to better understand how pain impacts everyday life globally. The questionnaire evaluates the five dimensions of mobility, self-care, pain, anxiety, and activities of daily living [18]; the 36-Item Short Form Survey (SF-36) [19] was collected: an overall health-related QoL measure extensively used to discriminate, evaluate, and predict outcomes in several health and pathologic conditions [20]; the Hamilton Rating Scale for Depression (HAM-D) was included in the survey [21], due to the relevance of depressive symptoms on pain perception and on the SCS success rate.

Stimulation management

A percutaneous lead with eight contacts was placed under direct fluoroscopic guidance in the epidural space. The correct position was determined using intra-operative stimulation and was deemed successful if the induced paraesthesia had an adequate overlap with the painful area. After the surgery, the patients were randomly assigned to one of the four arms (in a 1:1:1:1: ratio), where they received a one-month combination of tonic, HD, HF and burst stimulation including one treatment modality per week and varying the order of the modality received within the four possible combinations. We used different types of adapters to connect the same provisory lead extension with the various trial stimulators.

The length of the trial period was 39±18 days. At the end of the trial, patients were classified into two groups, success and failure group. Each patient in the success group decided to proceed to the permanent implantation of the device that showed the highest delta VAS score, calculated as the difference between baseline VAS and VAS with any of the four devices tested.

Statistical analysis

We analysed the following factors: age, sex, duration of pain and the validated scales scores. The significant difference between VAS scores was evaluated through the Friedman test. Univariate analysis was performed to investigate the presence and the strength of any predictor factor on the trial outcome to identify those factors to be included in the logistic regression analysis. Then, the Generalised Linear Model (GLM) was developed. Receiver Operating Characteristic (ROC) curve analysis was performed to identify the best cut-off of the most significant predictor variable specified with the previous analysis. All statistical analysis has been completed with R Core Team 2020 software (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results

Successful trial stimulation was reached in 15 out of 20 patients (75%). No significant differences at VAS score were registered among the four devices, whereas a significant reduction ($p<0.05$) in the VAS score compared to baseline VAS was observed in the whole success group, Fig. 1.

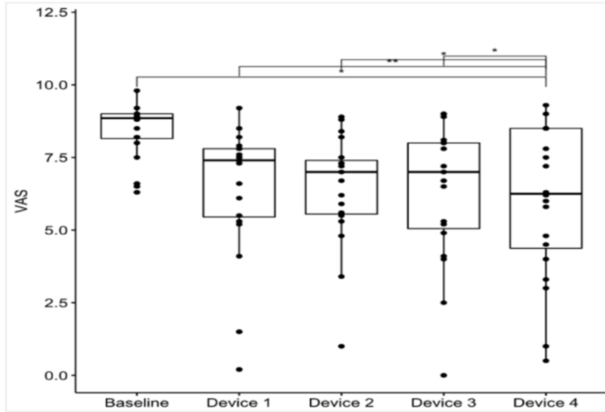

Figure 1. Preoperative VAS (Baseline) and VAS distribution for each Device tested

To investigate those factors associated with the success of trial stimulation, data were fit into a logistic regression model to verify whether any of the scores of the variables collected preoperatively correlated with the trial stimulation outcome. All the data are summarized in Table 2.

	Significance	Beta	P-value	SSE
VAS Baseline	Borderline	-	0.0811	85%
Degree of pain duration (years)	No	-	0.401	-
EQ-5D-3L	No	-	0.915	-
HAM-D	No	-	0.8087	-
ODI	Borderline	-0.1772	0.08	44.3%
PCS	No	-	0.914	-
PCS subscale - Pain Helplessness	No	-	0.970	-
PCS subscale - Pain Rumination	No	-	0.287	-
PCS subscale - Pain Magnification	Yes	-0.7292	0.0308	69.1%
SF-36 Physical Functioning	No	-	0.2620	-
SF-36 Physical role Limitations	No	-	0.1734	-
SF-36 Bodily pain	No	-	0.4491	-
SF-36 General Health Perceptions	Borderline	0.0567	0.0598	74%
SF-36 Energy/Vitality	No	-	0.573	-
SF-36 Social Functioning	No	-	0.589	-
SF-36 Emotional Role Limitation	No	-	0.2420	-
SF-36 Mental Health	No	-	0.804	-

Table 2. Logistic Regression
Logistic regression analysis on independent variables collected at baseline as predictor variables of trial outcome. SSE: Summary Squares Error.

Univariate analysis revealed that four of the analyzed independent factors were associated with the trial stimulation outcome. Therefore, we developed a GLM named "Comprehensive Model", which included ODI, Pain Magnification subscale, General Health subscale of SF-36 and preoperative VAS (model SSE 34.77%). However, the ANOVA test on the Comprehensive Model revealed that the deviance explained by General Health and preoperative VAS were not statistically significant (p=0.959 and p=0.299, respectively). Therefore, we removed these two variables from the Model and generated a simpler model, named PMO model, which included only two variables, i.e., the Pain Magnification and ODI (model SSE 39.9%). The equation of the PMO model is as follows with β_1 = -0.49853 as estimated parameter of the Pain Magnification predictor variable and β_2= -0.14349 as the estimated parameter of the ODI predictor variable and $\alpha =$6.27127:

$$\eta = \alpha + \beta_1 \times (Pain\ Magnification\ Score) + \beta_2 \times (ODI\ Score)$$

$$P(Trial\ failure) = \frac{e^{\eta}}{1 + e^{\eta}}$$

To further reduce the complexity of the model, we developed a univariate parsimonious predictive model based only on the ODI variable (model SSE 44.3%). The equation of the ODI model is as follows with β_1 = -0.1772 as estimated parameter of ODI predictor variable and α = 5.4513:

$$\eta = \alpha + \beta_1 \times (ODI)$$

$$P(Trial\ failure) = \frac{e^{\eta}}{1 + e^{\eta}} = \frac{e^{\alpha + \beta_1 \times (ODI)}}{1 + e^{\alpha + \beta_1 \times (ODI)}}$$

$$P(Trial\ failure) = \frac{e^{5.4513 - 0.1772 \times (ODI)}}{1 + e^{5.4513 - 0.1772 \times (ODI)}}$$

The predicted probability of trial failure based on the univariate ODI model is reported in Table 3. In the "minimal disability" category (ODI ≤20), the predicted probability of the trial failure increases drastically, while in the "severe disability" category (ODI ≥60) it is strongly avoided.

Therefore, to confirm the correlation estimated by the ODI model and identify the ODI best cut-off that shows the greatest correlation with the trial outcome, we developed a ROC curve analysis that

revealed that a ODI score of 38 is the best cut-off with the highest accuracy or optimal sensitivity (100%) and specificity (85.7%) in our case series. Hence, highest ODI scores (i.e., worse disability perception) are associated with higher SCS trial success.

ODI	0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75
P (failure)	.996	.99	.975	.942	.871	.735	.534	.321	.163	.074	.032	.013	.006	.002	.001	0

Table 3. ODI Score Predicted efficacy on SCS trial
Predicted probability of trial failure based on the univariate ODI model.

Discussion

SCS is a reliable technique in treating chronic pain, improving patients QoL and with a low rate of complications [6]. Nevertheless, the heterogeneity of patients and their symptomatology makes it often difficult to establish which patients are eligible for this treatment. Indeed, many conditions may expose to the risk of no SCS success in reducing pain [22]. Psychosocial factors such as dysfunctional coping, poor daily activity level and psychological distress are considered relevant for SCS selection [23]. To this purpose, when patients are determined to be eligible and potential candidates for SCS, a psychological assessment, including subjective pain intensity, mood and personality, daily activity interference, pain beliefs and coping, is required to help identify the ideal patient to achieve maximum benefit from an implanted device [24-26]. However, the interaction of clinical and psychosocial factors in determining the eligibility of patients with chronic pain to SCS implantation has led to a lack of clarity in selection criteria, and often poor consistency among surgical centers [23].

Patients typically undergo a trial stimulation to determine SCS efficacy and drive clinical judgment regarding appropriateness for permanent implantation. Overall, many factors are likely to play a role in shaping pain outcomes of SCS, nevertheless, no consensus exists on what factors are most consistently predictive of these outcomes. Reliable data are still missing and the available guidelines [27-29], due to the great heterogeneity of patients, are quite clear in their recommendations [30-34].

Beyond non-modifiable risk-factor of non-success, such as older age or long pain duration [32], it is crucial to better understand how psychological conditions may play a role in the SCS efficacy in pain reduction, to maximize patients' QoL [35].

To identify any predictive factors associated with the success of SCS trial stimulation, we evaluate, in a cohort of patients treated at our institution, the preoperative patients' self-perception of pain and disability, as well as more global aspect of wellbeing, including QoL and mental health scale.

In line with the literature data [32], the 75% of the sample reached a successful SCS trial, with a significant postoperative reduction in the pain level measured through VAS. Therefore, based on the preoperative data on the self-administered questionnaire, we design a predictive model on SCS trial outcome. It came out that the degree of perceived pain (VAS) and the General Health score of SF36 questionnaire, both measured at baseline, seem to play a marginally significant role in the SCS trial success in our representative case series. Interestingly, the analysis also identifies the pain magnification scale as a predictor of SCS success. This result is not surprising, due to the role of pain catastrophizing in negatively affecting pain-coping behavior [7,8]. However, considering that pain mentalization may have divergent impact on other dimension of QoL, and depressed mood [36], investigating the unique contributions of each PCS subscales could be crucial to predict the therapies success rate. Here emerged that the idea "that something serious may happen", associated to pain magnification, mainly could lead to a poor efficacy of SCS trial.

Furthermore, the patients' self-perception of disability, measured through ODI scale, results to be the strongest predictor of SCS trial success in our model. This result shows the role of patients' daily abilities level in affecting SCS outcome and identify the ODI score of 38 as the best cut-off in predicting SCS success, with optimal sensitivity and high specificity. That is, moderate or severe disability is related to grater SCS success. In other words, SCS may be more efficient on those patients with a worse

perception of their functional status related to the pain. This result could be seen in term of greater reward with respect to pain relief in those patients with a higher degree of perceived disability compared to those with a preserved functional status, in which the degree of pain reduction could be weaker.

Although the patients' mental health, such as depression or psychological distress, is thought to have a major influence on the SCS success, our results suggest the importance to take into account even the patients' own perception of their functional status in the routinely SCS eligibility evaluation. Not secondarily, the ODI scale is a self-administered scale, fast and easy to collect, that do not require clinical judgment and may be easily implemented in the clinical practice.

Taken together these evidences suggests the crucial importance of an extensive evaluation on patients' candidates for SCS with a multidisciplinary model of care and aims at proposing the adoption of self-administered scales in the routine clinical assessment as a good tool in investigating the patients' perception of health quality, overcoming the more disease-specific aspects of clinical evaluations.

Although further research is needed to clarify the role of self-reported scales in a larger cohort of patients and though the impact of several subjective determinants on SCS outcome is still unclear and these factors are still rarely studied, our preliminary data highlight that pain and disability perception may become routinely measures when evaluating consensus to SCS implantation.

Beyond the undoubtful limitation of our study is the reduced sample size, the main advantage is the heterogeneity of the sample, being representative of patients' profiles in a clinical setting, so it is considered to be the environment best suited for developing a predictive model, taking into account the great heterogeneity in SCS treatments.

Our preliminary data suggest that pain and disability perception may become routinely measures when evaluating consensus to SCS implantation. The self-administered scale, fast and easy to collect, may help predicting SCS trial success and may drive clinicians' consensus to permanent implantation.

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Efficacy of neuronavigation guided biopsy in deep seated brain lesions

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ABSTRACT

Localisation of brain lesions and prevention of damage to vital structures are important goals in the operation of brain pathologies, which can be aimed after the development of many techniques (e.g. angiography, MRI, sonography, frame base stereotaxy). In spite of current developments in radiological imaging techniques, accurate histological diagnosis is required to determine the appropriate treatment methods for intracranial lesions.

The study was conducted in the Department of Neurosurgery, Dr Ram Manohar Lohia Institute of Medical Sciences, over a period of 18 months. Descriptive statistics (frequencies and percentages) were used to interpret the collected data. After editing, data was entered into SPSS free versions for statistical studies. The results from various sites of the biopsy were compared based on sensitivity, specificity, positive and negative predictive values.

In this study, 4 patients were found to be below 20 years, 7 patients in the 20 – 40 years age group, 10 patients in the age group of 40 to 60 years and 4 patients were above sixty years. 22 (88%) patients were found to have positive yield when the biopsy was taken from the core area while 3 (12%) patients were not having any positive results from the biopsy. Sensitivity, specificity, positive predictive value, and negative predictive value of various sites of the biopsy were calculated Sensitivity of the periphery came out to be 68.2 % while specificity was 67.7%. The positive predictive value of the periphery was found to be 93.8 % while the negative predictive value was

22.2%. The sensitivity of the contrast-enhanced area came out to be 72.7 %, with specificity being 67.7%. The positive predictive value of periphery in such cases was found to be 94.1 % and the negative predictive value was 25%. The most common system-related complication was the inability to show choline peak properly, which was present in 7 patients.

Hence, it can be concluded safely that the use of neuronavigation is beginning to have a vital role in a variety of intracranial procedures with precise localisation of both intracranial as well as spinal lesions and prevention of damage to vital structures intraoperatively thereby significantly reducing procedure-related morbidity and mortality.

INTRODUCTION

Recently, there has been an increasing trend in most branches of surgery towards a reduction in the morbidity of a procedure by limiting surgical entry. This usually involves the application of technology such as laparoscopic cholecystectomy in general surgery[1]. A new era of neurosurgery has recently been unveiled with advent of image guided surgery..

Nowadays, a lot of of patients suffering from neurological focal deficiency or symptoms of increasing intracranial pressure or even for patients with slighter symptoms are being correctly diagnosed due to advent of technique such as computed tomography (CT) scan and magnetic resonance imaging (MRI) [,2,3,]. Furthermore, advances in the therapeutic methods and increasing number of survival in patients with systematic diseases, resulted in the development of metastasis into the central nervous system or high incidence of CNS infections, which are partly due to high confrontation with immune system deficiency (due to Acquired Immunodeficiency Syndrome (AIDS) or following immunosuppressive treatment in the recipients of transplantation or in patients under chemotherapy for systematic cancer); diversity and the number of CNS neuro-pathologies has increased requiring the needs for the more accurate detailed differential diagnosis of histology and cytology of cerebral space-occupying lesions (SOLs)[4,5]. In most of the patients, it is possible to diagnose the brain lesions accurately through clinical and laboratory findings. Examples are multiple sclerosis, secondary infectious and parasite diseases, metastatic tumors and brain involvement of systemic disease. But ,numerous brain lesions that are diagnosed in CT scan or MRI are the only provable documents for the disease and their treatment designing depends on the histological diagnosis[6,7]

MATERIALS AND METHOD

The study was conducted in Department of Neurosurgery, Dr. Ram Manohar Lohia Institute of Medical Sciences, over a period of 18 months.Total of 25 patients admitted in Neurosurgical wards underwent thorough examination and investigation. The inclusion and exclusion criteria used for study are as follows:

Inclusion Criteria

- Deep seated Lesions situated in basal ganglia, internal capsule, corpus callosum, periventricular areas, brain stem
- Lesions located in eloquent areas.
- Lesions refractory to an empirical therapy given previously.
- Diagnosis could not be ascertained by radiology (e.g., multiple lesions)

Exclusion Criteria

- Large lesions in non-eloquent and easily accessible areas amenable to surgical excision.
- Lesions producing mass effect and neurological deterioration
- Lesions near the surface of brain

Contrast enhanced CT scans/ MRI of the patients was taken in neuronavigation protocol one day prior to surgery. Histological examination was performed in the Department of Pathology. Radiological support was provided by Department of Radio diagnosis at institute. CT and MRI were done according to feasibility based on location of tumor, status of stent or metallic stents. The data was stored in CD. DVD in DICOM format and transferred to workstation for planning. Descriptive statistics (frequencies and percentages) were used to interpret the collected data.. After editing, data were entered into SPSS Free versions for statistical studies and analysis of the data was done by comparing all the details in the form of tables, texts and charts. Finally,the results from various sites of biopsy were compared on basis of sensitivity, specificity ,positive and negative predictive value.

RESULTS AND OBSERVATIONS

Table 1. Sex ratio of patients

Sex	Number of patients
Male	15

Female	10
Total	25

Table 1 shows the distribution of patients according to gender between. 10 patients were found females and 15 patients were found male.

Table 2. Age distribution of patients

SN	Age distribution	Number
1	0-20	4
2	20-40	7
3	40-60	10
4	60 and above	4

Table 2 showing that 4 patients were below 20 years. 7 patients were found in 20 – 40 years age group, 10 patients were found in the age group of 40 to 60 years and 4 patients were above sixty years.

Table 3. Histological diagnosis

SN	Histology	Number
1	GBM	6
2	Grade 3 Astrocytoma	4
3	Low Grade glioma	3
4	TBM	4
5	Abscess	2
6	NHL	2
7	Demyelinating disease	1
8	Negative	3

Table 4. Histological diagnosis from various sites of biopsy

Table 4A. 22 (88%) patients having positive yield when biopsy was taken from core area 3 (12%) patients were not having any positive result of biopsy. Out of this 22 patients 13 (52%) were diagnosed to be glioma, 2 (8%) were having abscess, 2 (8%) were diagnosed as NHL, 4 (16%) were heaving TB and 1 (4%) patient was diagnosed as Demyelinating disease.

CORE	Freq.	Percent	Cum
No lesion	3	12.00	12.00
Glioma	13	52.00	64.00
Abscess	2	8.00	72.00
NHL	2	8.00	80.00
TB	4	16.00	96.00
Demyelinating disease	1	4.00	100.00
Total	25	100.00	

Table 4B. 16 (64%) patients having positive yield when biopsy was taken from periphery area 9 (36%) patients were not having any positive result of biopsy. Out of these 16 patients 9 (36%) were diagnosed to be glioma, 3 (12%) were having abscess, 2 (8%) were diagnosed as NHL and 2 (8%) were having TB.

PERIPHERY	Freq.	Percent	Cum
No lesion	9	36.00	36.00
Glioma	9	36.00	72.00
Abscess	3	12.00	84.00
NHL	2	8.00	92.00
TB	2	8.00	100.00
Total	25	100.00	

Table 4C. 17 (68%) patients having positive yield when biopsy was taken from periphery area 8 (32%) patients were not having any positive result of biopsy. Out of these 17 patients 11 (44%) were diagnosed to be glioma, 2 (8%) were having abscess, 2 (8%) were diagnosed as NHL and 2 (8%) were having TB.

CONTRAST ENHANCED PORTION	Freq.	Percent	Cum
No lesion	8	32.00	32.00
Glioma	11	44.00	76.00
Abscess	2	8.00	84.00
NHL	2	8.00	92.00
TB	2	8.00	100.00
Total	25	100.00	

Table 4D. Due to registration error and inability to get MRI in few patients, only 12 (48%) patients underwent biopsy from Choline Peak voxals. While in 13 patients study was not possible. Out of these 12 patients in 3 (12%) biopsy results came out as Glioma, while in 9 (36%) patients having no positive yield.

MRS MARKED SITE (VOXALS)	Freq.	Percent	Cum
No lesion	9	36.00	36.00
Glioma	3	12.00	48.00
NA	13	52.00	100.00
Total	25	100.00	

Table 5. Sensitivity, specificity, Positive predictive value, Negative predictive value of various sites of biopsy

Table 5A. Sensitivity of periphery came out to be 68.2 % while specificity was 67.7% and Positive predictive value was 93.8 % and Negative predictive value of periphery was 22.2%.

	Positive	Negative
Positive	15	1
Negative	7	2

Table 5B. Sensitivity of contrast enhanced area came out to be 72.7 % while specificity was 67.7% and Positive predictive value was 94.1 % and Negative predictive value of periphery was 25%.

	Positive	Negative
Positive	16	1
Negative	6	2

Table 6. Patient related complication

SN	Complication	Number
1	Unintentional ventricular puncture	1
2	Intraoperative haemorrhage	0
3	Post operative neurological deficit	0
4	Post operative seizures	0
5	Surgical site infection	0

During this study only one patient had unintentional ventricular rapture while no other complication such as post operative neurological deficit, seizures, Intraoperative haemorrhage or surgical site infection was noted. All biopsy were taken in single attempt.

Table 7. System related complication

SN	Complication	Number
1	Registration error	3
2	System shut down	0
3	Inability to show contrast film properly	0
4	Inability to show choline peak are properly	7

During this study the most common system related complication was Inability to show choline peak properly, which was present in 7 patients while registration error was the second most common system related complication present in 3 patients.

Discussion

Image guided neurosurgery (neuro-navigation) or frameless stereotactic surgery has made a tremendous impact in the recent years. It gives a patient specific three-dimensional (3-D) Anatomy for preoperative planning and intra-operative navigation thus helping the surgeon to perform complicated procedures with improved accuracy and safety[8] Stereotactic biopsy for intracranial lesions is a realistic relatively safe procedure and is also a very efficient method especially in patient who need histological confirmation for the treatment. The overall diagnostic accuracy varies from 80-99%[9] In this study, out of 25 cases 22 biopsy (88%) came out to be positive and 3 cases (12%) came out to be negative which was comparable to previous studies showing positive yield of 89% and negative yield of 11%[10] in deep seated lesions.

In one more study a diagnostic yield of 86.16%[11]was found which was comparable to present study and in two other studies on frameless navigation guided biopsy, positive yield of 99%[12,13] was found. There was a study based on frame-based navigation guided biopsy which was showing positive yield of 84.21%, which was comparable to present study with positive yield of 88%[14]. In previous studies, discrepansy was noted in results of biopsy taken from central hypodense and well contrast enhanced area .So we took biopsy from various sites to look for efficacy from different areas, biopsy from core revealed 22(88%) positive results while 3(12%) were negative.In positive 22 cases, 6 cases of GBM, 4 cases of grade 3 anaplastic or grade 3 giomas, 3 cases of Low Grade Gliomas, 4 cases of TBM,2 cases of NHL, 2 cases of abscess and 1 case of demyeliting disease while 3 having negative biopsy.Biopsy taken from periphery sites having 16 (64%) positive results while (36%) were negative in positive results 9 cases were glioma, 3 were abscess, 2 were NHL and 2 were T.B. In contrast enhanced area 17 cases (68%) were positive while 8(32%) were negative, in which 11(44%) were glioma, 2(8%) were NHL ,2 were abscess and 2 (8%) were TB.In MR marked (voxols) there were only 12 cases out of which 3 (25%) were positive and 9(75%) were negative and these are all gliomas.

In our study 22 (88%) patients were having positive yield which was taken from core region while on comparing periphery region biopsy from core region biopsy, periphery was having 16(68%) yield with sensitivity of 68.2% specificity of 67.7% positive and negative predictive value of 93.8 and 22.2% in comparision to core while contrast enhanced area having a positive yield of 17(72.5%) with sensitivity of 72.7% specificity of 67.7% positive and negative predictive value of 94.1% and 25% respectively. In comparision to core, only 12 cases underwent biopsy

of MRS with choline peak voxals as few patients were not co-operative so MRI was not possible in these cases and also in few patients there was problem in marking Choline Peak area accurately in neuro-navigation system.

The complications in this series range from registration error, accurately localizing Choline peak area on navigation machine, Unintentional ventricular puncture, intra-operative haemorrhage, post operative neurological deficit, post operative seizures, surgical site infection etc. Registration error of 2.2 to 6 mm have been reported by Roessler et al (1998)[15], in our system it provides more accurate localization but a registration error of 1 mm was considered to be acceptable in view of brain shift. In initial cases we also had difficulty in registering Choline peak voxals. In our series there was 1(4%) patient associated with unintentional ventricular puncture, 3 patients had problem of registration error and 7 patients had problem of inability to show Choline peak area properly.

In various other previous studies complication such as symptomatic haemorrhage, morbidity due to neurological deficit, and mortality was observed with rates of 5.1%, 3.7%, 0.6% respectively but in our study, we had no cases of symptomatic haemorrhage, neurological deficit associated morbidity and mortality.

STUDY LIMITATIONS

Relatively low number of patients and short follow-up periods are the limitations of our study.

CONCLUSION

Neuronavigation guided biopsy has proved beyond benchmark of technology for various deep seated lesions along with added advantages of safety, cost effectiveness, accuracy, ease of use ,decreaed duration surgery, reduced post surgery complications such as neurological deficit, intracerebral haemorrhage and reduced hospital stay.

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Focal cerebritis with vasculitis mimicking a high-grade glioma. A case report

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ABSTRACT
Cerebritis is an inflammatory reaction in the brain which can be localized or diffuse and can be secondary to various etiologies like granulomatous demyelinating infections, vasculitis or neoplastic. Identifying the aetiology is very essential for the proper treatment. We report a case of 24 years male patient, who came with a history of headaches for 3 months. CT scan revealed intra-axial hypodense lesion suggesting high-grade glioma, which on histopathological examination revealed reactive gliosis with diffuse lymphocytic infiltrate and perivascular lymphocyte collection.

Keywords
cerebritis,
vasculitis,
tumour like lesion

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INTRODUCTION

Differentiation between tumor like lesions and tumors of central nervous system is very essential for selecting the mode of treatment and prognosis. Both have similar features in ultrasound (US), computerized tomography (CT), and magnetic resonance imaging (MRI) studies. Misinterpretation leads to delay in the treatment of malignant tumors or over-treatment of tumor – like benign lesions. On imageology, tumor presents as focal density or signal alteration displacing or infiltrating adjacent structures surrounded by vasogenic edema and with or without matching contrast enhancement. But many tumor like lesions such as abscess, vascular malformations, resolving hematomas, tumefactive multiple sclerotic (MS) plaques also present with similar features. Development of functional MRI sequences such as Magnetic resonance spectroscopy, Diffusion tensor imaging (DTI), perfusion weighted imaging, PH weighted MRI and susceptibility weighted imaging (SWI) helps in differentiating tumor like lesions and tumors.[1] Histopathological examination of biopsied tissue can give confirmed diagnosis.

Case report

A 24-year-old male patient came to neurology OP with chief complaints of headache and paresthesia on right side since 3 months. In 2014, he had history of diplopia and headache. In 2018, patient had transient ischemic attack. Patient had no history of vomiting, seizures, fever, neck stiffness, photophobia, double vision or jaw deviation. He had no history of hypertension, diabetes, tuberculosis, chronic obstructive pulmonary disease, or chronic kidney disease.

On examination patient was conscious coherent, with no pallor, icterus, cyanosis, clubbing or pedal edema. Patient was afebrile with pulse rate 85/minute, blood pressure of 110/80mm Hg and respiratory rate of 20/minute.

CNS examination revealed Glasgow coma score of 14/15. Higher mental functions and cranial nerves were normal. Motor examination revealed normal bulk, tone and power. Sensory system examination revealed intact cerebellar signs and no meningeal signs. No abnormality was detected in skull and spine.

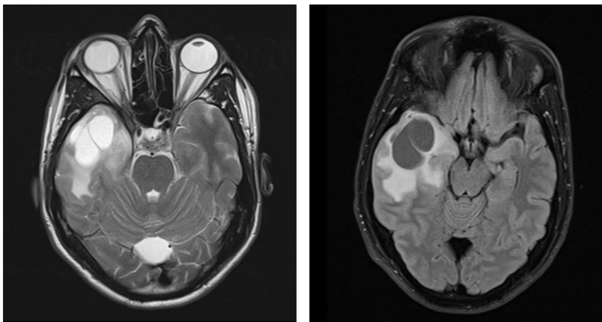

Figure 1. Pre and post IV contrast MRI Brain showing well defined peripherally enhancing lesion with perilesional edema in the right temporal region which is hyperintense on T2W image, supressed on FLAIR, hypointense on T1W images with evidence of enhancing pachymeninges adjacent to the lesion.

CT scan revealed intra axial hypodense lesion measuring 3.5X2.9cm in the right temporal lobe with adjacent perilesional edema in the surrounding white matter of the right temporal and parietal lobes. MRI scan with contrast study revealed ill-defined mixed signal intensity lesion with solid and cystic components. Solid component was T2/FLAIR (Fluid Attenuated Inversion Recovery) hypointense (Figure 1), and isointense on T1 in the right anterior and medial temporal lobe which was showing no evidence of restricted diffusion on DW1 with diffuse contrast enhancement. Cystic component was T2/FLAIR hyperintense and hypointense on T1 with no evidence of restricted diffusion on DWI (Diffusion Weighted magnetic resonance Imaging) with evidence of peripheral contrast enhancement. Medially the lesion was invading the cavernous sinus. Irregular T2 hyperintensity was not suppressed on FLAIR showing no evidence of contrast enhancement in perilesional region involving right temporal lobe, insular cortex, right external capsule and posterior limb of internal capsule suggesting edema. Lesion was causing mass affect in the form of midline shift of 5mm towards left side. Imageology suggested the clinical diagnosis of high-grade glioma.

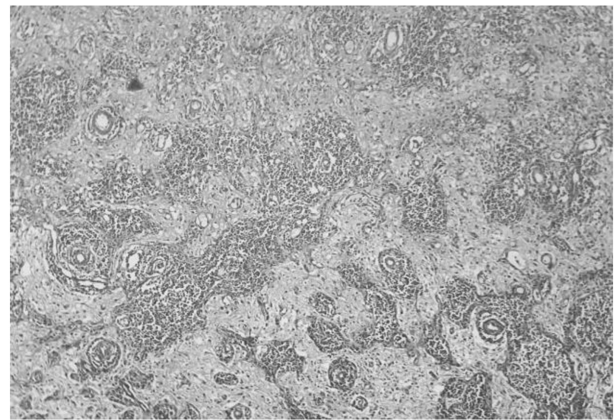

Figure 2. Glial tissue showing diffuse lymphoplasmacytic infiltrate and perivascular lymphocytic cuffing (H&E,X40).

All the hematological investigations were with in normal limits except for Erythrocyte sedimentation rate which was 82mm/1st hour.

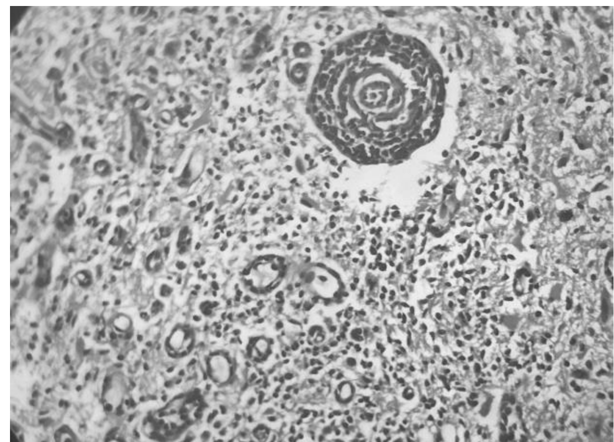

Figure 3. Glial tissue with vessels showing lymphocytic infiltration in the vessel wall (H&E,X100).

Patient underwent right fronto temporo parietal minicraniotomy and right temporal pole excision. Excised tissue was sent for histopathological examination. We received multiple grey, brown soft tissue bits altogether measuring 2X1.5X1cm. Sections studied shows glial tissue with diffuse lymphoplasmacytic infiltrate. Adjacent foci showed reactive gliosis with gemistocytes. Perivascular lymphocytic cuffing was noted (Figure 2). Some of the vessels showed lymphocytic infiltrate into the vessel wall (Figure 3). Few vessels showed fibrinoid necrosis of the wall. Dense lymphocyte predominant lymphoplasmacytic infiltrate was seen in the meninges.

Immunohistochemistry showed LCA, CD3 and CD20 positivity in the dense inflammatory infiltrate indicating the polyclonal nature of lymphocytes. GFAP and S-100 showed positivity in glial tissue. CD 68 was positive in scattered histiocytes. CD138 was positive in plasma cells. Ki67 was seen positive in some inflammatory cells. Special stains for acid fast tubercle bacilli and fungal elements were negative. Due to the above histopathological and immunohistochemical features diagnosis of cerebritis, probably secondary to vasculitis was considered.

Discussion

Cerebritis is an inflammatory reaction in the brain which can be due to systemic or local etiologies and can mimic neoplasm. [2] Imaging features of various tumor like lesions like resolving hematoma, tumefactive MS plaque, vascular malformation and abscess are similar and are difficult to differentiate. [1] Solitary lesion in various demyelinating diseases including acute disseminated encephalomyelitis, progressive multifocal leukoencephalopathy and multiple sclerosis may mimic tumor. Histopathological examination is gold standard for diagnosis.

Idiopathic focal cerebritis could be secondary to infectious disease, vasculitis, granulomatous or demyelinating diseases. Tumor like mass lesions are reported in patients having systemic vasculitis such as SLE (systemic Lupus Erythematosus), and primary angiitis of CNS. Huang et al reported a large temporal mass lesion mimicking tumor in 14-year-old boy with systemic lupus erythematosus.[3] Molloy et al described a solitary tumor-like mass lesion in a subset of primary angiitis of CNS presenting with edema and contrast enhancement. [4] Mohamad Ezzeldin at al described idiopathic focal cerebritis, presenting as tumor like lesion in right posterior parietal lobe in 35-year-old male. In this case ESR, C reactive protein (CRP) and Anti-nuclear antibodies (ANA) were normal and had no involvement of arteries. In our case, ESR was raised, and vessels showed lymphocytic infiltrate indicating possible cause may be vasculitis leading to cerebritis.

Differential diagnosis for this condition on imageology is focal cortical dysplasia, ganglioglioma, oligodendroglioma, Dysembryoplastic neuroepithelial tumor (DNET). [5] Focal cortical dysplasia type 1 occurs in adults with changes in the temporal lobe. Type 2 occurs in children and presents in frontal lobes with severe clinical symptoms. MRI may show focal cortical thinning or thickening with increased signal on T2 and gray and subcortical matter tapering towards ventricles on FLAIR weighted images. [6] Gangliogliomas contain cystic, solid and calcified components which gives inhomogeneous appearance to tumor. [7] Oligodendrogliomas commonly arise in frontal lobe, has well defined margins and with frequent calcifications. On MRI, T1 weighted images of tumor are hypointense and T2 weighted images of tumor are hyperintense. Surrounding vasogenic edema is uncommon [5]. DNET shows hypointensity on T1 weighted images and hyperintensity on T2 weighted images, without or with minimal mass effect and with surrounding vasogenic edema. 30% of cases show contrast enhancement. [7]

However histopathological examination is gold standard for diagnosis. Microscopically focal cortical dysplasia are two types. Type I shows cortical architectural abnormality (Type Ia) with hypertrophic neurons and immature neurons (Type Ib). Type II shows dysmorphic neurons with dislayering abnormalities (Type IIa) and with balloon cells (Type IIb). [6] Gangliogliomas are well differentiated benign neuroepithelial tumors. Histologically these tumors show combination of glial and neuronal elements exhibiting marked heterogeneity. [8] Oligodendroglioma is a low grade gliocytoma (WHO grade II) composed of monotonous cells having uniform round nuclei with perinuclear clearing (fried egg appearance) and thin branching vasculature (chicken wire vasculature). [9] Dysembryoplastic neuroepithelial tumor is characterized by presence of

abundant mucinous background with small round oligodendroglial like cells without dysplasia.[10]

Cerebritis secondary to vasculitis can be confused with lymphoma as in both the conditions diffuse lymphocytic infiltrate can be present. [11] Immunohistochemistry helps in differentiating polyclonality of lymphocytes which rules out the possibility of lymphoma.

Conclusion

Focal cerebritis can present as neoplasm on imageology. Focal cerebritis can be idiopathic or can be secondary to infectious disease, vasculitis, granulomatous or demyelinating diseases. Correct diagnosis and appropriate treatment are essential for prognosis. Proper awareness in neurologist and radiologist is essential regarding the tumor like lesions of brain. Histopathology is the gold standard for diagnosis.

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Haemorrhagic progression of contusions after traumatic brain injury in orally anticoagulated patient. The Rule of (6I's)

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Keywords
intracerebral hemorrhage,
contusion,
traumatic brain injury

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ABSTRACT

Traumatic brain injury carries a high risk of neurological disability and fatality[1-8]. The extent of the injury to the neuronal tissue following a head impact defines the primary injury. The acceleration energy delivered at the time of impact provokes this injury. There are numerous secondary responses to the injury that mostly intensify the primary injury. When a head impact causes a contusion, the hemorrhagic injury frequently progresses over the first few hours after impact, either growing or developing new, non-contiguous hemorrhagic lesions, a condition known as the hemorrhagic progression of a contusion[1,2,4,7,9-14].

ILLUSTRATED CASE

An 88-year-old woman was admitted with a severe headache, multiple emetic episodes, and a brief loss of consciousness after falling while doing housework. Her past medical history included anticoagulation with warfarin for atrial fibrillation (international normalized ratio (INR): 3.75). She had normal vital signs and a grossly intact neurological examination on admission. A cranial computed tomography (CT) scan was performed 45 minutes after arrival to the emergency department, which revealed small bifrontal contusions (Fig 1). It was decided to transfer her to the intermediate care unit with non-invasive hemodynamic monitoring, analgesia, continuous neurological evaluation, and neurosurgical evaluation. At 18 hours, she started

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having emetic episodes and drowsiness. An emergent follow-up cranial CT scan showed extensive bifrontal and bitemporal contusions with intraventricular bleeding (Fig 2). Due to rapid deterioration of the respiratory pattern, the airway was protected with a sequence of rapid intubation, sedation, protective mechanical ventilation, osmotherapy, fresh frozen plasma, and prothrombin complex concentrate. The patient progressed to coma and expired 36 hours after her presentation.

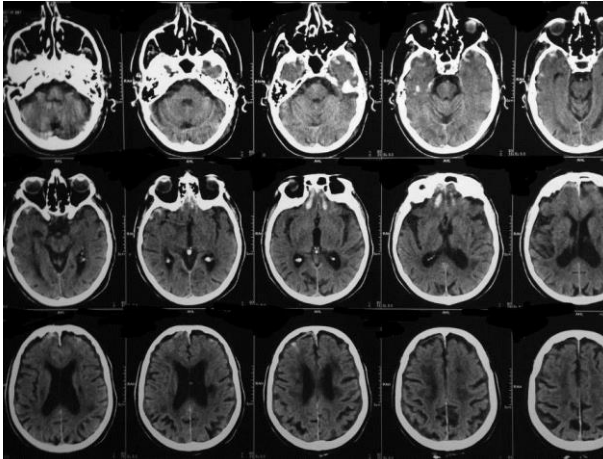

Figure 1. CT scan head on admission

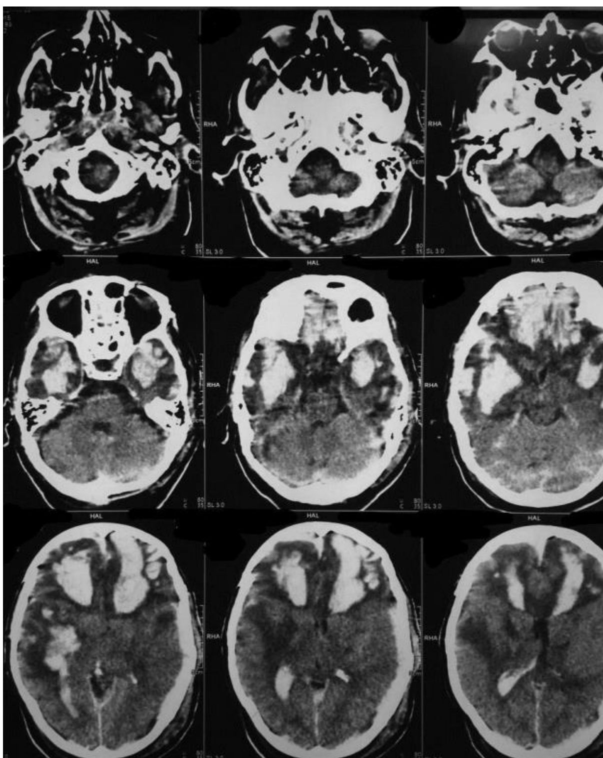

Figure 2. Follow-up CT scan showing marked changes with extensive intracerebral bleeding

Anticoagulant-associated ICH

Anticoagulated patients represent a major neurocritical care burden, as anticoagulation is one of the leading risk factors for intracranial hemorrhage (ICH) after a head impact.[15] The risk of developing ICH after a head injury is 42.2 times higher in patients on oral anticoagulants than in control patients.[16] Aggravating factors associated with anticoagulant-induced bleeding complications include older age, alcohol abuse, renal and hepatic insufficiency, uncontrolled anticoagulant, the targeted intensity of anticoagulant, prior stroke, concomitant anti-platelet therapy, and hypertension.[6,8,9-13] As a result, prompt screening strategies, and interventions that promote better neurological outcomes in the anticoagulated population after head impact are critical.

Warfarin versus direct oral anticoagulants (DOACs)

Recent randomized trials on orally anticoagulated participants for atrial fibrillation have demonstrated a 50% reduction in the incidence of ICH with DOACs compared to warfarin.[17-20] Nevertheless, given the high prescription rates of DOACs and unavailability of the specific reversal agents, ICH development with DOACs has become an important issue and can result in permanent disability and fatality, as with warfarin.[18-21] In a randomized clinical trial by Hankey et al[22] (2014), the fatality rate from anticoagulant-associated ICH was 49% (85/172), and among 85 participants who experienced fatality due to anticoagulant-associated ICH, 50% (54/85) were assigned with warfarin and 48% were assigned with rivaroxaban (31/85). Given the fact that there is an insignificant difference in fatality rate between DOAC and warfarin, the natural history of DOAC-associated ICH should be broadly investigated, and prospective studies on hematoma expansion in this specific group are warranted.

European Federation of Neurological Societies (EFNS) guidelines

In 2002, EFNS set guidelines targeting all anticoagulated participants with normal initial CT scans after sustaining a minor head impact.[4-6] The EFNS guidelines entailed one-day admission for close neurological observation, and a second head CT scan before discharge to rule out delayed ICH.[4-6] However, the growing body of research showed heterogenicity

to support EFNS recommendations for anticoagulated patients after minor head impacts.

A recently published meta-analysis by Puzio et al[7] (2021) estimated 2.43% (95% CI, 1.31-3.88%) and 2.31% (95% CI, 1.26-3.66%) for delayed ICH on DOACs and warfarin, respectively. Only a minority of 0.6% (2/1263) and 0.48%(8/1788) of those on DOACs and warfarin, respectively, reported fatalities, while the majority 86% (59/69) had no clinical complications. The authors concluded that screening for delayed ICH for those on oral anticoagulants is not warranted based on their estimated overall crude risk of fatality 0.36% (11/3051).[7]

In contrast, in a published study by Menditto et al[1] (2012) on the delayed ICH in orally anticoagulated participants, it was found that 6% (5/87) of participants with normal initial scans, developed delayed ICH, which was evident in a CT scan performed 24 hours after the trauma. The estimated relative risk of delayed ICH with an initial INR greater than 3.0 was 14 (95% CI, 4-49).[1] In a meta-analysis by Betchelor et al[14] (2012) the estimated higher odd ratio of fatalities in patients on warfarin with the head impact was 2.0008 (95% CI, 1.634-2.467). Accordingly, the authors supported the advisability of a second head CT scan as advocated by EFNS guidelines.

CONFOUNDING FACTORS OF HAEMORRHAGIC PROGRESSION

The challenges in defining the confounding factors of hemorrhagic progression in specific patients on oral anticoagulants include a paucity of relevant clinical data. However, various predictors have been reported in the literature concerning post-traumatic hematomas associated with trauma in general participants.

I. Increased age

In a published study by Melamed et al[23] (1980) and Purkayastha et al[24] (2014), increased age has been associated with contusion progression through several mechanisms. Increased age induces structural weakness in the cerebral microvasculature, endothelium loss, and reduced resting cerebral blood flow, which can consequently contribute to contusion progression.[23,24]

II. Intractable headache and emesis

The most common symptoms of a cerebral contusion are headache, emesis, concentration problems, and memory loss.[25] Patients struggling with continued symptoms despite proper medical management should warrant a second screening with a CT scan as the progression of contusion is highly expected.

III. Increased systemic blood pressure (BP) at admission

In a retrospective study by Wan et al[8] (2017), hypertensive participants had 4.5 times the incidence of ICH progression compared to normotensive participants, which can be ascribed to increased baseline blood-brain barrier permeability.

IV. Inclined Glasgow coma score (GCS) at admission

The initial GCS has been a predictor for contusion progression. The contusion progression was reported with GCS <14 by White et al[9] (2009), GCS ≤5 by Qureshi et al[10] (2015), and GCS <8 by Carnevale et al[11] (2018).

V. INR level >1.2, Platelet count <100 × 10^9 /L

Regarding laboratory parameters, White et al[9] (2009) and Wan et al[8] (2017) demonstrated contusion progression three times in participants whose initial INR was>1.2 compared to participants whose initial INR was ≤1.2. It has been shown by Sharma et al[12] (2016) that contusion progression increases seven times for each unit increase in INR. Additionally, Juratli et al[13] (2014) showed a strong association between contusion progression and platelet count <100 × 10^9/L, about six times the increased risk.

VI. Intoxication by alcohol

Several studies have shown a higher frequency of contusion progression with alcohol intoxication.[11,13,26.27] Alcohol intoxication contributes to coagulopathy through several mechanisms, including impairment of platelet function and reduction of vascular tone; both counteract each other on contusion progression.[27] Although the association has been reported, the causality remains unknown.

6I's Rule

1.	Increased age
2.	Intractable Headache and emesis
3.	Increased systemic BP at admission
4.	Inclined GCS at admission
5.	INR Level >1.2, PLT < 100 × 109 /L
6.	Intoxication by alcohol

As a goal to prevent deaths in patients with head impact and oral anticoagulants, we proposed the 6 Is rule (Table 1). The presence of any of the (i) in context with the history of current oral anticoagulant use indicates admission and performance of serial CT scans after 24 hours or according to neurosurgeon criteria. Applying and spreading the rule of the (6Is) will facilitate the identification of high-risk individuals and thus early recognition of possible delayed ICH or contusion progression. This can be a potentially useful, and reliable objective screening tool for emergency physicians, nurses, and nursing assistants.

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Cerebello Pontine Angle Hemangiopericytoma - an aggressive tumour needs aggressive management. A case report

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ABSTRACT

Background: CP angle Hemangiopericytoma are rare tumors. Pre-operative suspicion and gross total excision are key for better management due to their aggressive nature.

Case presentation: 18-year-old male presented with signs of progressive brainstem compression. Contrast MRI showed a polycystic enhancing SOL in the right CP angle region compressing the brain stem and cerebellar lobe. Operated with histopathology and IHC indicating it to be a Hemangiopericytoma.

Conclusions: Hemangiopericytoma being an aggressive tumour with a high rate of recurrence compared to other common tumours at CP angle, complete resection with definitive pathological diagnosis and radiotherapy are needed for a better outcome.

Keywords
hemangiopericytoma, cerebello pontine angle, cystic enhancing tumor, CP angle meningioma, IHC

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BACKGROUND

Hemangiopericytomas (HPCs) constitutes <1% of primary brain tumors. Mostly supra tentorial and dural based. Rare in Cerebello pontine angle (CPA), mimics meningioma radiologically, but because most are grade 2 or grade 3, this aggressive nature makes their pathological differentiation important. [2,3,4,5,6,7,8,9]

We describe here an unusual case of CPA hemangiopericytoma presenting with brainstem and cerebellar signs

CASE PRESENTATION

An 18-year-old male presented with chief complaints of disequilibrium, Progressive weakness all 4 limbs (left>right), slurring of speech, and dysphagia for liquid for 2 months. On admission, his neurological examination revealed a left facial paresis(Hunt & Hess grade 3) with weak gag reflex and uvula deviated to right and asymmetrical palatal arches(left 9th and 10th cranial nerve paresis), and left side weakness

more than right with increased tone with left cerebellar signs present, suggesting the presence of the Millard-Gubler syndrome.

Head CT scan and an MRI of the brain demonstrated a solid cystic enhancing 2.8×3.5 cm sized right CPA lesion compressing brain stem with no internal acoustic meatus extension (Fig. 1).

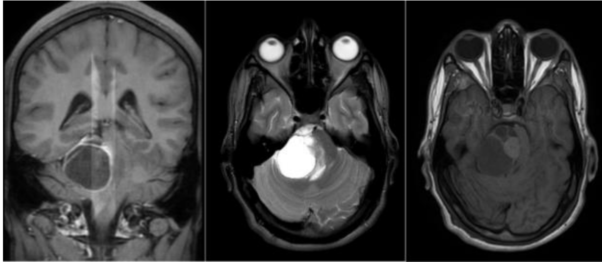

Figure 1. (A)Post-contrast magnetic resonance imaging of the brain in coronal views showing a cystic right cerebellopontine angle tumor with dural enhancement (dural tail sign); (B) T2 weighted image showing peritumoral CSF cleft; (C) T1 weighted image showing hyperintese nodule with septations in tumor.

As tumor was solid cystic with enhancement a diagnosis of cystic schwannoma was made with differential being pilocytic astrocytoma and hemangioblastoma, cystic meningioma.

A suboccipital retrosigmoid approach was attempted. During surgery, the tumor was solid and cystic, soft to firm, greyish pink, was suckable highly vascular, capsule was attached to cranial nerves passing in left cp angle with dural attachment superiorly . Tumor was not extending to or coming out from internal auditory canal . It was removed in parts by Cavitron Ultrasonic Surgical Aspirator (CUSA). Somatosensory evoked potentials, brainstem auditory evoked responses, and intraoperative facial nerve monitoring were used to minimise the damage intraoperatively.

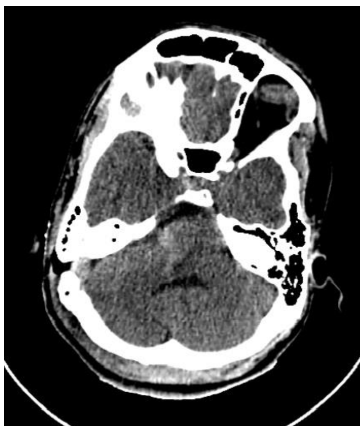

Figure 2. Post operative CT of Patient showing decompression of cystic part and a small residual attached to the brain stem.

The patient had CSF discharge from tissue drain more than 100ml on 3rd post op day for which lumbar drain was inserted and tissue drain removed on following day. Surgical wound healed and lumbar drain removed on day 5. No leak or pseudomenigocoele formation. Patient discharged on 8th post op day without fresh neurological deficit and improved cerebellar and brain stem signs.

The histopathology sections revealed moderately cellular neoplasm with closely opposed cells with round nuclei arranged in a haphazard pattern with limited intervening stroma. Nuclei are oval to spindle with dense chromatin and scanty cytoplasm. There was mild nuclear atypia with mitotic activity (<5/HPF). Cyst formation also seen. There was numerous slit like vascular spaces. Vimentin CD34 and CD99 are positive with STAT-6 strongly nuclear positive. Ki-67 is less than 5%. Immunomarkers favoured a grade 2 hemangiopericytoma. While negative for EMATLE, SOX10. (Fig. 3, Fig. 4, Fig.5, Fig.6).

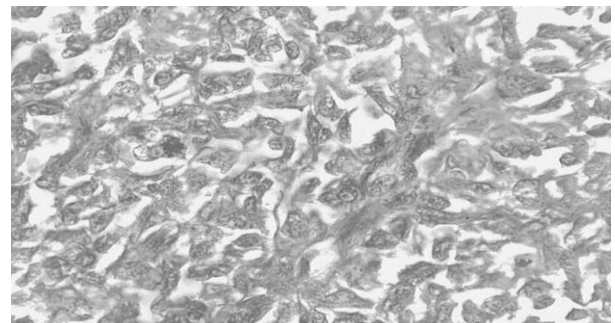

Figure 3. Photomicrographs of the tumor specimens showing. A: Diffuse sheets of relatively uniform population of cells interspersed by staghorn vascular channels (H&E, original magnification, ×10). B: Round to oval cells with finely dispersed nuclear chromatin and moderate cytoplasm and no signs of anaplasia (H&E, original magnification, ×20). H&E, haematoxylin and eosin.

Figure 4. Immunohistochemical staining showing diffuse positivity with CD34 (original magnification, ×100).

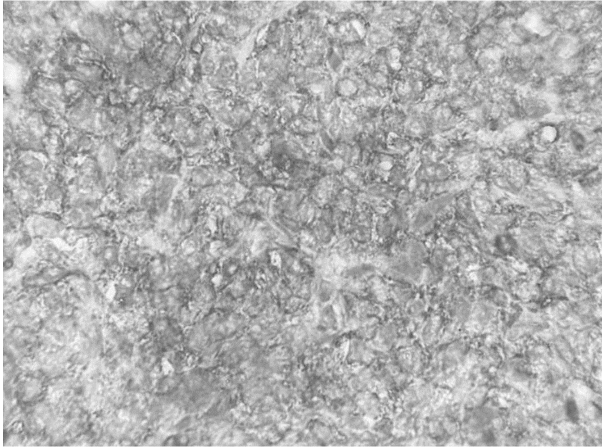

Figure 5. CD 99 STAINING (oil immersion; original magnification ×1000).

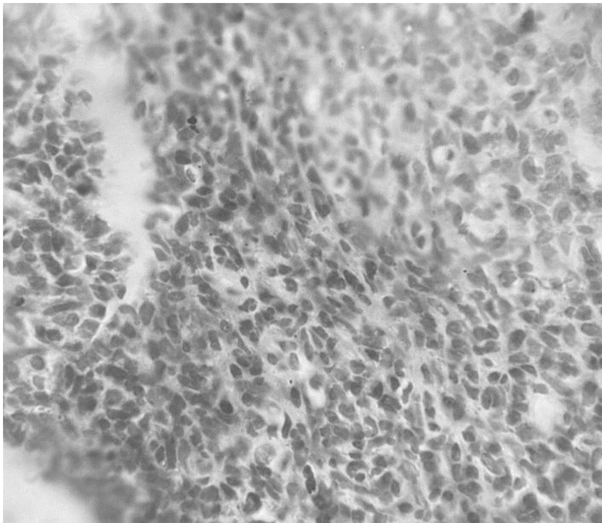

Figure 6. STAT 6 STAINING (original magnification ×100)

Metastatic workup including CT of the chest/abdomen/pelvis did not reveal any evidence of extracranial HPC. Adjunctive radiation therapy was advised but he was lost to follow up since a month post-surgery.

Discussion

HPCs are rare, and are aggressive neoplasms that arise from the pericytes of Zimmerman, which are contractile spindle cells surrounding capillaries and post capillary venules [4]; and most often involve the musculoskeletal system and skin [1].Intracranial HPCs constitute just 0.4% of all intracranial tumors [10] and approximately 2% to 4% of all meningeal tumors [5].

Immunohistochemistry has major role in diagnosis of HPC. It also helps in differentiation between meningioma and HPC, where HPC is positive with CD34, CD99 and STAT-6 [5].

In the present case, the morphological features were distinctive enough to place the lesion in the category of an HPC. Fairly uniform cellularity of the tumor and the high mitotic activity was more supportive of this lesion being labelled as grade II HPC instead of a cellular SFT

The similarity between meningioma and HPC is limited to radiology and gross morphology. In fact, with a mean survival of 84 months from the time of initial diagnosis [5], a local recurrence rate as high as 91% and a 15-year risk of distant metastasis approaching 70%; intracranial HPCs harbour one of the most aggressive biological/clinical behaviours [16].

In present scenario gross total resection followed by radiotherapy is standard of care.

Radiation therapy has in fact extended the mean time of local recurrence from 34 to 75 months, and the survival from 62 to 92 months [1].

Conclusions

In conclusion, HPC being aggressive tumor with high rate of recurrence and metastasis, it should be included as a differential diagnosis in dural Based extra axial CPA tumors in age-appropriate cases.

A high index of suspicion on radiology imaging is essential to plan for complete excision, and role accurate histopathological diagnosis can't be overemphasised. As postoperative recurrence seems unavoidable, long-term follow-up with serial imaging should be considered in all cases.

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Surgical outcome of endoscopic third ventriculostomy compared to ventriculoperitoneal shunt in non-communicating or obstructive hydrocephalus: A study from tertiary care centre of a low-middle-income country

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Keywords
hydrocephalus,
endoscopic third ventriculostomy,
ventriculoperitoneal shunt,
low-middle-income country

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ABSTRACT

Objectives: To assess and compare the effectiveness of Endoscopic Third Ventriculostomy over Ventriculoperitoneal shunt in terms of rate of revision in non-communicating or obstructive hydrocephalus at a tertiary care centre in a low-middle-income country.

Materials and methods: A Prospective Cohort Study was conducted from January 2019 to December 2020 at PIMS/SZABMU, Islamabad, Pakistan. A total of 104 patients of either gender under the age of 12 years diagnosed with non-communicating/obstructive hydrocephalus were enrolled in this study. They were allocated into two equal groups of 52 by the lottery method. One group underwent Ventriculoperitoneal Shunt (Group I) and another group underwent Endoscopic Third Ventriculostomy (Group II). They received routine treatment of one-week postoperative prophylactic broad-spectrum antibiotics. They were discharged on the third postoperative day and were instructed for follow-up on the 4th, 12th and 24th postoperative week. Clinically, successful outcomes were defined as no event occurring during or after the surgery that could result in reoperation or any significant postoperative complication.

Results: There were 55.8% males and 44.2% females in group I while 50.0% males and 50.0% females were in group II. The mean age of Group I was 0.89 years ± 1.5 SD while 2.3 years ± 2.8 SD in group II. During the procedure, the overall complication rate was 0% in group I and 4.1% in group II. In the 4th postoperative week, the overall complication rate was 5.9% in group I and 4.1% in group II. At the 12th postoperative

week, the overall complication rate was 17.6% in group I and 2.0% in group II. On the 24th postoperative week, the overall complication rate was 9.8% in group I and none in group II. During the procedure, reoperation was needed in 0% in group I and 4.1% in group II. In the 4th postoperative week, reoperation was needed in 5.9% of patients in group I and 2.0% in group II. In the 12th postoperative week, reoperation was needed in 17.6% of patients in group I and 2.0% in group II. At the 24th postoperative week, reoperation was needed in 9.8% of patients in group I and none in group II. The overall mortality rate was 5.9% in group I and 4.1% in group II.

Conclusion: Endoscopic Third Ventriculostomy procedure was found to be better than the Ventriculoperitoneal shunt in terms of reoperation and complication rate at the 4th, 12th and 24th week after the procedure in infants and children with non-communicating/obstructive hydrocephalus.

INTRODUCTION

Hydrocephalus is an abnormal ventricular dilatation secondary to excessive buildup of cerebrospinal fluid (CSF) in the cranial cavity. Normal CSF production is mostly by choroid plexus and to a lesser extent by interstitial space and ependymal lining of the ventricles and the nerve sleeve dura. It is absorbed into the venous circulation by arachnoid granulations.[1] Causes of hydrocephalus are congenital or acquired. Congenital causes include neural tube defects and those causing aqueductal stenosis. Post-traumatic, Post-hemorrhagic and posterior fossa tumors (Fig. 1) are some of the acquired causes.[1,2]

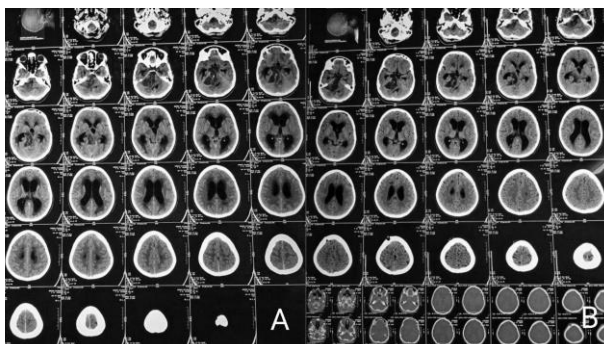

Figure 1. A: Preoperative CT Brain Plain of an 11-year-old boy with Hydrocephalus secondary to Posterior Fossa Tumor. B: Postoperative CT Brain Plain following ETV.

There are four types of hydrocephalus including Communicating, Non-communicating, Ex vacuo and Normal pressure hydrocephalus. Impedance of CSF flow after it exits the ventricles causes communicating hydrocephalus. Obstruction of CSF flow within the ventricular chain causes non-communicating also called Obstructive hydrocephalus. Hydrocephalus Ex vacuo occurs after stroke or traumatic brain injury. Normal pressure hydrocephalus is a chronic type usually present in adults and is mostly idiopathic.[1]

Usual presentations of hydrocephalus in children include progressively enlarging head size, drowsiness, vomiting, seizures and sunsetting of eyes. In adults, it may present with headache, visual impairment, poor balance, urinary incontinence, personality changes or mental impairments. Diagnosis is by clinical examination and neuroimaging techniques like; Ultrasonography, Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and intracranial pressure monitoring techniques.[1,3] Various treatments for this condition include surgical and non-surgical management. Conservative measures work with variable success and often these measures serve only to temporize hydrocephalus until shunt placement. Approaches include head wrapping, pharmacological treatment and intermittent CSF removal.[4] Surgical management includes Non-shunting and Shunting procedures. Non-shunting procedures include Endoscopic Third Ventriculostomy (ETV), resection of obstructing lesions when possible and choroid plexus coagulation. Shunt involves placement of a ventricular catheter into the cerebral ventricles in order to bypass flow obstruction/malfunctioning arachnoid granulations and drain the excess fluid into other body cavities where it is absorbed. Most shunts drain fluid into peritoneal cavity therefore called ventriculoperitoneal shunts.[4,5]

Shunts generally work well but they have inherent complications such as disconnection, blockade, infection, overdrainage or underdrainage. All these complications lead to multiple shunt revisions in a patient's lifetime. It is of particular importance that shunt systems are generally very expensive and cost about all of a month's income of a family in a developing country like ours.[6-10] Alternative treatment for obstructive hydrocephalus is ETV. Surgeon makes a burr hole just anterior to the coronal suture about three centimeters lateral to midline and inserts an endoscope through it inside the ventricles. Endoscope assisted opening is made in the floor of third ventricle, which allows the CSF to flow directly to basal cisterns thereby shortcutting any obstruction as in aqueductal stenosis.[6-10,11,12]

Complications of ETV include hemorrhage, injury to neural structures and late sudden deterioration. Infection, hematoma and CSF leak may present in the postoperative period. Failure of ETV may occur due to occlusion of Ventriculostomy that may need revision.[12,13] A huge advantage of ETV over implantation of shunt is the absence of foreign body. This technique is cost effective but if made with correct surgical expertise it does not need revisions and overall patient morbidity is lower than that caused by multiple shunt issues. Multiple studies have shown that ETV treated patients have better neurological outcome.[2,3,6-13] In this study, we compared the surgical outcome of ETV to VP shunt in terms of rate of reoperation and the complications of primary procedure.

MATERIALS AND METHODS

Study design: Descriptive Observational Study

Setting: Department of Neurosurgery, Pakistan Institute of Medical Sciences (PIMS)/Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU), Islamabad, Pakistan.

Duration of Study: 2 years (January, 2019 to December, 2020).

Sample size: A sample size of 104 patients was included in this study according to WHO sample size calculator, using the following parameters:

- Level of significance: 5%
- Power of test: 80%
- Anticipated population proportion of unfavorable outcome with ETV, p1: 4%
- Anticipated population proportion of unfavorable outcome with VP shunt, p2: 18%

Sampling Technique: Non-probability based consecutive sampling.

Sample Selection:

A. Inclusion Criteria:

- All the patients of any gender under the age of 12 diagnosed with non-communicating/obstructive hydrocephalus by radiology (CT/MRI), clinical correlation and advised for surgical treatment were included.

B. Exclusion Criteria:

- Patients already treated (VP shunt or ETV)
- Active intracranial infection
- Patients with communicating hydrocephalus

Data Collection Procedure: Permission from ethical review board was taken for this study. After obtaining informed consent, patients of any gender under the age of 12 years diagnosed with non-communicating/obstructive hydrocephalus on CT/MRI brain, with clinical correlation and advised for surgical treatment were included in this study. The sample size for this study was 104 patients. Informed consent for surgery and inclusion in the study was taken from the parents or their closest available relative. Patients were randomly allocated into two equal groups of 52 by lottery method. Group I patients underwent Ventriculoperitoneal shunt while Group II patients underwent Endoscopic Third Ventriculostomy. All included patients had their history taken and relevant physical examination done preoperatively. They also had routine baseline investigations done preoperatively including Chest X-ray, full blood counts, liver and renal function tests, serum electrolytes, coagulation profiles and hepatitis B and C screening. Patients received routine treatment of one-week postoperative prophylactic broad-spectrum antibiotics to avoid infection and analgesia according to WHO pain ladder for pain control. They were discharged on the third postoperative day or later depending on their clinical condition and recovery. Trainee residents recorded data on proforma as Per-op, at 4th, 12th and 24th postoperative week of follow-up. CT/MRI Brain was done preoperatively for diagnosis. Follow-up CT/MRI brain scans were done as required. Clinically, successful outcomes were defined as no event occurring during or after the surgery that would result in an alternate surgical procedure or significant postoperative complication. All complications related to the procedures were analyzed. The time to complication was noted as well as the type of complication (infection, mechanical failure of the shunt or non-functioning ETV). The diagnosis of a non-functioning ETV/shunt was made according to clinical criteria in patients with signs of raised intracranial pressure or growing head circumference and increase in ventricular size on imaging (CT/MRI brain). Complications of surgical

treatment and need for re-operations were recorded during the study period.

Data Analysis Procedure: Data was analyzed using SPSS version 23. Mean and standard deviation was calculated for quantitative variables like age. Frequency and percentages were presented for qualitative variables like gender, presenting complaints, need for reoperation and complications. Chi-square test was applied to compare outcome and complications between both the groups. P-value < 0.05 was considered significant.

Results

Demography of the selected population:

There were 55.8% (n=29/52) males and 44.2% (n=23/52) females in group I while 50.0% (n=26/52) males and 50.0% (n=26/52) females in group II (Table 1). Age distribution was also comparable in both groups. Mean age of Group I patients was 0.89 years ± 1.5 SD while it was 2.3 years ± 2.8 SD in group II patients (Table 2).

Table 1. Gender distribution in both the study groups

Gender	Groups		Total
	VP Shunt	ETV	
Males	29 (55.8%)	26 (50%)	55 (52.9%)
Females	23 (44.2%)	26 (50%)	49 (47.1%)
Total	52 (100%)	52 (100%)	104 (100)

Table 2. Age distribution in both the study groups

Groups	n	Mean Age (years)	± SD (years)
VP Shunt	52	0.89	1.5
ETV	52	2.3	2.8

Excluded patients:

We enrolled 104 patients and a total of four patients were excluded from the study (3 from ETV group and 1 from VP shunt group). Two patients from ETV and one patient from VP shunt group were excluded as lost to follow up. One patient from the ETV group was excluded as procedure aborted due to opaque 3rd ventricular floor.

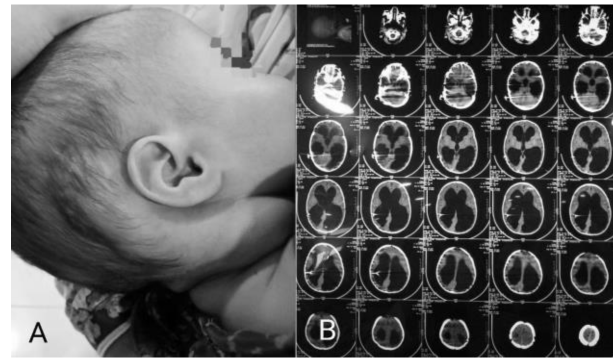

Figure 2. A: Surgical site swelling in a child with shunt blockade. B: CT Brain Plain of the same child with shunt blockade.

Outcome analysis of treatment in both groups:

Complications:

During the procedure, overall complication rate was 0% (n=0/51) in group I and 4.1% (n=2/49) in group II (P=0.145, Table 3). At 4th postoperative week, the overall complication rate was 5.9% (n=3/51) in group I and 4.1% (n=2/49) in group II (P=0.680, Table 3). At 12th postoperative week, overall complication rate was 17.6% (n=9/51) in group I and 2.0% (n=1/49) in group II (P=0.009, Table 3). At 24th postoperative week, overall complication rate was 9.8% (n=5/51) in group I and none in group II (P=0.025, Table 3). Overall complication rate was higher in patients who underwent VP shunt procedure as compared to those who underwent Endoscopic Third Ventriculostomy at 4th, 12th and 24th week after the procedure. The difference was not significant at 4th week (P>0.05), however, it was significant at 12th (P=0.009) and at 24th postoperative week (P=0.025).

Table 3. Complications rate Per-op, at Week 4, 12 and 24 in both study groups

Complications		Groups		Total	P-Value
		VP Shunt	ETV		Chi-square
Per-op	Present	0 (0%)	2 (4.1%)	2 (2%)	0.145
	Absent	51 (100%)	47 (95.9%)	98 (98%)	
Week 4	Present	3 (5.9%)	2 (4.1%)	5 (5%)	0.680
	Absent	48 (94.1%)	47 (95.9%)	95 (95%)	
	Present	9 (17.6%)	1 (2%)	10 (10%)	0.009

Week 12	Absent	42 (82.4%)	48 (98%)	90 (90%)	
Week 24	Present	5 (9.8%)	0 (0%)	5 (5%)	0.025
	Absent	46 (90.2%)	49 (100%)	95 (95%)	

Table 4. Reoperation rate Per-op, at Week 4, 12 and 24 in both study groups

Reoperation		Groups		Total	P-Value
		VP Shunt	ETV		Chi-square
Per-op	Present	0 (0%)	2 (4.1%)	2 (2%)	0.145
	Absent	51 (100%)	47 (95.9 %)	98 (98%)	
Week 4	Present	3 (5.9%)	1 (2%)	4 (4%)	0.327
	Absent	48 (94.1%)	48 (98%)	96 (96%)	
Week 12	Present	9 (17.6%)	1 (2%)	10 (10%)	0.009
	Absent	42 (82.4)	48 (98%)	90 (90%)	
Week 24	Present	5 (9.8%)	0 (0%)	5 (5%)	0.025
	Absent	46 (90.2%)	49 (100%)	95 (95%)	

Reoperation:

During the procedure, reoperation was needed in 0% (n=0/51) patients in group I and 4.1% (n=2/49) in group II (P=0.145, Table 4). At 4th postoperative week, reoperation was needed in 5.9% (n=3/51) patients in group I and 2.0% (n=1/49) in group II (P=0.327, Table 4). At 12th postoperative week, reoperation was needed in 17.6% (n=9/51) patients in group I and 2.0% (n=1/49) in group II (P=0.009, Table 4). At 24th postoperative week, reoperation was needed in 9.8% (n=5/51) patients in group I and none in group II (P=0.025, Table 4). Reoperation rate was higher in patients who underwent VP shunt procedure as compared to those who underwent Endoscopic Third Ventriculostomy at 4th, 12th and 24th week after the procedure. The difference was not significant at 4th week (P>0.05), however, it was significant at 12th (P=0.009) and at 24th postoperative week (P=0.025).

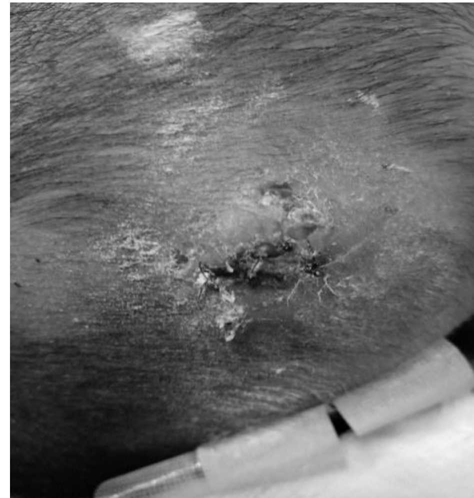

Figure 3. Ventriculoperitoneal shunt hardware exposure.

Details of complications and reoperations:

Details of complications and reoperations are mentioned in Table 5.

- Hardware exposure (Fig. 3) was the most frequent complication noted in VP shunt group followed by shunt blockage/breakage/malposition (Fig. 2), meningitis and intestinal obstruction. VP shunt revision was the most frequent reoperation procedure followed by shunt removal and External Ventricular Drain (EVD) placement (Table 5).
- In the ETV group, intraventricular hemorrhage was the most frequent complication followed by CSF leak and subdural hygroma. EVD placement was the most frequent reoperation procedure (Table 5).

Table 5. Complications and Reoperation details Per-op, at Week 4, 12 and 24 in both study groups

Time	Complications and Reoperation details				
		VP Shunt		ETV	
Per-op	Intraventricular hemorrhage	0	-	2	EVD placement
Week 4	Increased head size	1	Shunt revision	0	-
	Shunt malposition	1	Shunt revision	0	-

	CSF leak	1	Shunt distal end revision	1	Conservative management
	CSF hygroma	0	-	1	B/L subdural shunt placement
Week 12	CSF leak	0	-	1	VP Shunt
	Hardware exposure	4	Shunt removal	0	-
	Meningitis	3	Shunt removal + EVD	0	-
	Intestinal obstruction	2	Distal end of shunt exteriorized	0	-
Week 24	Shunt blockade	3	Shunt revision	0	-
	Shunt breakage	1	Shunt revision	0	-
	Meningitis	1	Shunt removal + EVD	0	-

Mortality:

Overall mortality rate was 5.9% (n=3/51) patients in group I and 4.1% (n=2/49) patients in group II. The difference was not statistically significant (P=0.680, Table 6). In the VP shunt group, two patients died due to meningitis and one patient died of a burst abdomen due to intestinal obstruction. In the ETV group, one patient died due to intraventricular hemorrhage and one due to subdural hygroma.

Table 6. Overall mortality rate in both the study groups

Mortality	Groups		Total	P-Value
	VP Shunt	ETV		Chi-square
Present	3 (5.9%)	2 (4.1%)	5 (5%)	0.680
Absent	48 (94.1%)	47 (95.9%)	95 (95%)	
Total	51(100%)	49 (100%)	100 (100%)	

Discussion

CSF shunts have long been the standard treatment for hydrocephalus in children.[14,15,16] ETV is an alternative approach that has several advantages over CSF shunting in that it is relatively low-cost, durable, and potentially avoids the long-term complications that frequently occur with VP shunts.[17] In the present study, we aimed to compare both the techniques in terms of rate of reoperation and the complications of primary procedure. In our study, the overall complication rate was higher in patients who underwent VP shunt procedure as compared to those who underwent Endoscopic Third Ventriculostomy. Hardware exposure was the most frequent complication noted in the VP shunt group followed by shunt blockage/breakage/malposition, meningitis and intestinal obstruction. Delayed presentation of hydrocephalus in low-middle-income countries like Pakistan is a reason that patients present with very large head size and thin scalp, which may be the cause of hardware exposure. We suggest that paediatric shunts with small reservoirs should be used in such patients.

Hardware exposure leads to CSF leak from cranial end. If present, CSF leak can become a drastic complication. Increased operative time or contact of shunt hardware with skin of patient is the most common cause of shunt infection.[18,19] In ETV group, intraventricular hemorrhage was the most frequent complication followed by CSF leak and subdural hygroma. Intraoperative hemorrhage is the most dreadful and major complication of ETV. Although severe hemorrhages are rare, the neurosurgeon needs to be aware of them and has to establish strategies for their management. Most hemorrhages can be stopped by constant irrigation and coagulation. In the other rare cases, the dry field technique is a safe and reliable technique and can be easily incorporated into endoscopic surgery. A 2° basilar artery hemorrhage will inevitably lead to EVD placement per-operatively and later death. And to avoid it beforehand MRI brain sagittal cuts are done to know the thickness of third ventricular floor and relation of basilar artery.[20] Patients having thin cortical mantle who underwent ETV had poor outcome (chances of subdural hygroma formation). Kamel et al proposed that the prolonged ventricular dilatation leads to the compression of the thin cortical mantle, causing an alteration in the cerebral viscoelastic properties. Thus, there would not be adequate spacing in the cortical mantle following the ETV, favoring the collection formation in the increased subdural space.[21,22] After piercing floor of

third ventricle, membrane of liliequist needs to be cut effectively in order to establish a pathway between ventricle and basal cisterns. It is known that its fenestration in microsurgeries for ruptured cerebral aneurysm clipping reduces the risk of the occurrence of postoperative hydrocephalus, however, it increases the formation of subdural collections. Cartimill and Vloeberghs attributed the occurrence of spinal subdural hematoma in a 9-year-old child to the very same mechanism.[23,24]

Our findings are comparable with other similar studies cited in the literature. Lu L conducted a meta-analysis to compare ETV and VPS in patients with obstructive hydrocephalus. They included 4 trials involving 250 patients. Their pooled results showed that ETV was associated with lower incidence of postoperative infection (risk ratio [RR] 0.09, 95% confidence interval [CI]: 0.02-0.32, P=0.0002); postoperative hematoma (RR 0.26, 95% CI: 0.08-0.88, P=0.03); and blockage (RR 0.28, 95% CI: 0.13-0.60, P=0.001) compared with VPS.[25] Jiang L et al in their meta-analysis demonstrated that ETV was associated with lower incidence of infection (RR: 0.20; 95% CI: 0.06-0.69; P=0.010). They further highlighted that patients who received ETV had shorter duration of surgery (SMD: -1.71; 95% CI: -3.16 to -0.27; P=0.020) and hospital stay (SMD: -0.91; 95% CI: -1.45 to -0.38; P=0.001).[23] In our study, we did not take into account duration of procedure and hospital stay as our outcome variables.

Complications of ETV were described in a 2012 systematic review of 24 case series reporting outcomes of >2500 ETV procedures in children and adults with hydrocephalus due to a variety of etiologies. The overall complication rate was 8.8 percent, including intraoperative hemorrhage (3.9%), infection (1.8%), CSF leak (1.7%), and other surgical complications.[26] The analysis was on ETV only and no comparison with VP shunting was performed. Jiang L et al compared ETV and VP Shunting for patients with non-communicating hydrocephalus in 10 observational studies. Their pooled analysis revealed that ETV was associated with lower incidence of major complications when compared with VPS (RR: 0.31; 95% CI: 0.17-0.56; P<.001). ETV was also associated with lower incidence of infection (RR: 0.20; 95% CI: 0.06-0.69; P=0.010).[27]

Our results further showed that reoperation rate was higher in patients who underwent VP shunt as compared to those who underwent ETV. During operation (0% vs 3.8%, P=0.145), at 4th week (5.9% vs 2.0%, P=0.327), 12th week (17.6% vs 2.0%; P=0.009) and 24th week (9.8% vs 0%, P=0.025). The difference was statistically significant at 12th and 24th postoperative week. VP shunt revision was the most frequent reoperation in VP shunt group followed by shunt removal and EVD placement. EVD placement was the most frequent reoperation procedure in the ETV group. Kulkarni AV et al compared ETV and shunt in infants (<24 months old) with symptomatic triventricular hydrocephalus from aqueductal stenosis. They reported that actual success rates for ETV vs shunt at 3, 6, and 12 months were: 68 vs 95 %, 66 vs 88 %, and 66 vs 83.[6] The trend appeared in both studies is comparable with higher success rate for ETV at 6 months (24 weeks). We, however, did not follow our patients till 12 months. In our opinion, ETV success is almost always dependent on surgeon expertise with endoscope. We believe for ETV procedure to be successful, the learning curve is steep and good outcome of ETV depends on surgical expertise. Casual attitude of surgeons towards placement of shunt is a factor which leads to increased rates of infection and causes shunt failure.[28]

Some authors advocate that the ETV success score can be used to estimate the likelihood of early success. The score was developed and validated using a dataset of 618 consecutive ETV procedures performed at 12 international institutions.[8] Older age at the time of the procedure (i.e, >1 year old) is the strongest predictor of success; other important predictors include non-infectious hydrocephalus etiology (e.g, aqueductal stenosis, tectal tumor, myelomeningocele, intraventricular hemorrhage), and lack of previous shunt.[29] In one study, investigators compared outcomes of ETV and shunting using ETV scoring in a cohort of children with newly diagnosed hydrocephalus.[30] Among patients with high predicted ETV success (i.e, ETV success score ≥80), cumulative reoperation-free survival at 36 months was greater with ETV compared with shunting (72% vs 54%). However, among patients with moderate and low ETV success scores, outcomes were similar with the two procedures. For patients with moderate ETV success scores (i.e, 50 to 70), reoperation-free survival at 36 months was approximately 50% in both groups; and for those with low ETV success scores (i.e, ≤40), reoperation-free survival at 36 months was

approximately 38% in both groups. In the present study, we did not use such scores.

Other studies compared ETV and VP shunting in other causes of hydrocephalus. Aranha A et al compared ETV and VP shunt in the treatment of hydrocephalus in tuberculous meningitis and reported the success rate for ETV 65.4% compared to the 61.54% success rate in VP shunt group.[31] Gonda DD et al treated patients with hydrocephalus related to cerebral metastases by either ETV or VP shunting and analyzed the clinical outcomes. The overall efficacy of symptomatic palliation was comparable in the ETV and VPS patients (ETV=69%, VPS=75%). The overall complication rate for the two groups was comparable (ETV=12.6%, VPS=19.4%), although the spectrum of complications differed.[32] The results of both studies are comparable to our study results. There are some ongoing clinical trials as well, which are evaluating outcomes with ETV compared with shunting in children with communicating[33] and non-communicating hydrocephalus[7]. Long term follow-up results are awaited.

In summary, both ETV and VP shunting are practical treatment options for non-communicating/obstructive hydrocephalus. Criteria for selection of patients for ETV versus shunting are not standardized and practice varies considerably. The 2014 evidence-based guidelines of AANS and the CNS concluded that outcomes of the two procedures are generally equivalent and they did not advocate for one approach over the other. ETV is generally not performed for treatment of obstructive hydrocephalus in infants <3 months old due to low success rates in this age group. For children in whom ETV is unsuccessful, a shunting procedure is generally performed, because repeating the ETV acutely is not likely to be successful. Present study results and several other studies cited in the literature showed that ETV when performed in a carefully selected group of patients is more effective and associated with lesser complication rates. ETV technique is cost effective and if made with correct surgical expertise it does not need revisions and overall patient morbidity is lower than that caused by multiple shunt issues. Our study design is the major strength of the study as we used stringent inclusion and exclusion criteria, though this study has some limitations as well. Firstly, the sample was relatively smaller, yet sufficient enough for interpretation. Secondly, our duration of follow up was relatively shorter and we did not follow the patients beyond 6 months, while studies in the literature showed longer duration of follow up even up to 5 years after the procedure. Thirdly, we didn't do ETV success scoring, which is an established score predicting the success of ETV and finally we did not take into account the duration of procedure, length of hospital stay and neurological outcome as our outcome measures.

Conclusion

Endoscopic Third Ventriculostomy was found to be better than Ventriculoperitoneal shunt in terms of reoperation and complication rate at 4th, 12th and 24th week after the procedure in infants and children with non-communicating or obstructive hydrocephalus. We suggest future studies taking larger sample sizes, with longer duration of follow up and taking into account other outcome variables like duration of procedure, length of hospital stay and neurological outcome.

List of Abbreviations

CSF: Cerebrospinal fluid
CT: Computed Tomography
EVD: External Ventricular Drain
ETV: Endoscopic Third Ventriculostomy
MRI: Magnetic Resonance Imaging
VP: Ventriculoperitoneal
VPS: Ventriculoperitoneal shunt
SD: Standard Deviation
RR: Risk Ratio
CI: Conference Interval
SMD: Standardized Mean Difference
P: P-value

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Comparison of levels of toxic trace elements in two most common spinal pathologies in three different tissues

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ABSTRACT

Aim: The toxic trace element levels in serum, bone (lamina), and intervertebral disc tissues of patients with lumbar spinal stenosis and lumbar herniated nucleus pulposus (HNP) which are the two most common spinal pathologies were determined, and it was investigated whether they have a role in the pathophysiology of these pathologies.

Materials and methods: Cadmium (Cd), aluminium (Al), arsenic (As), mercury (Hg), and lead (Pb) levels in serum, intervertebral disc, and bone (lamina) tissue of patients with HNP (=20) and 30 with lumbar spinal stenosis (LSS) (n=30) were determined by Inductively Coupled Plasma Mass Spectrometry technique.

Results: LDH group Cd serum level was found to be significantly higher than LSS group Cd serum level (p=0.024). Al disc level in the HNP group was found to be significantly higher than the Al disc level in the LSS group (p=0.038). While As serum level increased in LDH group, it was determined that As bone level increased very significantly (r= 0.699, p=0.001). In the LSS group, it was determined that the Hg disc level increased significantly as the Hg serum level increased (r=0.608, p<0.01). On the other hand, as the Hg serum level increased in the LDH group, the Hg disc level also decreased significantly (r= -0.579, p<0.01).

Conclusion: The difference in toxic trace element levels seen in these pathologies has been discussed in terms of possible causes in light of current literature. The findings of our study support the hypothesis that toxic trace elements may be effective in lumbar disc degeneration.

Keywords
trace element,
lumbar spinal stenosis,
lumbar disc herniation,
inductively coupled plasma
mass spectrometry

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INTRODUCTION

It is known that some environmental factors and especially toxic trace elements that are not essential for human health pass into the human body with contamination and cause physiological and pathological

negative effects (1). However, there is not adequate and satisfactory information about the effects of presence of these toxic elements in the human body in acceptable amounts or what kind of effects they have on the organism in the amounts below the permissible levels in food, drinking water or air. Moreover, the accumulation of these toxic elements in the body and the possibility that they may play a role in the pathophysiology of some different diseases that occur in chronic degenerative processes or may appear as predisposing factors should not be forgotten.

In this study, it was investigated whether five toxic substances (aluminum, arsenic, mercury, lead, cadmium) have an effect on lumbar herniated nucleus pulposus and chronic intervertebral disc degeneration. For this reason, two patient groups with lumbar HNP and LSS thought to be caused by intervertebral disc degeneration but with different pathogenesis were compared (2). In the HNP, disc degeneration generally develops in a shorter time due to axial loading and annulus fibrosis tears. However, in LSS degenerative changes are thought to be due to a more chronic inflammatory process which affects ligaments, bones, discs and facet joints (3,4). In LSS, it is predicted that the process occurs mostly with biomechanical effects as a result of instability developing on the basis of degenerative changes due to the aging process of the spine (5). Although intervertebral disc degeneration is a common feature in both diseases, it is assumed that they have different pathophysiological basis due to their histopathological differences (6). In this way, toxic trace elements in both groups of diseases were determined in serum, bone and disc tissue, and the effects of these substances on the degenerative process were investigated.

Material and method

After receiving the approval of the Yozgat Bozok University Clinical Research Ethics Committee (12.10.2016 / 68 dated 12.10.2016), the blood, bone (lamina) and intervertebral disc samples were collected from the patients who had undergone lumbar spine pathology operation in the Department of Neurosurgery of Yozgat Bozok University Faculty of Medicine between 2016-2017. Trace element levels in the samples were measured by ICP-MS (Inductively Coupled Plasma - Mass Spectrometry). The patients were divided into two groups as lumbar spinal stenosis (LSS) and lumbar disc herniation (LDH) by preoperative magnetic resonance imaging (MRI). Patients with rheumatic diseases such as rheumatoid arthritis and ankylosing spondylitis, under the age of 18, with missing file information or missing radiological images, and who underwent surgery due to trauma were excluded from the study. Patients with the possibility of prolonged or intense exposure to the trace elements mentioned in the study were excluded from the study. The diagnosis of LSS or HNP was made according to clinical and radiological findings. 20 out of 50 patients were diagnosed with L-HNP and 30 with LSS. Patients who underwent discectomy in addition to total laminectomy in the LSS group were included. In LSS group, patients who underwent only laminectomy and did not undergo discectomy were excluded from the study. Patients who use cigarettes and alcohol, and patients with diseases that require continuous drug use such as hypertension, diabetes, and goiter were excluded from the study.

Statistical Analysis: These measured levels were grouped according to radiological findings. Three replicates were obtained for each sample analyzed and their mean value was taken into account for the concluded assessment. If the required statistics are given, it is evaluated by SPSS 20.0 statistical program. A normality test was used to determine whether sample data of groups a normally distributed. The correlations between toxicological variables among groups were assessed with Pearson correlation test. The parametric and nonparametric tests were carried out to determine the association of main parameters concerning among groups. All tests were considered significant at $p < 0.05$.

Results

Median age was 53 years old (mean:53.84, std: ±12,55, min: 25, and max: 76). In L-HNP (n=20) median age was 35 and 9 of them were female and 11 were male. In LSS group (n=30), mean age was 54 and 18 of them were female and 22 were male. Mean, median, standard deviation, minimum, and maximum levels of 5 toxic trace elements were showed in three different tissue presented in Table 1.

Table 1. General descriptive values of the study

n=50 Unit - [µg/L]	Age	Cd			Al			As			Hg			Pb		
		Bone	Serum	Disc	Bone	Serum	Disc	Bone	Serum	Disc	Bone	Serum	Disc	Bone	Serum	Disc
Mean	53.84	0.31	0.49	0.54	27.13	30.57	2.47	0.82	0.53	1.16	0.26	0.21	0.03	14.76	5.93	6.34
Median	53.00	0.32	0.51	0.45	26.32	31.00	2.22	0.65	0.49	0.37	0.02	0.17	0.03	12.91	2.93	3.09
Std. Deviation	12.55	0.11	0.06	0.43	18.14	2.01	1.40	0.66	0.59	2.10	0.41	0.14	0.03	8.59	12.54	8.76
Minimum	28.00	0.02	0.26	0.07	8.64	21.15	0.39	0.03	0.00	0.02	0.00	0.00	0.00	1.75	0.06	0.34
Maximum	76.00	0.48	0.58	1.81	149.01	33.67	5.73	3.77	3.89	12.30	2.28	0.53	0.12	47.72	81.65	41.41

Table 2. The comparison of the toxic trace elements in between LSS and L-HNP groups

		LSS (n=30)		LDH (n=20)		p
		Mean	SD	Mean	Sd	
Cd	bone	0.30	0.10	0.32	0.12	p>0.05
	serum	0.47	0.07	0.51	0.04	**0.024***
	disc	0.57	0.47	0.50	0.35	p>0.05
Al	bone	28.20	23.24	25.54	4.44	p>0.05
	serum	30.39	2.25	30.85	1.58	p>0.05
	disc	2.14	1.25	2.97	1.50	**0.038***
As	bone	0.79	0.58	0.88	0.77	p>0.05
	serum	0.44	0.28	0.66	0.86	p>0.05
	disc	1.54	2.62	0.57	0.53	p>0.05
Hg	bone	0.30	0.46	0.19	0.33	p>0.05
	serum	0.22	0.16	0.18	0.11	p>0.05
	disc	0.03	0.03	0.03	0.02	p>0.05
Pb	bone	15.76	9.81	13.26	6.28	p>0.05
	serum	7.84	15.97	3.06	1.29	p>0.05
	disc	6.82	9.88	5.61	6.93	p>0.05
LSS-Lumbar Spinal Stenosis; HNP-Herniated Nucleus Pulposus; SD- Standard Deviation; *significant						

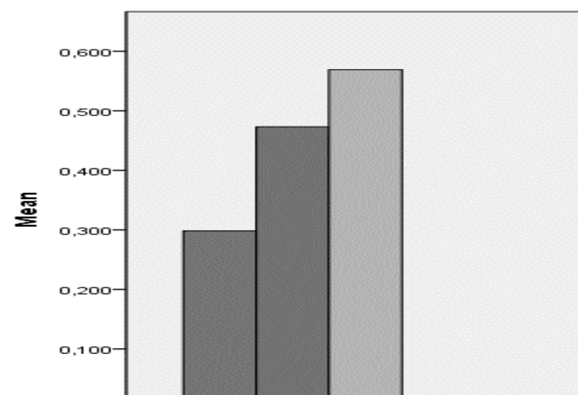
Cadmium (Cd) evaluation:

The lowest Cd level was observed in bone tissue in both LSS and HNP groups (0.30±0.10 µg/L and 0.32±0.12 µg/L, respectively). While the Cd serum level in the L-HNP group was found to be significantly higher than the Cd serum level in the LSS group (0.51±0.04 µg/L and 0.47±0.07 µg/L, p=0.024, respectively), the Cd bone level was also found to be higher, although not significantly, in the HNP group (p>0.05). On the other hand, Cd disc level was higher in the LSS group (p>0.05). However, for both groups, it was observed that Cd accumulated more in disc tissue rather than bone. In addition, while Cd serum and bone levels were inversely proportional in the LSS group, this was directly proportional in the HNP group.

Table 3. Correlations of Cd levels in bone, serum and disc tissues in both groups

Groups		Cd_Bone [µg/L]	Cd_Serum [µg/L]	Cd_Disc [µg/L]
LSS (n=30)	Cd_Bone [µg/L]	1	-,119	-,036
	Cd_Serum [µg/L]	-,119	1	,106
	Cd_Disc [µg/L]	-,036	,106	1
HNP (n=20)	Cd_Bone [µg/L]	1	,182	,284
	Cd_Serum [µg/L]	,182	1	,319
	Cd_Disc [µg/L]	,284	,319	1

Graphic 1. Graphical view of mean Cd levels in bone, serum and disc tissues



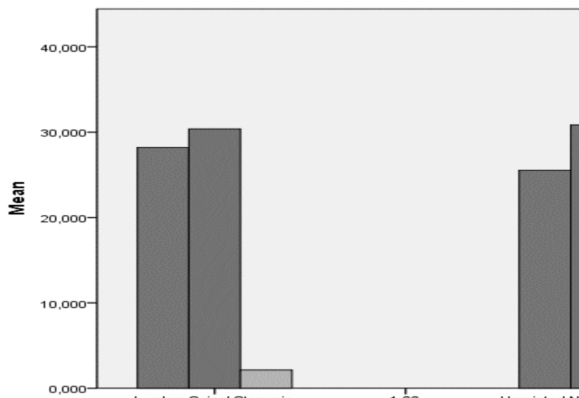
Aluminum (Al) evaluation:

The lowest Al level was observed in the disc tissue in both LSS and HNP groups (respectively, 2.14±1.25 μg/L and 2.97±1.50 μg/L). Al disc level in the HNP group was found to be significantly higher than the Al disc level in the LSS group (respectively, 2.97±1.50 μg/L and 2.14±1.25 μg/L, p=0.038). In both groups, the means were close to each other for each matrix. However, Al was found to accumulate in the bone tissue for both groups.

Table 4. Correlations of Al levels in bone, serum, and disc tissues in both groups

Groups		Al_Bone [μg/L]	Al_Serum [μg/L]	Al_Disc [μg/L]
LSS (n=30)	Al_Bone [μg/L]	1	,062	,269
	Al_Serum [μg/L]	,062	1	-,001
	Al_Disc [μg/L]	,269	-,001	1
HNP (n=20)	Al_Bone [μg/L]	1	-,053	-,205
	Al_Serum [μg/L]	-,053	1	,202
	Al_Disc [μg/L]	-,205	,202	1

Graphic 2. Graphical view of mean Al levels in bone, serum, and disc tissues



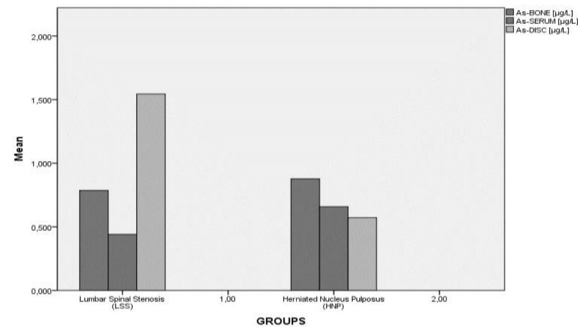
Arsenic (As) evaluation:

In LSS group, when as serum level increased, As bone level decrease was detected (r= - 0154, p=0.416). Whereas in L-HNP group, As serum level increased in HNP group, As bone level increased significantly (r= 0.699, p=0.001). LSS group As mean levels were found to be approximately 3 times higher than HNP group As mean levels.

Table 5. Correlations of as levels in bone, serum and disc tissues in both groups

Groups		As_Bone [μg/L]	As_Serum [μg/L]	As_Disc [μg/L]
LSS (n=30)	As_Bone [μg/L]	1	-,154	-,200
	As_Serum [μg/L]	-,154	1	,320
	As_Disc [μg/L]	-,200	,320	1
HNP (n=20)	As_Bone [μg/L]	1	**,699****	,288
	As_Serum [μg/L]	**,699****	1	,156
	As_Disc [μg/L]	,288	,156	1

Graphic 3. Graphical view of mean As levels in bone, serum and disc tissues



Mercury (Hg) evaluation:

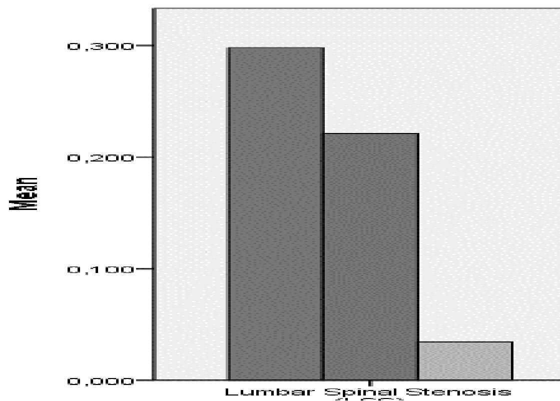
The lowest Hg levels were observed in the disc tissue in both the LSS and HNP groups (0.03±0.03 μg/L and 0.03±0.02 μg/L, respectively). The highest Hg levels in all tissues were detected in bone tissue in both groups (0.30±0.45 μg/L and 0.19±0.33 μg/L, respectively). Although not statistically significant, the Hg level in the LSS group was found to be higher in all three tissues than in the HNP group (p>0.05). In the LSS group, as the Hg serum level increased, the Hg disc level increased significantly (r=0.608, p<0.01). On the other hand, as the Hg serum level increased in the HNP group, the Hg disc level decreased significantly (r= -0.579, p<0.01). Again, an increase in Hg bone level was detected with the increase in Hg disc level in both groups (p>0.05).

Table 6. Correlations of Hg levels in bone, serum and disc tissues in both groups

Groups		Hg_Bone [μg/L]	Hg_Serum [μg/L]	Hg_Disc [μg/L]
LSS (n=30)	Hg_Bone [μg/L]	1	,190	,053

	Hg_Serum [μg/L]	,190	1	**,608****
	Hg_Disc [μg/L]	,053	**,608****	1
HNP (n=20)	Hg_Bone [μg/L]	1	**-,579****	,023
	Hg_Serum [μg/L]	**-,579****	1	,348
	Hg_Disc [μg/L]	,023	,348	1

Graphic 4. Graphical view of mean Hg levels in bone, serum and disc tissues



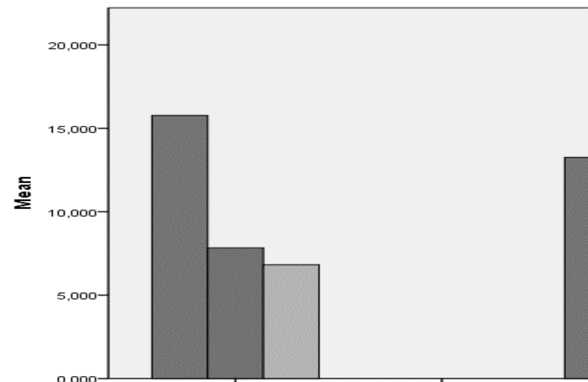
Lead (Pb) evaluation:

It was detected that the Pb bone level was approximately 2 times the Pb disc level for both the LSS and HNP groups (15.76±9.81 μg/L and 6.82±9.88 μg/L for LSS, respectively; 13.26±6.28 μg/L and 5.61±6.93 μg/L for HNP). The highest Pb level in all tissues was detected in bone tissue in both groups (15.76±9.81 μg/L and 13.26±6.28 μg/L, respectively). Although not statistically significant, it was observed that as Pb serum level increased in both groups, Pb bone and Pb disc levels decreased (p>0.05). Again, an increase in Pb bone level was detected with the increase in Pb disc level in both groups (p>0.05). While the lowest Pb level was observed in the disc tissue in the LSS group, it was found in the serum in the HNP group.

Table 7. Correlations of Pb levels in bone, serum and disc tissues in both groups

Groups		Pb_Bone [μg/L]	Pb_Serum [μg/L]	Pb_Disc [μg/L]
LSS (n=30)	Pb_Bone [μg/L]	1	-,302	,341
	Pb_Serum [μg/L]	-,302	1	-,148
	Pb_Disc [μg/L]	,341	-,148	1
HNP (n=20)	Pb_Bone [μg/L]	1	-,189	,109
	Pb_Serum [μg/L]	-,189	1	-,060
	Pb_Disc [μg/L]	,109	-,060	1

Graphic 5. Graphical view of mean Pb levels in bone, serum and disc tissues



DISCUSSION

Mechanical effects, aging, genetic, systemic and toxic factors are held responsible for the pathophysiology of intervertebral disc degeneration (7). However, the accumulation of toxic trace elements in intervertebral discs and the effects they may create have been little studied in the literature. Kubaszewsk et al. compared a number of trace element levels in intervertebral disc and bone tissue and concluded that disc tissue provides a more stable environment for elemental analysis (8). In another study, Nowakowski et al. determined the trace element in the degenerative intervertebral disc and pointed out that the levels are very different from the levels in other tissues and the existence of positive and negative correlations between the elements (9). Although several trace element level determinations and comparisons have been made in the literature in the form of human and animal studies, especially for bone, in this study, which we have done for the first time, the amount of toxic trace elements in intervertebral disc degeneration, which is thought to develop with different pathophysiological mechanisms in two different diseases, has been compared (10-12).

The effects of essential and non-essential trace elements on human bone and their toxic threshold limits are stated in plasma, blood, and urine, and it is said that no toxic side effects are observed below

these amounts (13). However, the effects of these trace elements on body metabolism at under the toxic levels and their relationship with some chronic diseases have not been clearly demonstrated yet. In our study, the serum, bone and intervertebral disc levels of five toxic trace elements (Cd, Al, Pb, Hg, and As) were compared and the results were tested to see if they were statistically significant. Cd element was found to be lowest in bone in both LSS and HNP groups (0.30±0.10 µg/L and 0.32±0.12 µg/L, respectively).

On the other hand, it was found that it accumulated more in the intervertebral disc tissue than in the bone in both groups and was slightly higher in the LSS group. The serum level of Cd in the HNP group was significantly higher than the serum level of the LSS group. In addition, while Cd serum and bone levels were inversely proportional in the LSS group, this situation was found to be directly proportional in the HNP group. It is known that the Cd can have toxic effects in many organs in humans (14). Osteotoxic and osteoporotic effects were observed especially in the male and female groups made on bone (15,16). Experimental cell culture studies have shown that the Cd element triggers the apoptosis effect on rat osteoblasts with its mechanisms (17).

Again, in experimental studies, it was determined that the Cd element decreases the bone collagen content and increases the collagen solubility (18). In another experimental study performed on male rats, it was concluded that the compact bone microstructure was changed, the bone weight was affected due to decreased the vascular structure which resulted in secondary osteoporosis and decreased potential bone mechanical properties (19). The higher Cd element in the intervertebral disc in our study suggests its relationship with degenerative processes.

Studies have shown that Cd element increases osteoclastic differentiation and turns the process in favor of degeneration (20). Disc degeneration is a multifactorial process, and effects such as the initiation of disc degeneration by one or more of these factors and the insufficiency of the regeneration process, especially in HNP cases developing as a result of axial loading with acute process, by preventing regeneration with the negative effect of the Cd element, rapidly expanding the annulus tear and as a result suggesting the hypothesis that the disc may be mechanically protruding. The high level of serum Cd in the HNP group in our study supports this hypothesis. In addition, it has been determined that the Cd element has a vasoconstrictor effect on the vascular system (21). For this reason, it was thought that the nutrition of the intervertebral disc may be impaired secondarily and accelerate the degenerative process. Since the osmotic supply of the intervertebral disc would be disrupted, it has been hypothesized that the Cd element may continue to accumulate in the disc space and increase the degenerative process. As a result, it is predicted that the Cd element may directly initiate the degenerative process, either as a cofactor or as a predisposing factor in this process.

Aluminum (Al), another toxic trace element, was found to be higher in the intervertebral disc of the HNP group than in the LSS group in our study (2.97±1.50 µg/L and 2.14±1.25 µg/L, respectively, p=0.038). Al element is known to cause dementia, osteomalacia and microcytic anemia especially in dialysis patients at toxic doses (22). However, the effects on the human body in amounts below toxic limits and in chronic processes have not been clearly determined yet, and the perception of a safe metal with little effect on human health continues (23). Al element is found in almost all human body organs and tissues. The highest concentration was found in the bones after the lungs, and it was reported that nearly half of the body Al element was in the skeletal system (24). Although these rates change in patients exposed to excessive Al, such as dialysis patients, the amount of Al may also change with osteoporosis that develops with aging, and the increase in osteoclast cell activity and resorption.

There are also studies showing that it is not associated with the development of osteoporosis in elderly patients exposed to normal amounts of Al (25). In our study, bone Al element levels in both groups were found to be higher than other tissues, which is consistent with the literature. However, the fact that Al element, which was found significantly in our results, was at higher levels in the intervertebral discs belonging to the HNP group, again suggests that it may cause a degenerative event in the formation of disc herniation in the acute period, as well as the fact that the intervertebral disc, which has degenerated for some reasons and lost its normal osmotic nutrition feature, may have accumulated more Al element.

The second possibility seems more logical since there was no significant difference in bone and serum levels of Al element.

Another toxic trace element, arsenic (As), can have a toxic effect on almost all body organs and tissues (26). Although the effect of the As element, which can be stored in the bone, on the bone has not been clearly demonstrated clinically, it has been shown to cause osteoporosis by inhibiting osteoblastic activity in a few experimental studies (27,28). In our study, while there was no significant difference between the element levels between the two patient groups, it was found that while the serum level of As increased in the HNP group, the bone level also increased in direct proportion. As mentioned before, the degenerative event in the LSS group is not limited to the intervertebral disc, but develops as a result of an osteoporotic degenerative process that also affects the facet joints and the spine. On the other hand, the HNP group is a group that causes intervertebral disc degeneration and protrusion of the nucleus in a shorter time, but no osteoporotic degeneration of the bones is observed. Therefore,

As toxic element forms apatite arsenate and possibly other calcium arsenate crystals by competing with the phosphate groups in hydroxyapatite crystals via alkaline phosphatase in the HNP group where bone turnover continues (29,30). In the LSS group formed on an osteoporotic background, it will not be possible for the As element to form crystals in the bone as a result of loss of mineralization and the shift of metabolism to catabolism. For this reason, it was thought that the increase of As element in bone tissue of HNP group along with the increase in serum level may be due to the increase in arsenate crystals in the bone. In support of this assumption, in the literature, in an elderly female patient who was chronically exposed to As element, with the dissolution of calcium arsenate crystals as a result of increased bone resorption during and after menopause, As blood levels increased to toxic levels and gave clinical symptoms and signs as a result of many organ damage (31).

The other toxic trace element mercury (Hg), which we investigated in our study, was found to be the lowest at the disc level for both groups. In the literature, there is no clear data or many studies on the effects of Hg element on human bone, and bone toxicity is not mentioned. In a study conducted on men, no correlation was found between the increase in Hg level in the blood and lumbar bone mineral density, and even as in some studies, it was observed that the incidence of bone fracture development decreased with the increase of the Hg element level in the blood (32,33,34). Another data we obtained is that as Hg serum level increases in the LSS group, the Hg disc distance level also increases, and it decreases inversely with the serum level in the HNP group. Although these data suggest that the bone density is tried to be preserved with Hg increase in the LSS group, which is an osteoporotic group, this would be a weak assumption that needs proof.

Our last toxic trace element lead (Pb) was found in the bone and in the intervertebral disc distance in both groups, approximately twice its levels. It is known that Pb element has many systemic effects and is stored more in the bone in adults (35). In a study on growing rats, it was found to impair bone development (36,37). The result we found is that the Pb element is mostly found and stored in the bone tissue.

As a result, today toxic elements pose a great threat to the environment and human life (38,39). Determining the standard amounts of toxic trace elements in different organs and tissues in the human body presents difficulties. In the literature, toxic trace element amounts have been detected in some tissues obtained from cadaver studies (40,41). However, within the framework of ethical rules, it is obvious that toxic trace element research can be done and a connection with diseases can be made in materials such as biopsies taken in some diseases that require surgery. Supporting meaningful results from clinical studies with experimental studies will accelerate research on toxic elements.

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Cervical Chondrosarcoma: A critical review with an illustration of a rare technically challenging case

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ABSTRACT
Chondrosarcoma of the cervical spine is an extremely rare tumour. The indolent course and neglected behaviour of the patient often give enough time for tumour expansion. The surgical management of these types of tumours is challenging. En bloc resection is a proven ideal treatment but it is not always feasible in this region because of the proximity to vital neurovascular structures which explains the recurrence and poor prognosis of this tumour. The role of radiation and chemotherapy in these tumours is limited. We are highlighting unique huge cervical chondrosarcoma which is not mentioned in literature and its management along with a review of 34 cases, published so far.

Keywords
cervical chondrosarcoma,
treatment,
recurrence,
prognosis

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INTRODUCTION

Chondrosarcoma (CHS) comprises a heterogeneous group of cartilage matrix producing neoplasms.[1] After myeloma and osteosarcoma, chondrosarcoma is the third most common primary malignancy of bone.[2] The majority of these types of tumors are benign and metastasis occurs rarely. Incidence of CHS of the spine is 7-12% of all primary spine tumor with male predominance and usually presents at the third to fifth decade of life.[3] Most commonly it occurs in the thoracic spine (60%) followed by lumbar (20-39%) and less frequently in the cervical spine (19-20%).[4] These slow growing insidious lesions are often voluminous at the time of discovery and diagnosis is usually delayed which pose difficulty in management. Surgical treatment is ideal for these types of tumors.[5,6] However, especially in the cervical spine, due to the proximity of tumors with vitals neurovascular structures and the intricate anatomy of this region , these tumors cause great difficulty for a surgeon. We discuss a case of unique huge cervical chondrosarcoma of C3 to C5 and to the best of our knowledge, such a large tumor has not been reported in the literature. Successful complete resection of the tumor was achieved using combined posterior to anterior approach with 360 degree stablisation. We also present review of the literature of 34 cases of cervical chondrosarcomas published so far.

CASE DESCRIPTION

A 50-year-old male patient presented in our department with painless, progressive enlarging right side neck swelling for the last 5 years and weakness of all 4 limbs for the last 4 months. He was unable to walk and wheelchair-bound for the last 2 months. He also had bladder and bowel incontinence. On local examination, he had approx 8X8 cm, nontender, hard, immobile swelling over the right side of the neck,between mastoid and clavicle (Figure 1). Neurologically he had spastic quadriparesis with exaggerated deep tendon reflexes and ankle clonus . The sensation was otherwise intact. Paradoxical respiration was absent and single breath count was 15 and breath-holding time was 17 seconds. His gag reflex was intact and had no other significant neurological deficit.

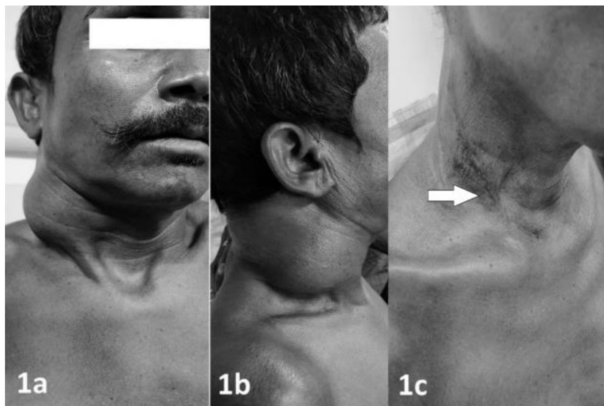

Figure 1. (a,b) Preoperative photograph of patient which shows a mass on the right side of neck; (c) postoperative photograph shows utility incision by white arrow on right side of neck with no apparent neck mass.

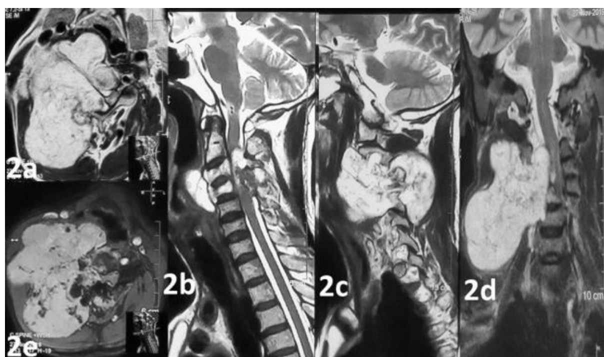

Figure 2. Preoperative magnetic resonance imaging of cervical spine (a) axial; (b,c) sagittal; (d) coronal T2 weighted images showing large hyperintense well defined lobulated predominantly exophytic lesion involving right side of vertebra with significant compressing and pushing the spinal cord on left side; (e) axial GRE sequence shows punctuate blooming foci inside the lesion.

Noncontrast computed tomography (CT) of cervical spine suggestive of the osteolytic lesion filling on the right side of the neck with C3-C5 bony destruction on the side of the tumor with irregularly mottled calcification. The vertebral artery could not be visualized on CT angiography on the right side and the internal carotid artery was pushed anteriorly (Figure 3). Magnetic resonance imaging (MRI) of the neck revealed T1 hypointense, T2 hyperintense and punctuate blooming foci on GRE sequence with large well defined lobulated predominantly exophytic lesion arising from the body and right lateral posterior arch of C3 and C4 vertebra (Figure 2). Large 8X7X7cm exophytic extramural component of the mass on right paravertebral space found which was displacing the adjacent muscles peripherally. There was Intraspinal epidural extension of tumor mass through C3-C5 neural foramina into the spinal canal and significant cord compression. A metastatic workup was done to rule out any other primary neoplastic focus or metastasis. F-18 FDG whole-body positron emission tomography with contrast-enhanced CT was performed that showed increased uptake of radiotracer on the right side of the neck with no evidence of metastasis.

Surgical technique

Because of the huge tumor and multi-compartmental involvement, combined approach with ENT specialist were planned. Due to the destruction of the C3-C4 vertebrae, the posterior cervical approach was used first then it was decided to go from anterior with the help of ENT surgeons. The patient was first placed prone and head kept in a 3-pins Mayfield fixator with the neck in the neutral position. For prolong spine surgery in a prone position, we avoid horse-shoe fixator because it may cause postoperative vision loss (POVL) .[7] A skin incision was made from inion to the C7 vertebrae. Soft-tissue dissection was done subperiosteally. Posterior vertebral elements were exposed from C1-C6 up to the lateral mass laterally but on right side lamina and lateral mass were not identified from C3-C4 due to destruction by tumor tissue. The tumor was identified with major bulk on the right side from C3-C4. The tumor was well capsulated, soft, and moderately vascular. The tumor invaded the spinous

process and right side of the lateral masses/laminae/transverse process from C3-C4.

Tumor tissue which was approached from behind was debulked in piecemeal. En-bloc excision was not possible because the tumor encased the vertebral artery and spinal cord with nerve roots. Even tiny pieces of the tumor were excised to prevent a recurrence. The cervical spinal cord which was severely compressed by the tumor was decompressed. All nerve roots were preserved and freed from surround soft tissues. Bilateral C1 lateral mass, C2 pedicle screws were inserted. Left side C3-5 and right side C5 lateral mass were placed and all metallic implants were connected with rods. The wound was closed in anatomical layers and position changed from prone to supine after placing the patient's neck on the hard cervical collar. In supine and neck neutral position, using utility neck incision [8] begins "anteriorly at the level of the cricoid and carried laterally to the posterior border of the sternocleidomastoid, continuing its gradual curve upward to end behind the prominence of mastoid process".The sternocleidomastoid muscle was divided to ease for tumor excision. ICA was identified and separated with the tumor capsule.

The major bulk of Tumor tissue along with the capsule was excised from the different compartment of the neck to create a large cavity. This anterior tumor cavity joined with the cavity made posteriorly from the previous approach. After dissecting longus colli over the C3 and C4 vertebral body, anterior tubercles were exposed. C2-3, C3-4, and C4-5 discectomy were performed and posterior longitudinal ligament was also excised. Partially destroyed vertebral bodies of C3 and C4 were excised in piece-meal fashion with the help of rongeurs. Resection was performed carefully to avoid any remnants of the tumor. After preparing endplates of C2 and C5, a corpectomy titanium mesh cage was fixed in between vertebral bodies. Artificial bone graft placed in the mesh cage to enhance the fusion. Corpectomy screws in C2 and C5 were also inserted to achieve fixation. After careful inspection of tumor residuals and bleeding spots, wound closed in anatomical layers. Just after surgery patient was

neurologically the same as before, he was advised to wear a hard cervical collar. Before discharge on the fifth day, the patient developed signs of recovery in the form of a reduction in spasticity.

Histopathology

Histologically this tumor turn out to be well differentiated conventional CHS. Pathologically it is characterized by well circumscribed cartilaginous tumor with increased cellularity of chondrocytes with occasional bi to multinucleation. Moderate nuclear pleomorphism and cytoplasmic vacuolization within the chondroid matrix (Figure 5).

Follow-up

The patient was followed up clinically after 1, 3 and 6 months. The patient showed gradual improvement in his motor power of limbs. After a couple of months, he started walking and became independent after 3 months. Now the power in his upper and lower limbs is 4+/5 on MRC grade with improvement in bladder and bowel continence. As per our protocol, noncontrast computed tomography (NCCT) scan of the cervical spine was performed postoperatively to know the position of implants (Figure 4).

Table 1. Cervical Chondrosarcoma: review of 34 cases from literature

SN	Author / year	Case no	Age/sex	Level	Surgery	Grade ‡	Adjuvant radio-therapy	Follow up in months	outcome	Recurrence/duration in months
1	Arlen/1970[21]	1	56y/M	C5	STR	NS	RT	36m	death	Y/6m
		2	42y/M	NS	STR	NS	N	60m	death	Y/NS
2	Blaylock/ 1976[22]	1	43y/M	C2	GTR	Low grade	N	12m	Alive	N
3	Wronski/ 1974[23]	1	22y/M	C5-6	STR	Well diff	RT	2m	alive	N
4	Yang /2012[5]	1	29y/M	C7	STR	Low grade	N	46m	death	Y/21m

		2	32y/M	C6-7	En bloc resection	Low grade	N	140m	Alive	N
		3	42Y/M	C6	STR	Low grade	N	36m	Death	Y/24m
		4	22y/M	C7	GTR	High grade	RT	92m	Alive	N
		5	67y/M	C3	GTR	Low grade	RT	37m	alive	N
5	York / 1999[6]	1	64y/M	C4	STR	Average grade	N	7m	Death	N
		2	54y/M	C7	GTR/GTR#	Average grade	RT/N	67.2m	alive	Y/(3.7m/ 1.2m)
		3	51y/F	C7	STR/STR#	High grade	N/RT	10m	Death	Y/(4m/N)
		4	64y/F	C4	STR/STR/STR/STR†	Low grade	RT	3.5m	Death	Y/ (9/6/6/N)
6	Tessitore/ 2006[24]	1	22y/F	C7	STR	Clear cell	Proton beam therapy	12m	Alive	N
7	Ohue/ 1995[25]	1	48y/M	C5-6	GTR	Low grade	N	36m	Alive	N
8	Simsek/ 2009[16]	1	18y/m	C3	GTR	NS	N	12m	Alive	N
9	Foweraker / 2007[26]	1	43y/F	C1	STR	Well differ	RT	107m	Alive	N
10	Dejean / 1998[27]	1	64y/M	C7	STR	Average grade	N	30m	Alive	Y/24m
11	Finn / 1984[28]	1	45y/M	C7	GTR	Low grade	N	228m	Alive	N
		2	64y/M	C4	GTR	Average grade	N	8m	Death CHF	N
12	Merchant / 2014[29]	1	30y/M	C5-7	GTR	Low grade	N	12m	Alive	N
13	Boriani/ 2000[15]	1	13y/M	C7	En bloc resection	NS	N	236m	Alive	N
		2	31y/M	C5-7	En bloc resection	NS	N	40m	Alive	N
14	Strike / 2011[30]	1	60y/F	C2-4	GTR	NS	N	24m	Death due to pul mets	NS
		2	37y/ F	C4-C5	STR	NS	Proton beam therapy	48m	Death due to pul mets	NS
		3	79y/M	C5-C6	GTR	NS	N	48m	alive	N
		4	46y/M	C1-C2	GTR	NS	N	78m	alive	N
15	Sakayama/ 2004[31]	1	58y/M	C2	STR	Average grade	N	36m	alive	Y/12m
16	Gebhart/ 2008[32]	1	30y/M	C4	En bloc resection	Low grade	N	132m	Alive	N
17	Camins/ 1978[33]	1	20y/F	C5-6	GTR	Low grade	RT	1m	Alive	N
18	Shives/ 1989[10]	1	33y/F	C4	STR	Average grade	RT	14m	Death due to disease	NS

	2	58y/ M	C7	STR	Average grade	N	60m	Death due to disease	NS
	3	35y/ F	C7	STR	Low grade	RT	233m	Death due to disease	NS
	4	59y/M	C5	STR	Low grade	N	43m	Death due to disease	NS

NS- not specified; M-male, F-female; GTR- gross total resection, STR- subtotal resection; Grade: NS- not specified, RT-radiotherpay, N-no radiotherapy, m- months; recurrence (Y- yes, N-no recurrence), NS- not specified; # 2 surgical procedures in the same patient; † 4 surgical procedures in the same patient; ‡ histological grade according to Thomson and Turner-warwik11 (low, average and high grade).

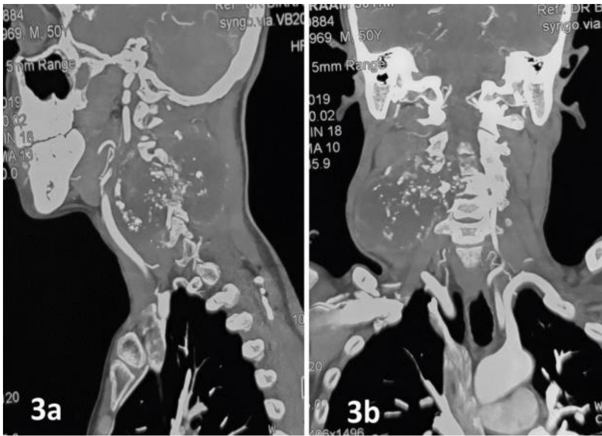

Figure 3. Preoperative computed tomography angiography (a) sagittal view shows mottled calcification within large osteolytic lesion with anteriorly displaced carotid artery; (b) coronal view shows dominant left vertebral artery without visualization of right vertebral artery with partial destruction of multiple vertebrae.

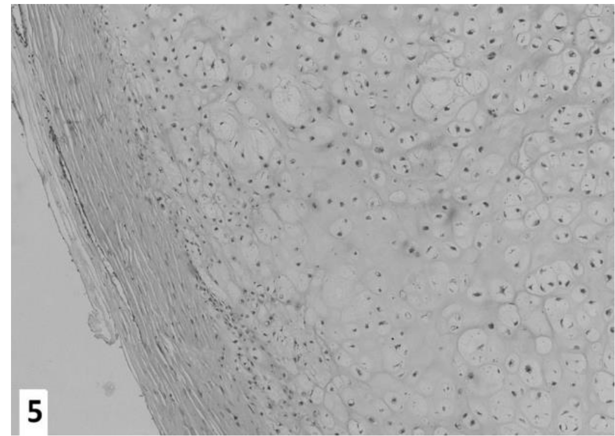

Figure 5. H&E stain 100x: shows the well circumscribed cartilaginous tumor with increased cellularity of chondrocytes with occasional bi to multinucleation, moderate nuclear pleomorphism and cytoplasmic vacuolization within the chondroid matrix.

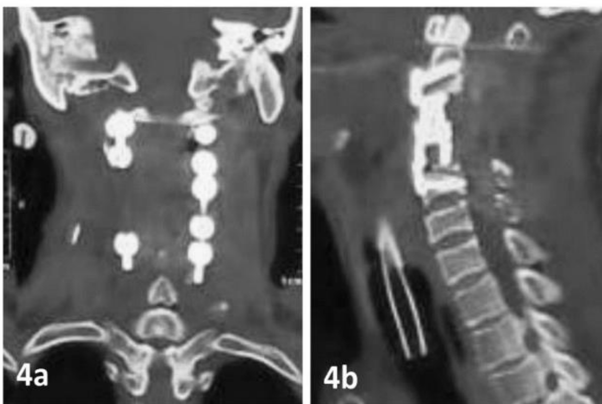

Figure 4. Postoperative computed tomography of cervical spine (a) coronal view showing metallic construct consist of bilateral C1 lateral mass and C2 pedicle screws, left side C3,5,6 and right side C6 lateral mass screws fixation with rods; (b) sagittal view showing distractable interbody cage in C2-C5 vertebral space with plate/screws.

Discussion

Spinal chondrosarcoma is a rare entity, out of the vertebral column cervical spine is the least common site affected.[3,5,6] We reviewed 34 cases of cervical chondrosarcomas in literature published by 18 authors so far (Table 1). Demographically mean age of presentation is 43.5 years and males are more commonly affected than females (25:9). Presenting feature of CHS patients showed indolent growth pattern and most common presenting symptom is local site pain.[6] Neurological features are not uncommon and present as myelopathy or radiculopathy.[9] As the tumor grows further from the vertebral body or posterior elements, it appears as a palpable mass in the neck or back. Yang et al reported in his study that the duration between the symptoms and diagnosis ranges from 3-60

months.[5] Our patient had a history of 5 years, the reason for this long-duration presentation was ignorance. The majority of tumors arise from the normal bone without any association of any benign cartilaginous pathology.[10] Various allelic losses and nonrandom genetic aberration occur in a majority of tumors (70%), Several mutations are associated with malignant degenerations of chondroma which includes amplification of c-Myc oncogene and a gain of chromosome 8. The loss of chromosome 6 and the gain of 12q12 also related to high-grade CHS. [3,4]

Yang et al reported that the tumor originated most commonly from the posterior part of the vertebral bodies (73.3%) as compared to posterior elements of the vertebra. Extraosseous paravertebral involvement also occurred in the majority of cases in his case series.[5] Our case review showed that the C5-7 vertebral region is most commonly affected by the tumor. However, no specific cervical level for common occurrence is mentioned in literature. Radiological diagnosis includes characteristics CT findings of bony destruction with irregularly mottled calcification with low attenuation of the mass lesion due to the water content of the cartilage matrix. MRI is also very useful to know the extent of soft tissue invasion.

T1-weighted images showed hypointense and T2-weighted demonstrate hyperintense images of a lesion with heterogeneous or peripheral ring type of enhancement on intravenous gadolinium injection.[3] Increased uptake of radiotracer in the region of tumors is often shown in bone scanning. Despite the lower proportion of the malignant nature of CHS, PET CT is a useful tool to diagnose the extent of disease spread. It helps in the planning of management. PET CT did not demonstrate any secondary deposition or evidence of metastasis in our patient.

Previously Thomson and Turner-Warwik classified the CHS histologically into low, average and high grade.[11] The world health organization (WHO) described CHS as nonmeningothelial, mesenchymal neoplasm.[12] Based on histologic features such as tumor cellularity, mitosis nuclear atypia, and stromal content, the grading system is used by WHO. It ranges from grade I(low grade) to grade IV (high grade). One of the most important prognostic indicators of CHS is WHO grade. In low-grade CHS, 10 years survival is 90% where it is 30-40% in high grade.[4] In our review of cases we also found 47% of cases were low grade CHS which was the most common histological type among them. Chondrosarcomas are also classified into several subtypes based on stereotypic histologic features which include conventional, mesenchymal, clear cell and dedifferentiated types.[13]

Conventional CHS is the most common subtypes (around 80%) and almost all of them are of low grade. Malignant degeneration of low-grade conventional CHS gives rise to a dedifferentiated type. Mesenchymal CHS is very much similar to dedifferentiated CHS and it has a poor prognosis with a 5-year survival rate of 50%. Finally, clear cell CHS have a better prognosis than mesenchymal or dedifferentiated subtype (McLoughlin).[3]

In tumor management, histopathological diagnosis is required. Percutaneous CT guided biopsy can be performed in this type of tumor but it requires careful interpretation. Lis et al reported 24% false-negative results in these types of sclerotic lesion.[14] Hence it was decided to undergo the excision of the tumor without a biopsy. Due to the ineffectiveness of conventional chemotherapy and radiotherapy, surgical management in the form of en-bloc resection is the only ideal method for the treatment of CHS.[5,6] Out of 34 patients in case review, en bloc resection was achieved in 4 patients. Gross total resection was associated with a better outcome as compared to STR. GTR performed in 13 and STR in 17 patients. Local recurrence is reported in 9 patients, out of which 88.9% associated with STR. Mean follow up was 58.4months. Out of 14 deaths, 12 deaths (85.7%) are recorded among those patients who underwent STR of the tumor.

Boriani et al. reported the outcome difference of en-bloc resection and intralesional excision of CHS in his study.[15] He found no local recurrence in 9 patients who were treated with en-bloc resection with wide or marginal margin whereas, there was local recurrence in all 13 patients treated with piece-meal or intralesional excision. However, due to the proximity of vital structures and technical obstacles like bleeding or spinal cord injury, it is not always possible to secure en-bloc-resection. Many case report also suggests that circumferential excision of cervical CHS could provide preserved neurological status with a long recurrence-free survival period.[16,17] Preoperative planning with a multidisciplinary approach is very essential in these

types of huge tumors. Because of the destruction of long segment vertebral column, postoperatively spinal instability would be expected as experienced by many authors, hence tumor excision along with reconstruction was decided. [16,18]

Because of huge size of tumor and restriction of neck movements, intubation itself was a challenging task. Initially we tried en-bloc resection but due to nonvisualization of vertebral artery in imaging which was untraceable even on intraoperative ultrasound and circumferential involvement of spinal cord and nerve roots, enbloc surgical decision was not feasible, hence piecemeal excision of tumor tissue along with its capsule was performed. We successful preserved all nerve roots without injury to major vessles. Follow up radiology is required to detect the local tumor recurrence or distant metastasis and it is decision making in future adjuvant therapy if possible.

Most studies reported that the adjuvant chemotherapy (CT) and radiotherapy (RT) has only limited role in CHS treatment.[5,6,15,19] Our case review also supports the limited role of RT as adjuvant therapy. RT received in 13 patients out of which 6 patients did not survive. This ineffectiveness may be due to that chemo or radiotherapy both acts on fast dividing cells and chondrosarcoma are slow growing tumors with low fractions of dividing cells. In addition to slow grade, chondrosarcomas have a rich extracellular matrix and poor vasularity, which produce hindrance of chemotherapy drug penetration.[5] Hence adjuvant therapy is not included in standard treatment recommendation.[2] Nevertheless, high dose radiotherapy or proton beam therapy may be useful to slow tumor growth and tumor recurrence but the long term results of this therapy are still unknown. Gwak et al reported that hypofractionated cyberknife stereotactic radiation therapy can potentially provide promising results in these types of radioresistant tumors.[20]

Despite the massive size of tumor and involvement of large areas of the neck and cervical spine, we successfully achieved the goal of surgery by doing complete tumor excision and restored the spine integrity by 360-degree spinal fixation. Our case is unique from all the cases reported in the literature that no case exists with so much extensive involvement of the cervical spine.

Conclusion

Huge cervical chondrosarcoma is rare and usually, these massive tumor presents with neurological deficits. Management of neglected cervical chondrosarcoma is technically challenging but adequate anatomical knowledge and detailed surgical planning in the form of a multimodality approach can prevent permanent disability and increase disease-free survival period.

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Intradiploic meningioma. A series of two cases and literature review

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ABSTRACT
Intradiploic meningioma is a rare subtype of primary intraosseous meningiomas. The convexity and the skull base are the two primary locations for intraosseous meningiomas. They usually present as a painless expansile mass without any neurological findings. Intradipoic meningiomas are seldom correctly diagnosed preoperatively and are usually mistaken for primary bone tumours. CT scan head with bone windows and contrast-enhanced MRI brain should be done for diagnosis and evaluation. Intraosseous meningioma should be considered in the differential diagnosis of patients presenting with osteoblastic or osteolytic skull lesions as the treatment of choice is resection, which is potentially curative.

Keywords
primary intraosseous meningioma, intraosseous meningioma, intradiploic meningioma

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INTRODUCTION
Primary intraosseous meningioma is the most uncommon manifestation of meningiomas.1 The extradural or ectopic meningiomas form 1-2 % of all meningiomas, which was first described by Winkler, in 1904 [5,8]. Most of the intraosseous meningiomas arise from cranial bones, although a few cases in the mandible have been reported [4]. Intradiploic meningioma is a term to describe the purely calvarial meningioma. Preoperative diagnosis of Intradiploic meningioma is very difficult and often diagnosed as bone tumours or metastasis. Here we are reporting two cases of intradiploic meningioma presented with painless scalp swelling and surgically treated with good outcome.

CASE REPORT
Case 1
A 45-year-old man presented with a painless scalp swelling in right fronto-parietal region. The scalp swelling was present for last 6 years and had gradually increased in size. There was no history of trauma. Physical examination revealed a swelling in the right fronto-parietal region about 3 cm in diameter. Swelling was non tender, immobile and not adhered to the overlying skin. The patient had no neurologic deficit.

The laboratory studies were unremarkable. CT head revealed a right-sided fronto-parietal intradiploic mass expanding the calvaria with marked thinning of both inner and outer tables with areas of cortical breach. The lesion was protruding extra cranially causing focal bulge over the scalp. The intracranial component was causing compression of underlying brain parenchyma. MR imaging showed a solitary calvarial mass lesion of the frontoparietal region that was hyper intense on T2-weighted images, hypo intense on T1-weighted and was showing marked post contrast enhancement. MR imaging also demonstrated intracranial but extradural extension of the lesion. (Figure 1) Preoperative diagnosis of primary or secondary malignant osteolytic lesion was made. Complete workup was done to rule out calvarial metastasis but no primary could be found. Per-operatively scalp was easily elevated from tumour and there was destruction of both the inner and outer tables of the claverium with extradural extention. Total tumour removal with a wide surgical resection followed by cranial reconstruction was done. Final histo- pathological diagnosis of Intra-diploic meningioma was made. At one year follow up, patient was doing well without any evidence of recurrence.

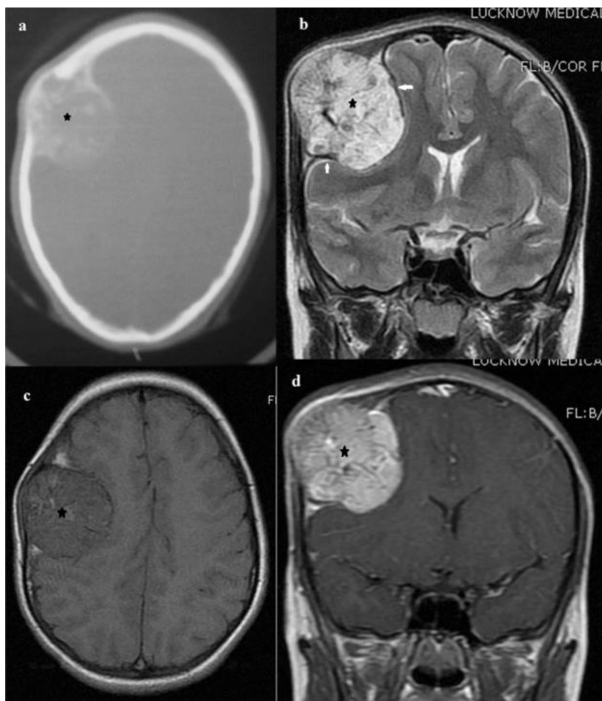

Figure 1. (a) axial image of NCCT Brain in bone window shows right-sided fronto-parietal intra-diploic mass (*) expanding the calvarium with large intra and extra cranial components causing marked thinning of both inner and outer tables with areas of cortical breach. MRI brain shows large intra-diploic expansile lesion (b) hyper-intense on coronal T2WI, (c) hypo-intense on axial T1WI, and (c) marked enhancement on coronal fat supressed T1WI. Displacement of duramater and compression of underlying brain parenchyma by the intracranial component of the lesion is clearly visible (arrow).

Case 2

A 50-year-old man presented with a painless progressive swelling of scalp the right frontal region and headache for eight years. There was no history of trauma. Physical examination revealed a swelling of about four cm diameter in the right frontal region. Swelling was non tender, nonmobile and not adhering to the overlying skin.

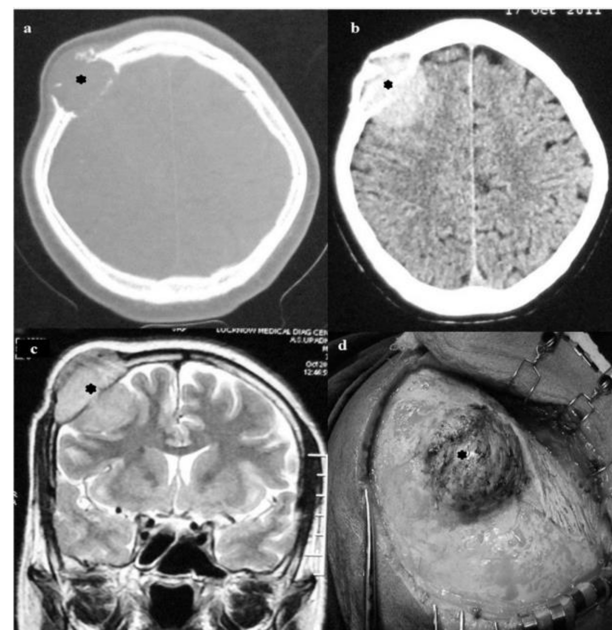

Figure 2. (a) axial image of NCCT Brain in bone window and (b) soft tissue window shows right-sided frontal intra-diploic expansile lesion (*) with intra and extra cranial components causing destruction of both inner and outer tables. MRI brain shows large intra-diploic expansile lesion (c) T2WI of MRI brain in coronal plane shows hyper-intense lesion causing compression of underlying brain. (d) Per- operative image showing extra- calvarial component of the lesion.

The patient had no signs of neurologic deficit. The laboratory investigations were within normal limits. CT Scan of head revealed a right-sided frontal intradiploic mass expanding the calvaria with destruction of both inner and outer tables. The lesion was extending both intra- and extra cranially.

MR imaging showed a solitary calvarial mass

lesion of the frontal region that was hypo intense on T1-weighted and hyper intense on T2-weighted images with post contrast enhancement. The lesion showed intracranial but extradural extension of the lesion. (Figure 2) Preoperative diagnosis of primary or secondary malignant osteolytic lesion was made. Complete workup was done to find out primary lesion anywhere else in the body, however tests were negative. Per-operatively scalp was easily elevated from tumour and there was destruction of both the inner and outer tables of the calvarium with extradural extension of the lesion. Total tumour removal with a wide surgical resection followed by cranial reconstruction was done. Histo-pathological features were suggestive of Intra- diploic meningioma. On six months follow up patient was well without any evidence of recurrence.

Discussion

Primary intraosseous meningioma is a subtype of extradural meningiomas that arise in bone and does not involve the underlying dura [7]. Approximately 68% of the primary extradural meningiomas involved the calvaria. Intraosseous meningiomas most commonly involve the fronto-parietal and orbital regions. Primary extradural meningiomas occur approximately with equal frequency in both sexes. Primary intradural and extradural meningiomas occur predominantly during later decades of life with a second peak incidence in younger patients (especially during the second decade) in primary extradural meningiomas [3]. Lang et al. classified interosseous meningiomas as type I- purely extracalvarial, type II- purely calvarial and type III- calvarial with extracalvarial extension. The type II and III are further divided as convexity (C) or skull base (B) forms [3]. Thus, intraosseous meningiomas could be considered Type II or III primary extradural meningiomas based on whether extracalvarial extension is observed or not, while intradiploic meningiomas are type II only [3].

There are three explanations for the origin of primary intraosseous meningioma. First being the trapping of arachnoid cap cells in the cranial sutures during birth and head molding suggested by Azar-Kia, et al. It is thought that the formation of small meningoceles containing arachnoid cells during that period which got entrapped within the cranial sutures and give rise to intraosseous meningiomas later in life [1]. Second postulated theory states that lesions are secondary to previous trauma which was first described by Cushing and Eisenhardt [2]. Thirdly it has been postulated that meningiomas may arise from mesenchymal precursors, in reaction to a yet unknown stimulus [9].

Usually, the Neurological signs and symptoms are absent in the patients. A painless expansile mass without any neurological finding is usually the initial symptom. The symptoms are dependent on tumor location, size, and involvement of the neighbouring structures. Meningiomas presenting with scalp swelling and extracranial soft-tissue masses are more aggressive in nature than others [10]. Osteolytic meningiomas associated with a soft-tissue component must be considered malignant until proven otherwise [6].

Although calvarial meningiomas have been observed to be benign and slow-growing, but they are more prone to develop malignant changes (11%) compared with intracranial meningiomas (2%) [3]. Bone remodelling and calvarial thickening at the site of origin of the meningioma are frequent with these tumors. In calvarial meningiomas osteolytic skull lesions are also known to occur. Hyperostosis is the most common radiographic finding (reported in 59% of the cases) but osteolysis, as in our case is also reported in 35% of the cases. Mixed picture of hyperostosis and osteolysis is reported in 6% of the cases in the literature [2]. Scalp swelling with osteolytic skull lesions and extracranial soft-tissue masses suggest the aggressiveness of meningioma.

CT scan head with bone windows is necessary to detect the tumor, cortical destruction, and both intra- and extraosseous extension. MRI brain provides a better anatomic delineation in the evaluation of the soft tissue component and extradural extension of the lesion. Although rare, intraosseous malignant meningioma should be excluded in an osteolytic skull lesion associated with soft-tissue component.

Complete tumour excision with a wide surgical resection followed by cranial reconstruction is the treatment of choice in symptomatic primary intra-diploic meningioma. In subtotal resection due to involvement of critical structures within the orbit, paranasal sinuses, or skull base radiological follow up is mandatory [2]. In symptomatic residual lesions and lesion showing evidence of progression adjuvant radiation therapy is recommended [2].

Conclusions

In the patient having osteolytic calvarial lesions associated with a soft-tissue component, a primary intraosseous meningioma should be considered. Osteolytic meningiomas associated with a soft-tissue component must be considered malignant until proven otherwise. CT scan head with bone windows and MRI brain should be done for diagnosis and evaluation. By keeping the defferential diagnosis in mind while evaluation, this can be treated with good outcome. Complete excision with a wide surgical resection followed by cranial reconstruction should be done.

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Cervical carotid artery vasospasm during cerebral angiography

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Keywords
cerebral angiography,
internal carotid artery,
vasospasm

ABSTRACT

Background: Vasospasm occurs commonly in the intracranial arteries as a complication of subarachnoid haemorrhage. On the other hand, extracranial Internal carotid artery (ICA) vasospasm is scarce, and it may occur due to mechanical manipulation during cerebral angiography. We report a case of cervical carotid artery vasospasm during diagnostic cerebral angiography, which caused anterior cerebral artery territory hypoperfusion, to discuss potential risk factors.

Case description: For a 22-year-old female with a ten-year history of epilepsy on multiple drugs, brain magnetic resonance imaging (MRI) showed frontal periventricular developmental venous anomaly. Diagnostic catheter cerebral angiography was used to better identify the vascular abnormality. In the procedure, extra steps were performed, including instruments being sterilized with CIDEX® OPA Solution (phthalaldehyde as the active ingredient), the reuse of the set including the catheters more than twice or triple times, and cold temperature of normal saline that was used in the flushing procedure. Under conscious sedation, the procedure went uneventful until the catheterization of the left carotid artery was performed, where severe vasospasm was noticed in the extracranial ICA, followed by cessation of flow in the ipsilateral ACA. Pulling the catheter to a more proximal location in the extracranial ICA was performed to alleviate the vasospasm. It took twelve minutes for the circulation to be restored, and that was under continuous irrigation and flushing. The patient did not develop any symptoms throughout the procedure or post-procedural course.

Conclusion: Chemical irritation from the sterilizing agent and reuse of the catheters could cause extracranial ICA vasospasm.

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INTRODUCTION

Vasospasm in the intracranial arteries is a common complication of subarachnoid hemorrhage, cerebral vasculitis, and reversible cerebral

vasoconstriction syndrome (RCVS) (6,20). Extracranial internal carotid artery (ICA) vasospasm, on the other hand, is rare, and its potential causes may include ergot poisoning or mechanical manipulation (2,16,8). Regarding mechanical irritation, it can attribute either to external manipulation or intraluminal stimulation. Intraluminal stimulation can be seen during catheter cerebral angiography, and it may trigger vasospasm in the ICA (1,10). However, extracranial vessels vasospasm can occur due to various causes depending on the procedural setting and the patient's condition. We report a case of cervical carotid artery severe vasospasm that causes anterior cerebral artery (ACA) territory hypoperfusion during diagnostic cerebral angiography with a discussion of potential factors.

CASE SCENARIO

A 22-year-old female with a ten years history of epilepsy on multiple drugs. Brain magnetic resonance imaging (MRI) showed frontal periventricular developmental venous anomaly (DVA). Diagnostic catheter cerebral angiography to better identify the vascular abnormality. The angiography procedure went with the typical steps used in every case in our institution. It is noted that we are obligated to reuse the instruments because of the cost-related issues and the absence of an insurance system in Iraq. That is why only the additive step that procedural set was reused more than two times at least after the sterilization with CIDEX® OPA Solution (phthalaldehyde as the active ingredient).

Underwent conscious sedation, the procedure went uneventful until the catheterization of the left carotid artery was performed, where severe vasospasm was noticed in the extracranial ICA, followed by cessation of flow in the ipsilateral ACA. We tried to pull the catheter to a more proximal position (2 cm below the skull base) in the ICA along with irrigation with warm normal saline multiple times was done, and it didn't work. So, the subsequent trial was to put the catheter in an even more proximal site at the left common carotid artery, and an irrigation procedure was performed again. It took twelve minutes for the ACA circulation to be restored, and that was under continuous irrigation and flushing (Figure 1). During these events, the patient was assessed clinically because she was under conscious sedation, and fortunately enough, the patient didn't develop any symptoms throughout the procedure and during the post-procedural course.

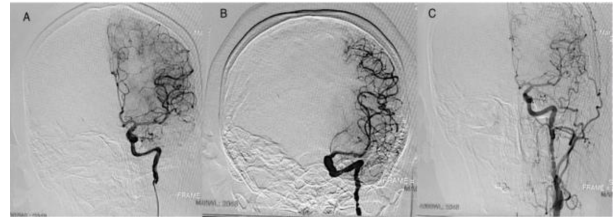

Figure 4. Cerebral angiography images. (A) is showing the left ICA (anteroposterior view) showing the normal (pre-vasospasm) ICA with its branches. While (B) is showing ICA (anteroposterior view) showing spasm in the cervical of the ICA with ipsilateral ACA flow absence. (C) shows left ICA (anteroposterior view) showing partial resolution of the vasospasm in the cervical ICA with reestablishment blood flow in the ACA.

DISCUSSION

Intracranial vasospasm is temporary, focal, or diffuse narrowing in the caliber of intracranial arteries that mainly contribute to the arterial wall's smooth muscle contraction (17). It can be classified into intracranial or extracranial, depending on the ICA segments. Intracranial vasculatures are prone to vasospasm compared to extracranial (5,9). However, extracranial vasculatures vasospasm was also reported (2,16). Extracranial ICA vasospasm can be attributed to many factors that may be procedural-associated or patient-related.

In cerebral angiography, advancing the catheter and wires in the ICA may induce mechanical vasospasm. Ishihara H et al, examined 147 patients who underwent therapeutic neuro-endovascular procedures; severe vasospasm was noted in up to 40% of the sample (8). Individuals with significant anxiety, having a history of vasospasm in diagnostic angiography, and increase vascular tortuosity with a degree ≥ 30° vessel bends were all potential risk factors for severe vasospasm (12). Patients with high anxiety have a high probability of developing vasospasm in both general anesthesia and conscious sedation because of the increase in the sympathetic response in the body during the procedure (8,12). The history of diagnostic angiography and the increase in vascular tortuosity may cause vasospasm because of mechanical irritation of the vascular lumen.

Based on the literature review, the intracranial location of the catheter within the ICA is a well-known cause of irritation in the form of pain or vasospasm (2,8,9). However, extracranial ICA vasospasm is either not well reported or usually doesn't affect the distal flow (9). During the procedure, the wire may induce vasospasm if it reaches the skull base. However, in our case and our practice, we localize the wire in the proximal portion of the cervical carotid. Here, we describe a case with apparent distal flow affection in the form of ipsilateral ACA flow cessation due to cervical carotid vasospasm.

Vasospasm due to mechanical irritation caused by sterilizing material is not described in the literature. In our case, after exclusion of the above risk factors, we propose the following points as potential causes for severe vasospasm, 1) chemical irritation with the use of CIDEX® OPA Solution, which has phthalaldehyde as the active ingredient, the primary tool for the sterilization of the procedure tools 2) re-sterilization of the equipment in the procedure and the set may be used twice or triple times 3) cold temperature of normal saline that was used in the flushing during the procedure. In the procedure, the reuse of the catheters has obvious advantages from a cost perspective and has several disadvantages because catheters are made for single-use (15). The practice of reusing catheters in cerebral angiography is common, and in Iraq, the re-usage can occur particularly when there is a limitation of resources.

The treatment of vasospasm in the setting of subarachnoid hemorrhage is well established by using calcium channel blockers (4,7). Mechanical irritation-related-vasospasm treatment needs further studies because it is clinically significant, and it is difficult to pinpoint the cause. There are a few reports on the efficacy of intra-arterial injections of calcium channel blockers, papaverine, and lidocaine in the mechanical irritation-related-vasospasm. Still, no comprehensive studies have been conducted on this topic (3,14). Reports listed that deep anesthesia or muscle relaxants may effectively reduce vasospasm and others suggested warm compression, especially while using the radial access (11). We propose different steps in the management of vasospasm in the setting of neuro-endovascular procedure, 1) dragging the catheter in a more proximal portion within the affected artery (in our case, the cervical carotid), 2) copious irrigation with normal saline, 3) administration of vasodilators as discussed above, 4) the use of angioplasty. The use of one of these steps or a combination may result in the resolution of the vasospasm. In our case, continuous irrigation with warm normal saline was sufficient to resolve the vasospasm and restore the distal circulation.

As for prevention, vasospasm is expected to be relieved by prophylactic treatments in patients with risk factors such as sedative drugs and warm compresses (3,12). Also, using the optimum sterilization technique is needed as well as utilizing the tools once only is the preferable setting. While in limited resources setting where re-usage represents the only viable option, sufficient irrigation to ensure clearance of any sterilizing agent is mandatory. Flushing and the irrigating fluid' temperature can be monitored to use the fluid with body temperature as much as possible.

Clinical assessment of the patient is quite ready if the patient is under conscious sedation, and this fits well for diagnostic cerebral angiography. However, in certain cases, general anesthesia can be applied. Sriganesh K et al, proposed that the Bispectral index BIS might be utilized to detect and monitor substantial changes in regional cerebral blood flow following neuro-endovascular procedures with general anesthesia (19). In our case, the patient was on conscious sedation, the assessment of vasospasm was imminent, and it was carried out radiologically and clinically during the procedure.

In summary, vasospasm may occur in diagnostic cerebral angiography due to mechanical manipulation, chemical irritation, equipment usage, and temperature fluctuations in normal saline. The treatment options include the administration of intra-arterial calcium channel blockers or papaverine, or lidocaine. Prevention can be achieved by targeting the risk factors. Vasospasm as a complication during endovascular management should be highlighted and kept in mind during the explanation of the procedure to the patient, and it should be disclosed as there is a plurality of causes of this condition; we haven't scratched its surfaces yet.

Conclusion

Cervical carotid artery severe vasospasm is a rare complication during diagnostic cerebral angiography. Chemical irritation from the sterilizing

agent and re-usage of the catheters should be kept in mind as potential causes of vasospasm.

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Coil migration during pressure-cooker technique for cerebral AVM. A case report

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Keywords
arteriovenous malformations, pressure cooker technique, endovascular embolization

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ABSTRACT

Introduction: In recent decades, the endovascular treatment of cerebral arteriovenous malformations (AVMs) has advanced. However, it still carries risks of unanticipated complications. Coil migration is a reported complication of aneurysmal coiling procedures. Herein, we report a case of early intraprocedural coil migration during pressure cooker technique embolization of right thalamic AVM, discussing the management and potential explanations. The literature showed no report of coil migration after the pressure cooker technique in the form of coil-augmented Onyx injection technique (CAIT).

Case description: An otherwise healthy 26-year-old female suddenly developed a severe headache with no loss of consciousness. Computed tomography (CT) scan of the head illustrated intraventricular haemorrhage. Magnetic resonance imaging (MRI) showed the bag of worms' sign in the right thalamic area. The size and location of the AVM prompted the decision for multistage endovascular embolization using onyx. In the anterior circulation, the right A5 arterial feeder has a high flow which indicates the pressure cooker technique embolization in the form of CAIT. In the procedure, early detachment and migration of the coil occurred in the medial prefrontal branch through the anterior cerebral artery. No intervention to retrieve the coil was carried out because the detachment piece is small and lodged distally. Onyx was injected directly without the coil because of the risk of radiation to the patient. Otherwise, the intraprocedural and postprocedural courses went uneventful.

Conclusion: This is the first report of coil migration during the pressure cooker technique with CAIT for the right thalamic AVM.

INTRODUCTION

Therapeutic embolization of cerebral arteriovenous malformations (AVMs) was documented for the first time by Luessenhop and Spence in 1960 (3). Since then, endovascular treatment has advanced

significantly in recent years, particularly for AVMs, and it is now utilized as a preoperative adjuvant before microsurgery or radiosurgery and as a curative option (11). However, this treatment still carries the potential for unanticipated complications (5,15). Coil migration is a reported complication of aneurysmal coiling procedures with up to 6% of the cases (4). However, the literature showed no report of coil migration after the pressure cooker technique in the form of coil-augmented Onyx injection technique (CAIT) or balloon-assisted embolization of AVM. Herein, we report a case of early intraprocedural coil migration during CAIT of right thalamic AVM with a discussion about the management and potential explanation.

Case description

An otherwise healthy 26-year-old female suddenly developed a severe headache which made her seek the private clinic. Her initial Glasgow coma scale (GCS) is 15/15 and muscle power grade 5 bilaterally on the Medical Research Council of Canada (MRC) scale. Her initial computed tomography (CT) scan of the head illustrated intraventricular hemorrhage in the lateral ventricles. Her magnetic resonance imagining (MRI) showed the bag of worms' sign in the right thalamic area. She was advised to undergo diagnostic catheter angiography, which showed right thalamic arteriovenous malformation with multiple arterial feeders from both anterior and posterior circulations (Figure 1). The patient doesn't have other associated abnormalities such as aneurysm, varix, stenosis, and steal phenomenon.

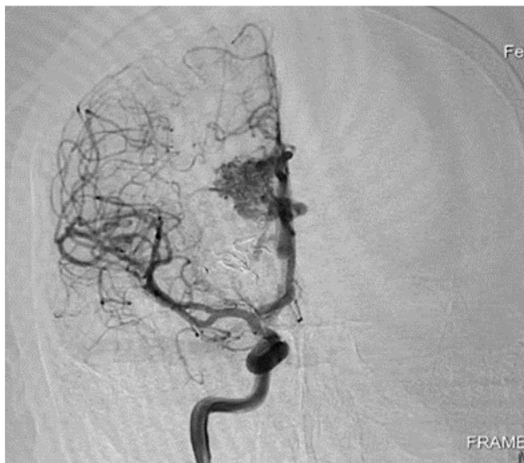

Figure 1. DSA with anteroposterior right Internal carotid artery (ICA) and its branches showing right thalamic AVM with feeders from ipsilateral ACA with Onyx from the first embolization procedure.

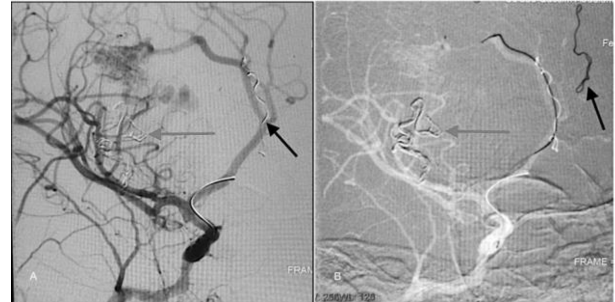

Figure 2. DSA with the AP view of the right ICA showing (A) the detached coil in the contralateral collosomarginal branch of the right ACA (Black arrow) with Onyx from the previous embolization (Red arrow). (B) The detached coil migrated more distally in the contralateral ACA (Black arrow) in the road map image.

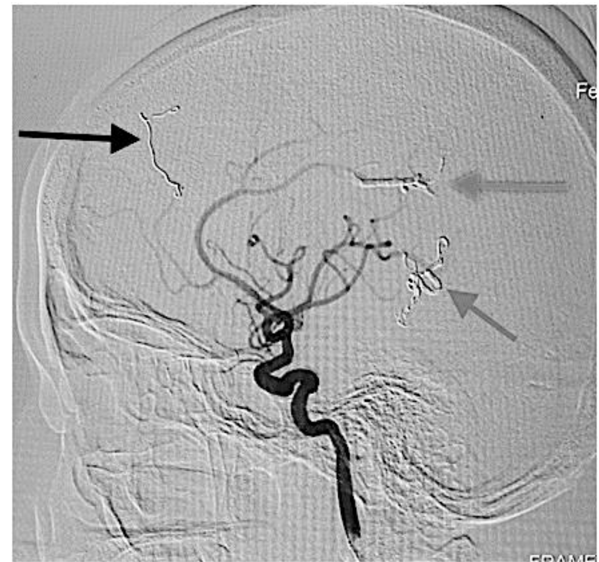

Figure 3. DSA of AP view of right ICA showing the coil migration in a distal branch of ACA (back arrow). It also shows complete obliteration of the AVM nidus with embolization of the arterial feeder from A5 (Yellow arrow). The first stage embolization Onyx is also noted (Red arrow). Note: the CMA in this case is a segmented artery with the 2 segments originating separately from the pericallosal artery.

The size and the location of the AVM prompted the decision for multistage endovascular embolization using onyx. The first stage was performed through embolization of the posterior choroidal artery by passing through the posterior cerebral artery and utilizing onyx as the liquid emblazing agent. Two weeks later, the second stage was contemplated. However, in the anterior circulation, the right A5

arterial feeder has a high flow. Right A5 Feeder coiling was considered prior to the onyx to raise proximal resistance and facilitate plug formation, leading to improved reflux control and better distal penetration. All these steps are with the pressure cooker technique in the form of CAIT. Balloon-assisted embolization was one of the options, but the high cost of this method and lack of medical insurance in Iraq make the utilization of this option unlikely. In the procedure, early detachment and migration of the coil occurred in the prefrontal medial branch through the contralateral callosomarginal branch of the anterior cerebral artery (ACA) (Figure 2).

Distal migration of the coil happened pre-onyx injection, and no intervention to retrieve the coil was carried out because the detachment piece is small and lodged distally (Figure 3). Onyx was injected directly without the coil because of the risk of radiation to the patient. Postprocedural digital subtraction angiography (DSA) imaging exhibits 90% obliteration of the AVM. Otherwise, the procedure went uneventful. Postprocedural examination showed GCS 15/15 and MRC grade 5 bilaterally. Patient follow-up includes antiepileptic drugs, diagnostic catheter angiography three months after the second stage of embolization, and referral for gamma knife radiotherapy.

Discussion

Treatment of cerebral AVMs successfully is a major challenge (14). Embolization has become more essential in the therapy of cerebral AVMs as endovascular materials and experience have improved (1). Nidus reduction before surgery or radiosurgery, as well as curative embolization, are the two main goals of AVM embolization. The goal of Nidus reduction is to reduce operative difficulty and risk during surgical removal (18). Curative embolization aims for the entire obliteration of the AVMs, and in the cases of partial occlusion, embolization can reduce the volume of the nidus, allowing radiosurgery to be attempted (10). Similarly, while waiting for the delayed occlusion accomplished by radiosurgery, embolizing the feeding artery can lower the risk of hemorrhage (3,10). The pressure cooker technique as CAIT of AVM and balloon-assisted coiling has specific indications, which are highlighted with AVM of high flow feeders and large caliber such as in the current report. CAIT, according to Gao X et al has several advantages, including 1), the microcatheter used for coil infusion is far more navigable than the balloon, 2), the coil can provide sufficient proximal resistance to enable plug formation and obtain better distal penetration, allowing more Onyx to be injected from a single feeding pedicle while reducing procedure time and radiation exposure (8). In our case, CAIT was used because, in the anterior circulation, right A5 was a high flow feeder. In addition, balloon-assisted coiling was off the choice because healthcare insurance in Iraq is immature, making costs significantly elevated for the patient.

The hemodynamics of the AVM in the arterial system is working as a suction device in which the majority of the flow is in the direction of the main feeder. When the navigation is performed by microwire, microcatheter, or coiling, it is easy to carry out within the flow of the main feeder as it has negative pressure. In our case, the presence of the microcatheter in the proximal part of the feeder (in our case, right ACA) may result in a decrease in the feeder's flow and a change in the hemodynamics of the AVM, which was apparent in the migration of the coil in the contralateral ACA. This could be unexpected if the hemodynamics of the AVM is unchanged and all pressure is within the nidus direction.

AVM embolization can result in significant treatment-related morbidity and mortality (6). Complication rates associated with AVM embolization have been observed to range from 5% to 15% (7). According to a recent meta-analysis by van Beijnum et al., complications after AVM embolization resulted in irreversible neurological impairments or death in 6.6 percent (range 0–18 percent) of patients (16). After 846 embolizations in 408 individuals, Baharvahdat et al. observed an 11 percent procedural complication rate. After embolization, 7.6% and 1.6 percent of patients, respectively, reported persistent, new impairment and mortality due to hemorrhage (2). In addition, coil migration is a potential complication in CAIT in the AVM, which was not reported in the literature yet. In the present report, coil migration occurred pre-onyx injection and migrated distally to the prefrontal medial branch through the contralateral callosomarginal branch of ACA. However, the patient was assessed clinically and radiologically

intraoperatively, which was unremarkable, and stayed asymptomatic through the follow-up period.

Our experience in coil migration in terms of classification is based on general principles mainly derived from the studies in aneurysmal coiling. Migration can be categorized into acute procedure migration and delayed postprocedural migration depending on the time the migrated coil was identified (1). Coil migration found after the coiling technique was completed is referred to as delayed migration (1,12). The period between endovascular coiling and detection of the migrating coil should be noted. The location of the migrated coil is classified as proximal or distal. The mentioned classifications are more related to the endovascular coiling in aneurysms, but the general principle can be applied to the CAIT of the AVM. Although, in CAIT of AVM with high caliber and flow feeders, as in the case, the potential migration of the coil after its detachment may occur before or after the onyx injection, and the migration was acute procedural with distal migration.

In general, coil migration management differed depending on the timing of migration (acute or delayed), the location of the migrated coil (proximal or distal), the target vessel's patency, and the vascular territory's eloquence (1,4). When a migrated coil relocates intraprocedurally, lodges in a proximal or eloquent position, and/or there is a concomitant accessible vascular obstruction, migrated coil retrieval should be performed endovascularly or by open surgery (9,17). In contrast, distal migration requires conservative treatment (1,13). In the present report, the management of coil migration depends on the principles that were extracted mainly from the literature on aneurysmal coiling. In AVM with high vessel caliber and increased flow feeders, as in the current study, distal migration was managed conservatively. Otherwise, early assessment of the patient within the procedure and after the procedure, along with early intervention, may lead to better management of the patient's condition.

In summary, endovascular embolization by CAIT may result in size reduction in AVM nidus or complete obliteration, especially for the arterial feeder with the high flow as in our case. We report a case of coil migration in CAIT of AVM. In this report, contralateral ACA distal coil migration was managed conservatively.

Conclusions

Coil migration is a rare complication in aneurysms. This report is the first case of coil migration during the pressure cooker technique with CAIT for the right thalamic AVM.

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Impact of dome projection on operative steps during clipping of a ruptured pure posteriorly directed posterior communicating artery aneurysms

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ABSTRACT
Background: Ruptured posterior communicating artery (PCoA) aneurysms are common; they usually present with subarachnoid haemorrhage (SAH) and oculomotor nerve palsy. The aneurysmal dome projection may influence the safety access and aneurysmal neck clipping. Here, we discuss additional intraoperative steps that may be required to widen the surgical field to ensure safe surgical clipping of a rupture pure posteriorly directed PCoA aneurysm.
Case description: A previously healthy 38-year-old male reported sudden severe headache and disturbed level of consciousness with a Glasgow coma scale (GCS) of 13. His initial computed tomography (CT) scan of the head showed SAH in the basal cistern. 3D-constructed CT angiography (CTA) revealed a left pure posteriorly directed PCoA aneurysm.
In the surgery, through the left pterional approach, all intraoperative steps were carried out. Additional steps were performed as well. Three additional intraoperative steps were contemplated because a pure posteriorly directed PCoA aneurysm is not well appreciated and is often hidden behind the supra cliniold internal carotid artery (ICA). First, the extension of Sylvian fissure dissection to include the distal part and the proximal. Second, temporal pole mobilization is performed by cutting small anterior temporal veins. Third, a brain retractor is placed on the temporal lobe to gently tract the superficial part of the lobe. All these steps widened the surgical corridor to ensure the aneurysm's safe clipping.
Conclusion: Surgical clipping is influenced by the aneurysmal dome projection. In a ruptured pure posteriorly directed PCoA aneurysm, further intraoperative steps may facilitate complete access and safe clipping of the aneurysm.

Keywords
intracranial aneurysms, posterior communicating artery, microsurgical clipping

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INTRODUCTION

Posterior communicating artery (PCoA) aneurysms represent 25% of all aneurysms and 50% of the entire internal carotid artery (ICA) aneurysms [3]. Ruptured PCoA aneurysms frequently present with subarachnoid hemorrhage (SAH) and oculomotor nerve palsy [4]. Surgical clipping and endovascular coiling are two therapeutic options for ruptured PCoA aneurysms, and the outcome of the endovascular has a slight advantage compared to surgical clipping [8]. In the surgery, intraoperative clipping of PCoA aneurysms is influenced by the dome projection, which includes lateral and posterior directions [9]. PCoA aneurysm's surgical clipping carries surgery-related nuances [12]. In pure posteriorly direct PCoA aneurysm may render peculiar intraoperative steps [10,12]. Here, we discuss the procedure-related surgical steps in a ruptured pure posteriorly directed PCoA aneurysm.

CASE DESCRIPTION

An otherwise healthy 38-year-old male presented with a sudden onset of severe headache, disturbed level of consciousness (Glasgow coma scale (GCS) 13, E3, M6, V4), right-sided weakness grade 2 (Medical Research Council (MRC) scale), left partial oculomotor nerve palsy, and neck stiffness. A non-contrast cranial computed tomography (CT) scan revealed SAH in the basal cistern. 3D-reconstructed CT angiogram (CTA) revealed a left pure posteriorly directed aneurysm with a wide neck arising from the Supracliniod ICA in the junction with PCoA (Figure 1).

The surgery was advised to the patient because of the unavailability of the endovascular choice in Iraq and the high cost to the patients. Through the left pterional approach with all the steps contemplated to reach the aneurysm, including using a retractor on the frontal lobe and deep part dissection of the Sylvian fissure. Because the PCoA aneurysm is not well appreciated due to its projection as a pure posteriorly directed and its neck is hidden behind supra cliniod ICA. Here, additive steps were performed, including first, lengthening the Sylvian fissure dissection to encompass the distal part (wide Sylvian dissection). Second, temporal pole mobilization was carried out by releasing the anterior part of the temporal pole from small bridging veins connecting it to the sphenoparietal and cavernous sinuses. Third, using the temporal lobe retractor mainly on the superficial part of the temporal lobe to minimize the risk of early rupture Here, the operative field widened, and the surgeon had full access to the aneurysmal neck. The aneurysm was exposed, dissected then clipped safely without incident (Figure 2). PCoA patency was checked. The postoperative course was uneventful. On the follow-up, the patient was conscious (GCS 15), with no neurological deficit aside from improving his right-side weakness (MRC grade 4).

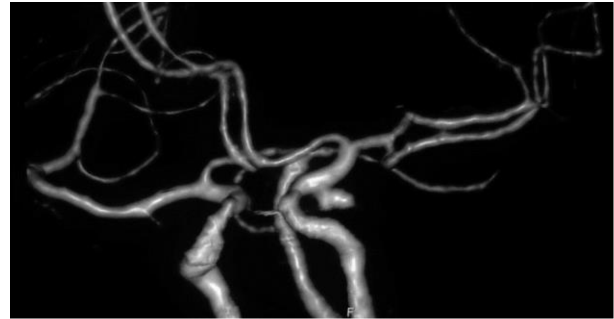

Figure 1. Left anterolateral CT angiogram showing left pure posteriorly directed PCoA aneurysm.

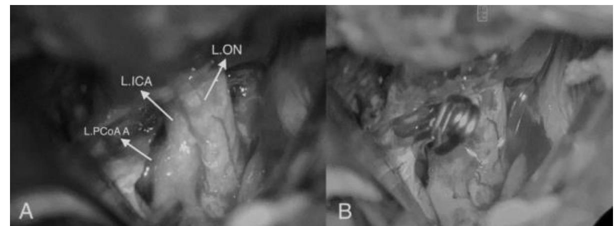

Figure 2. Intraoperative images through the left pterional approach show (A) before clipping. (B) after clipping insertion. L.PCoA A: Left posterior communicating artery aneurysm. L.ICA: Left internal carotid artery (Supracliniod) L.ON: Left optic nerve.

DISCUSSION

Ruptured PCoA aneurysms represent 13-25% of all intracranial aneurysms, and the unruptured aneurysms are proportionally lower [2]. In a meta-analysis study, Clark et al, estimated the risk of rupture of PCoA aneurysm (0.46%) yearly, and it regularly presents with SAH [1,4,13]. However, the oculomotor nerve palsy may present with ruptured or unruptured aneurysms in 19-38% of PCoA aneurysm patients, and it may be partial or complete [4,5,7]. In the treatment of PCoA aneurysm, Molyneux et al, 2005 trial found endovascular coiling increased the survival rate independently by one year compared to surgical clipping; and the survival benefit extended for seven years with the former

option [8]. With limited resources, hospitals such as the status in Iraq and the high cost to the patients made endovascular options off the choice in most of the cases as well as in our example here.

The Intraoperative surgical steps of PCoA aneurysm clipping may be affected by the dome projection [4,5]. The lateral or the posterolateral projection, which is the most common projection of the PCoA aneurysm, is particularly operated with regular steps of 1) pterional craniotomy and dura opening, 2) positioning of the brain retractor on the frontal lobe; however, some surgeons prefer retractor less surgery [6]. Obviously, this is not always possible in ruptured aneurysm cases with an expected tense brain, 3) proximal Sylvian fissure dissection, 4) identification and dissection of supracliniod ICA and its bifurcation, optic nerve, PCoA (proximal to the aneurysmal neck), and anterior choroidal artery (distal to the aneurysmal neck), 5) dissection of the neck of the aneurysm then placement of the aneurysmal clip to exclude the aneurysm from the circulation, 6) oculomotor nerve decompression by opening and shrinking the aneurysmal dome [4,6]. On the other hand, with a pure posteriorly directed PCoA aneurysm, there are further steps required to reach the neck of the aneurysm due to technical difficulties. Because first, the major segment of the aneurysm is positioned posterior to the supra clinoid ICA, thus it will be hidden from the surgeon's view during the typical pterional approach [4,5]. Second, PCoA is commonly arising proximal to the aneurysm and course posteromedial in addition to the possible presence of perforator branches in the area close to the neck [4]. These reasons may render further steps mandatory for the neurosurgeon to ensure adequate surgical view, thus ensuring complete safe clipping of the aneurysm.

In our case, three additional steps were contemplated, which include a) extended dissection of the Sylvian fissure to include the distal part in addition to the proximal one to widen the operative corridor. b) The mobilization of the temporal pole is performed carefully by cutting the small anterior temporal veins, thus releasing the temporal lobe and gaining extra space for the operating surgeon. c) placing a retractor on the temporal lobe to enlarge the surgical view in these cases of the tight brain due to ruptured aneurysm and the consequences of SAH. Although Nadar et al, advised not to use a retractor on the temporal lobe, we only retracted the superficial part of the temporal lobe gently to gain a better surgical view and at the same time to prevent early rupture of the aneurysm [9].

In summary, the modification of the pterional approach by these three additional steps intraoperatively allowed better access and safe clipping of pure posteriorly directed PCoA Aneurysm's neck.

Conclusions

Ruptured PCoA aneurysm clipping is affected by the dome projection. A ruptured pure posteriorly directed PCoA aneurysm may require additional intraoperative steps to improve the operative view and widen the surgical field, thus ensuring complete and safe clipping.

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The impact of coagulation profile derangements and their effect on the outcome of head injury patients. A prospective study

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ABSTRACT

Background: In traumatic brain injury patients, coagulation disorder causes secondary brain injury, thereby increasing mortality and morbidity.

Aim: This study aims to know the impact of coagulation profile derangements and their effect on the outcome of head injury patients.

Materials and methods: A total of 100 patients admitted with traumatic brain injury were included in the study. Samples of complete haemogram (CBC), prothrombin time (PT), partial thromboplastin time (PTTK), D-Dimers and fibrinogen were obtained. Coagulopathy was defined as platelet counts < 100,000 cells/mm2 and PTI >15 seconds or a DIC (Disseminated intravascular coagulation) score of more than 4. The outcome in each group was measured according to the Glasgow outcome score. The data were analysed with the Chi-square test and independent t-test.

Results: In patients with severe and moderate traumatic brain injury, there was no significant difference in the Haemoglobin, Fibrinogen and D-Dimer between the patients with and without coagulopathy. But the platelet count was significantly lower in the patients with coagulopathy and the PT and PTTK were significantly higher in the patients with coagulopathy in comparison to the patients without coagulopathy ($p<0.05$). There was no significant difference in the Fibrinogen and D-Dimer between the expired and discharged patients. But the platelet count was significantly higher in the discharged patients and the DIC score, PT and PTTK were significantly lower in the discharged patients ($p<0.05$).

Conclusion: Coagulation profile derangements are seen in patients with traumatic brain injury. Early diagnosis and prompt management can make remarkable improvements in the mortality of these patients.

Keywords
coagulation,
head injury

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INTRODUCTION

Traumatic brain injury (TBI) is one of the most important causes of death and long-term disability in young adults (Boto et al. 2006). TBI has also been found to be a significant factor behind the deaths occurred in the very first day after trauma (Shackford et al. 1993). The incidence of coagulopathy in different types of TBI ranges from 10 to

97.3% (Lustenberger et al. 2010, Harhangi et al. 2008) and in case of acute brain injury, coagulopathy leads to hemorrhagic lesions (Oertel et al. 2002, Allard et al. 2009, Tian et al. 2010) and increased chances of mortality (Talving et al. 2009, Wafaisade et al. 2009).

Although the pathophysiology of TBI induced coagulopathy has not been completely understood, the following factors have been proposed to be responsible for the same: release of tissue factors (Goodnight et al. 1974, Keimowitz et al. 1973, Scherer et al. 1998), disseminated intravascular coagulation (Stein et al. 2004, Stein et al. 2002, Hulka et al. 1996), thrombocytopenia or platelets dysfunction (Carrick et al. 2005, Schnu¨riger et al. 2010, Nekludov et al. 2007, Engstrom et al. 2005), activation of protein C pathways (Cohen et al. 2007, Frith et al. 2010).

Early recognition of coagulopathy is of value in predicting the occurrence of delayed brain injury and may contribute to prevention of bleeding disorders (Stein et al. 1992). Most studies, however, report a mixture of early and delayed coagulopathy in isolated TBI, and knowledge about the prognostic value of acute, early diagnosed coagulopathy is therefore limited. A recent evaluation of a large German trauma registry revealed that 23% of patients with isolated TBI are presented with acute coagulopathy upon arrival of the emergency department, which was associated with increased morbidity and mortality (Wafaisade et al. 2010). Although the prevalence of coagulopathy increases in the period after admission to the emergency department, there are only limited data available about the evolvement of hemostatic parameters and the relative number of patients that develop delayed coagulopathy in the first days post-trauma (Carrick et al. 2005, Zehtabchi et al. 2008).

Therefore, the aim of the present study was to know the impact of coagulation profile derangements and their effect on the outcome of head injury patients.

MATERIALS AND METHODS

This prospective observational study was carried out on 100 patients of head injury admitted in the Neurosurgery department of SMS Medical College Attached Hospital, Jaipur, Rajasthan from June 2020 to September 2021. Ethical approval was obtained from the institutional ethical committee and informed consent was taken from the patient attendants.

The inclusion criteria for the patients was that they should be within the age range of 1 to 70 years. The exclusion criteria for the patients were: i) patients having other associated injuries such as chest injury, bony injury, abdominal solid and hollow viscus injury etc., ii) patients having known case of hypertension, diabetes or any other chronic disease, iii) patients having pre-existing coagulopathy, taking anticoagulants or drugs which interfere with the laboratory testing and iv) patient have history of chronic alcohol intake, ongoing liver disease; history of of hepatotoxic drug intake and history of long time anti-inflammatory drug intake.

All the selected patients were divided based upon their GCS into two groups based on their GCS. There were two subgroups of patient moderate head injury (GCS 9-13) and severe head injury (GCS < 9). Initial resuscitation and subsequent management was done as per Advanced Trauma Life Support (ATLS). Samples for complete haemogram (CBC), prothrombin time (PTI), partial thromboplastin time (PTK), D-Dimers and fibrinogen were drawn. The blood was collected by venepuncture in EDTA vacutainers as well as PT tubes containing anticoagulant sodium citrate and processed immediately. Based on results of these blood investigations, DIC score was calculated and severity of the DIC was graded. DIC score was calculated (Table 1). After calculating the DIC score severity of the DIC was graded (Table 2).

Table 1. DIC score

	Platelet count (in lac)	PT Time (in secs)	APTT (in secs)	D-Dimer (µg/dl)	Fibrinogen (g/l)	Score awarded
Normal	>1.5	13.5	26-34	<1000	>1	0
Mild derangement	1-1.5	13.5-15.0	>34	1000-2000	<1	1
Moderate derangement	0.60-1.0	15-18	>39	2000-4000	<1	2
Severe derangement	<0.60	>18	>54	>4000	<1	3

Table 2. Severity of DIC

DIC Score	Inference
0-3	Normal
3-6	Mild derangement
7-10	Moderate derangement
>10	Severe derangement

Outcome was defined by the GOS (Glassgow outcome Score) and the comparison of presenting GCS was done with the GOS and DIC score was done. Coagulopathy- Coagulopathy was defined as platelet counts < 100,000 cells/mm2 and PTI >15 seconds or a DIC score more than 4. The outcome in each group was measured as discharged (GOS- 5) or vegetative state (GOS-2) or dead (GOS-1). During follow up of the patients GCS, cranial nerve palsy, haematoma formation (surgically operated), local surgical site infection and fever were noted.

Statistical Analysis

The data was tabulated in Microsoft excel software and analysed with SPSS v.24 software Statistical analysis was done by using chi square method and independent t-test. The p-value of <0.05 was considered as statistically significant.

RESULTS

A total of 100 patients of isolated head injury were included in the study and were further categorized into moderate and severe head injury on the basis of GCS. The patients with GCS 3-8 were categorized as Severe Head injury (n=54) and patients with GCS 9-13 were categorized as moderate head injury (n =46). Among severe head injury (GCS 3-8) group, 31 (57.4%) patients out of 54 developed coagulopathy and in moderate head injury group 18 (39.1%) patients out of 46 developed coagulopathy. The demographic parameters, hospital stay and in-house mortality of the patients with severe and moderate TBI are shown in tables 3 & 4. In both the tables, there was no significant difference in the age and gender between the groups. But, total stay, ICU stay and outcome (death) were found to be significantly higher in the patients with coagulopathy (p<0.05).

The laboratory parameters of the patients with severe TBI was shown in table 5. There was no significant difference in the Haemoglobin, Fibrinogen and D-Dimer between the patients with and without coagulopathy. But, the platelet count was significantly lower in the patients with coagulopathy and the PT and PTTK were significantly higher in the patients with coagulopathy in comparison to the patients without coagulopathy (p<0.05).

The laboratory parameters of the patients with moderate TBI was shown in table 6. There was no significant difference in the Haemoglobin, Fibrinogen and D-Dimer between the patients with and without coagulopathy. But, the platelet count was significantly lower in the patients with coagulopathy and the PT and PTTK were significantly higher in the patients with coagulopathy in comparison to the patients without coagulopathy (p<0.05).

Table 7 shows the comparison of total DIC scores and the laboratory parameters of expired and discharged patients with severe TBI. Out of the 54 patients, 34 expired and 20 were discharged. There was no significant difference in the Fibrinogen and D-Dimer between the expired and discharged patients. But, the platelet count was significantly higher in the discharged patients and the DIC score, PT and PTTK were significantly lower in the discharged patients (p<0.05).

Table 8 shows the comparison of total DIC scores and the laboratory parameters of expired and discharged patients with moderate TBI. Out of the 46 patients, 5 expired and 41 were discharged. There was no significant difference in the Fibrinogen and D-Dimer between the expired and discharged patients. But, the platelet count was significantly higher in the discharged patients and the DIC score, PT and PTTK were significantly lower in the discharged patients (p<0.05).

Table 9 shows the comparison of total DIC scores and the laboratory parameters of expired and discharged patients with coagulopathy. Out of the 49 patients who developed coagulopathy, 35 expired and 14 were discharged. There was no significant difference in the platelet count, PT, PTTK, Fibrinogen and D-Dimer between the expired and discharged patients. But, the DIC score was significantly higher in the expired patients (p<0.05).

Table 10 shows the comparison of total DIC scores and the laboratory parameters of expired and discharged patients without coagulopathy. Out of the 51 patients who did not develop coagulopathy, 4 expired and 47 were discharged. There was no significant difference in the DIC score, PT, PTTK, Fibrinogen and D-Dimer between the expired and discharged patients. But, the platelet count was significantly lower in the expired patients (p<0.05).

Bivariate analysis was carried out to identify the risk factors associated with the development of coagulopathy (table 11). On bivariate analysis, severity of TBI, effaced basal cisterns on CT scan and low haemoglobin level were found to predict the development of coagulopathy (p<0.05).

Table 3. Association of demographic parameters, hospital stay and in-house mortality of severe TBI in presence or absence of coagulopathy

Parameters	Patients with coagulopathy (n=31)	Patients without coagulopathy (n=23)	P value
Age (years)	30.5±7.1	31.8±8.4	>0.05
Male:/Female	27:4	18:5	>0.05
Total stay (days)	13.4±2.7	6.8±1.5	<0.05*
ICU stay (days)	8.1±2.3	4.9±1.8	<0.05*
Outcome (Deaths)	20 (64.5%)	11 (47.8%)	<0.05*

Table 4. Association of demographic parameters, hospital stay and in-house mortality of moderate TBI in presence or absence of coagulopathy

Parameters	Patients with coagulopathy (n=18)	Patients without coagulopathy (n=28)	P value
Age (years)	33.5±8.6	29.2±6.4	>0.05
Male:Female	16:2	25:3	>0.05
Total stay (days)	12.7±3.5	7.1±2.9	<0.05*
ICU stay (days)	6.7±2.1	4.4±1.3	<0.05*
Outcome (Deaths)	8 (44.4%)	3 (10.7%)	<0.05*

Table 5. Association of laboratory parameters in severe TBI in presence and absence of coagulopathy

Parameters	Patients with coagulopathy (n=31)	Patients without coagulopathy (n=23)	P value
Hb	10.4±2.1	11.9±2.4	>0.05
Platelet	1.45±0.3	2.18±0.7	<0.05*
PT	20.2±4.4	14.6±4.1	<0.05*
PTTK	36.1±7.2	26.5±6.3	<0.05*
Fibrinogen	0.68±0.2	0.37±0.1	>0.05
D-Dimer	2761±884	2519±729	>0.05

Table 6. Association of laboratory parameters in moderate TBI in presence and absence of coagulopathy

Parameters	Patients with coagulopathy (n=18)	Patients without coagulopathy (n=28)	P value
Hb	11.2±2.7	12.9±3.1	>0.05
Platelet	1.52±0.4	2.37±0.8	<0.05*
PT	20.8±4.5	14.1±3.8	<0.05*
PTTK	35.7±7.3	25.9±6.9	<0.05*
Fibrinogen	0.73±0.2	0.42±0.1	>0.05
D-Dimer	2837±895	2489±706	>0.05

Table 7. Comparison of total DIC scores and the laboratory parameters of expired and discharged patients with severe TBI

Parameters	Expired (n=34)	Discharged (n=20)	P value
DIC Score	5.9±2.2	3.6±1.4	<0.05*
Platelet	1.72±0.4	2.61±1.3	<0.05*
PT	19.6±3.5	15.2±2.8	<0.05*
PTTK	34.3±7.1	24.1±6.4	<0.05*
Fibrinogen	0.75±0.2	0.47±0.1	>0.05
D-Dimer	2768±831	2504±634	>0.05

Table 8. Comparison of total DIC scores and the laboratory parameters of expired and discharged patients with moderate TBI

Parameters	Expired (n=5)	Discharged (n=41)	P value
DIC Score	7.6±3.1	3.4±1.1	<0.05*
Platelet	1.03±0.2	1.95±1.2	<0.05*
PT	18.7±3.2	14.2±2.4	<0.05*
PTTK	33.8±6.6	25.2±5.8	<0.05*
Fibrinogen	0.77±0.3	0.51±0.1	>0.05
D-Dimer	3015±912	2461±527	>0.05

Table 9. Comparison of total DIC scores and the laboratory parameters of expired and discharged patients with coagulopathy

Parameters	Expired (n=35)	Discharged (n=14)	P value
DIC Score	7.6±2.2	4.1±1.3	<0.05*
Platelet	1.26±0.2	1.57±0.5	>0.05
PT	35.1±7.2	31.7±4.3	>0.05
PTTK	36.7±8.4	34.2±7.1	>0.05
Fibrinogen	0.77±0.3	0.65±0.2	>0.05
D-Dimer	2806±793	2752±785	>0.05

Table 10. Comparison of total DIC scores and the laboratory parameters of expired and discharged patients without coagulopathy

Parameters	Expired (n=4)	Discharged (n=47)	P value
DIC Score	2.9±0.8	2.5±0.6	>0.05
Platelet	1.28±0.7	1.84±1.1	<0.05*
PT	16.5±3.1	14.7±2.2	>0.05
PTTK	28.4±6.1	25.7±5.9	>0.05
Fibrinogen	0.61±0.4	0.57±0.2	>0.05
D-Dimer	2513±844	2422±785	>0.05

Table 11. Risk factors for development of coagulopathy following isolated TBI

Parameters	Unadjusted odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
GCS ≤ 8	3.8 (1.6-5.9)	<0.05*	2.5 (1.4-4.8)	<0.05*
Effaced basal cisterns	2.1 (1.2-4.2)	<0.05*	2.5 (1.6-5.5)	<0.05*
Hb ≤10g/dl	2.4 (1.1-4.9)	<0.05*	2.9 (1.2-5.3)	<0.05*

*Statistically significant difference exists between the groups

Discussion

Traumatic brain injury is associated with activation of the coagulation cascade through fulminant cerebral tissue factor release, contributing to disseminated intravascular coagulation and cerebral microthrombi. This process is independent of bleeding. The subsequent disparity between clot formation and fibrinolysis in combination with coagulopathy may increase the risk for secondary bleeding and mortality. The present study showed a male predominance (86%) in the patients with TBI. This is in accordance with the studies done by Talving et al. in 2009 (78% males) and Affonseca et al. in 2007 (69.1% males).

In the present study, mortality was 39% which was at par with Affonseca et al. in 2007 and Greuters et al. in 2011. Coagulopathy was developed in 49% patients in our study which was in concordance with Affonseca et al. in 2007, but more than the mortalities reported in the studies by Greuters et al. in 2011 where it was 54% and by Harhangi et al. in 2008 where it was 33%.

The present study showed that the mean platelet count in the severe head injury group patients was lower than in patients of moderate head injury patients in our study. This finding is supported by the results of the study by Engstrom et al. in 2000, were they observed thrombocytopenia to be an independent risk factor for traumatic brain injury. In the present study, the mean PT in the severe head injury group was higher in the expired patients than the discharged patients. Saggar et al. in 2009 reported similar findings in their study.

In the present study, the mean D-dimers value was higher in the patients with severe than the patients with moderate head injury. Similar results were reported in the study by Scherer et al. in 1998 and Kuo et al. in 2007. They also reported that increased D-Dimer values was associated with poor prognosis in head injury patients. 35% of the patients in the present study had moderate DIC scores. Selladurai et al. in 1997, observed that 38% of their patients had moderate to severe DIC scores while Saggar et al. in 2009 observed 63% of their patients had moderate to severe DIC scores. Plasma fibrinogen concentration was found to be significantly higher among the patients who developed coagulopathy. Jovan et al. in 1998 in their study also reported similar results.

In the present study, severity of head injury (GCS ≤ 8), effaced basal cisterns on CT scan and haemoglobin level less than 10 g/dl strongly predicted the development of coagulopathy. Talving et al. in 2009 had also reported GCS ≤ 8 and presence of cerebral edema, SAH, SBP < 90 mm Hg, midline shift as the factors, which independently predicted development of coagulopathy. Similar findings were also reported by Affonseca et al. in 2007 in their study on pediatric patients where they found severity of head injury, presence of brain swelling, and injuries to chest and abdomen being associated with the development of coagulopathy

Conclusions

The present study concludes that, traumatic brain injury is complicated by the coagulopathy. The mortality of the patients with moderate or severe TBI can be predicted with the presence of coagulopathy and the severity of head injury. Early diagnosis and prompt management can make remarkable improvement in the survival rate of these patients.

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Coexistence of ipsilateral ulnar and median nerve entrapment

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ABSTRACT
Objective: Carpal tunnel syndrome (CTS) and Cubital tunnel syndrome (CuTS) are the median nerve compressions under the carpal ligament and ulnar nerve at the wrist, the most common peripheral nerve entrapment of the upper extremity. The fatty tissue due to the high body mass index (BMI) differs the severity of the entrapment symptoms. The study aims to evaluate the association between BMI and symptoms of CTS and CuTS by analyzing the patients whose entrapments are at the same extremity and onset at the same time.
Method: The patients were divided into two groups according to the neuropathy sit (CTS and CuTS) and four subgroups according to the BMI (Overweight, grade 1 obese, grade 2 obese, and morbidly obese). All patients were followed up with EMG and performance scale before and after surgical treatment.
Results: A total of 31 patients were included in the study. The mean BMI of the patients was 29.63 kg/m^2. The average BMI of male patients was 29.02 kg/m^2, while the average BMI of female patients was 30.3 kg/m^2.
Conclusion: In contrast to the previous hypotheses that claim the high body mass index increases the severity of CTS but reduces the formation of CuTS, our study revealed that body mass index was not related to the severity of symptoms.

Keywords
peripheral nerve,
carpal tunnel,
cubital tunnel,
entrapment,
body mass index

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INTRODUCTION

Entrapment neuropathies occur when nerves are exposed to pressure during their course in rigid anatomical structures. Carpal tunnel syndrome (CTS) occurs due to compression of the medial nerve under the flexor retinaculum ligament in the wrist, while compression of the ulnar nerve at the elbow level causes cubital tunnel syndrome (CuTS). While CTS is the most common neuropathy among entrapment neuropathies (annual incidence 424/1000000), CuTS is observed in the 2nd frequency (annual incidence 20.9 / 100000) [1,2].

In the initial phase of peripheral entrapment neuropathies, epineural blood flow is reduced due to ischemic block. As a result, the nerve slowed down the conduction velocity, and a conduction block may develop. At this stage, Wallerian degeneration has not yet begun, and the patient benefits from conservative treatment. In the late stage,

epineural edema, endoneurial edema, and segmental demyelination begin to develop. As this situation becomes chronic, Wallerian degeneration now occurs, and clinical findings such as sensory defects and muscle atrophy can be seen [3].

Patients with CTS complain of pain, numbness, and tingling in the first three fingers of the hand, while patients with CuTS have pain in the medial of the elbow and arm, numbness in the 4th and 5th fingers, and loss of strength in the intrinsic muscles of the hand. The definitive diagnosis of both syndromes is made by electromyography (EMG) and neurological examination.

Conservative treatment is given primarily to patients with mild and moderate nerve compression. In addition to anti-inflammatory drugs, splits restricting wrist movements for CTS and elbow movements are used for CuTS. Surgical intervention is required for cases resistant to conservative treatment, severe hypoesthesia, atrophy, and loss of strength. The trap channel is surgically opened, and nerve compression is decompressed.

In individuals with a high body mass index, the amount of adipose tissue around the median nerve increases, which increases the risk of entrapment neuropathy [4].

Studies have shown the coexistence of CTS and CuTS, but the frequency of median and ulnar nerve entrapment neuropathy in the same extremity and at the same time has not been reported [5,6]. In this study, it was aimed to compare the severity of entrapment neuropathies and to evaluate their demographic structure according to the body mass index of patients who were admitted to our clinic with ipsilateral CTS and CuTS complaints at the same time and who were treated with surgical intervention in the same session.

MATERIAL AND METHODS

CTS and CuTS patients who were treated with ipsilateral surgical intervention between January 2015 and December 2019 in the Neurosurgery Department of our hospital were retrospectively analyzed. The local ethics committee approved each stage of the study, and consent was obtained from all patients.

Patients with numbness, weakness, and thenar muscle atrophy in the 1st, 2nd, and 3rd fingers due to median nerve entrapment, and patients with the same symptoms in the 4th and 5th fingers and hypothenar muscle atrophy due to ulnar nerve entrapment, and whose symptoms started on the same side and at the same time were included in the study.

Cubital tunnel and carpal tunnel syndromes were diagnosed according to the patients' neurological examination and EMG results. Numbness, tingling, and pain sensation in the palmar face of all the fingers were questioned. Tinel test was performed on the median nerve at the wrist and the ulnar nerve at the elbow, and the Phalen test was also performed on patients with suspected carpal tunnel syndrome. Patients with carpal and cubital tunnel syndrome at the same time were determined by evaluating physical examination findings and EMG results together. Cervical pathologies were excluded by performing a cervical magnetic resonance imaging. Among these patients, patients whose complaints did not recover despite using medical treatment and splint and who underwent ulnar nerve and median nerve decompression surgery under local anesthesia in the same session were evaluated.

Patients with symptoms of the CTS and CuTS occur at different times, in different extremities, patients with cervical vertebral root lesions and/or discopathy findings in cervical magnetic resonance imaging, patients with thoracic outlet syndrome and polyneuropathy, cases secondary to trauma such as fractures, nerve injury and tumor and cases with CTS and CuTS secondary to pregnancy were excluded from the study.

Parameters evaluated

Data of the patients were collected to evaluate the age, gender, which side of the surgery, presence of atrophy, smoking, diabetes, presence of thyroid disease, hypertension, educational status, occupation, and dominant hand. Preoperative EMG results of the patients were collected. Body mass index (BMI) was calculated in kg / m2 by measuring the patients' height and weight. Calculated BMIs were grouped using the World Health Organization (WHO) classification.

Statistical analysis

Spearman test was used to evaluate the correlation between BMI and severity of CTS and CuTS in statistical analysis. P <0.05 was considered statistically significant.

RESULTS

A total of 31 patients were included in the study (17 men (55%), 14 women (45%)). The average age of all patients was 51.29 ± 13.2 (Male 51.65 (min: 23-max: 70), female 50.86 (min: 14- max: 72). Nine patients were operated on from the left side, 22 from the right side, and the right/left ratio was 2.44. There was only one male patient with the left dominant hand, and the pathology of this patient was on the right side. Ipsilateral involvement of 30 right dominant patients was 22 (73.3%). Smoking was present in 17 (55%) of the patients. The number of patients with diabetes was 10 (32%). The number of patients with thyroid dysfunction was 6 (19%). The number of patients with hypertension was also 6.

The mean BMI of the patients was 29.63 kg/m2. The average BMI of male patients was 29.02 kg/m2, while the average BMI of female patients was 30.3 kg/m2. While 3 of the patients were morbidly obese, one was 2nd degree obese, and ten were first-degree obese. As a result, 45% of the patients were obese (Table 1).

Table 1. The distribution of patients according to the body mass index and gender

		Body Mass Index					Total
		Normal	Overweight	Grade 1 Obese	Grade 2 Obese	Morbid Obese	
Gender	Male	2	10	3	0	2	17
	Female	3	2	7	1	1	14
Total		5	12	10	1	3	31

The education level of the patients is that 3 of them did not go to school, 24 of them were primary school graduates, and 4 of them were secondary education graduates. 13 of the patients were housewives, 8 of them were workers, 5 of them were farmers, and the rest were in the other occupational groups (office worker, trader, students).

Physical examination of the patients revealed 17 thenar atrophy. In the EMG evaluation, 9 of the patients had mild, 14 had moderate, 8 had severe carpal tunnel syndrome, eight had mild, 15 had moderate, and 8 had severe cubital tunnel syndrome.

In carpal tunnel syndrome, the average BMI was found to be 29.86 kg/m2 in patients with mild EMG findings, 28.94 kg/m2 in moderate, and 30.59 kg/m2 in severe ones. While the mean BMI in mild cubital tunnel syndrome was 31.15 kg/m2, it was found to be 28.08 kg/m2 in moderate patients and 31.03 kg/m2 in severe ones (Table 2). According to body mass indexes and EMG findings, there was no significant correlation between carpal tunnel syndrome and cubital tunnel syndrome severity (P> 0.05).

Table 2. The severity of entrapment neuropathies in different body mass index groups

		Body Mass Index
		Mean
Cubital Tunnel Syndrome	Minor	31,15
	Moderate	28,08
	Severe	31,03
Carpal Tunnel Syndrome	Minor	29,86
	Moderate	28,94
	Severe	30,59

DISCUSSION

Carpal tunnel syndrome and cubital tunnel syndrome are the most common entrapment neuropathies of the upper extremity. It has been reported that 93% of patients benefit from decompression surgery [7]. There are epidemiological studies in the literature separately for these two syndromes, but there are few publications regarding the operation of these two syndromes in the same session. The most known risk factors for carpal tunnel syndrome are female gender, obesity, advanced age, and repetitive hand movements [8]. Risk factors for cubital tunnel syndrome have been reported as advanced age and high BMI for men, while low BMI for women [9].

It is known that diabetes mellitus is a risk factor for both carpal tunnel syndrome and cubital tunnel syndrome. Diabetes increases the severity of entrapment neuropathy after collagen solidifying after neural ischemia due to diabetic microangiopathy and non-enzymatic collagen glycolysis [10]. Naran et al. found DM in 23% of patients with cubital tunnel syndrome [11]. It was present in 32% of our patients.

In our study, the average age of all patients was 51.2, and the number of male patients was higher than female patients, similar to the literature. Carpal tunnel syndrome is more common in females than cubital tunnel syndrome [12,13]. 13 (41.9%) of our patients were housewives, 8 (25.8%) were workers, and 5 (16.1%) were farmers. 79% of female patients with carpal tunnel syndrome were determined to be

housewives in a study [14]. Consistent with our study, it has been shown that homemakers performing activities such as cleaning and handicraft intensively and male patients work in professions with intense, repetitive hand movements increase the risk of entrapment neuropathies [13,14]. The literature has reported that entrapment neuropathies are more common in the dominant hand and arm. Wilson et al. claim that while ulnar entrapment was determined in the left side with a rate of 51.8%, entrapment was observed in 53% of the dominant arm [15]. In our study, the right side/left side ratio was found to be 2.44, and the entrapment rate on the dominant side was 73.3%.

In the literature, it has been suggested that a high body mass index increases the severity of CTS. It has been thought that supportive fat tissue around the nerve may cause stenosis in the carpal canal in people with high BMI [4,10]. Also, they showed that the fatty tissue in the carpal canal increased hydrostatic pressure [16]. The situation is the opposite in cubital tunnel syndrome. It has been thought that the increased fatty tissue at the height of the BMI creates a protective filling around the nerve against external effects [9]. In our study, no significant correlation was found between body mass index and the severity of entrapment neuropathy. While only 5 of our patients had average body weight, other patients were overweight and obese. Contrary to expectations, mild entrapment neuropathy in EMG results is observed in patients with high BMI (29.86), Severe entrapment neuropathy was observed as a result of EMG in patients with CuTS with high BMI (31.03), and it is not compatible with the hypotheses in the literature. The study results of Sahin et al. were consistent with ours, and no significant difference was found between increased BMI and the severity of carpal tunnel syndrome [17]. There are not many publications examining the association of carpal and cubital tunnel syndrome in the literature. Similar to our study, Cross et al. applied decompression procedures to patients with cubital and carpal tunnel syndrome in both pathologies in the same session [18]. Surgical intervention in two entrapment neuropathies in the same session prevents the patient from receiving anesthesia twice, decreases the duration of hospital stay, and decreases workforce loss.

Conclusions

When CTS and CuTS patients are evaluated separately in the literature, although it is hypothesized that high body mass index and thick adipose tissue increase the severity of CTS by increasing the median nerve compression, but the same adipose tissue reduces the formation of CuTS, in our study when patients with the same extremity and simultaneous onset of symptoms were evaluated, it was revealed that body mass index was not related to the severity of symptoms. Although BMI does not change the severity of neuropathy, it is an important etiological factor in entrapment formation.

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Commentary: Controlling high blood pressure with intravenous sedation in mechanically ventilated neurosurgical patients in the intensive care unit. Is it a correct practice?

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ABSTRACT
This commentary discusses the effect of misuse of intravenous sedation regimens in lowering the systemic blood pressure in mechanically ventilated neurosurgical patients in the intensive care unit.

Intravenous sedation regimens are widely used in a neuro-intensive care unit (neuro-ICU) for specific neurologic purposes.[1-4] Among these purposes are intracranial pressure control, seizures management, targeted temperature management, reduction of pain, agitation control, and patient-ventilatory asynchrony.[1-4] The effect of sedatives on blood pressure is that they lower systemic blood pressure.[5] Thus, some would intensify sedation intending for systemic blood pressure control.[5] The problem is, when the sedatives are stopped, the risk of systemic rebound hypertension will exacerbate intracranial pressure in patients with low brain compliance.[6] Improper management of systemic blood pressure (BP) can ultimately lead to encephalopathy, cardiac and renal complications.[7,8] Moreover, the misuse of sedatives in neurocritical patients has deleterious effects in terms of eliminating neuro-assessment and potential cardiovascular depression; thus, it increases hospital stay, morbidity, mortality and delays the clinical decision process.[1-4]

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Prompt BP control in mechanically ventilated patients with neurological emergencies in neuro-ICU is necessary.[7-10] Nicardipine, labetalol, clevidipine, and urapidil are examples of fast-acting, soluble intravenous medicines that are feasible and recommended as first-line antihypertensive medications.[8] Invasive BP monitoring is required, especially in the setting of intracranial hypertension.[8,9] The 2013 American Stroke Association (ASA) guidelines state no exact BP target for which intravenous antihypertensive agents should be started.[10] When the systolic BP surpasses 220 or the diastolic BP surpasses 120 during the first 24 hours after an acute ischemic stroke, the ASA recommends reducing the blood pressure.[10] When fibrinolytic therapy is attempted, the recommended BP target is a systolic BP less than 180 or diastolic BP less than 110.[10]

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Madjid Samii: Omagium
When hard work, excellence, and love for patients collide

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pneumencephalotomography,
cranial nerves,
skull-base,
WFNS,
president,
future

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ABSTRACT

Prof. Madjid Samii is an internationally recognized neurosurgeon who has conquered the highest levels of 21st-century neurosurgery. Born in Iran, he decided to take medical courses at the University of Mainz, Hanover, Germany. He earned his medical degree in 1963, marking the highest achievable score, and started his residency, guided by Emeritus Professor Dr Kurt Schurmann. Numerous various surgeries and studies that reshaped the field of neurosurgery describe his career. Starting with a publication regarding a new technique, pneumencephalotomography, he has steadily been ascending, studying and writing about cranial nerves, developing the surgery of the skull base and proving that the transnasal approach is preferred in clivus chondromas. Prof. Madjid Samii founded, 1990, the Foundation of National and Continental Skull Base Societies and, and since 2001, he has been the Honorary President of the World Federation of Neurosurgery Societies (WFNS). Not only was he successful in his scientific path, but he also gave an example for the future generation of what astonishing results can be obtained with hard work, commitment, and a leader's spirit. He wanted to take worldwide neurosurgery to a whole new level, so he came up with an idea, the concept of an international neuro-excellence centre, which quickly became the reality of the International Neuroscience Institute of Hanover.

BRIEF PRESENTATION OF THE EVOLUTION OF NEUROSURGERY

Taking a trip down memory lane, neurosurgery is a surgical specialty that set about to develop at the beginning of the 20th century. Since

then, it has been in a progressive evolution, swayed by the contributions of grand names such as Harvey Cushing (1869-1939) and Gazi Yasargil (1925-).

Harvey Cushing (Figure 1), remembered as the father of modern neurosurgery, was an American pioneer of modern operative techniques in brain surgery. His significant contributions have made neurosurgery more approachable and understandable for future generations.

Gazi Yasargil (Figure 1) is a Turkish neurosurgeon who managed to revolutionize brain surgery by introducing micro-neurosurgery. He was the founder of micro-neurosurgery and trained countless surgeons in the micro-neurosurgical anatomical laboratory in Zürich, Switzerland.

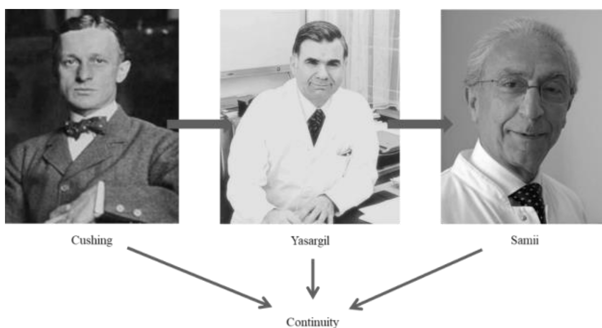

Figure 1. Harvey Cushing, Gazi Yasargil, Madjid Samii (golden triangle of neurosurgery)

We considered reminiscing these two names as a glimpse of recognition for their scientific and spiritual influences that push neurosurgery to reach new horizons nowadays.

Certainly, the highest level of 21st century global neurosurgery has been conquered by Prof. Madjid Samii (born in 1937, Teheran), not only through his surgical activity but also through his innovative and societal actions.

Madjid Samii - life, career and achievements

Prof. Madjid Samii (Figure 2) is a neurosurgeon who dedicated his career to solving the hardest and most complicated cases, to educating future neurosurgeons, and to publishing an astonishing number of statistics.

He was born on the 19th of June 1937 in Tehran, Iran. After graduating high school in Iran, he moved to Germany, where he studied medicine at the University of Mainz.

Earning his medical degree from the University of Mainz in 1963 by marking the highest achievable score in the final medical examination made him the recipient of the prize of the Iranian Science Ministry for the best Iranian student in Europe.

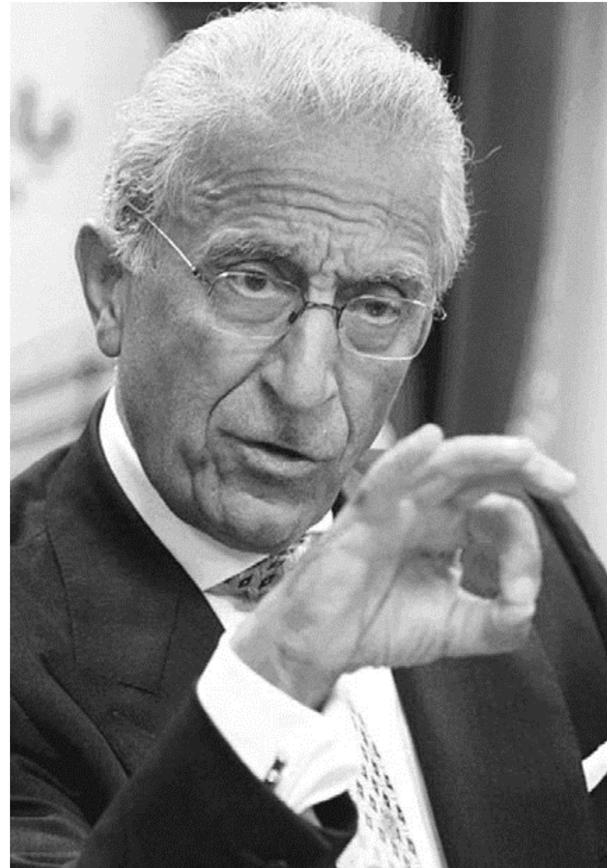

Figure 2. Prof. Dr Med. Madjid Samii (WFNS-President)

Prof. Madjid Samii finished his neurosurgical residency at the same university, learning from the Emeritus Professor Dr. Kurt Schurmann, who provided him with de Cushing's motto: "Through Valor and Divine Aid" and receiving his board of neurosurgery in 1970.

Being inspired by what was known at that time: pneumoencephalography-Walter Dandy (1886-1946) and cerebral angiography-Egas Moniz (1927-2017), Prof. Madjid Samii thought about a new technique and published his first paper, named "pneumencephalotomography", together with Prof. Schurmann in 1965.

Three years later, his innovative thinking was brought back to light. He used the previous technique, developing a more advanced one-"Combined ventriculo-lumbar puncture" and, by

using it, he realized the first radiologic diagnosis of Hydrocephalus occlusus. Furthermore, this technique was performed by him in the treatment of a case of Dorsum sallar Chiasma Compression Syndrome (1972).

Prof. Madjid Samii was one of the first to use a microscope in the operating room, back in 1969. Afterwards, he dedicated his time to the study of peripheral and cranial nerves, focusing on nerve grafting and nerve transfer operative techniques. Two years later, he achieved the success of a hand reimplantation surgery. During the same year, he published "The Cranial Nerves" book.

He also developed the surgery of the skull base. In 1970, he built the first interdisciplinary team in Hanover, consisting of neurosurgery, ear, nose and throat (ENT) and maxillofacial surgery doctors. As a result of his hard work, in 1989, he published "Surgery of the Skull Base-An Interdisciplinary Approach" book. Regarding the skull base surgery, Prof. Madjid Samii founded in 1990 the Foundation of National and Continental Skull Base Societies and the Foundation of German Skull Base Society (of which he is president).

His statement is, "The only real treasures a neurosurgeon can have in his life are his patients". It may explain his commitment to studying, innovating, and discovering during his entire career. Thus, he studied all the approaches for clivus and proved that the transnasal approach is preferred in clivus chondromas (using an endoscope and microscope).

In 2013, he published the "Surgery of Cerebellopontine Lesions" book, in view of presenting his professional experience between 1968 and 2013 (more than 6000 surgeries).

His work and discipline encourage surgeons from all around the world to manage the most difficult cases with extreme precision and determination. He gave lectures that represented a major contribution to the progress of neurosurgery, while publishing numerous papers and statistics.

In 1977, Prof. Madjid Samii became chairman of the Neurosurgical Department at Nordstadt Krankenhaus, in Hanover, Germany. He also accepted the chair of Neurosurgery at Hanover School of Medicine.

Between 1997-2001, he was elected president of the World Federation of Neurosurgery Societies (WFNS) according to his societal and humanitarian contributions worldwide through his work. Since 2001, he has been the honorary president of WFNS and the honorary president of the WFNS Foundation.

THE INTERNATIONAL NEUROSCIENCE INSTITUTE OF HANOVER

Prof. Madjid Samii's considerable capacity for leadership gives Hanover, Germany, one of the most recognized centers of excellence in neurosurgery in the world, raising European neurosurgery to a more advanced level.

He managed to fulfill his idea of creating a comprehensive neurosurgical center, the International Neuroscience Institute of Hanover. **In 2000, at the World Expo** event, the International Neuroscience Institute of Hanover was officially inaugurated, becoming rapidly the best center for treating neurosurgical conditions.

Although the project was realized by the "Siemens" Company, the ideas of Prof. Madjid Samii were vigorously taken into consideration, the interior and exterior designs of the building being decisively influenced by his suggestions.

Shaped as a "futuristic" human brain, the International Neuroscience Institute of Hanover (Figure 3) is a unique architectural landmark, enhancing the suggestion that any pathology of the nervous system can be cured.

Figure 3. International Neuroscience Institute of Hanover (Open in 2000)

The main areas of the Institute consist of three separate but synergetic departments: Neurology, Neurosurgery, and Interventional Neuroradiology.

For an elitist final result, it was mandatory to build a team formed by the most competent neurosurgeons. In this matter, Prof. Madjid Samii's imposing personality helped the Institute to quickly have the brightest neurosurgeons for each neurosurgical subspecialty practicable.

The Institute is also focused on skill-improvement specialized training as well as on clinical research, having various laboratories for scientific experiments with successful results spread worldwide.

Compared to developing countries, the International Neuroscience Institute of Hanover uses highly technological devices for paraclinical analysis, such as: 3 Tesla MRI,functional MRI, a 128-slice CT scanner, and a biplane angiography system.

The International Neuroscience Institute of Hanover was soon followed by the International Neuroscience Institute of China (Beijing) and the International Neuroscience Institute of Iran (Teheran).

Romanian Neurosurgery at the International Neuroscience Institute of Hanover

Last but not least, we have to mention that Prof. Madjid Samii is a real friend of the Romanian Neurosurgical Society, as he answers positively to the many congress invitations. He built a strong relationship with the greatest Romanian neurosurgeons.

A special bond was created in 2014, when Prof. Madjid Samii invited Prof. Alexandru Vlad Ciurea to the International Neuroscience Institute of Hanover (Figure 4). Prof. Alexandru Vlad Ciurea presented a truly complex medical study regarding the embriology and development of the human brain, afterwards being awarded by Prof. Madjid Samii with the title of "**Visiting Professor**".

Figure 4. Prof. A.V. Ciurea & Prof Madjid Samii

As Prof. Madjid Samii reaches the age of 85, we would like to pay tribute to his major innovative, scientific, and humanitarian contributions to the field of international neurosurgery

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