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PAEDIATRIC MENINGIOMAS: A CLINICO-PATHOLOGIC EVALUATION OF SEVEN YEAR EXPERIENCE WITH OWN SERIES, ILLUSTRATION OF FIVE RARE CASES AND REVIEW OF THE LITERATURE

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Abstract: **Meningioma is one of the most common tumors of the central nervous system in adulthood, constituting 20–30% of all intracranial primary neoplasm. [1, 2]. Meningiomas occur most commonly in the fifth decade of life in adults. Paediatric meningiomas are relatively uncommon and rare. They compose no more than 3% of all childhood primary intracranial tumors [2–5]. Previous literatures reported that paediatric meningiomas have different clinical features and prognosis compared with those of adults [6]. The information about the entity of paediatric meningiomas is poor, only several studies have attempted to analyze the characteristics of childhood meningiomas. Although they are uncommon in infancy and childhood, some features of childhood intracranial meningiomas, such as male predominance or lower frequency of dural infiltration have been well described in the literature [8, 10,23]. Absence of dural attachment is more common in children than in adult patients. Childhood meningiomas have a low recurrence rate. They are frequently associated with neurofi- bromatosis, which is the most important factor influencing outcome. Many controversies exist and a definitive description of childhood meningiomas still requires much more broader experience.**

Objective: To retrospectively analyze and review the epidemiological profile, clinical features and characteristics, radiological findings, type of excision, histopathological findings, treatment consideration, and overall management profile and prognosis of paediatric meningiomas. The findings were compared with those of other studies in children and in adults.

Materials and Methods: Review of the literature with MEDLINE / PUB-MED / EMBASE search was done to study and analyze the published data about paediatric meningiomas for the last 25 years.

Nineteen consecutive cases of meningioma patients, who were admitted, operated and followed up at our institution between the years 2006 and 2013, were included in this study. This article reviewed 19 cases of surgically treated intracranial and intraspinal meningiomas in children under 18 years of age, who were followed up during a period of 7 years.

Additionally, five rare cases of paediatric meningioma were presented with illustration of specific uncommon findings: One case in the anterior cerebral fossa, two cases of the pineal region, one case of cerebro-spinal infiltration and a case of lepto-meningeal dissemination.

Results: The mean age of patients at presentation to our hospital was 12.81 years (range from nine months – 18 years, 11 boys and 8 girls). The male to female ratio was 1.38:1. The median preoperative duration of symptoms

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was 1.2 years. An increased incidence was seen in patients with neurofibromatosis. Intraventricular and skull base locations were common. Total tumor excision was achieved in all cases.

Seven patients were in the first decade of life and 12 patients were in the second decade. The most common symptoms were related to increase of intracranial pressure (ICP) such as headache (33. 3%) and epilepsy (25%), followed by cranial nerve dysfunction: distortion of commissures, vision disorder and disturbance of sensorium level up to unconsciousness. In spinal tumors, muscular weakness with paraparesis / monoparesis with or without sensitive dysfunstion were the main symptoms. The size of lesions was ranged 25–65 mm (mean 42.3 mm). Of these 19 patients, 11 were diagnosed as WHO class I meningiomas, 5 were WHO class II, and 3 manifested WHO class III. Two of 19 patients (10.5%) met the criteria, that theyvhad tumor recurrence within follow-up of seven years.

The specific findings of the five additional cases were illustrated and discussed in details.

Conclusion: Paediatric meningiomas usually have larger size, higher pathologic grade, and unusual location. The influential factors for recurrence include lesion location, histological features and extent of removal. A higher incidence of atypical and aggressive meningiomas is seen in children. Children with complete resection and a typical benign histology have a good prognosis. Complete tumor resection is the best choice to treat the symptoms, improve the prognosis and prevent recurrence.

Keywords: **Paediatric Meningioma, Craniotomy, Laminectomy, Laminoplasty, Castleman's syndrome, Linear accelerator (LINAC), Central Nervous System (CNS), paediatric neoplasms, Neurofibromatosis, Cerebello-Pontine Angle (CPA) tumor, Cranio-Spinal Leptomeninges, CSF-Dissemination, cerebral or spinal digital subtraction angiography (DSA), Positron emission tomography (PET), Univariate and multivariate odds ratios (ORs), GOS (Glasgow Outcome Score), (KPS) Karnofsky performance index / score, Gorlin syndrome, Positron emission tomography (PET), Leptomeningeal carcinomatosis, Intraventricular, Malignant, en plaque Meningiomas, Radiation-induced meningiomas (RIM), Spontaneous meningiomas (SM), Ionizing radiation, Hemangiopericytomas in children, Relapse-free survival (RFS), Generalized tonic clonic seizure (GTCS), Within normal limits (WNL), Intracranial Pressure (ICP), High power field (HPF), Anaplastic meningioma, World health organization (WHO), Atypical meningioma, Brainstem dysfunction, Multiple cranial nerve palsies, Vimentin, Cerebrospinal fluid (CSF) dissemination, Intraventricular meningioma (IVM), Vascular endothelial growth factor (VEGF), Estrogen, Progesterone, Cytoplasm, Nucleus, Hormone binding, Infratentorial meningioma (ITM), chemotherapy, leukemia, lymphoma, The South West Oncology Group (SWOG), Tamoxifen, Mifepristone, Radio-surgery (RS), Radiation therapy (RT), Morbus von Recklinghausen, Alpha feto protein, (AFP), beta subunit of human chorionic gonadotropin (HCG), Glial fibrillary acidic protein (GFAP), Epithelial membrane antigen (EMA), Growth factor (GF), Epidermal growth factor (EGF), Sporadic meningioma (SM), paediatric meningioma (PM).**

1. INTRODUCTION

Meningiomas are uncommon childhood tumors with special features relating to the clinical characteristics, biological behavior and outcome of this interesting and almost benign pathology, which rarely occurs in the first two decades of life. Cushing and Eisenhardt [13, 18, 23, 28, 33-39, 44-49] encountered six (1.9%) children among 313 meningiomas documented in their classic 1938 monograph. Among 750 intra-cranial tumors reported by Matson 1969, only 3 (0.4%) were meningiomas [44]. Since then, several series have been published, yet the reported incidence remains unaltered making these tumors an interesting and distinct clinical entity. Paediatric meningiomas vary considerably in their histopathological, topographical and gender distribution throughout childhood and adolescence, reflecting different tumor dynamics as compared to adults.

Meningiomas are most commonly encountered after the second decade of life. However, they may occur at any age or even during foetal development. Amirjamshidi et al. in 2002 compiled in a list of 329 published cases of childhood meningiomas, to which they added 24 more patients. A recent report from the Central Brain Tumor Registry of the USA states that only 2.5% of all primary paediatric CNS tumors were meningeal in origin, whereas for all age groups combined, 22% of tumors were of meningeal origin [1-3]. Generally, paediatric meningiomas are commonly quoted as constituting 1.5-1.8% of all meningiomas and 0.4-4.1% of all childhood brain tumors [19, 20, 22, 26, 34, 40, 49, 52, 57, 59, 60, 65, 66, 71]. Multifocal tumors, usually encountered in the context of NF2, are a recognized feature [14, 19-36, 36-52, 77-90, 101-119] within the paediatric population, underscoring further differences from their adult counterparts. Even though meningiomas are uncommon in the children, they constitute a challenging issue for neurosurgeons, because of their different behavior as compared with adult meningiomas [150-165, 177-200].

There are no large series of paediatric meningiomas because of the rarity of these tumors. [1-14] However, it is possible to analyze meningiomas in children by reviewing the available series collectively. For the purpose of this study, we reviewed the pertinent literature for articles containing cases of meningioma in childhood published between 1913 and

2001. All together, 107 articles were selected, containing 587 cases of meningioma in children (563 spontaneous meningiomas and 24 radiation-induced meningiomas). In the present survey, 147 cases lacked complete information or were intraorbital, excluding them from the present analysis. [14,36-48,65,77-78,97,104,108-119, 140-161, 179, 192, 199-204] Therefore, 467 intracranial meningiomas were analyzed, including the own cases (448 spontaneous meningiomas and 19 radiation-induced tumors).

Most of the reports concerning meningioma in children describe the particular findings of these tumors, with special emphasis placed on the differences from meningiomas in adults. Our review, including the own cases, confirms most of the previously reported peculiar characteristics of paediatric meningiomas, but it challenges the concept that these tumors have a poorer prognosis than their counterpart in adult patients. On the other hand, many reports suggest a more aggressive behavior of meningiomas in children than in adults. [97-98]

Various causes have led to this controversy. To begin, the clinical results should be interpreted distinguishing the different histologic forms of meningiomas. Many authors have included anaplastic meningiomas, papillary meningiomas, and melanotic tumors in their reviews. [1, 8, 12-13, 16-18, 32, 59] These histologic variants of meningeal tumors, classified according to the modified World Health Organization classification, [21] are malignant and clearly have a poorer prognosis than classic meningiomas. Second, in the past, the malignant behavior of these meningiomas was interpreted not only from a stringent histologic point of view, but also more generically because of the tendency of the tumor to recur. [92, 99] This obviously implies that aggressive meningiomas were identified improperly. In fact, it is universally accepted that postoperative meningioma recurrence is related to both the microscopic pattern of the meningioma and the adequacy of the original surgical removal. [112-116] Subtotal or partial removal is associated with a high recurrence rate. From our review of the literature, almost all children with meningioma recurrence had malignant histologic variants or partial or subtotal removal. [17, 32 ,52 ,92, 99]

Advances in neuroimaging and development of microsurgical and anaesthesiological techniques have allowed an increase in complete tumor removal rates. This was demonstrated in the own series: the total removal rate before 1970 was 55% versus 88% after 1970. Children in this series with subtotal removal have always had meningioma regrowth. This datum might be erroneously interpreted as the malignant behavior of the tumor.

Third, affected children often have history of NF 2 or previous cranial irradiation for tinea capitis, leukemia, or brain tumors. [11-12, 14, 59, 98, 117-118] The association with neurofibromatosis 2 can be a poor prognostic factor for the progression of syndrome-associated lesions. [119-121, 134-149, 151-169, 174-188]

Postirradiation meningioma is a rare event in children, with only 18 cases reported in detail in the available literature by a MEDLINE search. [109, 120-133] Radiation-induced meningiomas in children are often atypical or malignant. This could be explained by the hypothesis that the radiation-induced degenerative changes tend to evolve toward anaplasia. Another element to considering a meningioma aggressive could be the multiplicity of the lesions. However, the incidence in the computed tomography and magnetic resonance imaging era of multiple meningiomas in children is very low in spontaneous meningiomas (2.4%) and zero in postirradiation ones. [83,91,134-135]

The analysis of 419 cases considered here confirms some general aspects of spontaneous meningiomas in children, namely the male predominance, frequent intraventricular location, cystic appearance, and lack of dural attachment. In addition, the analysis of 21 patients with postirradiation meningiomas evidences some clinical features specific to children.

The greater incidence among male patients rather than the female patients in paediatric meningiomas contrasts to the female prevalence of meningiomas seen in adults. This phenomenon might be related to an absence of the effect of sex hormones on corticosteroid receptors in meningioma cells for low blood concentrations. [11,136-139] This suggests that different pathogenetic factors might account for the occurrence of this tumor in children and adults. Some studies on genetic aberrations in meningiomas in children show no differences from meningiomas in adults. The frequency of intraventricular meningiomas is very high (12%) if compared with 0.5% to 4.5% in adults. [29,59,60,68,140, 163-179, 180-204] This propensity for growth into the ventricular system could be explained by the inclusion of arachnoid cells in the choroid plexuses and velum interpositum.

A high frequency of intra- or peritumoral cysts (15%) results from this analysis, whereas in the adult population, cystic forms are present in 2% to 4% of all meningiomas. [2, 17, 32, 91, 92, 102, 108, 109] Cystic prevalence in the first 2 years of life can be ascribed to the tendency of cystic tumors to manifest earlier than solid ones. Effectively, we have found the average duration of the clinical history of meningiomas in paediatric patients (1.2 years) to be shorter than meningiomas at other ages (2.8-3.5 years). [3,6,45] Lack of dural attachment is another frequent occurrence in paediatric meningiomas (28.5%), whereas it is extremely rare in adults. [12,13,17,54,59,60,78] The lack of dural attachment is probably due to derivation of the tumor from leptomeningeal elements lodging within the parenchyma or in or near the ventricles rather than from the dura mater. [91, 101, 109] Histologically, the meningiomas were mainly meningothelial (32%), [19-23, 91, 94, 97, 99, 102, 104, 106-110] followed by fibrous (25%), [9,19-20,91,99,100,101,104] transitional (22%), [19-20, 97, 99, 103-109] anaplastic (9%), [19,20] angiomatous (6%), [19,20,104,107] psammomatous (2%), [99,104] atypical (1.2%), [99-100, 105, 108] papillary (0.9%), [19,20,104] chordoid (0.6%), [95, 107] microcystic (0.3%), [108] clear cell (0.3%), and lymphoplasmacytic (0.3%). [108] Surgical treatment was reported in 412 children, with a total operative mortality of 7%. Precisely, 63 patients were operated on before 1970, with an operative mortality of 26.7%; 119 patients were operated on between 1970 and 1989, with an operative mortality of 10%; and 260 children were operated on between 1990 and 2004, with an operative mortality of 0.3%. [14-20, 91-111] The marked operative mortality decreasing in the last decades is relative to the early diagnosis and progress in microsurgical and anesthesiologic techniques.

The clinical outcome was available in only 267 cases, with a mean follow-up of 4.2 years. In 13% of these cases, tumor recurrence is described. Recurrence seems to be strictly related to incomplete resection and/or the histologic subtype of the meningioma: 54% of the recurring meningiomas were removed subtotally and 46% totally. Most of the latter were malignant or malignant variants; more precisely, 31% were anaplastic, 15% atypical, 10% papillary, and 10% sclerosing with brain invasion. The remainder were angiomatous (5%) and not invasive (26%). One of these latter cases was previously irradiated. One of the patients and another one reported in the literature [45-49, 56, 59, 69-77, 92-113, 119-127, 144-165] were affected by von Recklinghausen disease. He had bilateral acoustic neurinoma 15 years after the operation without recurrence of meningioma. Nno other factors were found predisposing patients to the development of meningioma. With regard to radiation-induced meningiomas, there are some differences when compared with both the spontaneous counterpart and radiation-induced meningiomas in adults. First, in paediatric postirradiation meningioma, there is a female to male ratio of 1.7:1. This female predominance is similar to that of meningiomas in adults, but it contrasts to the absence of a sex predominance observed in spontaneous paediatric meningiomas. Second, the rate of postirradiation meningiomas in children with aggressive behavior is similar to that in adults (15% vs 18.8%) but contrasts to the behavior of spontaneous paediatric meningiomas. Third, the latency period between irradiation and the diagnosis of meningioma tends to be shorter in paediatric patients than in adults. The latency period between RTtherapy and clinical onset of meningioma in the paediatric population is 9 years (2-15 years) versus 21.9 years in adults. Modan et al followed 10,834 children irradiated for ringworm of the scalp with low doses (1-2 Gy) using the Adamson-Kienboch technique. [111-117]. These children showed a significantly higher risk of both malignant and benign head and neck tumors, including brain tumors, compared with age-matched controls. A further 10-year period of observation in this group of patients estimated that the relative risk compared with the control populations was 6.9 for all tumors, 8.4 for neural tumors of the head and neck, 9.5 for meningiomas, and 2.6 for gliomas. At the moment, large investigations outside the era of irradiation for tinea capitis are not available, so it's not known, how many patients develop radiation-induced meningioma following irradiation for other central nervous system tumors. However, it was found in a recent study, by a MEDLINE / PUB-MED / EMBASE search, 80 cases of high-dose radiation-induced meningiomas in adults [140] and 21 similar paediatric cases (mean dose 38.8 Gy). The marked rarity of paediatric post-irradiation meningiomas compared with their adult counterparts could be due to the fact that meningioma is a slow-growing tumor that manifests late. However, in paediatric radiation-induced meningiomas, it was found a mean age at irradiation of 1.4 years versus 16.2 years in adult radiation-induced meningiomas. In addition, the latency period tends to be shorter in patients in whom irradiation was performed at a young age. The low age and the short latency period probably reflect the marked vulnerability of the immature nervous tissue to the oncogenetic action of ionizing radiation. In the paediatric population, the primary disease was mainly a malignant tumor: medulloblastoma, seven cases (36%); glioma, four cases (21%); ependymoma, three cases (15%); acute lymphoblastic leukemia, two cases (10%); pineoblastoma, one case; (5%); histiocytosis, one case (5%); and cutaneous angioma. Ron et al. found a strong dose-response relationship for brain tumors. [119-141, 189] Similarly, Harrison et al., in a

review of the literature, reported a relationship among radiation dosage, latency period, and age at the appearance of the meningioma: for doses more than 20 Gy, the age at diagnosis and the latency period are reduced. [129-142]

2. EPIDEMIOLOGY

The incidence of meningiomas among primary intracranial neoplasms in adults is ca. 20 – 30 % and the reported incidence per 100,000 population varies from less than 1% to more than 6%. The incidence of intracranial meningiomas rises with increasing age with 3.5 times higher in patients older than 70 years age than in younger patients, regardless of sex [40, 42, 50-55]. Paediatric meningiomas are commonly quoted as constituting 1.5-1.8% of all meningiomas and 0.4-4.1% of all childhood brain tumors [19, 20, 22-26, 34, 40, 49, 52, 57, 59, 60, 65-66, 71]. The incidence of paediatric meningiomas increases with age and more are reported in the second decade of life compared to the first. The male to female incidence ranges from 1:1.4 to 1:2.8. [21-23] In contrast to adult meningiomas, there is no female preponderance among paediatric meningiomas, and in certain series male subjects appear to outnumber their female counterparts [19, 25, 49]. Ferrante et al. [25, 29, 40-44] reviewed 178 examplesand foun d a marginal male preponderance (M:F 1.3:1). The male predominance in childhood meningiomas is more marked in infants than in adolescents, and characteristically it seems to be absent in patients affected by neurofibromatosis [19]. However, some authors like Glasier [28] and Darling [15] quote an equal incidence and others like Rochat [42, 54] have found a female predominance as in adults. The sex hormone binding characteristics of paediatric meningiomas have not yet been well-characterised, and it is unclear to what extent the hormonal status affects the sex predilection [1, 54]. Meningiomas are multiple in 5-40% of patients, especially when they are associated with NF II [23].

3. ETIOLOGY / SPECIFIC FEATURES / MANAGEMENT

3.1. Trauma

Although numerous case-control studies have reported an increased association between a history of head trauma (vs. no head trauma) and the development of meningiomas, Annegers et al (1979) [6] found no significant increase of any intracranial tumors in a prospective study of 2953 patients with head injuries. Similarly, a population based cohort study conducted in Denmark with 228055 patients who were hospitalized with head injuries between 1977 and 1992 found no significant increase in the subsequent incidence of meningiomas [37].

3.2. Irradiation

Exposure to ionizing radiation is a known etiological factor in the development of meningiomas. An increased rate of meningioma formation has been seen in patients after irradiation for tinea capitis, in patients after treatment for primary head and neck malignancies, and in survivors of radiation exposure from the atomic bomb explosions in Hiroshima and Nagasaki. The causal relationship between radiation and paediatric meningioma is also well established. Current findings suggest a nearly ten-fold relative risk for children with radiation exposure over those without such exposure [29, 46]. Radiation induced meningiomas typically present at an earlier age, arise within the prior irradiation field, are more likely to be multifocal, have different cytogenetic characteristics, are more biologically aggressive with higher degrees of atypia and mitosis and are more likely to recur. Due to dose effect; with higher levels of radiation exposure being associated with shorter latency periods for development of meningiomas [29]. Sheffield et al. reported about a sufficient time between the radiation and the development of the meningioma.

3.3. Genetics and Molecular biology

Thirty to eighty percent of SM and nearly all neurofibromatosis-related meningiomas have mutations in the NF-2 gene located in chromosome band 22q12, that result in mutations in the protein merlin. Chromosomal banding techniques have identified chromosome subband 22q12.3-qter, which is near the NF-2 gene but is believed to represent a separate and distinct locus in meningioma formation. The genetic factors involved in the tumorigenesis of meningiomas are currently a subject of investigation to inform screening and prediction of risk for tumor progression to atypical or anaplastic disease. The possibility of NF2 should be considered in any child with a meningioma and approximately 25-40% of children with meningiomas have NF2 [7, 49, 50]. The more severe ("Wishart") variant of NF2 is more likely to present with paediatric meningioma [49]. In Perry's series [49, 50], sporadic and NF2-associated paediatric meningiomas were histopathologically similar with the exception that brain invasion was nearly exclusive to the sporadic tumors, a difference that reached

statistical significance. Both NF2-associated and sporadic paediatric meningiomas frequently had demonstrable 1 p and 14q deletions, alterations commonly associated with tumor progression in meningiomas. The large size of some paediatric meningiomas mentioned in several series and especially in those including NF pedigrees, implicates NF as a stigma suggestive of rapid tumor growth. Beside NF, Gorlin syndrome also known as multiple basal cell carcinoma, is another familial tumor condition with autosomal dominant inheritance with an association with meningiomas [41-55]. Loss of expression of another tumor suppressor gene, DAL-1, which is located in 18p11.3, has been found in 30-70% of meningiomas and is thought to play a role in both early tumorigenesis and meningioma evolution. Other tumor suppressor genes implicated in the development or progression of meningiomas are SMARCB2 (22q11.2), p53 (17p), and CDKN2B (9p21). The fact, that malignant and atypical meningiomas tend to have more chromosomal aberrations than benign tumors do, suggests progressive loss of tumor suppressors and potential activation of oncogenes. Some of the genes implicated in meningioma oncogenesis are c-sis, C-inyc, Ha-ras, K-ras, c-fos, c-erbB and S6k. A variety of other chromosomal aberrations have been implicated in the formation and progression of meningiomas including losses on 1p, 2p, 6q, 10q and 14q and gains on 1q, 9q, 12q, 15q, 7q and 20. Alteration on chromosomes 1, 10, and 14 and reactivation of the telomerase subunit hTERT seem to be practically important in the progression of more biologically aggressive meningiomas.

Radiation induced meningiomas have been shown to express genetic alterations that are different than those of sporadic meningiomas. In particular, there are fewer losses of genetic material on chromosome 22 and more losses on chromosomes 1 p, 6q, 9q, 18q and 19q.

3.4. Gonadal steroid hormones and receptors

Estrogen receptors have been reported in 0-94% of meningiomas and progesterone receptors in 40-100%. Recent studies using modern experimental and laboratory techniques have revealed minimal amounts of functional estrogen receptor. This finding is supported by the generally disappointing results of anti-estrogen agents (Tamoxifen and Mepitiostane) in treating meningiomas. Most investigators have identified high levels of progesterone receptors in meningiomas, and the presence of these receptors has correlated with less aggressive tumor biology, more favourable prognosis and a lower incidence of recurrence. Antiprogesterone agents used to treat meningiomas have yielded varied results; the most recent phase-Ill double-blind, randomized, placebo-controlled trial of Mifepristone reported no significant benefit [32]. Though one might not expect paediatric meningiomas to be hormonally driven, progesterone receptor (PR) is expressed with similar frequency, regardless of age at presentation. There is a roughly inverse association between PR expression and tumor grade in meningiomas of children and adults alike [18, 54]. Androgen receptors are found in meningiomas with about the same frequency as progesterone receptors and are expressed in 69% of males and 31% of females [9]. Testosterone stimulates in vitro meningioma cell growth, and it has been speculated that androgen receptors may help modulate progesterone receptor activity.

3.5. Other receptors and Growth Factors

Using polymerase chain reaction analysis (PCR), Carrol et al. (1996) detected D1 receptor mRNA in meningiomas, particularly in females, as well as D2 receptor mRNA and prolactin receptor mRNA, but the functional importance of these findings is unclear. Somatostatin receptors, particularly type 2a (hsst2a) receptors have also been reported at high levels in meningiomas. There have been a few reports of success using somatostatin analogues to treat meningiomas, but the role of somatostatin receptors in tumor progression or growth is still unclear. GH receptor mRNA is ubiquitiously expressed in meningiomas. GH receptor blockade by Pegvisomant has been shown to result in decreased growth rates of primary meningioma cell cultures and reduced tumor growth and regression in an in vivo animal model. Westphal and Hermann (1986) discovered functionally intact EGF receptors, a product of the oncogene c-erb, and reported increased DNA synthesis after EGF treatment of meningioma cell cultures. Weisman et al (1986) noted a modulatory effect on this receptor by platelet derived growth factor (PDGF) and revealed near maximal levels of DNA synthesis in meningioma cell cultures when PDGF and EGF were added together. The finding of c-erb/EGF receptor expression in meningiomas prompted searches for other oncogene receptor- mitogen systems. Using Northern-blot analysis, Maxwell et al 1990 demonstrated that meningiomas express both: The c-sys/ PDGF-2 proto-oncogene and the PDGF receptor (PDGFR) gene. Further studies revealed that PDGF-f3 is expressed in meningiomas, that PDGF-BB increases c-fos expression in meningioma cell cultures, and that over-expression of PDGF- f3 and PDGF-BB is associated with higher grade and

proliferative activity in meningiomas, which supports concept of PDGFR activation by an autocrine-paracrine loop and the idea that PDGFR activation contributes to tumor cell proliferation or malignant transformation. VEGF levels are associated with increased angiogenesis, edema and frequency of recurrence in meningiomas. Fibroblast GF factor and insulin-like GF 1 have also been identified in meningiomas and implicated in tumor progression. Many of the GFreceptors (PDGFR, EGFR and VEGFR) are protein tyrosine-kinase receptors that activate and associate intracellular cascades, which mediate cellular proliferation, differentiation and transformation.

3.6. Clinical Features

There is no single symptom or sign that identifies patients, who harbour intracranial or spinal meningiomas. A variety of presenting features depend primarily on the tumor's size and location; these features include headache, paresis, seizure, personality change or confusion and visual impairment. Headache and paresis are the most common symptoms and signs respectively and each might occur in a third of patients. Meningiomas in particular locations may produce a consistent set of signs and symptoms. Tumors of the olfactory groove have been associated with the Foster-Kennedy syndrome (anosmia, ipsilateral optic atrophy and contralateral papilloedema); Tuberculum sellae meningiomas may cause significant and early visual loss (typically a chiasma syndrome with optic atrophy and an incongruent bitemporal hemianopia). Cavernous sinus meningiomas may result in proptosis, diplopia or primary aberrant oculomotor degeneration and foramen magnum tumors often have associated nuchal and suboccipital pain with step-wise appendicular sensory and motor deficits. Childhood meningiomas are characteristically known to have non-specific symptoms and diagnosis is often difficult. The elasticity of skull and non-cooperation among children compounds the problem. Quite often a local swelling of the cranial vault may be the first sign. Common clinical manifestations of paediatric meningiomas include signs of increased intracranial tension, focal neurological deficits, seizures and other signs based on their location.

3.7. Radiological Diagnosis

3.7.1. Radiological Findings in the Computed Tomography (CT scan)

From the material, available there is no distinctive imaging feature differentiating anaplastic meningioma from its equally malignant rhabdoid forms. Since more than 30 years ago, CT scan findings to characterize malignant cranial meningiomas. Such endeavor has since been revisited. Thus, presence of intra-tumoral low densities, a sign of necrosis, is suggestive of malignancy. Similarly, skull vault erosion by a heterogeneously enhancing mushroom-shaped tumor with fringed margins is strongly indicative. In critical clinical situations where a firm diagnosis hinges on histopathology, such CT findings are essentially an expression of lesional aggression. In the context of 40 malignant meningiomas in this review, such notions are hardly justified as only showed skull vault and scalp erosions on CT or Magnetic Resonance Imaging (MRI). Since a paper by Mattei T., et al. in 2005, it has become routine practice to correlate histologically benign and malignant meningiomas with the extent of peritumoral oedema depicted on CT and MRI in adult patients. Similar guidelines are adopted in “sub-typing” meningiomas among children and adolescents. Indeed, it has been observed that most lesions of the WHO Grade III class are surrounded by extensive white matter oedema [20, 27, 47-51]. Some youngsters with this “ominous” sign succumbed, while others had survived with the aid of surgery and radiotherapy Contrarily, where peritumoural oedema was absent or at a minimum, the patients’ clinical course had progressed satisfactorily. This is demonstrated in the case study of a 2-year-old girl whose histologically confirmed right cerebello-pontine angle malignant meningioma was completely removed. Radiotherapy was not offered because of her age; she remained alive and well 5 years post-surgery [53]. The other concerned a 3-year-old boy with a large rhabdoid meningioma in the right middle cranial fossa. Contrast enhanced MRI showed the lesion had straddled the sylvian fissure and encased the ipsilateral middle cerebral artery. In consequence, his tumor was incompletely excised; only adjunct chemotherapy was given on account of his age. Significantly, his condition was stable at follow-up at 33-months post therapy.

The incidence of calcification and hyperostosis in CT scan is high especially in the paediatric meningiomas associated with NF. On CT scanning, hyperostosis of the overlying bone is seen in 50% of tumors and 50% have intra-tumoral calcification. [32-39, 44-48, 51, 55, 59, 65-78, 81, 99, 104-119].

Computed Tomography (CT) (Figure 1) with contrast can detect most meningiomas. CT optimally detect bone involvement involving both hyperostosis and bone erosion or remodeling. On enhanced CT scans, meningiomas are generally

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homogenously isodense or slightly hyperdense compared with normal brain. Because small tumors can be missed contrast studies are indicated.

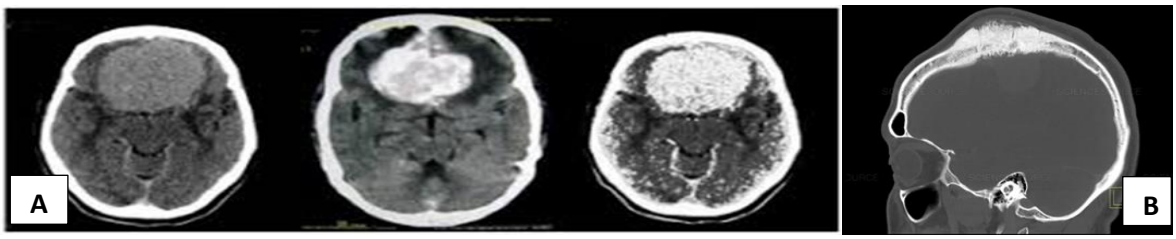

Figure 1 A and B: CT scan of a bi-frontal mid-convexity olfactory groove meningioma showing contrast enhancement (1A) and hyperostosis (1B). Notice: Different patients.

Calcification may range from tiny punctuate areas to dense calcification Qf the entire lesion. With intravenous contrast, meningiomas typically enhance homogenously and often demonstrate morphologic features such as sharp demarcation and a broad base against bone or free fural margins. Approximately 15% of benign meningiomas have an unusual appearance on CT images. Areas of hyperdensity, hypodensity or non-uniform enhancement may be seen. These areas may represent haemorrhage, cystic degeneration, or necrosis respectively.

3.7.2. Radiological Findings in the Magnetic Resonance Imaging

The advent of Magnetic Resonance Imaging (MRI) opened a new vista in precision radiology. It has led to correct identification of intracranial meningiomas and their clear delineation from adjacent brain [54]. MRI's supreme soft tissue resolution means the size and locations of intracranial tumors can be gauged with precision. The case study of a 15-year-old girl illustrates the point. A large multi-cystic papillary meningioma had, at various stages of its 4-year clinical course, occupied the supra-tentorial compartment and the ipsilateral infra-temporal fossa. At the fifth year of follow-up, after surgery and radiotherapy, MRI clearly delineated the exact extent of tumor recurrence [45]. By virtue of the sensitivity of its pulse sequences, MRI is an excellent modality in the post-therapy monitoring for recurrent disease.

The introduction of T1, T2 and Diffusion Weighted MRI (DWI) (Figures 2-4) in recent years makes it possible to differentiate WHO Grade I meningiomas from those in the higher grades. Recent papers by Surov et al. and Nagar et al. have shown, in adult patients, that WHO Grade II and III tumors had lower mean apparent diffusion coefficient (ADC) values than Grade I meningiomas. It has been postulated the marked decrease in ADC values in malignant meningioma is due to its hypercellularity and multifocal areas of necrosis resulting in reduction of extracellular matrix / fluid and space that in turn is manifested as reduced ADC values.

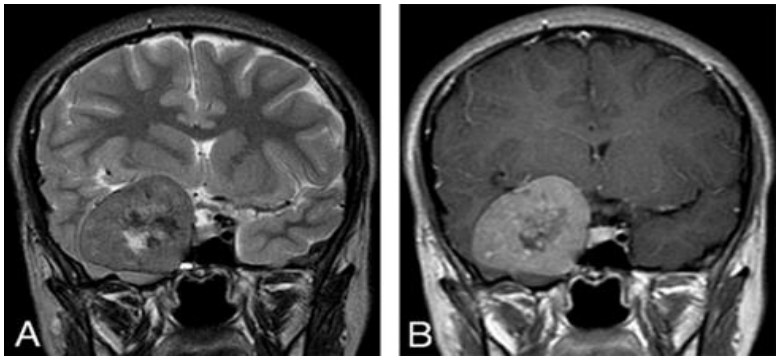

Figure 2: T 2 without contrast (A) and T1 with contrast (B)

Benign tumors retain their intracellular water; in consequence, their ADC values remain high [57]. The use of diffusivity of water in tumor tissue forms the basis of how chordoid meningiomas can be differentiated from those of other WHO grades. Thus, the presence of mucoid stroma gives rise to relative increase in extracellular free water motion resulting in elevated ADC values. In addition, a chordoid tumor's characteristic decrease in nucleus-to-cytoplasm ratio further contributed to an increase in diffusivity of water [58]. Research along such themes has so far not been done in the paediatric population.

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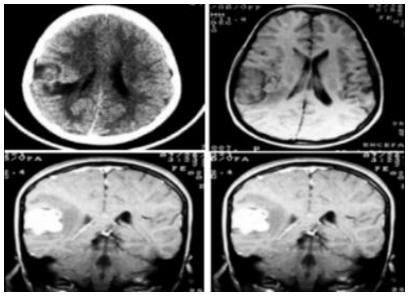

Figure 3: Right parietal meningioma with appearance in CT scan (left upper view) and in MRI without contrast (right upper view) and contrast enhanced (lower views).

The MR imaging characteristics of typical meningiomas are homogeneous well-enhancing mass exhibiting high or iso-signal intensity (SI) / on T2-weighted images (T2-WI) and low or iso- SI on T1 weighted images (T1-WI). They can be observed at the convexity or in the parasagittal region with a significant dural tail. The meningotheliomatous subtype is most common [8, 11-19, 22-32, 45-59, 64-69, 73-87]. In contrast to meningiomas of adulthood, fewer radiologic and histopathologic findings have been reported in childhood. Findings reported include; larger tumors, cysts, unusual sites such as the lateral ventricles and posterior cranial fossa, a lack of dural attachment, and a more malignant nature. The duration of follow-up was 6 months to 8 years (median 4 years).

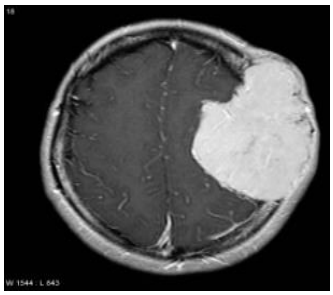

Figure 4: T1 with contrast enhancement and dura- and bone invasion of 6 years old male patient

The MRI characteristics of meningiomas are generally consistent. On T1 weighted images, 60-90% of meningiomas are isointense and the reminder are mildly hypointense compared to grey matter. On T2 weighted images, 30-45% of meningiomas have increased signal intensity and approximately 50% are isointense compared to grey matter. Their typical extraparenchymal location heightens the neuroradiologist's ability to diagnose these tumors. There is increased interest in using MRI characteristics to subtype meningioma tissue before surgery. The results of these studies have been variable. A high signal intensity on T2 weighted images has been correlated with microscopic hypervascularity and soft tumor consistency. Contrast enhanced MRI provides the most sensitive and specific means of detecting meningiomas. Most meningiomas enhance intensely and homogenously with intravenous contrast material, and in 10% cases, small additional meningiomas are encountered that are missed on un-enhanced MR images. Post-operative enhanced MRI has also been found to be sensitive and specific in detecting residual or recurrent meningiomas. Thick and nodular enhancement has a high correlation with recurrent or residual neoplasm. [Figures 5+6] Early post-operative enhanced MRI has also been found to be sensitive and specific in detecting residual or recurrent meningiomas. Thick and nodular enhancement has a high correlation with recurrent or residual neoplasm.

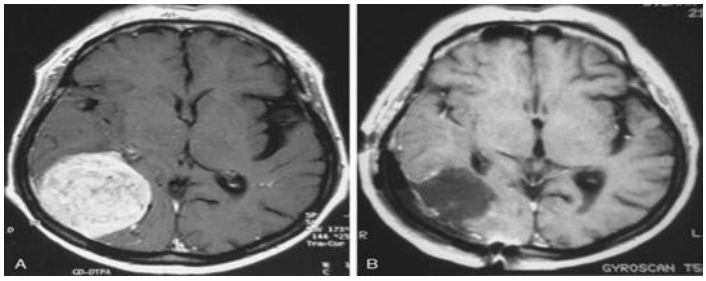

Figure 5: Pre- and postoperative MRI of a 9 years old male patient with right parietal meningioma

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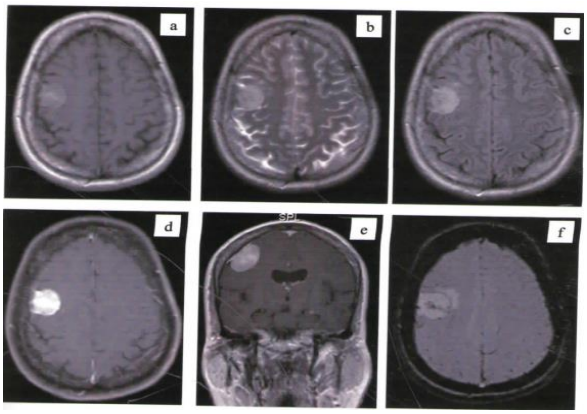

Figure 6: Right frontal mid-convexity meningioma: Isointense on T1 (a), hyperintense on T2 (b) and FLAIR (c), homogenously enhancing on contrast (d), coronal imaging (e) showing dural tail, susceptibility artifacts on SWI (f).

In vivo, MR spectroscopy (MRS) (Figure 7) is an evolving area of study. Compared with the MR spectroscopy of a normal brain, the typical MR spectra for meningiomas reveal a markedly increased choline peak and reduced N-acetyl aspartate and phosphor-creatine / creatine peaks. An additional peak present in some meningiomas at 1.47 ppm has been attributed to Alanine. Childhood and adolescence meningiomas have variable imaging characteristics. Cystic and calcified variants are known to occur frequently. Apart from the known spectra and metabolites such as choline, creatine and N-acetyl-aspartate (NAA), Buhl R et al. (Neurol Res. 2007 Jan;29(1):43-6) have shown that lactate and alanine were often found in necrotic tumor tissue.

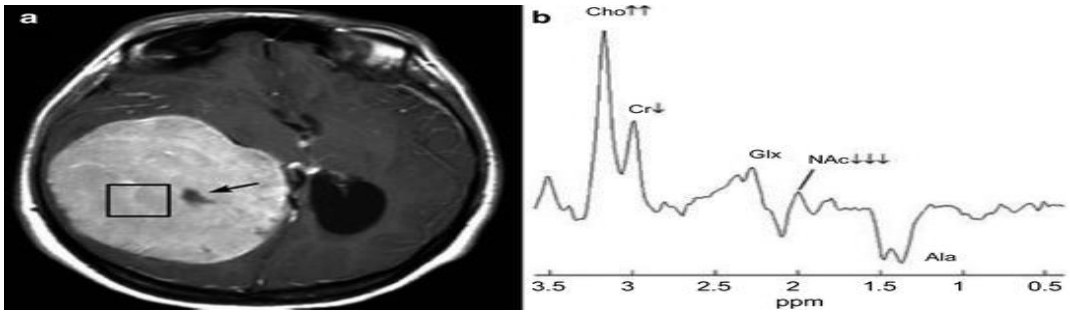

Figure 7: MRS of 9 years old male patient with right parietal huge meningioma

Contrast enhancement (dural tail / attachement) of the dura mater extending away from the margins of the mass is typical of meningiomas, although this pattern can be seen with other dural based lesions. This dural tail can represent either tumor extension or reactive change, and its resection is important to reduce the risk of recurrence. (Figure 8) MRI characteristics of paediatric and adilt meningiomas are similar. On MR imaging, the tumors are usually isointense to hypointense on T1 , iso- to hypointense on T2 and exhibit good contrast enhancement [32]. T2 hyperintensities if seen, denote microcystic changes, dilated blood vessels, and high cellularity and usually suggest a syncytial / syncytium or angiomatous variant. Although its role in diagnosing meningiomas has changed, angiography still remains an important pretreatment evaluation technique; it also demonstrates the tumor's vascularity and its feeders in preparation for preoperative embolization in cases of giant tumors (22, 192-204), (Figure 9).

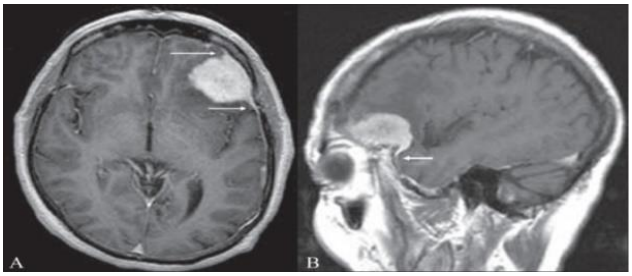

Figure 8: Dural tail signs of meningiomas

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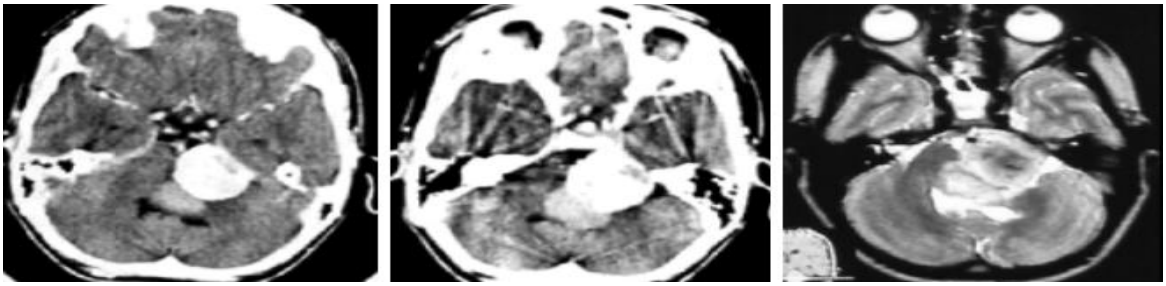

Figure 9: Meningioma in the posterior fossa; T1 image with / without contrat and T2 in the last view.

3.8. Anatomical distribution

Of all intracranial meningiomas, 85% are located supratentorially, (Table 1) one-third to half of which are located along the base of the anterior and middle fossa. (104-119, 146-186) Parasagittal and convexity meningiomas are the most frequent sites for meningiomas in both adults as well as in several series of paediatric meningiomas (25, 53-66). However, paediatric meningiomas are known to favour uncommon sites like skull base and posterior fossa locations (19, 22, 25, 49, 53, 66, 90-106). A second feature that seems to be typical of the paediatric age, is the higher incidence of meningiomas located within the ventricular system or lacking any apparent dural attachment like deep in the sylvian fissure.

Table 1: Common sites and relative incidence of intracranial meningiomas in adults

Site	Relative incidence (%)
Parasagittal or falcine	25
Convexity	19
Sphenoid ridge	17
Tuberculum sella	9
Posterior fossa	8
Olfactory groove	8
Middle fossa or Meckel's cave	4
Tentorial region	3
Peritorcular region	3
Lateral ventricle	1-2
Foramen magnum	1-2
Orbital or optic nerve sheath	1-2

In their review, Herz et al. (34), found that 28% of children with NF had intraventricular meningiomas (Figure 10). Incidence of multiplicity was significant in some series (66). Other unique aspects reported for paediatric meningiomas are large tumor size, cyst formation and tendency to recur. Cystic changes are reported to occur in 13-50% of paediatric patients against 2-4.6% in adults meningiomas (11, 35, 48). Cyst formation was rare as noted in Amirjamshidi's (151-159) series of 24 patients with no case of cystic meningiomas being reported. Spinal meningiomas (Figure 11) typically arise from arachnoid cap cells in the dura mater near the region of the nerve root. They may also originate from meningiothelial cells making up the arachnoid villi near the dorsal root ganglia. This anatomic arrangement explains why these tumors frequently arise .in a lateral location within the spinal canal. These tumors occur with approximately equal frequency as the nerve sheath tumors representing approximately 40% of intradural extramedullary tumors.

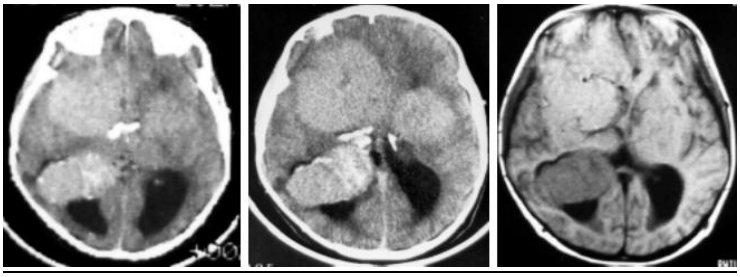

Figure 10: Intraventricular meningioma.

Most spinal meningiomas occur after the fourth decade of life and have a significant predeliction for males (75-85% of cases). Meningiomas arise primarily in the thoracic region in approximately 80%. The cervical region is affected less often and lumbar and sacral tumors are relatively rare. These tumors typically grow in a globoid configuration with a region of dural attachment. Rarely, they grow as a carpet like plaque (en plaque meningiomas). Meningiomas tend not to invade the pia mater, which improves the ability to resect them safely.

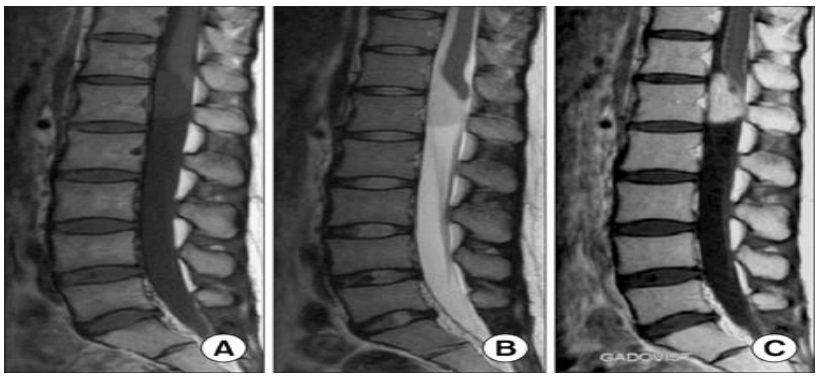

Figure 11: Spinal meningioma in L1 level with hypodensity in T1 (A), hyperintensity in T2 (B) and contrast enhancement (C)

3.9. Pathology / Histopathology

Microscopically, meningiomas have a varied but characteristic histopathologic appearance. This diversity forms the basis for their pathologic classification. Based on the WHO classification, which associates suffiently histopathology with information on recurrence and aggressiveness, there are three grades of meningiomas; Grade I meningiomas are associated with a low risk of recurrence and aggressive growth, whereas Grade II and III meningiomas have a greater likelihood of one or both of these characteristics.

3.9.1. Grade (I) Meningiomas

Of the 9 subtypes of Grade I meningiomas, the three most common are meningiothelial, fibrous and transitional. (Figures 12-13)

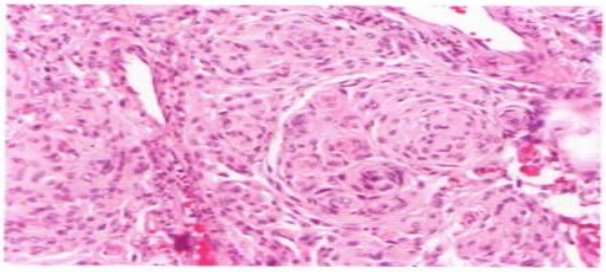

Figure 12: Meningiothelial meningioma with cells arranged in whorls.

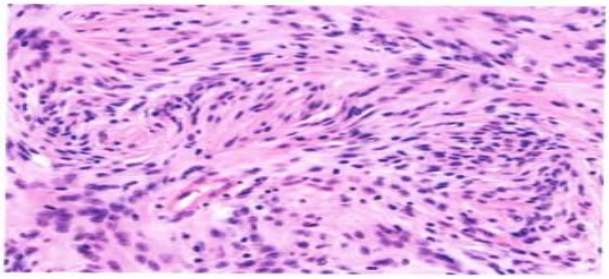

Figure 13: Transitional variant of meningiomas.

Although it is important that these and the other subtypes are recognized, the prognostic significance of each one is unclear. But they are currently considered equivalent.

3.9.2. Grade (II) Meningiomas

WHO Grade II meningiomas (Atypical cranial meningiomas, the Chordoid and the Clear Cell forms). In accordance with WHO grading in 2007, an atypical meningioma is defined primarily by presence of 4 to 19 mitosis per 10 high power fields. Brain invasion and hyper-cellularity with prominent nucleoli are other primary determining factors. In using the latest WHO criteria, it was found that atypical meningiomas made up to 30% of all cranial meningiomas. The older set of criteria dating back to year 2000 was more conservative: Retrospectively, a similar subset of atypical meningiomas had an incidence of 4.7% to 7.2%. The use of brain invasion as an adverse factor had caused this discrepancy. Patients in WHO Grade I, but showing brain invasion, were moved to a higher grade [7-19, 23-45, 69-88, 110, 118, 123-132, 143-155, 167-170, 180, 186-192]. A paper by the group in Sydney Children's Hospital reported on a 16-month old boy diagnosed as an atypical meningioma on histological grounds [65]. They made a detailed study of atypical meningioma in children and came to the same conclusion, that its histomorphology was identical to that in adults. Despite the findings of microscopic brain invasion, they still considered their case to be that of Grade II. Added to this concept is the modern thinking that brain invasive meningiomas have a greater incidence of recurrence and mortality rates [54-60, 67, 70, 77-79, 84-91, 111-119, 157-179, 183-200]. In most large paediatric series, the incidence of atypical meningiomas ranges from 9.1% [66] to 26% [67-71]. There is also a greater propensity for recurrent atypical cranial meningiomas to transform into a higher grade [5]. However, discounting the apparent unfavourable prognostication of recurrences, in one series the authors stated that both the atypical meningiomas and their WHO Grade I counterparts had a low recurrence rate and their respective survival rates were excellent [58, 63-66, 68, 71-85, 91-111, 132-156, 170-179, 183-201].

Chordoid Meningioma is a malignant variant of meningioma with an incidence of 0.5% of all meningiomas in adults. The tumor belongs to the WHO Grade II class and is uncommonly encountered in paediatric practice. The most common clinical presentation is headache, followed by visual and gait disturbances [69]. In the largest series of the present review [70-79] only 2 of 42 patients affected were children. In another series of 12 children with WHO Grade II cranial meningiomas [6-9, 11-18] only 1 had the chordoid form. The only exception was in the work of Kepes JJ., et al. who described 7 children and adolescents who were afflicted with chordoma-like intracranial tumors associated with a systemic syndrome of fever, hypo-chromic anaemia and lympho-proliferative state akin to Castleman's Disease [71]. Their 7 cases were a collection of case-reports from sources round the globe. The tumor's histological pattern and CT features were analysed in detail. The basic histo-morphologic structure consisted of a meningothelial cellular pattern mixed with tumor cells with multiple intracytoplasmic vacuoles some of which were large. They gave an apparent impression of being "physaliferous" cells. Nonetheless, CT showed the lesions were uniformly enhancing following injection of intravenous contrast; and were characteristically based against the skull vault or adjacent to the surface of the falx cerebri or the tentorium. Kepes paper established chordoid meningioma as a distinct histological entity [71-77, 80-88]. It remains essentially a tumor of the adult population. In accordance with a survey by a Canadian group in 2014 [62-69, 72, 74-78, 80-88], no paediatric patients were encountered in their institution. In their patients, dural infiltration was common, although brain invasion was only noted in one case with recurrence. The classic chordoid morphology consists of cords and lobules of vacuolated cells separated by fibro-vascular septae within a sea of myxoid stroma simulating chordoma. Positive staining of cells for vimentin and epithelial membrane antigen confirm diagnosis of meningioma [70-73]. The clinical diagnosis of a chordoid meningioma can be difficult when it is complicated by presence of tuberose sclerosis, a condition where coexisting subependymal giant cell astrocytomas (SEGA) are common. Such was the extremely rare report by Lee J., et al. that illustrated almost similar MRI features (of obstructive hydrocephalus) between an intraventricular chordoid tumor and a large SEGA [74]. But intraventricular chordoid meningiomas have a higher recurrence rate [75]. This is probably due to the mucoid quality of the stroma, somewhat akin to that of chordoma on the ventricular wall making it difficult to achieve complete removal [75]. The intraventricular forms are prone to metastases. Adjuvant radiotherapy was offered for this category of patients, although it had been stressed that such decision is made on a case-by-case basis. As a general rule, radiotherapy would be given for recurrent chordoid meningiomas and for those that received a prior subtotal resection since these lesions are the most prone to turn malignant [75-79]. This is illustrated by their report of an 11-year-old boy who had remained disease free 5-years after the first surgery. Contrarily, the clinical course can be one of rapid aggression: In the only known case of death due directly to a chordoid meningioma, a 12-year old girl suffered from disseminated spinal meningeal disease despite subtotal resection of a left frontal tumor and radiotherapy to the whole of the neural axis [70-76, 79, 85, 88, 90, 100-121, 154-167]. Yet there are instances where the presentation was more sedate: Glasier., et al. described a 15-year old girl whose main complaint was headache and dizziness only to discover she harboured a tentorial

chordoid meningioma [77-90]. It was uncertain her past history of surgical excision and irradiation of an abdominal Wilms tumor had any relevance to her cranial lesion. In summary, there is lack of consensus in the therapeutic approach for chordoid meningiomas in the paediatric and adolescent population. However, in a series of 221 patients with a mean age of 45.5 years [61-78, 88-99, 110-132, 144-155, 160, 179, 184-188] in which the age group comes closest to that of children, gross total resection (GTR) is considered the strongest predictor of tumor control while tumors that were sub-totally resected accompanied by an MIB-1 labelling index > 5% are at risk for greater recurrence, a situation where radiotherapy is required.

Clear Cell Meningiomas (CCM)

CCM is another histologic variant of meningioma and was classified as WHO Grade II on account of its aggressive biological behaviour. The main characteristic of CCMs is their propensity to affect those in the first 3 decades of life. The tumor has a predilection for the posterior fossa and cranio-vertebral regions [79]. An early series that included 14 examples of CCM in a mixed cohort of adults and children (mean age 29-years) confirmed the tumors biological aggression in which 3 patients died of the disease. There is however a bias as 50% of the lesions were within the spinal column [80-82, 119, 129, 138-144, 150-167]. Cytologically, whorled syncytial architecture with bland-looking nuclei are possessed by CCM. Contrary to the conventional benign meningioma, CCM contains sheets of polygonal cells with clear glycogen-rich cytoplasm. The cells can be vacuolated but mitosis is infrequent. Cell morphology needs to be differentiated from metastatic renal cell carcinoma, clear cell ependymoma, oligodendroglioma and haemangioblastoma [80-88].

Immunohistochemical analysis will reveal positivity in the Vimentin and epithelial membrane antigene while S-100 staining is negative. Ki-67 proliferative index can be elevated to 10% in some cases but may not necessarily correlate with tumor aggressiveness [79-90, 93, 96, 110, 119-129, 133-149, 170, 198-204]. While describing CCM's rather innocuous histological appearance, one group [67-81, 88-93, 119-125, 136-145, 169-179, 200] had warned of its inordinate biological aggression. In their own case of an 11-year-old boy with a 1-month history of headache, contrast enhanced MRI depicted a huge right sided dural based extra-cerebral tumor that had extended through the middle cranial fossa into the ipsilateral infra temporal space. It needed a two-staged procedure for its complete extirpation. As tumor excisions had been complete, adjuvant irradiation was withheld.

One of the basic principles of surgery in children is to be aware of the neuro-cognitive complications and development of late malignancies. And only in case of repeated recurrences despite multiple surgeries would radiotherapy be offered [81-88]. A complex form of CCM is illustrated in a case study on an 11-year old boy presenting with anaemia and fever of unknown origin [65-82]. The main clinico-laboratory finding was that of an inflammatory reaction. The discovery of an elevated polyclonal gamma globulin, raised serum level of C-reactive protein and the presence of a tumor at the cerebello-pontine angle on MRI were strongly indicative of Castleman's syndrome. Excision of the tumor resulted in resolution of the boy's fever and his biochemical abnormalities. A literature search by Raffalli-Ebezant., et al. documented 25 cases of paediatric CCM in the past 20 years [9, 27, 179-199]. The uniqueness of childhood and adolescent CCM is that in only 4 instances were the tumors situated in the supra tentorial compartment. The CP angle is site of origin in up to 48% of cases [9-28, 177-200]. In a similar vein, 5 of the 6 cases of CCM in the series by Wang X Q., et al. were situated in the CP angle [9-18, 27, 190-200]. Follow-ups had ranged from 5-72 months with 8 (32%) patients suffering recurrences compared to 61% in the Zorludemir et al. [80] series. Despite its relatively benign histologic features, CCM has a tendency to metastasise through the subarachnoid spaces. This feature was demonstrated radiologically by Lee W., et al. [83]. Their case of a 17-year-old youth had suffered multiple recurrences in the cranio-spinal leptomeninges over 21 months. He survived after repeat surgery and a course of irradiation to the cranio-spinal axis. That none of the patients succumbed from the disease in the multiple case-reports in the Raffalli-Ebezant series has justified the tumor's WHO Grade II classification [59-79]. This research group had identified a mutation of the SMARCE1 gene that could implicate in establishing peculiar clear cell histology of CCM. Apart from brain invasion and metastatic spread which define malignancy, certain features of Grade II meningiomas that may be seen by light microscopy suggest increased tumor aggressiveness and increased recurrence rate. Among these atypical features, are loss of architectural pattern, high cellularity, increased number of mitotic figures (>4 mitoses per 20hpf), necrosis, prominent nucleoli and nuclear pleomorphism. The three subtypes of grade II meningiomas are atypical, chordoid and clear-cell type. (Figure 14)

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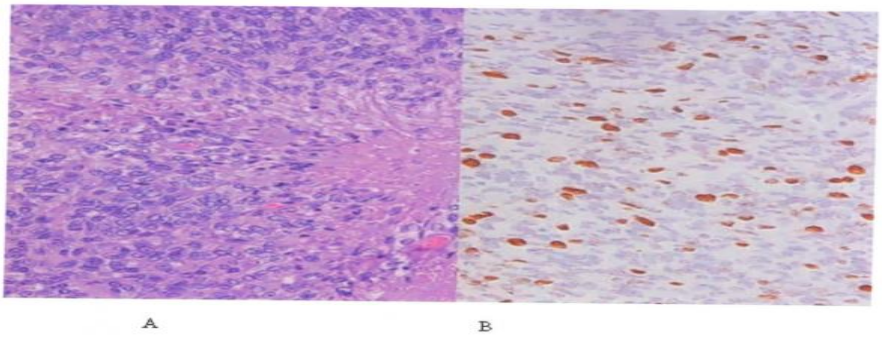

Figure 14: A. H&E stain showing high cellularity and sheets of meningothelial cells with a mitotic activity of 4 per 10 high power fields with foci of necrosis (center and lower right). (B) Ki-67 immunostaining with the MIB-1 antibody showing a labeling index of around 15%.

3.9.3. Grade (III) Meningiomas:

The diagnosis of a grade III (malignant) meningioma traditionally requires histologic evidence of brain invasion or distant metastasis which in most cases is accompanied by further evidence of biologic aggressiveness such as cellular sheeting, nuclear pleomorphism, increased cellularity and mitoses (>20mitoses per 20 high power fields), and necrosis. When dissemination occurs, the most common location for metastasis are the lungs and pleura, abdominal viscera (especially the liver), lymphnodes and bones. Patients with meningiomas associated with frank malignancy are reported to have only a 2-year median survival duration. The three subtypes of grade III meningiomas are anaplastic, papillary and rhabdoid. (Figure 15)

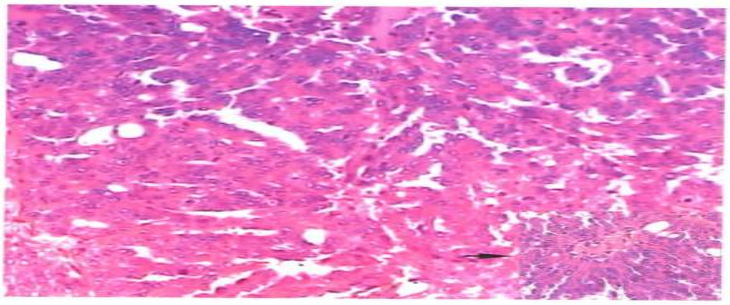

Figure 15: Papillary meningioma: Photomicrograph of the tumor showing sheets of tumor cells arranged in papillary pattern and a papilla with fibrovascular core (inset) (H&E, x200).

Childhood meningiomas are known to have a high incidence of atypical histopathology especially the clear cell and the papillary variants. Higher risk of malignancy (sarcomas 30%, papillary variant 40%) has been reported by some authors like Glasier [28]. Current evidence does not support this higher risk and most authors [46, 55, 112-119] accept an incidence of 2-5%. Similarly, chordoid meningiomas, rhabdoid meningiomas and a unique histopathological pattern termed "sclerosing variant" are reported to be more common in children [17, 50, 55].

3.10. Immunohistochemistry

EMA is useful in both age settings for confirming the meningothelial phenotype in anaplastic or sarcomatoid examples and GFAP highlights entrapped glial elements in those meningiomas with brain invasion(17, 50). MIB-1 (Ki-67) proliferative indices tend to correlate with tumor grade and to a lesser extent with the risk of recurrence in paediatric meningiomas, [44] (Figure 18) though the associations are weaker than in adult cohorts [18, 58]. Immunohistochemical proliferative markers have been studied by Sandberg et al. [44] in 14 meningiomas from children. They documented higher MIB-1 LI in atypical or malignant tumors (median 12.3%; range 7.0-31.6%) than those for tumors without atypia (median 7.0%; range 1.2-12.6%; p = 0.045). On the other hand, median MIB-1 LI for paediatric meningiomas without histological atypia did not differ significantly from that for adult meningiomas without atypia.

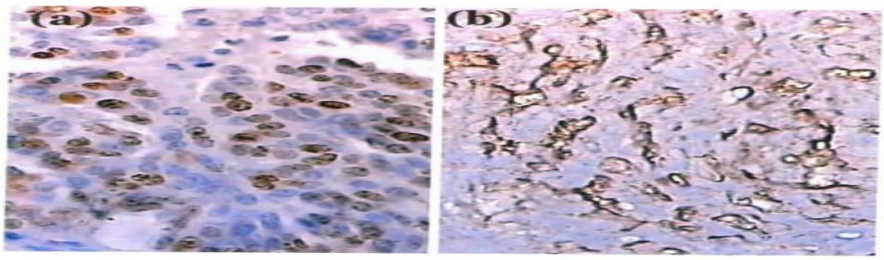

Figure 16: Tumor cells showing immunoreactivity to (a) MIB-1 and (b) EMA (*400).

3.11. Management

The treatment of a meningioma depends primarily on the size and location of the tumor, the age of the patient, the associated symptoms and neurologic deficits. The mainstay of treatment is surgical resection, although small, asymptomatic, incidental meningiomas can typically be managed with observation and serial imaging. After surgery, re-imaging is typically performed at 6 month intervals initially, which may be extended to longer intervals if there are no radiographic signs of tumor growth and the patient remains asymptomatic. Treatment should be initiated when symptoms arise or tumor growth is documented. Critical parameters that affect the ease of surgical removal include the tumor's location, size and consistency, vascular and neural involvement and in case of recurrence, prior surgery or radiotherapy. New and innovative approaches have been devised to reach and widely expose meningiomas in any location. Furthermore, a greater appreciation of risk factors for and patterns of tumor recurrence has changed surgical planning and goals. Surgically, with resectiong of the neoplasm and all involved dura mater, soft tissue and bone, the recurrence can be decreased. However, the tumor size and location and the involvement of adjacent structures may not allow all meningiomas to be completely resected in this manner.

3.11.1. Surgical Approach

The patient should be positioned to maximize the accesibility of the tumor, the chances of unimpeded venous drainage and the beneficial effects of gravity, the surgeon's comfort and above all, the patient safety. In any position that places the patient's head above heart level, monitoring for air-embolism should be used, particularly because many meningiomas are located close to the venous sinuses and their large tributaries.

To the surgeon's advantage, a layer of arachnoid usually separates meningiomas from the brain, cranial nerves and blood vessels. By accessing and staying within this surgical plane, the surgeon can minimize the chances of neural or vascular injury. Early extensive tumor debulking allows the tumor capsule to collapse inward, thus facilitating the definition of the arachnoid plane. The method used to debulk the tumor which may be suction, coagulation, sharp excision, ultrasonic aspiration or laser vapourisation, depends on the tumor's consistency, vascularity and location. Once the tumor mass has been resected, careful attention must be given to the resection of the involved dura mater and bone. The involved dura mater is resected as widely as possible and repaired with autologous pericranium, fascia lata or temporalis fascia or a dural graft. Vascularised pericranium, temporalis muscle or free tissue transfer is used to separate intracranial contents from the paranasal sinuses, aerodigestive tract and middle ear. Cranioplasty is performed as required to reconstruct calvarial defects.

The goal of surgical treatment of spinal meningiomas is gross total surgical excision with the intention of cure. Gross total excision / resection can be achieved in most cases, largely because these tumors tend not to invade the spinal cord or the bone surrounding the dura mater. Even so, the recurrence rate may be as high as 10-15%. Simple posterior laminectomy provides adequate exposure in almost all cases. The addition of facetectomy, a lateral extracavitary approach, or an extreme lateral approach in the region of the foramen magnum may be required to gain access to ventral meningiomas. Sectioning of the dentate ligament and suture retraction to rotate the cord may also help. Even with these extended approaches, it may be difficult to visualize the entire margin of a ventrally situated tumor. Fortunately, a protective layer of arachnoid pia mater between these tumors and the ventral surface of the cord is usually there. While dorsal and dorsolaterally situated meningiomas may be removed en bloc (including the site of dural attachment), for ventrally tumors, it’s generally piecemeal and resection of the dura mater may not be possible. When the tumor and the dura mater can be resected, a variety of dural patch materials (both natural and synthetic) are available for dural reconstruction.

3.11.2. Adjuvant radiation therapy (RT)

Although there have been no randomized, controlled or prospective studies with long-term follow up conducted to evaluate the efficacy of radiotherapy in treating meningiomas, the use of external beam irradiation has become an important part of the management of these tumors, particularly as adjuvant treatment for patients after subtotal tumor resection. In a prospective analysis of 140 patients with benign meningiomas treated by subtotal resection plus adjuvant radiotherapy over 23 years, Goldsmith et al. 1994 [30] reported 5 and 1 0-yr progression-free survival rates of 89 and 77 % respectively. In patients treated using CT planning (after 1980), the 5-yr progression-free survival rate was 98%. Recently, Soyuer et al (2004) [61] compared 92 patients with WHO grade I benign cerebral meningiomas who underwent gross total resection, subtotal resection plus adjuvant radiotherapy or subtotal resection plus delayed radiotherapy.

At a median follow up of 7.7 yrs, the 5-yr progression-free survival rates were 77%, 91% and 38% respectively. The overall 5 and 1 0-yr survival rates were not statistically different among the three groups or from the age-adjusted expected survival rate. Thus delaying RT until tumor recurrence without compromising overall patient survival is possible and may spare the patient from the potential toxicity of radiation. The data do not permit determination of which strategy is optimal. For meningiomas, which are considered to be inoperable because of their location, poor patient health, patient refusal of surgery, external beam RT would seem beneficial for aggressive (atypical or anaplastic) tumors, but few informations exist to support this theory.

Stereotactic irradiation in the form of radiosurgery or conformal, fractionated or intensity modulated radiotherapy has increasingly been used to treat meningiomas with improved efficacy and diminishing untoward effects. Stereotactic irradiation uses various forms of energy, the most common of which are photons from Cobalt-60 gamma-ray sources (gamma-knife) or linear accelerators (LINAC) and heavy particles (protons) from cyclotrons.

RS provides effective tumor control of small meningiomas. Kondziolka et al. 1999 (41) observed a 93% tumor control rate in patients, whose meningiomas were treated by gamma-knife RS and a 61% incidence of tumor shrinkage in 99 patients, who were followed for 5-10 years.

The incidence of new neurological deficits in this group of patients was 5%. In a recent retrospective study, Pollock et al. 2003 [51] reported that gamma-knife radiosurgery of small or medium sized beingn meningiomas, provided progression-free survival rates equivalent to that of complete surgical resection after a mean follow-up of 64 months.

Gamma-knife radiosurgery has also been shown to be an effective treatment for difficult to resect cavernous sinus meningiomas. Lee et al. 2002 [43], reported an actuarial tumor control rate of 93% at five years for benign cavernous sinus meningiomas; adverse effects of radiation were experienced by 6.7% of patients. LINAC based radiosurgery also offers effective control of small meningiomas. A recent study of 43 patients who underwent LINAC based radiosurgery for skull-base meningiomas, reported a 7-year local control rate of 89.7% [12]. This value correlated with the 5-yr control rate of 89% and a complication rate of 55 in a previous study of 127 patients [33]. Spiegelmann et al 2002 [62] reported that both the 3- and 7 -yr actuarial tumor growth control rates were 97% for cavernous sinus meningiomas treated by LINAC based radiosurgery. They also reported a low incidence of tong term cranial neuropathies. Despite the promising results of stereotactic irradiation, there are some limitations and uncertainities with this modality. The targeted tumor is limited to 35-40mm because this is the size at which the tumor can receive a single dose of appropriate strength with a 1% risk of radiation necrosis. However, the increased availability and use of fractionated delivery of stereotactic irradiation have overcome this size limitation. Alheit et al 1999 [4] reported a 1-yr progression-free survival rate of 1 00% in 24 patients who underwent fractionated stereotactically guided conformal radiotherapy for meningiomas. Seven of fifteen patients who had neurologic deficits before treatment improved, and two patients experienced early side-effects (one facial palsy and one Addisonian state). Other recent studies have reported benefit from stereotactic conformal radiotherapy for atypical and malignant meningiomas and for large cavernous sinus meningiomas. Intensity modulated radiotherapy delivers fractionaled, conformal radiotherapy more effectively than traditional techniques to tumors with complex shapes. Initial reports have shown that this method is effective in treating meningiomas and controlling tumor growth and carries a low risk of side-effects. Adjuvant RT appears to be beneficial after incomplete excision of meningiomas in adults, but it is rather risky to use radiotherapy for benign and partially excised cerebral lesions during childhood. Re-operation is thought to be better than adjuvant therapy [22]. Tumor behaviour following resection was difficult to predict and paediatric patients with histologically benign meningiomas deserve careful and extended clinical follow-up [27, 34].

3.11.3. Adjuvant chemotherapy

Few data are available regarding the efficacy of traditional antineoplastic agents against benign or malignant meningiomas. Adjuvant chemotherapy (intravenous or intra-arterial cis-platinum, dacarbazine or doxorubicin) against malignant meningiomas and for recurrent benign or atypical meningiomas has been administered to a small number of patients but has generally been unsuccessful despite its effectiveness against other soft tissue tumors. Hydroxyurea has been shown to arrest meningioma cells in the S-phase of cell cycle and to induce apoptosis in vitro. Although a similar beneficial effect has been seen in a small subgroup of patients with recurrent and unresectable meningiomas, subsequent studies have shown little, if any, benefit.

Interferon-α was reported to be effective in prolonging the time to recurrence in a small group of patients with aggressive meningiomas and, compared with traditional chemotherapeutic agents, to have a lower toxicity. SWOG used Tamoxifen to treat 19 patients with unresectable or refractory meningiomas and observed tumor progression in 10 patients, temporary stabilization of the disease process in 6 patients, and a partial or minor response in 3 patients [31]. A recent phase Ill, double-blind, randomized study of Mifepristone did not show any benefit [32].

3.11.4. Recurrence

The completeness of tumor resection is the primary factor influencing the recurrence rate. Stafford et al. [63] found a 25% recurrence rate at 10 years in patients who had undergone a gross total tumor resection and a 61% recurrence rate in those who had undergone partial resection. Jaaskelainen (Nov 1986) [38] found an overall recurrence rate at 20 years of 19%. Multivariate analysis showed that strong risk factors for recurrence included no coagulation of dural origin, invasion of bone and soft consistency of the tumor. The recurrence rate at 20years was 11% for patients with none of these risk factors, 15-24% for one risk factor and 34-56% for two risk factors. In a second study from the same group, the diagnosis of atypical and anaplastic meningioma carried an increased risk of recurrence of 38 and 78% at 5 years respectively [39]. The fact that cumulative relative survival rates (that is the observed to expected survival rates) at 1, 5, 10 and 15 years were 83%, 79%, 74% and 71% respectively, indicated increased mortality in patients with meningiomas. Using multivariate analysis, Stafford et al. 1998 [63] found that age younger than 40years, male sex, incomplete surgical resection, optic nerve involvement and four or more mitotic figures per ten high power fields were associated with a decreased progression-free survival rate. Other factors that have been implicated in the recurrence of meningiomas include mitosis, focal necrosis, brain invasion, syncitial tumors, hypervascularity, haemosiderin deposition, sheets of tumor cells, prominent nucleoli, nuclear pleomorphism and elevated proliferation index. The use of Ki-67 labelling to develop a proliferation index is a common immunocytochemical technique for predicting a tumor's biologic aggressiveness and potential for recurrence. Labeling indicates averaging 1%, 5.5% and 12% have been identified for benign, atypical and anaplastic meningiomas respectively [2]. The median MIB-11abelling index for paediatric meningiomas without histological atypia did not differ from that for adult meningiomas without atypia, in a study of 14 paediatric meningiomas by David Sandberg et al. [46, 58], suggesting that the more aggressive clinical features of meningiomas in children may be attributable to factors other than the rate of cellular proliferation. Other markers of proliferation currently being investigated are progesterone receptors, topoisomerase II a, telomerase, transforming growth factors, mitosin, survivin, and other apoptosis related proteins. PET scan of glucose utilization have also been used to assess a tumor's biologic aggressiveness and potential for recurrence.

3.11.5. Cerebral Angiography

The versatility of contrast enhanced MR angiogram has made it almost redundant to employ cerebral or spinal digital subtraction angiography (DSA) as a surgical road map in children. But in situations where the tumor is at the skull base or shown to be highly vascular on contrast enhanced MRI, then a preoperative embolization of the arterial feeders may be indicated. (Figure 17) However, interventionists ought to bear in mind the remote possibility of intratumoural bleeding as a complication [59]. Where the indication is crucial then the procedure is justified. Thus, in one case of a huge vascular rhabdoid meningioma of the right fronto-temporal lobe, pre-operative embolisation made the operating field cleaner and less tainted with blood [28]. And in a predictably difficult case of a 14-year-old girl, whose suprasellar meningioma had multiple feeders, a successful pre-operative embolization of the arterial feeders of the tumor was performed prior to complete excision of the tumor [5].

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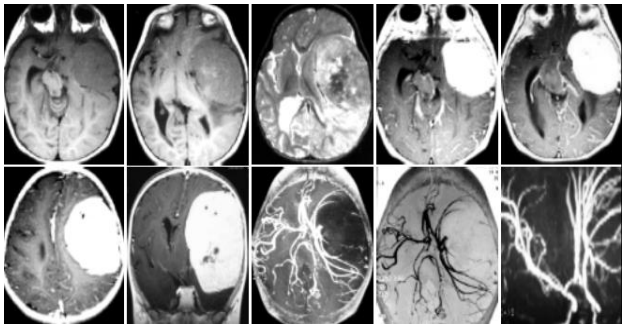

Figure 17: Huge left temporo-parietal meningioma with feeders in the DSA.

3.11.6. Prognosis

The clinical evolution of meningiomas in children is not reliably predictable and remains a problem. Consequently, childhood meningiomas are considered to carry a worse prognosis (35% 10 year survival rate) than meningiomas in the adult population [20, 59]. Statistical analysis of outcome prognosticators is difficult due to the limited number of patients in most of the published series. Location and extent of excision appear to be more important than histology in predicting outcome. The role of proliferative indices and biological atypical meningiomas are known to have long survival and benign ones are known to recur fast [54].

4. REVIEW OF THE LITERATURE ABOUT PAEDIATRIC MENINGIOMAS

The aim of the study was to report on a series of patients aged less than eighteen years with cranial and / or spinal meningiomas, focusing on the clinical profile of the patients, tumor pathology, complications and to attempt to determine the factors influencing the outcome following surgical excision. Search Strategy and Selection Criteria was performed with search in PubMed, Medline, and Embase for articles published from January 1989 to January 2015 that included the following terms: "meningioma,""childhood," "pediatric," "paediatric," and "adolescent." All single case reports and case series of radiation associated meningioma were excluded. No study was excluded on the basis of language. Two reviewers independently assessed full text copies of all case series for Morbidity in Paediatric Meningioma. Additional studies were traced by checking the references of the selected publications. Figure 18 illustrates the selection criteria of studies and patient data. Forty-six studies initially were identified, 5 of which were excluded 49-53 because they reported duplicate data. Morbidity was reported in 21 studies, all of which were exclusive to children and adolescents. Ten patients who had meningiomas that could not be categorized histologically according to the 2007 WHO grading system (eg, angioblastic, sclerosing) or that were of unknown histology were excluded. Eleven patients with radiation induced meningioma, 24 patients for whom outcome was unknown, and 3 patients, for whom there were duplicate data in another included publication also were excluded. Of the remaining 326 patients, 52 had died, and for the leaving 274 patients, who were eligible for the selection of individual patient data, further evaluation was performed.

4.1. Selection of Individual Patient Data

Corresponding authors of the 21 eligible studies were contacted. Variables for which data were requested included the extent of initial surgery (subtotal resection, gross total resection), use of upfront radiotherapy (no, yes), tumor grade according to the 2010 WHO classification system (WHO grade I, II, or III), tumor location (supratentorial, infratentorial, spinal), NF (no, yes), patient sex (male, female), patient age at diagnosis, and relapse: defined as either progression or recurrence. To allow a comparison with previously published data, seven identical categories were selected and included within the multivariate analysis for each variable. Data obtained for clinical endpoints included descriptions of reversible deficits suffered that were no longer apparent at last follow-up, including immediate postoperative complications (defined by the Ibanez classification system as occurring within 30 days of the procedure) that were subsequently treated or resolved; any long-term morbidity that existed at last follow-up; the timing at which the morbidity occurred in relation to surgery; and the overall length of follow-up. Nineteen studies (8-26) provided individual patient data for 261 patients. Morbidity was graded independently based on severity into three categories—none, mild, or moderate=severe (Tables 1+2).

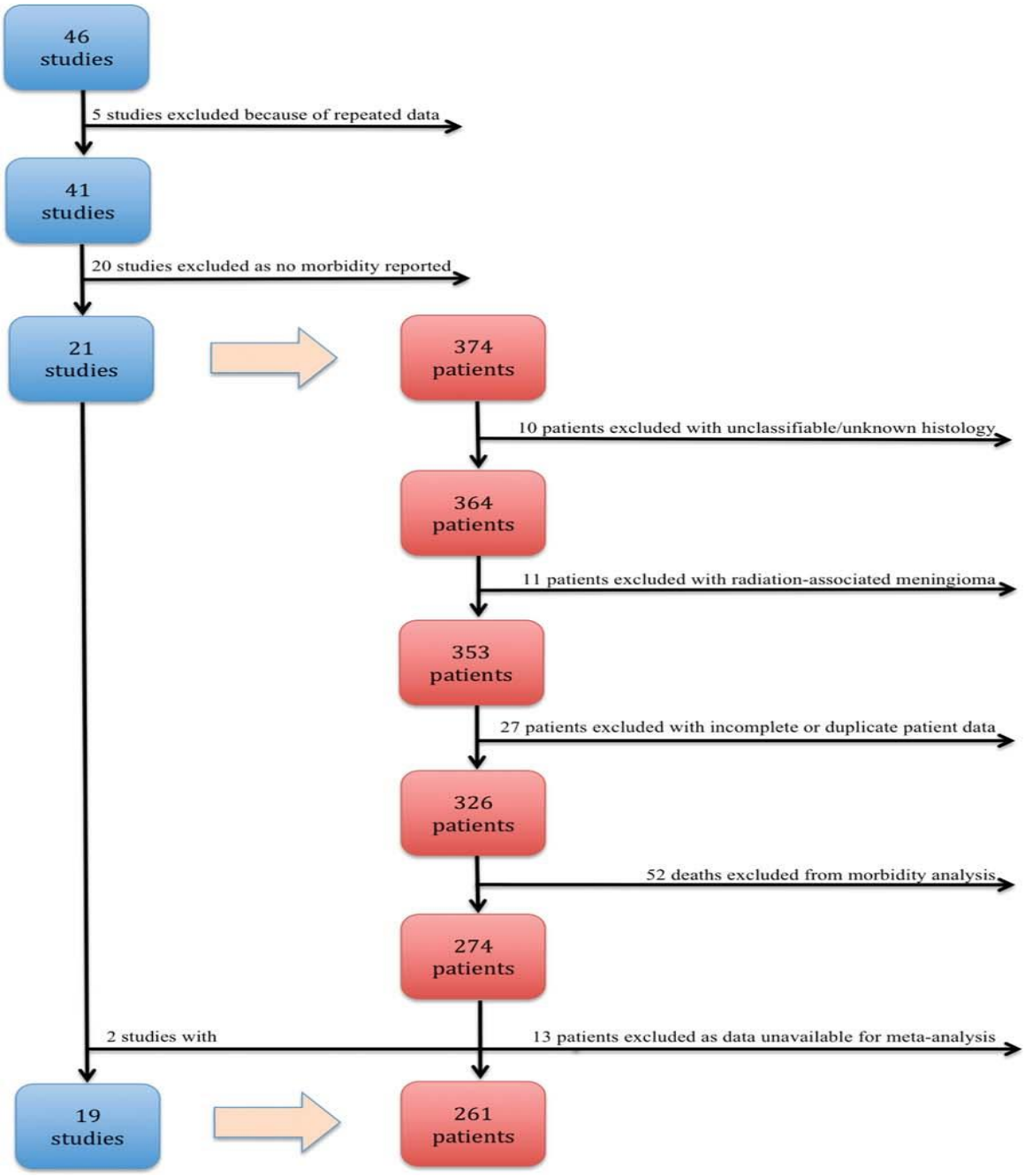

Figure 18: The selection of studies and patient data are illustrated.

4.2. Statistical Analyses

Patients were included in the meta-analysis. Data were collated and are presented as number (percentage), mean and range, as appropriate for the type of data. To assess whether these patients provided an appropriate representation of the previously published cohort, the survivors from the previously published cohort who were included in the current study were compared with those who were excluded using the chisquare test for sex, location, histology, extent of surgery, and relapse and using the t-test for age. Ordinal logistic regression models using the proportional odds assumption were used to assess the influence of prognostic factors on morbidity. Univariate and multivariate odds ratios (ORs) were calculated for each prognostic factor. Subgroup analysis to assess the effect of intracranial tumor location (re-categorized as skull base vs non skull base) on morbidity was performed using the chi-square test. P values <.05 were considered statistically significant. Analyses were done and provided with STATA statistical software.

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4.3. Results

From 19 studies, 261 patients were included; their characteristics are listed in table 2. It was determined, that the study was an appropriate representation of previously published data. The mean follow-up was 7.11 years. At last follow-up, 126 patients (48%) were reported as leading a completely normal life with no meningioma-associated morbidity or other comorbidity. There were 116 patients (44.5%) suffering from meningioma-associated morbidity, with 51 cases (19.5%) classified as mild and 65 (25%) classified as moderate=severe. The majority of patients with mild morbidity had minimal reductions in their KPS or GOS (KPS 90, 8.4%; KPS 80, 6.5%; and GOS 5 with deficit, 3.4%). The most frequently occurring morbidities in the moderate=severe category included visual deficit (6.9%), cranial nerve deficit (5.4%), seizure disorder (4.6%), GOS 4 (4.6%), and motor deficits (3.4%), such as hemiparesis and specific limb weakness (Figure 2). Meningioma relapse was identified as the long-term morbidity independent risk factor for on multivariate analysis (Tables 2-3), with a 4-fold increased risk in patients who relapsed compared with patients who did not relapse (OR, 4.02; 95% confidence interval [CI], 2.11-7.65; P .001). On univariate analysis (Table 2-4), NF was associated with an increased risk of long-term morbidity (OR, 1.90; 95% CI, 1.04-3.48; P 5.04). Subgroup analysis of intracranial tumor location revealed a significantly higher incidence of morbidity for survivors with skull base tumors (61%; n 545 of 74 patients) versus those with non skull base tumors (34%; n 553 of 155 patients; P .001). The timing at which the morbidity occurred was available for 70 of the 116 patients (60%) who suffered from meningioma-associated morbidity. In the majority (67%; n 547 of 70 patients), the morbidity was present before surgery, occurring as a consequence of the meningioma with subsequent failure of recovery from symptoms after therapeutic intervention and at last follow-up. In 20% (n 514 of 70 patients), the morbidity occurred as a direct result of treatment. Cranial nerve injury after surgery for skull base meningioma accounted for 64% (n 59 of 14 patients). The remainder (n 55) were individual patients with growth arrest secondary to radiosurgery, cognitive impairment after radiotherapy, severe neurologic disability after surgery for recurrence, chronic headache, and new-onset seizure disorder. The small patient group, who suffered morbidity as a consequence of therapy precluded a meaningful statistical analysis of therapy as a risk factor. In 13% (n 59 of 70patients), morbidity was related to multiple craniospinal tumors in patients with NF.

Table 2: Classification of Morbidity According to Severity

Morbidity Category	Inclusion Criteria
No morbidity	KPS 100 GOS 5 with no deficit No morbidity at last follow-up
Mild morbidity	KPS 80-90 GOS 5 with deficit Morbidity described as "slight" or "mild" at last follow-up
Moderate/severe morbidity	KPS ≤70 GOS ≤4 Persistent neurologic deficit at last follow-up, eg, visual deficit, hemiparesis, seizure disorder

Abbreviations: GOS, Glasgow Outcome Score; KPS, Karnofsky performance status.

Information regarding the presence of reversible postoperative deficits was available for 169 patients, and the occurrence rate was 22% (n 538 of 169 patients). Reversible postoperative deficits comprised infections (n 513), including meningitis and osteomyelitis; reversible motor deficits (n 58); seizure disorders, which subsequently resolved (n 57); intracranial hematoma (n 54); cerebrospinal fluid leak (n 52); hydrocephalus (n 52); pseudomeningocele (n 51); and urinary retention (n 51). When only considering the medical complications in these patients in addition to those that occurred in the 52 patients who died, the overall rate of medical complications was 8.1% (n 518 of 221 patients) and included infections (n 514), postoperative multiorgan failure (n 53), and urinary retention (n 51).

4.4. Discussion

Meningiomas are uncommon in the children <18 years and differ in various clinical and biological aspects from meningiomas in the adult population. It was reported that the frequency was less than 5% of all paediatric brain tumors. Its incidence as reported by Mendiratta et al. [67] is 1.5% of total meningioma. In this series of meningiomas in children, the incidence was 1.92%.

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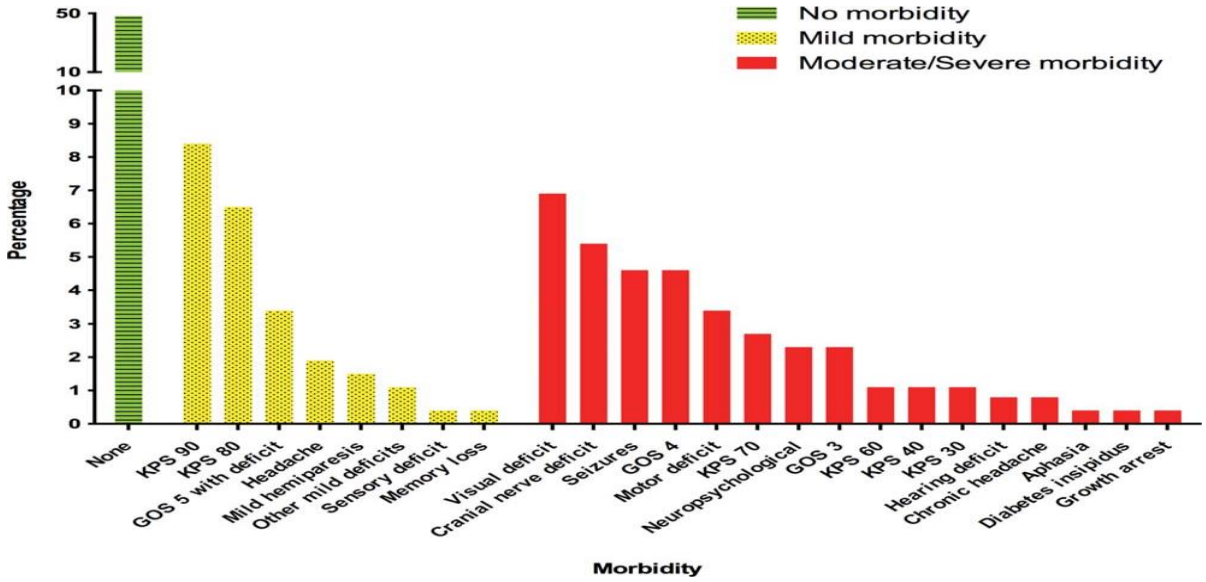
Table 3: Patient Characteristics

Characteristic	No. of Patients (n = 261)
Sex	
Male	150
Female	111
Age, y	
<3	13
3 to <12	90
≥12	158
Location	
Supratentorial	204
Infratentorial	33
Spinal	24
Histology: WHO grade	
I	200
II	41
III	20
Neurofibromatosis	
Yes	44
No	217
Initial surgery	
Gross total resection	204
Subtotal resection	57
Upfront radiotherapy	
Yes	27
No	234
Relapse	
Yes	48
No	213

Abbreviations: WHO, World Health Organization.

Patients with meningiomas present late in the first decade or early in the second decade of life. [10- 11, 18,-19] In this series, the mean age at presentation was 12.81 years. Infantile meningioma is extremely rare. Less than 30 cases of meningiomas in infants less than 12 months of age have been reported.

Diagram 1: Morbidity is illustrated among survivors of childhood and adolescent meningioma. KPS indicates Karnofsky performance status; GOS, Glasgow Outcome Score



The incidence of infantile meningiomas in different series of childhood meningiomas varies from 2.4% to 6.9% [8–10] In this series, only one case (5.5%) of infantile meningioma was seen. Signs and symptoms related to raised intracranial pressure are most common in childhood meningiomas. Meningiomas in children grow faster and occur more frequently in the ventricles than those in adults; therefore, cerebrospinal fluid circulation can be easily obstructed in the early stage, which results in increased intracranial pressure. [19-29] The incidence of seizure in childhood meningiomas(25%) [8–10] is lower than that in adult meningiomas (29-40%). [1] In our series, seizure was seen in 44.4% of cases (eight cases), i.e., an

incidence similar to adult patients. [14-29] Focal seizure occurs more commonly in adults, whereas generalized seizure occurs more in children. [20-26, 29, 33, 45, 60, 77-92, 119-133, 146-160, 170-188, 191-199] In our series, six patients presented with generalized seizures and only two patients presented with focal seizure. [10, 19-29, 33-49, 56-79, 146-178, 189-200] (Diagram 1) (Table 4)

Table 4 : Demographic data from I5 series of meningiomas of the first two decades of life

Authors & Year	No. of Cases	Incidence (%)	Age (yrs)		Sex (M:F)
			Range	Average	
Crouse & Berg, 1972	13	2.3	0.5–20	12.8	7:6
Cooper & Dohn, 1974	7		7–14	11.0	2:5
Merten, *et al.*, 1974	48*		0.3–19	10.9	27:21
Leibel, *et al.*, 1976	13		9–19	15.2	7:6
Herz, *et al.*, 1980	9		4–18	12.9	4:5
Sano, *et al.*, 1981	18	3.0	6–26		10:8
Deen, *et al.*, 1982	51†	2.5	7–20	15.0	25:26
Chan & Thompson, 1984	4	1.1	3–16	8.3	2:2
Drake, *et al.*, 1985–1986	13	1.0	3–16	11.6	10:3
Nakamura & Becker, 1985	7	0.7	8–16	11.6	4:3
Doty, *et al.*, 1987	13	3.2	2–16	8.8	7:6
Kolluri, *et al.*, 1987	18	4.2	5–15		9:9
Ferrante, *et al.*, 1989	19	2.8	0.5–16	9.1	13:6
Davidson & Hope, 1989	22		0.3–16		13:9
Germano, *et al.*, 1994	23	2.9	6–21	13.3	14:9
total cases	278			11.8	154:124
% of total		1–4.2			54:46

* Includes one case of spinal meningioma.
† Includes 10 cases of spinal meningioma.

4.5. Histological Findings

The histological subtypes of paediatric meningiomas are summarized in Table 6. It was showed, that 33% of the tumors had an increased number of mitoses, and 29% had small areas of circumscribed necrosis; 14% had invaded the adjacent brain. In one case, areas of papillary formations were seen, but most of the tumor had a well-preserved meningotheliomatous pattern. Immunohistochemical stains were negative for GFAP and positive for vimentin in all cases. Of 21 specimens available for resection and grading, 15 (71%) were Grade I, six (29%) were Grade II, and none were Grade III (anaplastic). Reticulin staining showed preservation of the architectural pattern in all cases.

Table 5: Pathological data from 15 series of menmgiomas of the first two decades of life

Authors & Year	No. of Cases	Location				Histology			
		Supra-tentorial	Infra-tentorial	Intra-ventricular	Orbital	Syncytial/ Meningothelial	Fibro-blastic	Transi-tional	Others
Crouse & Berg, 1972	13	7	6	0	0	0	1	6	5,* 1†
Cooper & Dohn, 1974	7	6	0	1	0	3	1	1	1 ("atypical")
Merten, *et al.*, 1974	48‡	24	9	8	6	0	0	0	0
Leibel, *et al.*, 1976	13	8	4	1	0	3	1	8	1*
Herz, *et al.*, 1980	9	5	0	4	0	3	2	2	1,* 1 (angioblastic)
Sano, *et al.*, 1981	18	13	2	2	1	5	5	1	6,* 1 (lipoblastic)
Deen, *et al.*, 1982	51‡	29	7	2	3	18	4	24	5 (papillary)
Chan & Thompson, 1984	4	4	0	0	0	0	2	1	1 ("atypical")
Drake, *et al.*, 1985–1986	13	12	0	1	0	1	0	11	1 ("atypical")
Nakamura & Becker, 1985	7	7	0	0	0	2	1	4	
Doty, *et al.*, 1987	13	11	0	2	0	4	1	5	2,* 1 (lipoblastic)
Kolluri, *et al.*, 1987	18	14	2	1	1	10	2	1	3,* 2 ("atypical")
Ferrante, *et al.*, 1989	19	17	2	0	0	4	11	0	3,* 1 ("atypical")
Davidson & Hope, 1989	22	13	5	1	3	7	0	6	7 (angioblastic), 2 not specified
Germano, *et al.*, 1994	23	16	3	3	1	9	6	8	0
total cases	278	186	40	26	15				
% of total		67	14.4	9.4	5.4				

* Meningeal sarcoma.
† Melanoma, hemangiopericytoma.
‡ Merten, *et al.*, and Deen, *et al.*, include one and 10 spinal meningiomas, respectively.

In different series in the literature, 0-41% of childhood meningiomas are associated with NF 2, [8–10] while it is only 0.35% for adult meningiomas. [21] In Erdincler et al. [16], 41% of paediatric meningiomas were associated with multiple neurofibromatosis, of which 58% were NF-1 and 42% NF-2. In this series, there was one case each with NF-1 and NF-2, i.e. an incidence of 11.11%. (Table 5), (Figure 18).

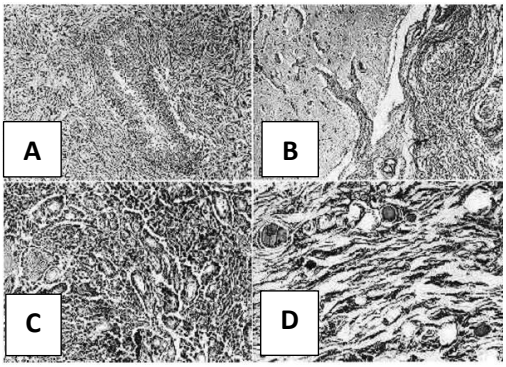


Figure 18: Photomicrographs of intracranial meningiomas that developed in the first two decades of life. A: Section showing a small area of focal necrosis. H & E, original magnification x 200. B: "Finger-like" cortical invasion by a meningioma is visualized. H & E, original magnification X 150. C: Section showing papillary formations in a meningothelial tumor. H & E, original magnification • 500. D: Intensely vimentin-positive cells (dark) are separated by collagen fibers in this fibroblastic meningioma. A few psammoma bodies are also seen (round). Immunohistochemical stain for vimentin, original magnification • 200.

4.6. Tumor Location

It has been suggested that the lateral ventricle is a favored site for childhood meningiomas. Intraventricular tumors constituted 17% of meningiomas in children and adolescents reported by Merten, et aL, 28 and 44% of those reported by Herz, et al. ;21 however, Crouse and Berg 4 and Ferrante, et al., found no meningiomas at this location. In this series, 13% of the tumors were IVM. In all paediatric series combined, 9.4% of meningiomas were IVM (Table 2). Recent studies have shown that 5% of adult meningiomas are intraventricular. There were no ITM arising in the first two decades of life in several series 2,13,14,29 and the percentage ranged from 19% to 46% in three others. Infratentorial meningiomas (ITM) accounted for 13% 4.9 28 of the tumors in our patients and 14.4% of tumors in all the paediatric series combined (Table 2). In adults, approximately 10% of meningiomas are infratentorial. Thus, although the great majority of meningiomas of the first two decades of life are supratentorial and extraventricular, they can occur more frequently in the ventricles and in infratentorial locations than meningiomas in adults.

4.7. Neuroimaging Characteristics

The MR imaging characteristics of meningiomas in adults have been well described. In many cases, there is a "dural tail," a small amount of contrast enhancement along the dura adjacent to the meningioma. Two similar features were seen in the cases evaluated by MR imaging. Pathological studies have shown the absence of a dural attachment in meningiomas of the first two decades of life. Further studies are necessary to investigate whether this will correspond to

4.8. Histological Considerations

Meningiomas are difficult to diagnose and classify because their histological appearance is highly variable and they may mimic glial tumors. Many tumors classified as meningiomas prove to be misdiagnosed; in one series, only 48 of 75 meningiomas were classified as such after careful review. Immunohisto-chemical stains can help establish the diagnosis. In the presented series, all tumors were positive for vimentin and negative for GFAP, supporting the diagnosis of meningioma. Meningiomas of the first two decades of life reportedly have a higher incidence of "malignant" changes than meningiomas in adults. The lack of universally accepted histological criteria to define aggressive behavior makes such comparisons difficult. In the presented series, necrosis was present in 29% of the tumors, an increased number of mitoses in 33%, and cortical invasion in 14%. However, 71% of the meningiomas in the patients of presented series were benign (Grade I), 29% were atypical (Grade II), and none was anaplastic (Grade III). In adults, 60% to 90% of meningiomas are benign, 5% to 20% are atypical, and approximately 10% are anaplastic. These findings suggest that meningiomas of the first two decades of life have histological features similar to those of adults and are not more malignant than their adult counterparts. Papillary meningiomas are considered more aggressive than other types of meningiomas and are reportedly more frequent in children. The 5-year survival rate for papillary meningiomas is about one-half that for the other types of meningiomas (40% vs. 80%). In a recent review of the literature, Pasquier, et al., found that 37 (80%) of 46 papillary meningiomas were in adults, whereas only one tumor in the presented series had a papillary pattern. Thus, papillary meningiomas appear to be much rarer in children than in adults.

4.9. Outcome

Surgical excision has been the treatment of choice for these tumors. Surgical management poses a formidable challenge considering their peculiar location, larger size at presentation, relatively less blood volume in children, and the risks of

prolonged surgery like hypothermia, massive blood transfusion, etc. (Table 6). The determinants of long-term survival after surgery for intracranial meningiomas are still being debated. Meningeal tumors such as sarcomas, hemangiopericytomas, and angioblastic and melanocytic tumors are more aggressive than classic meningiomas and have a poor prognosis? In their review of the literature, Drake and Hoffman reported that the 5-year survival rate increased from 76% to 84% when meningeal sarcomas were excluded. Classic meningiomas were included in the presented series; a similar criterion was suggested to be used in other retrospective studies so as to facilitate comparison of data. In adults with intracranial meningiomas, total excision seems to be the most important factor in decreasing the incidence of tumor recurrence. Barbaro, et al., showed that 96% of patients who underwent gross total resection of an intracranial meningioma were recurrence-free during a follow-up period of 5 to 15 years. The recurrence of meningiomas in the first two decades of life is difficult to assess. In one study of paediatric meningiomas, recurrence was shown to decrease the 5-year survival rate from 94% to 64%. In most series, however, the authors stated that the patients were "doing well," without specifying if the follow-up evaluation included radiological studies. Nevertheless, there have been no documented cases of recurrence after gross total resection of meningiomas developing in the first two decades of life. Because the growth rate of meningiomas is slow and variable, the length of the follow-up period is important in assessing recurrence. After a maximum follow-up time of 20 years in 69 adults with intracranial meningiomas, Jaaskelainen reported a recurrence rate of 19%. The data available in the young population (Table 6) do not suggest such a high incidence after gross total surgical resection, even in cases with more than 20 years of follow-up review. Although further studies are necessary to corroborate this observation, meningiomas in the young population do not, as previously suggested, appear to be more aggressive than those in adults. After incomplete resection, a tumor may continue to grow and become symptomatic. Regrowth after subtotal surgical resection in adults is thought to occur in 10% to 26% of cases. The available data on meningiomas of the first two decades of life (Table 6) do not allow to establish a clear rate of regrowth after subtotal resection for meningiomas in this age group. Several factors may influence regrowth. The histological subtype of meningioma does not correlate with the recurrence of subtotally resected meningiomas in adults, m Although histological features such as necrosis, invasion of adjacent brain, and mitoses may portend a more aggressive behavioring meningiomas lacking these features have recurred after subtotal resection, and many of the histological features of malignant meningiomas can be observed to a lesser degree or as isolated characteristics in benign tumors. More-over, benign meningiomas constitute the most frequent category of recurrence. Of 43 tumors that recurred in the series of Jaaskilainen, et al. , 23 56% were benign. These contradictory data on the importance of histological features on regrowth after subtotal resection in adults make it very difficult to make useful comparisons with the findings in younger patients. RT after partial resection of meningiomas appears to be beneficial in adults. Owing to the paucity of cases, it is difficult to establish the role of radiation therapy in the treatment of meningiomas of the first two decades of life. In our series, all 3 patients who underwent RT after subtotal resection are recurrence-free, as is one patient who did not receive radiation therapy.

Table 6: Regrowth, recurrence and outcome in cases with long follow-up period

*Regrowth, recurrence, and outcome in cases with a long follow-up period**

Authors & Year	STR	Regrowth	GTR	Recurrence	Follow-Up Period
Crouse & Berg, 1972	3	1 (2†)	—	—	3–9 yrs
Cooper & Dohn, 1974	—	—	—	—	—
Merten, *et al.*, 1974	20	20	28	28 well‡	10 mos–25 yrs
Leibel, *et al.*, 1976	9	6 (3†)	1	1 well‡	4 mos–17 yrs
Herz, *et al.*, 1980	—	—	—	—	—
Sano, *et al.*, 1981	—	—	—	—	—
Chan & Thompson, 1984	1	1	2	2 well‡	8–20 yrs
Drake, *et al.*, 1985–1986	7	3	6	0	5 mos–15 yrs
Doty, *et al.*, 1987	1	1	11	8 well‡	15 mos–11 yrs
Kolluri, *et al.*, 1987	—	—	—	—	—
Ferrante, *et al.*, 1989	3	3	12	12 well‡	6 mos–17 yrs
Davidson & Hope, 1989	1	1	8	0	2–12 yrs
Germano, *et al.*, 1994	4	0	6	0	3–22 yrs

* In the studies of Deen, *et al.*,[11] and Nakamura and Becker,[29] no distinction was made between subtotal resection (STR) and gross total resection (GTR); the "recurrence" rates were 39% and 43%, respectively. — = data not available.
† No follow-up information given.
‡ Authors stated that patients were "doing well" but did not state how recurrence was ruled out.

Leibel, et a1. (65), reported 3 patients who received radiation therapy and were "well" at follow-up review (6 to 17 years). Nevertheless, the adverse effect of radiation on the developing brain cannot be ignored. With the widespread availability

of MR imaging, frequent follow-up studies to document regrowth may be advocated before instituting RT. The frequency of intraventricular meningioma (IM) is high (12%) as compared to 0.5-4.5% in adults. The propensity for growth into ventricular system is explained by the inclusion of arachnoid cells in the choroid plexus and velum interpositum. In the presented series, 22.22% of cases had an IM. The lack of dural attachment is another frequent occurrence in paediatric meningiomas (28.5%), whereas it is extremely rare in adult patients. This lack of dural attachment is probably due to derivation of the tumor from leptomeningeal elements lodging within the parenchyma or in or near the ventricles rather than from the dura mater. An important feature distinguishing childhood meningiomas from adult meningiomas is their peculiar location. Convexity meningiomas are most common in adult meningiomas, while childhood meningiomas have other peculiar location that increases complexity in their management. Various series have also documented a high incidence of cystic changes in meningiomas in children. In the presented series, two patients were with cystic changes in meningiomas. In series of Tufan et al. [51], 4 out of 11 meningiomas showed cystic changes.

Nevertheless, with progress in microneurosurgical and anesthesiological techniques and considering the benign nature of disease, surgical excision remains the modality of choice. Also in children with residual tumor or regrowth, the risk of radiation to the developing brain favors redo-surgery over radiation therapy. (Table 7)

Table 7: Simpson classification for surgical management of meningioma

Grade	Tumor Resection	Recurrence Rate
I	Macroscopically complete removal of dura, bone	9%
II	Macroscopically complete removal, dural coagulation	19%
III	Complete tumor resection, dura not coagulated	29%
IV	Partial removal	44%
V	Simple decompression	

* Based on Simpson grade.[3]

The clinical outcome is available in only 267 cases, with a mean follow-up of 4.2 years. [14, 19, 20, 91-92, 95, 97-104, 106, 108, 110-111] In 13% of these cases, tumor recurrence is described. Recurrence seems to be strictly related to incomplete resection and/or the histologic subtype of the meningioma: 54% of the recurring meningiomas were removed subtotally and 46% totally. Most of the latter were malignant or malignant variants; more precisely, 31% were anaplastic, 15% atypical, 10% papillary and 10% sclerosing with brain invasion. The remainder were angiomatous (5%) and not invasive (26%). One of these latter cases was previously irradiated. Two patients were reported in the literature [92-99, 105, 109, 115, 119-128, 177-183] and were affected by von Recklinghausen disease. The patient had bilateral acoustic neurinoma 15 years after the operation without tumor recurrence of meningioma, and the patient described in the literature had a recurrence of tumor. With regard to radiation-induced meningiomas, there are some differences when compared with both the spontaneous counterpart and radiation-induced meningiomas in adults. First, in paediatric postirradiation meningioma, there is a female to male ratio of 1.7:1. This female predominance is similar to that of meningiomas in adults, but it contrasts to the absence of a sex predominance observed in paediatric meningiomas. Second, the rate of postirradiation meningiomas in children with aggressive behavior is similar to that in adults (15% vs 18.8%) but contrasts to the behavior of spontaneous meningiomas in children. Third, the latency period between irradiation and the diagnosis of meningioma tends to be shorter in paediatric patients than in adults. The latency period between radiation therapy and clinical onset of meningioma in the paediatric population is 9 years (2-15 years) versus 21.9 years in adults.

4.10. CSF Dissemination

Intracranial and intraspinal meningiomas with leptomeningeal were reported. (Figures 19-21)(Table 8). Ki-Su Park et al. showed in his presentation in the (J Korean Neurosurg Soc 57 (4): 258-265, 2015) five cases of intracranial meningioma with leptomeningeal dissemination (LD) and this group investigated the characteristics of this disease. It was showed, that intraventricular location / histologically aggressive features seem to increase the chance of LD of meningioma, whereas this tumors had no metastases in the usual extra-cranial organ such as the liver, lungs, pleura, and lymph nodes.

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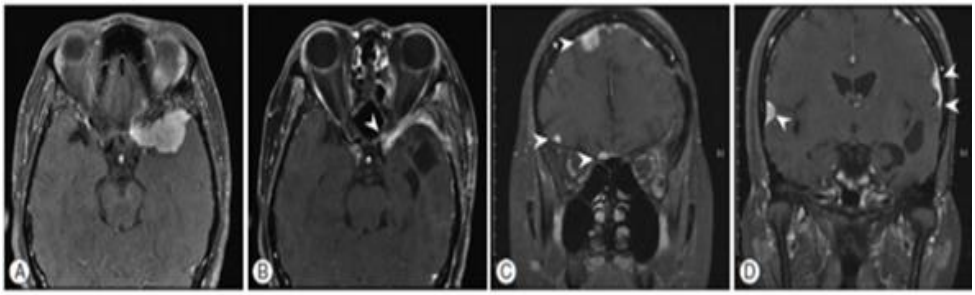

Figure 19: Preoperative MRI displaying a left sphenoidal ridge meningioma. B : Four months later, MRI showing the local recurrence (arrowhead). C and D : Approximately 18 months later, MRI revealing multiple meningiomas around bilateral convexity (arrowheads).

Table 8: Characteristic findings of leptomeningeal dissemination of meningioma in 5 patients

Case No.	Histological transformation	Metastases		Time to local recurrence	Time to CSF disease presentation	Treatment	Progression	OS/survival after LD	Death
		Cerebrospinal	Extraneuronal						
1	-	Suprasellar, posterior fossa, spinal	-	2.5 mo	2.5 mo	Surgery	PD	3.5/1 mo	Death
2	+ (I→II)	Both convexity	-	4 mo	1.8 yr	GK	SD	2.3/2 yr	Alive
3	-	Cavernous sinus, cervicomedullary, cerebellar convexity, spinal	Skull base, ribs, spines, pelvic bones	1.7 yr	1.7 yr	Surgery+ GK+RT	PD	4.3/2.5 yr	Death
4	-	Sylvian cistern	-	2.1 yr	3.8 yr	Surgery	PD	7.3/3.5 yr	Death
5	Unknowability	Suprasellar, ambient cistern	-	6.9 yr	6.9 yr	GK	PD	10.7/3.8 yr	Death

No. : number, RT : radiotherapy, GK : Gamma-Knife radiosurgery, PD : progression disease, SD : stable disease, mo : months, yr : years, LD : leptomeningeal dissemination, CSF : cerebrospinal fluid, OS : overall survival

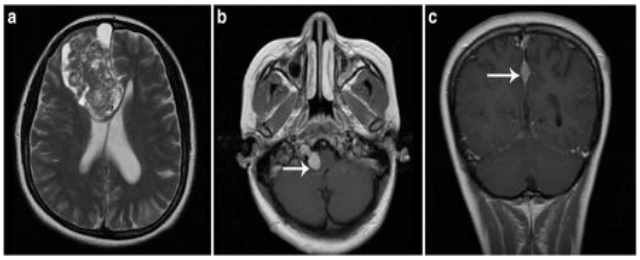

Figure 20: 1 a Axial T2-weighted MR showing a large Right frontal lobe meningioma in a 15-year-old girl with NF2. b, c Multiple nodosity NF2 was found in the cerebellopontine angle and cerebral falx (arrow)

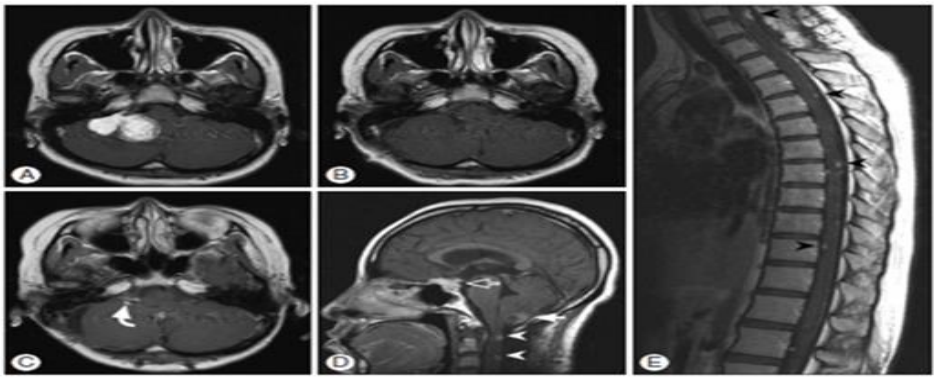

Figure 21: Preoperative enhanced magnetic resonance imaging (MRI) showing a right cerebellopontine angle meningioma. B : Postoperative MRI displaying Simpson grade II resection of the tumor. C and D : Approximately 2.5 months later, follow-up MRI revealing the local recurrence (curved arrow) and new lesions in the posterior fossa (closed arrow), suprasellar (open arrow) and spinal region (arrowheads). E : Spinal MRI demonstrating multiple leptomeningeal disseminations (arrow heads).

4.11. Radiation-induced meningioma (RIM) after high-dose cranial irradiation

RIM is known to occur after high and low dose cranial radiation therapy. Currently, RIM are the most common form of radiation-induced neoplasm reported. The largest series of RIM induced by high dose radiation reported was by The Royal Melbourne Hospital. Spontaneous meningiomas (SM) were treated between 2007 and 2011 with regard to age, gender, and histopathology and they were compared with the RIM. The female-to-male ratio was 1.88:1 in RIM compared to 2.37:1 for SM. Of the RIM, 86.5% were World Health Organization (WHO) grade I and 11.5% were grade II (atypical) meningiomas. There were no anaplastic or malignant RIM. Of the SM, 91.5% were WHO grade I, 7.1% WHO grade II, and 1.4% WHO grade III meningiomas. The characteristics of RIM induced by low dose radiation therapy have been well described. It is timely to consider RIM due to high dose radiation, which is now frequently employed in the management of various childhood and other malignancies.

4.12. Relapse free survival of in children and adolescents with meningiomas

A series of 35 cases completed over the past 21 years. Individual patient data were obtained from 30 studies. Primary outcomes were relapse-free survival (RFS) and overall survival. Prognostic variables were extent of initial surgery, use of upfront radiotherapy, age, sex, presence of neurofibromatosis, tumor location, and tumor grade. RFS and overall survival were analyzed using Kaplan-Meier survival curves and multivariable Cox regression models. From a total of 677 children and adolescents with meningioma, 518 were eligible for RFS analysis and 547 for overall survival analysis. Multivariable analysis showed that patients who underwent initial gross-total resection had better RFS (hazard ratio 0·16, 95% CI 0·10–0·25; p<0·0001) and overall survival (0·21, 0·11–0·39; p<0·0001) than those who had subtotal resection. No significant benefit was seen for upfront RT in terms of RFS (0·59, 0·30–1·16; p=0·128) or overall survival (1·10, 0·53–2·28; p=0·791). Patients with NF2 had worse RFS than those without NF (2·36, 1·23–4·51; p=0·010). There was a significant change in overall survival with time between patients with NF2 compared with those without NF2 (1·45, 1·09–1·92; p=0·011); although overall survival was initially better for patients with NF2 than for those without neurofibromatosis, overall survival at 10 years was worse for patients with NF2. Patients with WHO grade III tumors had worse RFS than those with WHO grade I (3·90, 2·10–7·26; p<0·0001) and grade II tumors (2·49, 1·11–5·56; p=0·027).

4.13. A heritable form of SMARCE1-related meningiomas

Gerkes et al. reported in Neurogenetics (2016) 17:83–89 about a 10-year-old boy, who was referred because of recent onset of hearing loss and tinnitus of the right ear. He complained about blurry vision. His medical history was unremarkable apart from treatment with methylphenidate because of ADHD. O/E of the ear, nose and throat showed no abnormalities apart from an abnormal Weber test to the left, and an asymmetric reaction of facial nerve. The audiogram showed a sensorineural hearing loss of the right ear, with a downsloping audiogram and complete loss of higher tones indicating damage to the acoustic nerve. The MRI scan of the brain showed a large extrinsic tumor in the right cerebello-pontine angle with severe compression and displacement of the brainstem. (Figures 22-25)

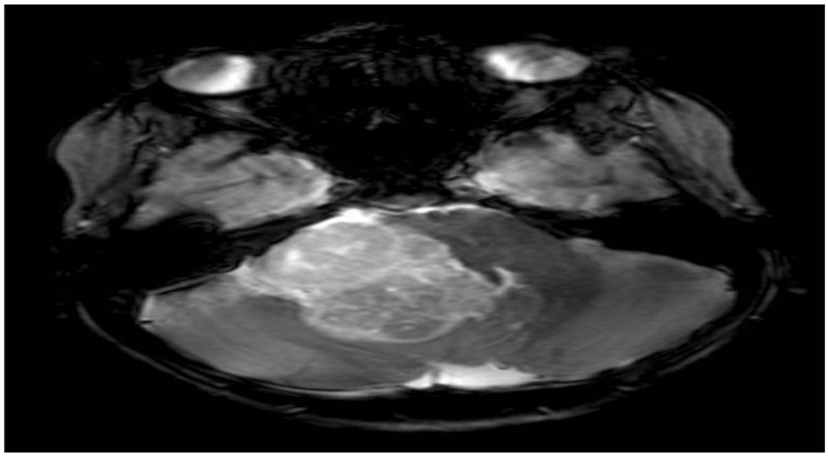

Figure 22: Heterogenous tumor within the right cerebello-pontine angle causing severe compression of the brainstem. This T2-weighted MRI image in the transversal plane illustrates the extrinsic nature of the lesion with a differential diagnosis of meningioma or Schwannoma

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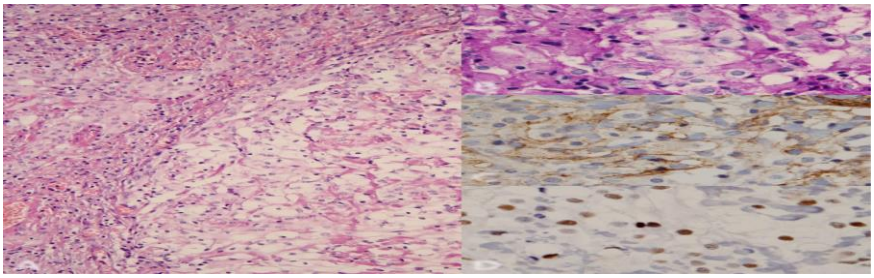

Figure 23: H & E staining ofthetumor (a, left, magnification ×20), partly consisting of clear cells on the right side. The asterisk indicates meningothelial cells. In (b) to (d) (from right up to right down), more detailed micrographs (magnification ×40) of the clear cell component after PAS, EMA and progesterone receptor staining, respectively

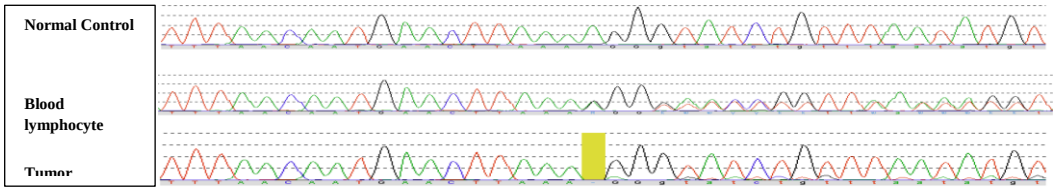

Figure 24: DNA sequencing chromatograms from the patient's blood lymphocyte DNA and tumor DNA from fresh frozen tissue, and a normal control for reference. The mutation locus of the SMARCE1 c.814delA frameshift mutation is indicated by the red arrows. In blood lymphocyte (germline) DNA, the mutation is present in heterozygous state, while in the tumor, it is present in homozygous state, indicating loss-of-heterozygosity (LOH) at the mutation locus. The minimal amount of wild-type sequence that is visible in the tumor sample is caused by a small amount of normal tissue mixed with the tumor cells (color figure online)

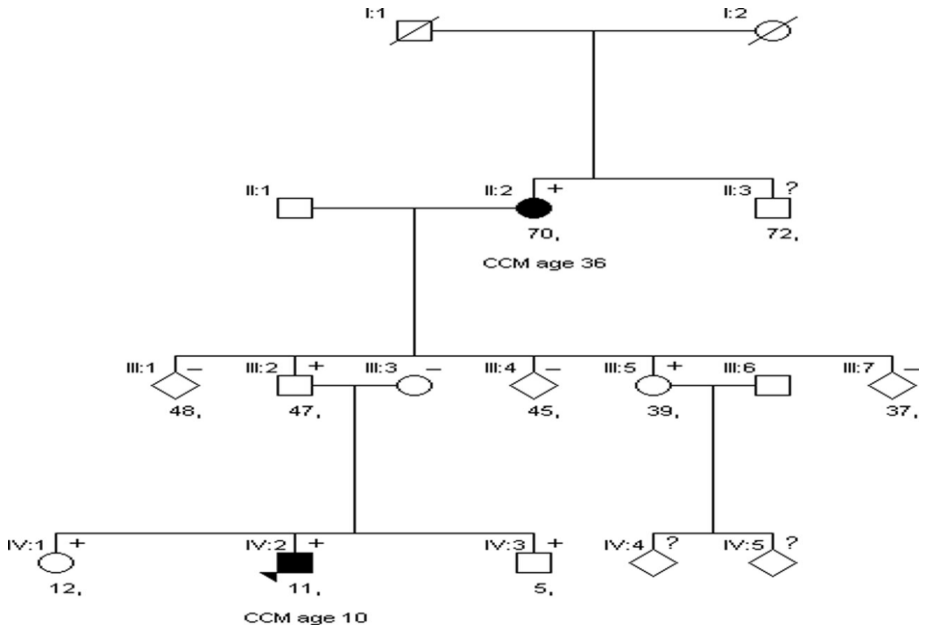

Figure 25: Pedigree of the family with the SMARCE1 mutation. Current age is mentioned below the square/circle. + = mutation positive, − = mutation negative. Solidblack=CCMpatient,ageof detection of CCM is mentioned below the current age. Solid white = clinically asymptomatic.? = testing not started yet

4.14. Estrogen / progestin binding by cytosolic / nuclear fractions of human meningiomas

Martuza RL et al reported in J Neurosurg. 1985 May; 62(5):750-6, about the work with frozen tissue samples were obtained from meningiomas in 42 patients. Both cytosolic and nuclear fractions were tested for estradiol and progestin binding using equilibrium binding assays. The results were correlated with the age of the patient and the histological type and cellular density of the tumor. Cytosolic estradiol binding was noted in 25 (60%) of 42 tumors, with eight (19%) of the 42 having levels over 10 femtomoles (fM)/mg protein. Nuclear estradiol binding was detected in 16 (57%) of 28 tumors, with six (21%) of the 28 having levels over 10 fM/mg protein. Cytosolic progestin binding was noted in 16 (73%) of 22

samples, with levels in nine (41%) of 22 being greater than 10 fM/mg protein. There was no correlation between the level of cytoplasmic progestin binding and either the level of cytoplasmic estradiol binding or the level of nuclear estradiol binding. In several specimens, level of cytoplasmic progestin binding in excess of 100 fM/mg protein were found in tissues demonstrating little or no estradiol binding by either the nucleus or the cytosol. This discrepancy differs from the situation found in other hormonally responsive tissues such as breast or uterus, and suggests either a possible derangement of the normal cellular hormonal control mechanism or that the measured hormone binder is a molecule other than a classical hormone receptor.

4.15. Paediatric meningiomas: 65-year experience at a single institution

Andrew J et al. evaluated in the Journal of Neurosurgery: Paediatrics, Jul 2017 / Vol. 20 / No. 1 : Pages 42-50 pa,ediatric meningiomas with the risk factors, pathological subtypes, and recurrence rates of paediatric meningiomas. Sixty-seven meningiomas in 39 patients were identified. Eight patients had NF2, 2 had a family history of meningioma, and 3 had prior radiation exposure. Of the 39 patients, 12 (31%) had WHO Grade II or III lesions, and 15 (38%) had recurrence after resection.

5. RETROSPECTIVE STUDY

The aim of this clinical retrospective study was to review the characteristics, therapy considerations and outcomes of paediatric meningiomas in our center and other previous published data are reviewed. Nineteen consecutive cases of meningioma in patients under 18 years of age admitted and operated at our institution (Barmherzige Brüder Hospital, Department of General Surgery, Neurosurgery Unit, Ludwigsburg / Neckar, Germany) between the 2008 and 2013 were included in the study. All cases were confirmed by radiological, operative, and histopathological findings. Retrospectively, following performance was done: To analyze the epidemiological profile, clinical features, radiological findings, type of excision, histopathological findings, and overall management profile of these patients. All patients/relatives were called for the follow- up or an attempt was made to at least get an interview on telephone. As and where possible, an attempt was done to determine the differentiating features between adult and paediatric meningiomas. Between January 2008 and April 2013, a total of 29 meningiomas were diagnosed in 19 patients aged less than 18 years. Twenty-seven tumors were surgically treated and these were histologically proven meningiomas. Their hospital records including follow-up notes and imaging studies were retrospectively reviewed.

5.1. Preoperative Examination

The preoperative workup included a detailed neurological examination to establish baseline characteristics of the patients. Imaging studies included high-resolution CT and MR imaging. If the internal carotid arteries or the vertebrobasilar system were involved by the tumor, a cerebral arteriogram was acquired and collateral blood flow was assessed through cross-compression studies.

5.2. Radical Excision

The surgical procedures were performed to accomplish total resection. A variety of approaches were used depending on the location and size of the tumor. The adequacy of resection was noted based on the surgeon's observation and findings on the postoperative MR and/ or CT studies.

5.3. Outcome and followup

Post-operative outcome of each patient was recorded using the Glasgow outcome score. The patients underwent regular follow-up and clinical examination at each visit. The follow-up period was defined as the period extending from surgery to the most recent clinical visit or patient contact. Patients with follow up period less than six months were considered as lost to follow up. Recurrent tumor was judged according to findings on imaging studies. All tumors were evaluated by a neuropathologist, and the diagnosis of meningioma was confirmed and classified in accordance with WHO classification of central nervous system tumors, 2000.

5.4. Data analysis

The outcome was analysed with respect to the following variables: age, gender, association with neurofibromatosis, extent of resection, tumor location, recurrence and the histopathological variant. Data was analyzed using SPSS software.

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5.5. Incidence

A total of 989 meningioma cases were analyzed between the years 2006 and 2013 at nine neurosurgical centres, of which 19 cases were in the age group of 9 months - 18 years and were treated at our institution. Thus, childhood meningiomas accounted for 1.92% of total meningiomas in this presented study.

5.6. Sex and Age

Age at diagnosis varied from 9 months to 18 years. Only one child was with presentation under 1 year of age. The maximum incidence of meningiomas was seen in the second decade of life. Thirteen out of 19 cases presented in the second decade. The mean age at presentation was 12.81 years. There were 11 males and 8 females in this series. The male-to-female ratio was 1.38:1.

5.7. Presenting symptoms and signs

The main presenting symptoms in intracranial meningiomas (mainly because of raised ICP) were seizure (8 patients), headache (6 patients), impairment of vision (2 patients), vomiting (3 patients), proptosis (2 patients), increased head size (1 patient), and occipital swelling (1 patient). Thoracic pains with low back pain and weakness in the lower limbs in 2 patients with spinal meningioma. The median pre-operative duration of symptoms was 1.2 years.

The most common clinical sign seen was papilloedema (7 patients) followed by monoparesis (4 patients), marked impairment of vision (4 patients), proptosis (2 patients), tense anterior fontanelle (2 patients), occipital swelling (1 patient), neurofibromatosis (3 patients).

5.8. Neuro-radiology

Patients were investigated with varied neuroradiological modalities such as plain X-ray of skull (2 patients with calcified tumor), DSA and pre-operative embolization (6 patients), CT scan (9 patients), MRI (2 patients), and CT scan + MRI (17 patients, 2 patient with cystic formation). (Figure 26-28)

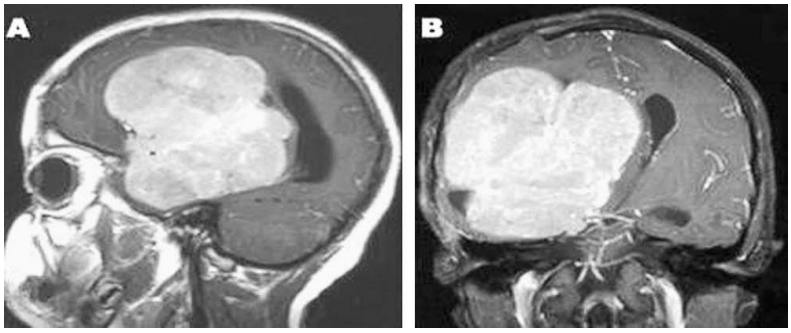

Figure 26: A 6 years male patient with severe headache and tonic clonic convulsions. Magnetic resonance T -weighted sequence (TR/TE = 4400/111 ms) reveals large, lobulated hyperintense lesion, suggestive of meningioma in right cerebral hemisphere. There is midline shift and compression of right lateral ventricle. (A) Sagittal view. (B) Coronal view.

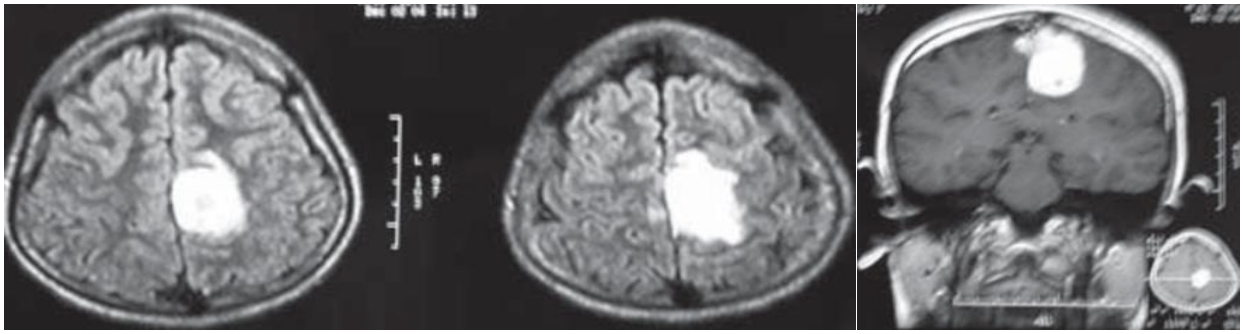

Figure 27: MRI Brain with Gadolinium: Axial view showing intensely enhancing falcine meningioma

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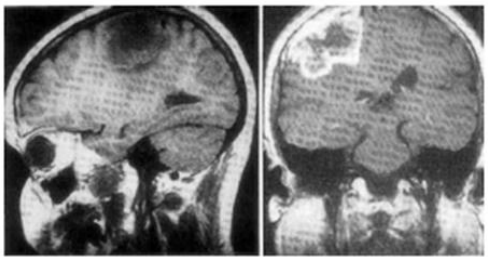

Figure 28: MRI Tl-weighted images (TR 600 msec, TE 20 msec). Left: Sagittal image showing a large hypointense extra-axial convexity mass. Right: Coronal image obtained after administration of gadolinium-diethylenetriamine penta-acetic acid showing heterogeneous enhancement, suggesting a necrotic or cystic core, and linear enhancement along the dura (a "dural tail"), suggestive of a meningioma.

5.9. Location

Fifteen cases were supratentorial, 2 cases was infratentorial and two cases in thoracic spine region. The tumors were located in the cerebral convexity in five patients, intraventricular in four patients, skull base in three patients, Falcine in two cases, parasellar in one patient, tentorial in one case, posterior fossa in one patient and thoracic spine in two patients.

5.10. Lesion characteristics

Tumor was homogenous in appearance in most of the cases visualized with CT/MRI. Intra-tumoral calcification was seen in three cases. Intra-tumoral cystic changes were seen in two cases. Hyperostosis was seen in three cases.

5.11. Tumor excision

Total excision of tumor was achieved in all cases. In 15 patients, total excision was achieved in one stage. Three patients required two-stage surgeries for total excision and one patient required three-stage surgeries to achieve complete excision.

5.12. Peri-operative mortality

One patient died postoperatively due to global severe cerebral edema. He was diagnosed to have malignant meningioma (WHO III). The mean peri-operative mortality was 5.2%.

5.13. Histopathology

Histopathology showed fibroblastic meningioma in three patients, meningothelial in two patients, transitional in eight patients, angioblastic in three patients, sarcomatous in one patient, aggressive syncitial in one patient, and malignant meningioma in one patient.

5.14. Adjuvant therapy

Postoperative adjuvant RT was given to four patients; three patients with histopathology suggestive of angioblastic meningioma and one patient with aggressive syncitial meningioma. One patient with sarcomatous meningioma could not be given radiation, as the age at diagnosis was only 9 months. However, patient had no recurrence even at 4 years of follow-up.

5.15. Follow up and recurrence

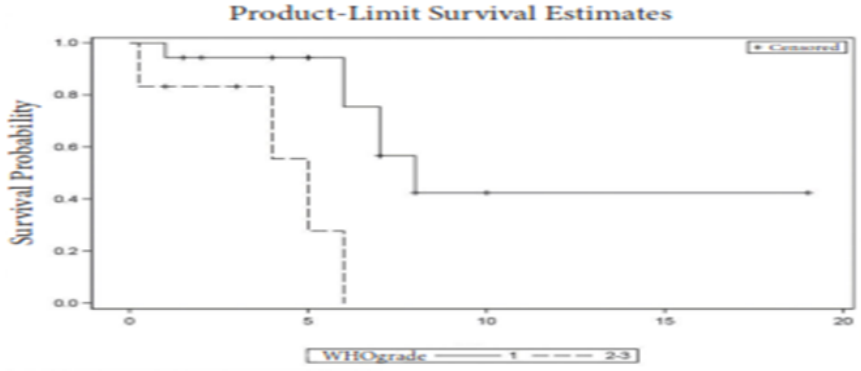

Diagram 2: (Left) Kaplan-Meier analysis of time to recurrence or progression. Difference between groups of WHO grade was compared by the two-sided log-rank test. A significant difference by WHO grade was noted (p=0.0009).

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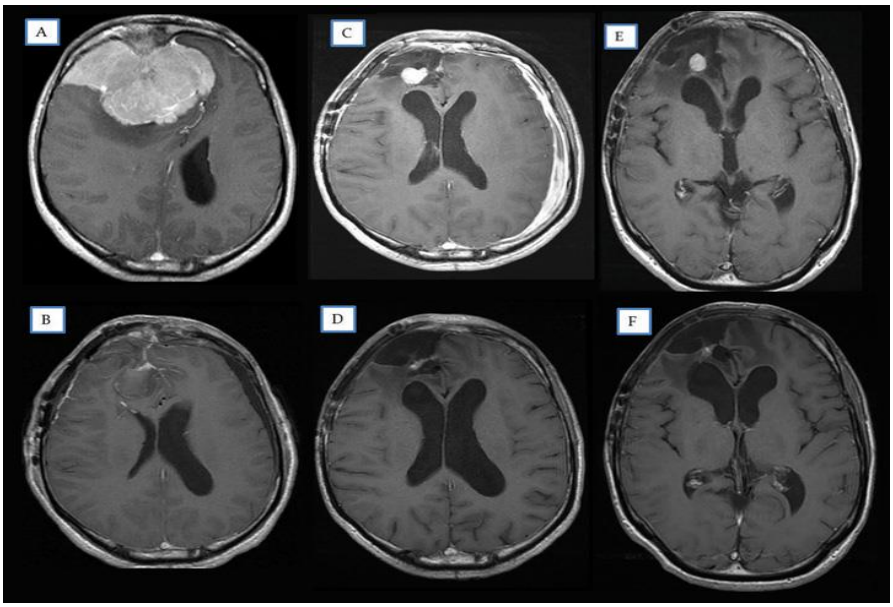

Figure 29: (Right)Initial presentation with large anterior cranial fossa lesion (A); Post-operative scan shows good resection (B); Recurrence of tumor at six months from surgery (C) that was treated with fractionated radiation therapy along with rest of tumor bed with regression of the recurrent tumor (D); Three years from surgery, small, asymptomatic recurrence without mass effect (E); treated with stereotactic radiosurgery with good response approximately three years after radiosurgery (F).

An attempt was made to get follow-up of all patients. The period of follow-up ranged from 1 to 7 years with a mean follow-up of 2.1 years. Two recurrences (10.5%) were documented in the presented series on follow-up. The histopathology in patients with recurrence was aggressive syncytial in one patient and transitional in the other patient. Both patients had a total excision during their first surgery. The patient with transitional meningioma had a huge falcine meningioma with extension up to the dura and hyperostosis. Some microscopic remnant must have been left behind, as falx was not excised. During the redo surgery, a total excision of the falx was achieved. The patient with aggressive syncytial meningioma, recurrence was seen after 2 years and in a patient with transitional meningioma, recurrence was seen after 5 years. (Figure 29 and Diagram 2)

6. CASE REPORTS

CASE 1: HUGE ANTERIOR FOSSA BASED MENINGIOMA

A 5 year old male patient presented with one episode of generalized tonic clonic seizure (GTCS) followed by unconsciousness. Removal of the tumor was done carefully. The biopsy report revealed atypical variety of meningioma WHO II. Despite that no recurrence is found in a F/U examination even after 2 years. Patient was moderately built and well nourished7 m years old male, complaints of one episode of GTCS followed by unconsciousness for 5 minutes. He had been delivered normally and was healthy otherwise. H/O excessive talk activeness and poor school performance. No neuro cutaneous marker was found. No sensory motor deficits, but plantar reflexes were down going. All laboratory values were WNL, chest x-ray normal. Preoperative CT scan of brain revealed a well defined heterogenous lesion of approximately 10cm×7 cm×6 cm in size, dural based, likely extra-axial right frontal SOL, which showed contrast enhancement with extension to left frontal region with evidence of compression over anterior horn of right lateral ventricle and dilatation of contra lateral ventricle. The midline septum was deviated to left side by 2 cm. Corpus callosum and brain stem were compressed from right side. Patient underwent bifrontal craniotomy and gross total excision of the mass. Histopathology report showed numerous meningothelial cells in whorling pattern, few of them were arranged in patternless sheets along with foci of small cells showing condensed nuclei. Mitotic activity: 4-5 /10 HPF along with early foci of necrosis. Stromal hyalinization and psammomatous calcification also present. Diagnosis was atypical meningioma WHO II. (Figures 30-32)

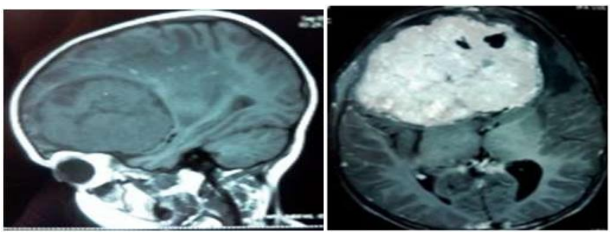

Figure 30: MRI of brain without contrast left and with contrast showing intensely enhancing meningioma in the bifrontal region with compression of the neuronal structures.

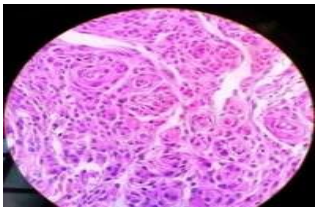

Figure 31: Microscopy: Sheets of meningothelial cells of the above mentioned tumor in whorling pattern, low power (Haematoxylin and Eosin stain, H & E, 10 X)

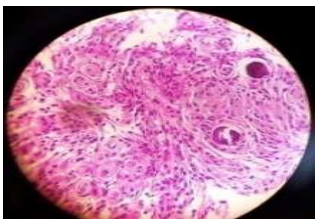

Figure 32: Microscopy: Sheets of meningothelial cells of the above mentioned tumor in whorling pattern with focal areas of psammomatous calcification, low power (H & E stain, 10 X)

The post-operative course was uneventful. No chemo-radiotherapy was given to the patient for atypia due to non co-operation. No recurrence in a follow-up examinations within seven years. No feature of neurofibromatosis was found in this case.

CASE 2: MENINGIOMA OF PINEAL REGION IN 5 YEARS OLD GIRL

Paediatric meningiomas in the pineal region may originate either from the velum interpositum or from the falcotentorial junction. A case of tumor in the pineal region is described, arising within the velum interpositum, with no dural attachment. Lack of dural attachment is one of the clinical characteristics of meningiomas in children: around 36% are not dural-based tumors. A 5 years-old girl presented with a 1 year history of occasional episodes of vomiting and progressive weakness of her right arm and leg. Her mother observed some irritability. Two weeks before admission, her relatives had noted an increase in pubic and axillary hairs. On examination, the child was calm, cooperative and oriented, with episodes of spontaneous weeping. She demonstrated increased pubic and axillary hairness, but without other signs of virilization. Fundus examination revealed bilateral papilledema. Her stance was unsteady, with evidence of hemiparetic spastic gait. She had global cerebellar and bilateral pyramidal syndrome. Plain skull radiographs revealed sutural diastasis and no calcification. Dosage of tumor markers AFP and HCG in serum were negative. Radiologic bone age was 6 years. Computed tomography (CT) showed a well-defined mass of slighly greater density than the surrounding brain, and uniform enhancement of the tumor was achieved with contrast injection. The tumor occupied the pineal region and compressed the posterior portion of the III ventricle. Marked ventriculomegaly was present. Abdominal ultrasonography study was normal (no suprarenal and ovary lesions were detected). Germinoma was thought to be the most likely diagnosis. Surgery was performed with the patient positioned in the “three-quarter prone”with the side-down position to minimize retraction of the occipital lobe. A large and encapsulated mass, with smooth surface, was completely removed through a righ occipital craniotomy and occipital transtentorial approach. There was no attachment of the tumor to the dura-mater of the tentorium, but the tumor was displacing the inferior portion of the tentoriun, the posterior half of the internal cerebral veins, and the inferior surface of the great vein of Galen. The tumor appeared to originate from the velum interpositum. Pecentral mesencephalic veins were occluded due to tumor involvement. Rosenthal vein on the right side

needed to be occluded, close to the great vein of Galen, while removing the last and small remaining portion of the tumor. The tumor did not invade or occlude the rectal sinus. Complete microscopic removal was achieved (Simpson Scale I). The neurological status improved, with gradual disappearance of the right hemiparesis and mental alteration. Histologic examination of the tumor revealed a fibroblastic type of meningioma. Child was discharged on the seventh post- operative day. After 5 years follow-up, a routine CT demonstrated a recurrence of the tumor, which was completely removed with no morbidity. Presently, patient is clinically stable. (Figures 33-34)

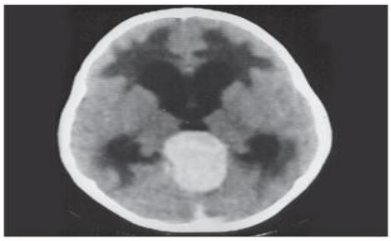

Figure 33: Case 1. Axial preoperative CT with contrast enhancement shows a round and well delineated mass, with high and homogeneous density, at the pineal region. The lesion is compressing the posterior part of the III ventricle. No peritumoral edema is demonstrated. Sign of acute obstructive hydrocephalus is present.

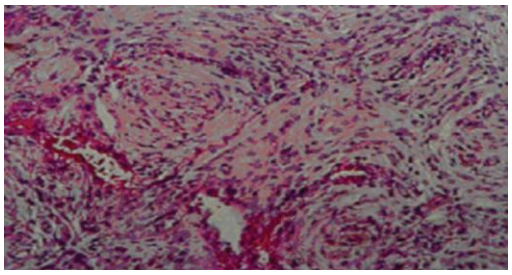

Figure 34: Case 2. Histological features of fibroblastic meningioma.

CASE 3: PINEAL MENINGIOMA IN A 13 MONTHS OLD BOY

The patient was admitted with H/O head trauma after RTA, where-after child became drowsy, developed vomiting, convergent strabismus and two episodes of GTCS. On examination he had no signs of external head injury. CT revealed enlargement of both lateral and III ventricles with a round, well-defined and high density mass in the pineal region, that enhaced homogeneously after injection of contrast. The tumor was slightly lateralized to the right, compressing the posterior portion of the III ventricles and the pulvinar thalamus on the right. In retrospect, his mother denied any abnormality with the child, he was feeding well, and his neurodevelopmental milestones were adequate. He underwent a frontal VP shunt insertion, with improvement of the sensorium and strabismus. Dosage of tumors markers (AFP and HCG in serum and CSF) was negative. Based on clinical data, neuroradiological findings, and negative tumor markers, the tumor was presumed to be germinoma, pineocytoma, or neuroepithelial tumors. The patient was operated on the "three-quarters prone" side-down position, through a right occipital craniotomy and suboccipital transtentorial approach.

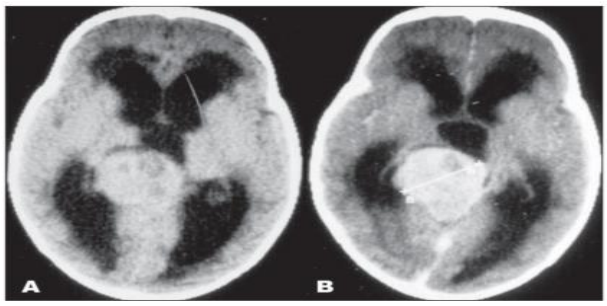

Figure 35: (A) Unenhanced CT scan reveals a round and slight high density lesion at the pineal region, compressing the posterior part of the III ventricle and the right pulvinar of the right thalamus. No peritumoral edema was seen. Ventricular dilatation and transependymal edema is demonstrated. (B) The tumor is markedly enhanced with contrast medium. Tumor size was 48 mm at the diameter indicated in the figure.

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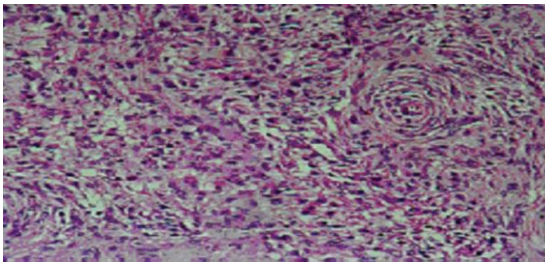

Figure 36: Case 3. Histological features of transitional meningioma.

Complete tumor removal was achieved (Simpson Scale I). (Figures 35-36) The tumor was relatively soft, mildly vascular, well circumscribed, encapsulated, with expansion to the III ventricle and posterior fossa, and no attachement of the tumor either to the dura-mater or the veins of the region was observed. After debulking of the tumor, and dissecting it away from the deep venous system, it was found that the tumor had an attachment to the tela choroidea right sided. Only the precentral-cerebellar vein was cauterized and divided without clinical postoperative consequences. Postoperative course was uneventful. Discharge with intact neurological status.

Histological examination demonstrated transitional type meningioma. Follow up course of 6 years, has shown no recurrence and he has done very well at school during all these years.

Discussion of cases 2 and 3

Diagnosis and recognition of meningioma among other tumors of the pineal region, despite advances in radiographic imaging, still remains unreliable. The majority of pineal region tumors occur during childhood and adolescence; on the contrary, meningiomas clearly predominate in adults over 40 years of age. Additionally, many histological types of tumors arise in the pineal region; more than 17 histologically distinct tumor types were recognized The most frequent tumors are germ cells tumors, pineal parenchymal tumors, and astrocytomas. Other types of tumors are less frequently observed. Meningiomas of the pineal region are extremely rare, especially in children. Incidence of meningiomas varies from 0.5% to 10.1% of all tumors in the pineal region, and of these, only about 8.1% correspond to children. Similar to all other meningiomas, those located in the pineal region predominate in female adults with a mean age of 39.3 years 8. Meningiomas may originate at the pineal region, either from the falcotentorial junction or from the velum interpositum. Falcotentorial meningiomas are more frequent than the ones originating from the velum interpositum [8,9], even though they may constitute less than 1% of all meningiomas; Meningiomas arising from the falcotentorial junction may demonstrate a different direction of growing and according to the extension; they may masquerade a pineal tumor. A review by Quinones-Hinojosa et al. found fewer than 50 cases of meningiomas of the falcotentorial junction. Typically these tumors also occur in adults with mean age of 42 years. Only one case of falcotentorial meningioma, a chordoid meningioma, occurring in a child of 15 years was found in the literature 13. Regarding meningiomas originating from velum interpositum, a review by Lozier and Bruce 14 collected only 27 cases. These meningiomas, like others, occur mainly in adults, with a presentation mean age of 32.6±19.7 years. Out of 27 cases, only four were reported in children less than 14 years of age. Owing to the rarity of meningioma at the pineal region in children, and relatively higher incidence of germ cell tumors of the pineal region, during the fi rst two decade of life, meningiomas are usually not considered at the first diagnosis. With very few exceptions, no clinical features can identify a specific tumor type at the pineal region. Usually these tumors present with increased intracranial pressure due to obstruction of CSF drainage, and compression of the mesencephalic tectal plate. Although benign tumors usually have a more insidious history these are not specific of meningiomas of the pineal region 10. Meningiomas of the pineal region may produce a rapid onset of symptoms related to aqueductal obstruction. When anterior, meningiomas from the velum interpositum, tend to occupy the III ventricle, causing obstruction of CSF at the Monro foramen. Posterior meningiomas grow to the pineal region, and compress the quadrigeminal plate, as do all pineal region tumors, and causing obstruction of the aqueduct giving rise to a rapid onset of symptoms. Meningiomas originating from the falcotentorial junction with inferior extension more frequently masquerade, clinically and radiologicaly, other pineal tumors 11. Endocrinological disturbances, as present in case 2, were unexpected and it was a disorienting point in the diagnosis, since virilization is more related to germ cell tumors, especially choriocarcinoma. Non parenchymal tumors were three times as likely to produce precious puberty, as were parenchymal tumors. Neuroophtamologic alterations (impairment of upperward gaze, abnormality of pupils, paralysis or spasm of

convergence, and nystagmus refractoris, and upper conjugate palsy) caused by compression of the mesencephalon, is very typical of this region, although not so frequent in children, but with only 11% with ocular disturbances.

CASE 4: MENINGIOMA WITH LEPTOMENINGEAL DISSEMINATION

A 9 years old boy was presented with severe headache, was operated on anaplastic meningioma WHO III and developed recurrence and leptomeningeal dissemination. (Figure 37)

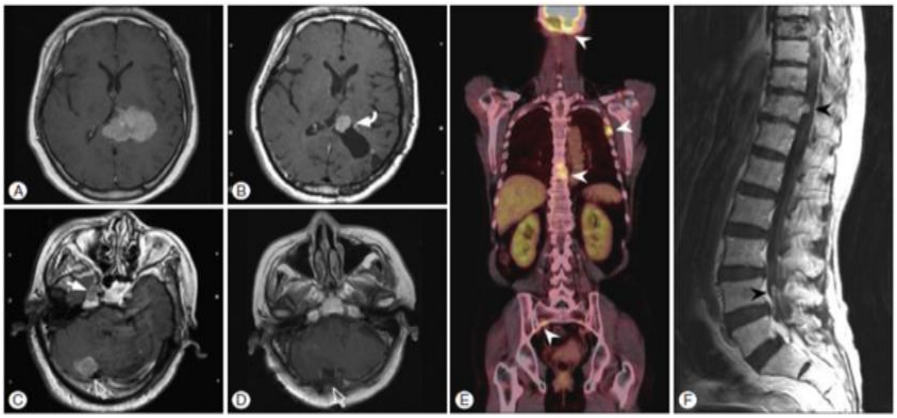

Figure 37: A : Preoperative MRI demonstrating a meningioma in the trigone of the left lateral ventricle. B : Approximately 1.7 years later, brain MRI showing the local recurrence (curved arrow). C : New lesions in the right cavernous sinus (closed arrow) and posterior fossa (open arrow) on enhanced MRI. D : Postoperative MRI after a second surgery for posterior fossa (open arrow). E : Four months later, positron emission tomography-CT showing multiple extraneuronal metastases in the skull base, ribs, spines and pelvic bone (arrow heads). F: Spinal MRI revealing leptomeningeal dissemination (arrow heads).

CASE 5: CSF DISSEMINATION OF INTRAVENTRICULAR MENINGIOMA

Progressive brainstem dysfunction and multiple cranial nerve palsies were seen in an 8-year-old boy, who was admitted because of double vision, right facial nerve palsy and truncal ataxia. Brain magnetic resonance imaging showed normal findings except for a tumor mass in the left lateral ventricle, which had been noted over 6 months previously. The patient developed hiccups, hyperventilation, and drowsiness, which worsened progressively, and did not respond to corticosteroid or intraventricular immunoglobulin therapy. CSF study revealed a mild elevation of protein, and cytology was negative. The patient died and an autopsy was performed. Postmortem investigation disclosed a malignant transformation of benign fibroid anaplastic meningioma WHO III with CSF dissemination of the malignant cells, diversely involving the surface of brainstem, cerebellum, and spinal cords, secondarily resulting in extensive ischemia in the brain parenchyma by vessel occlusion. The patient developed acute progressive decline of brainstem function caused by the CSF dissemination of intraventricular malignant meningioma. Here, we present the clinical and pathological data of the patient. (Figure 38-41)

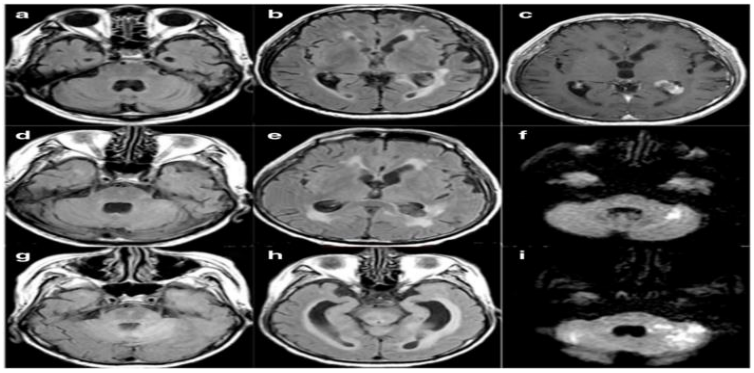

Figure 38: Brain MRI of the present patient at admission (a –c), and 17 days (d–f) and 40 days (g–i) after admission. Fluid attenuated inversion recovery (FLAIR) images at admission showed no gross abnormality, including in the brainstem and cranial nerves (a, b), although a mass-enhancing lesion was observed in the trigone of the left lateral ventricle on T1-weighted imaging (c). 17 days after admission, FLAIR images revealed slight hyperintensity in the exit for the trigeminal nerve and the left cerebellar hemisphere (d, e), and diffusion-weighted imaging (DWI) showed hyperintensity in the left cerebellar hemisphere (f). At the final MRI at 40 days after admission, diffuse high-intensity lesions and hydrocephalus were observed in the brainstem and cerebellum on FLAIR (g, h) and DWI revealed multiple hyperintense lesions in the bilateral cerebellar hemispheres (i)

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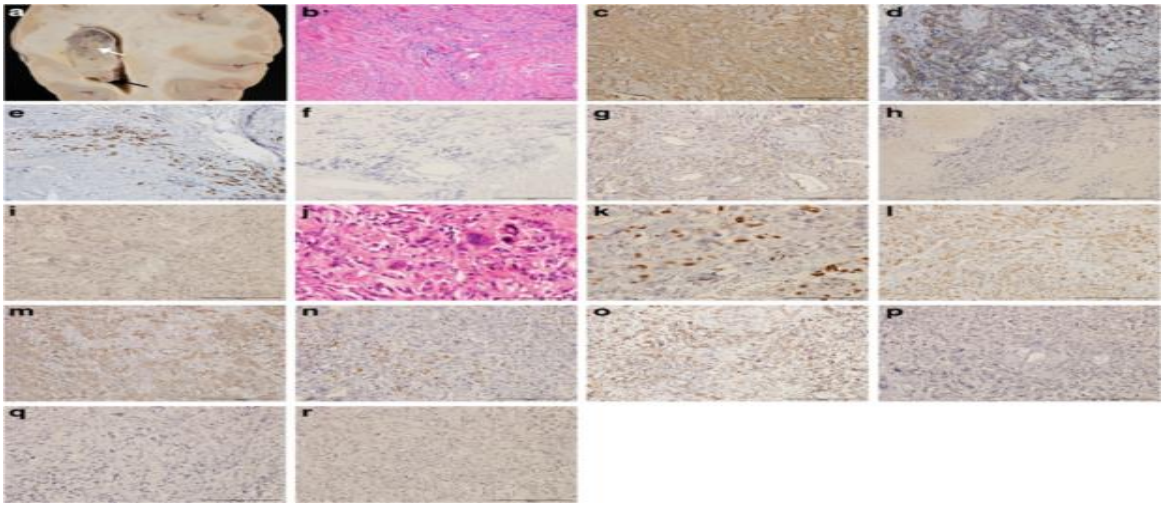

Figure 39: a: Macroscopic photograph of the intraventricular tumor. The main part of the tumor was encapsulated and solid (white arrow). The bottom part of the tumor became prominent and soft (black arrow). b-i: Histopathology of the main part shown with a white arrow in Fig. 2a. This region consisted of spindle-shaped fibrous cells, including a large amount of collagen deposits (b, hematoxylin & eosin (HE) stain). Using immunochemistry, the cells positively stained for vimentin (c), epithelial membrane antigen (EMA) (d) and S-100 protein (e), but were negative for cytokeratin (f), Schwann 2/E (g), GFAP (h), Olig2 (i) and lymphocytic markers (data not shown). These cellular profiles confirmed the histological diagnosis of the tumor as fibrous meningioma (WHO grade I). j-r: Histopathology of the part shown with a black arrow in Fig. 2a. This region showed increased cellularity, and cells were large, atypically shaped with multiple nuclei and prominent nucleoli (j). Mitotic cells were confirmed by examining more than 20 percent high-power fields on HE (j) and Ki67 stain (k). The cells with a malignant appearance were also positive for vimentin (l), EMA (m), S-100 protein (n) and cytokeratin (o), but negative for Schwann 2/E (p), GFAP (q) and Olig2 (r); This part of the tumor was diagnosed as anaplastic meningioma (WHO grade III).

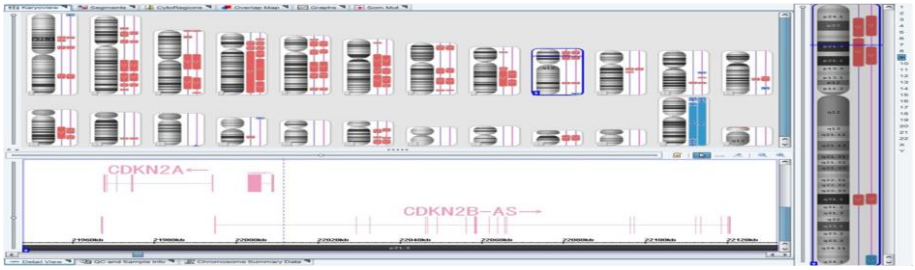

Figure 40: The chromosome analysis for the two tumor parts. The deletion of chromosome 9p21 was detected in the malignant region, the left side sample.

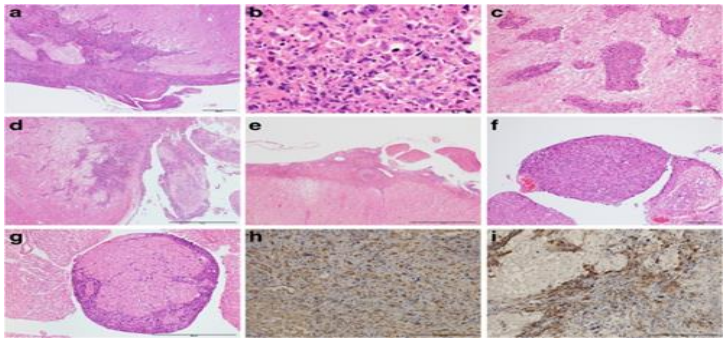

Figure 41: a-i: Histopathology of dissemination and infiltration of tumor cells. Copious cells invaded the surface, parenchyma and vessels of the brainstem (a, b; medulla oblongata, c; pontine base, d; pons and trigeminal nerve), spinal cord (e; dorsal part of T2) and nerve root (f;dorsalrootofL2,g;cauda equina). The cells invaded directly from the surface and damaged the tissue structures (a, d, f). Moreover, vascular infiltration of the cells caused ischemic necrosis around the vessels (c). The cells, which invaded the brainstem, pontine, spinal cord and nerve root, also showed the anaplastic meningioma with a highly increased mitotic ratio (b) and were positive for vimentin (h) and EMA (i).

As result and conclusion from this case, if a patient with an intraventricular tumor develops acute, progressive neurological symptoms, the possibility that it is be caused by cerebrospinal fluid dissemination of tumor cells, after malignant transformation, should be considered.

7. DISCUSSION

Meningiomas are usually slowly growing benign tumors originating from arachnoidal cap cells of the meninges [7]. They constitute 20–30% of all intracranial neoplasms in adulthood. These patients are most commonly in middle-aged and gerontal. Paediatric meningiomas are relatively rare. They account for less than 3% of all primary intracranial neoplasms in childhood. In our series, they range in age from 1 to 18 years, with a mean age of 13.7 years, similar with previous studies [1-2, 8–10]. The male-to-female ratio is 1:2 for adulthood meningiomas, with female predominance. Males were predominance in paediatric meningiomas with the ratio is about 2–3:1 [11, 12]. Of our 29 meningiomas in 19 patients, the ratio was 1.38:1, slight male predilection. While the reason is not clear, the sex hormones may play a role [3, 4, 13]. This suggests that the pathogenesis might be different between adulthood and childhood. Although there is no confirmed evidence for the pathogenesis of primary paediatric meningiomas, many risk factors may be relational, such as ionizing radiation and association with neurofibromatosis. Approximately 10% of paediatric meningiomas were associated with neurofibromatosis [14]. There is a clear association between paediatric meningiomas and NF-2 [15–17, 19, 21-28, 33-37].

Rushing EJ et al. reported that about 72% paediatric patients with meningioma had NF-2 gene deletion, the NF2 gene deletion is not somatic deletion, only in tumor tissues [18-19, 23-33, 59-61, 88-109]. This phenomenon suggests that these two kinds' neoplasm may be sharing the similar pathogenesis. Cranial ionizing radiation is one of the risk factors for meningiomas. The arachnoidal tissue in the meninges of children has higher radioactive susceptive, but radiation-induced meningiomas rarely manifest in childhood [18, 20, 33, 38-39]. No radiation induced signs in this series were detected. Meningiomas in childhood may develop anywhere in the cranium. They are usually observed in exceptional locations, such as: infratentorial, intraventricular, or skull base [10, 20, 25, 29-35, 40-53, 156-178]. Convexity of brain also is the most frequent location for paediatric meningiomas as adulthood. Intraventricular meningiomas are common in childhood, and most of them in the lateral cerebral ventricle. Arachnoid cells inclusions in the choroid plexus and velum interpositum may play a role [17-21]. The size of meningiomas is frequently larger in childhood than in adulthood [16]. More than 45% of the paediatric meningiomas are bigger than 5 cm in diameter 11. The mean diameter size of lesion was 5.4 cm in these 19 cases. The strong compensation ability of the cavitas cranii and the acataphasia of children may be the major reasons. Dural attachment or a dural tail sign on neuroimaging is usually absent, but cystic and calcified features are not rare Cysts were reported in 24% paediatric meningiomas compared with 2–7% in adulthood [14, 18- 20].

Dural attachment absence may be due to that the tumor genesis from leptomeningeal elements lodging within the brain parenchyma or the ventricles. MRI characteristics of paediatric meningiomas are similar to adulthood. On MRI, the tumors are usually isointense to hypointense on T1-weighted imaging, isointense to hypointense on T2-weighted imaging and exhibit good contrast enhancement [8]. Heterogeneous enhancement was seen in malignant meningiomas. The symptoms of paediatric meningiomas are nonspecific, variably according to its location and size. Headache is the most common symptom of paediatric meningiomas [9-19, 34-55, 61-79, 88-94, 158-169], and epilepsy is another common symptom. Previous literatures reported that the incidence of epilepsy was about 25–35%, and most related to the supratentorial cases [11, 13]. It is no noticeable physical characteristics to discriminate meningiomas from other diseases which could increase the intracranial pressure. Chronic increased intracranial pressure can also induce increased head circumference and late fontanel closure in younger children [11-13, 26, 30, 44, 50, 59-67, 78-85, 114-119, 125-136, 143-159, 168-177]. Cranial nerve dysfunction was caused by local compression and increased intracranial pressure, usually involving the II, III, IV, VI, VII and VIII nerves [11]. Surgical operation is the fundamental treatment for intracranial meningiomas. Complete tumor resection is the best choice to prevent recurrence and improve the prognoses. Surgical resection in paediatric meningiomas is a neurosurgical challenge considering their difficulty of early diagnosis, larger size at presentation, relatively less blood volume in children, occurrence of unusual location, tight adherence to vital vessels and nerves, and the various risks due to prolonged surgery like hypothermia, massive blood transfusion, etc. [11, 21]. Microsurgical techniques should be performed for each childhood tumor. The lesion and dural origin/attachment should be removed totally because the higher recurrence risk. Control of hemorrhage intraoperative and especial intensive care postoperative is necessary. The WHO classification divides meningiomas into three grades: grade I, benign; grade II, atypical; and grade III, anaplastic/malignant [2, 15]. The histology of the meningiomas is different between childhood and adulthood. The ratio of malignancy in paediatric

meningiomas is 7–16%, significantly higher than in adulthood [11, 20, 23]. The influential factors for recurrence include location, histological features and extent of surgical removal. [9-34, 56-76, 90-98, 114-132].

From previous studies, the prognosis of PM was worse than that of adults. A conservative therapy is unacceptable in PM. Meningiomas in children could grow very large without specific symptoms. It is usually too late to perfect operation until symptomatic appear. Adjuvant postoperative focal or systematic radiotherapy still remains controversial for younger patients. Uncertainty in prognosis, little evidence to support and the potential adverse long term effect on brain function were the major reasons. Ionizing radiation also is one of the important reasons for childhood neoplasm pathogenesis. Those patients should consider receive radiotherapy if their tumors were malignant or recurrent and couldn't be removed completely. Only one child underwent recurrence and anaplastic variant meningioma received radiotherapy, but died after 9 months because of cerebral hernia. Chemotherapy was not considered in the treatment of meningiomas.

PM are relatively uncommon and slight predominantly in males. These PM are rare in the first decade of life. They usually have larger size, higher pathologic grade and unusual location compared with adult meningiomas. Symptoms of PM are nonspecific, variably according to its location and size; influential factors of recurrence include location of the lesion, histological features and extent of surgery. Complete tumor resection is the choice to prevent recurrence and improve the prognoses.

Meningiomas are central nervous system neoplasms derived from arachnoid cap cells of the arachnoid villi [1-9]. They are the second most common brain tumors after gliomas, constituting 20% of all intracranial tumors. The annual incidence is 2.3-3.1 per 100,000, but many lesions are asymptomatic. Most of them (90%) are benign, slow-growing tumors that commonly arise between ages 40-70 years. There is a female-to-male predominance of 2:1 in adults [13-29]. Meningiomas are relatively uncommon in childhood, representing 1-2% of all intracranial tumors in children [4, 18, 33, 45-60, 77-89, 116-126, 138-144, 169, 177, 179]. Previous studies indicated that childhood meningiomas have different locations and behavior compared with those of adults.

Intracranial meningiomas in children and adolescents are rare tumors. In most large series, the incidence of meningiomas before the age of 16 years ranges from 0.4% to 4.6% of all primary brain tumors in this age group. [1-10] They account for 2% of all intracranial meningiomas. [2, 10-14] In the past, meningiomas in children have been considered histologically more aggressive than those in adults. [12-18] However, recent studies do not support this assertion; thus, we analyze all of the possible factors responsible for this discrepancy.

In addition, we described the peculiar aspects of meningiomas in children on the basis of a large pool of data obtained from a review of 440 cases collected from the pertinent literature, to which we added 19 of our own cases. Intra-axial (intraparenchymal) meningiomas are an extremely rare pathology with only dozens of cases reported. In children, the unusual characteristics of intraparenchymal meningiomas can easily create an atypical preoperative differential. A rare case of an otherwise healthy 14-year-old girl presenting with new-onset seizures and an intracranial lesion upon investigation. CT and MRI revealed a lesion both cystic and calcified in nature, residing completely within the brain parenchyma. Upon operative examination, the mass was found to be completely surrounded by cortex and to be of two disparate consistencies. Pathological analysis revealed the mass to be a meningioma. Despite the rarity in children, meningiomas must be kept on the differential for cystic, calcified lesions. The differential diagnosis based on imaging as well as the operative strategy taken are further discussed. In addition, the authors review the current understanding of paediatric meningiomas as compared with adult tumors. Imunohistochemically, the paediatric meningiomas are EMA and vimentin positive, GFAP negative, [13]. Surgical excision has been the treatment of choice for this kind of tumors. Surgical management poses a formidable challenge considering their peculiar location, larger size at presentation and relatively less blood volume in children. Overall, most series have shown a high incidence of atypical and anaplastic meningiomas in children as compared to the adult population. In the literature, adjuvant therapy has been advised in these patients in the form of radiation therapy [6-19, 23-45, 78].

Though, no chemotherapy or radiotherapy was given to patient despite the atypia due to non cooperation of the patient in case 1 of the huge anterior fossa tumor. Literature has shown that in different series recurrence rate of approximately 13% [9, 19, 146, 178-189, 199-204].

Recurrence seems to be strictly related to incomplete resection and/or histological subtype of the meningioma. Atypical, aggressive and meningiomas with cortical invasion show a higher rate of recurrence. This patient was followed up closely and had not shown any recurrence even after 4 years, might be due to total removal of the mass by the surgeons carefully.

Meningioma is usually attached to the dura and thought to arise from the arachnoid cap or meningothelial cells. It is reported that the frequency is less than 5% of all paediatric brain tumors [3-12]. Its incidence as reported by Mendiratta et al. [2-19, 67] is 1.5% of total meningiomas seen in the population. Children with meningiomas commonly present late in the first decade or early in the second decade of life [5-16]. Meningioma generally differs in various clinical and biological aspects from meningioma in the adult population [6-19]. Risk factors for meningioma include: radiation treatment, female hormones and inherited nervous system disorders. In contrast to adult meningioma, where a female preponderance is seen [7], paediatric tumors show a distinct male predominance [5]. The greater occurrence of meningioma in males could be related to an absence of the effect of sexual hormones on corticosteroid receptors in meningioma cells for low blood concentrations [8].This suggests that different pathogenic factors might account for the occurrence of meningioma in children and adults. Some studies on genetic aberrations in meningioma in children show no differences from meningioma in adults.

Signs and symptoms related to raised intracranial pressure (ICP) following obstruction of the cerebrospinal fluid circulation are most common in childhood meningioma due to the involvement of ventricles (12%) [9-19, 28-33, 35, 56, 78, 88, 99-112, 119, 123, 143, 200-204] as compared to 0.5-4.5% in adult [10-19, 28-44, 56-67, 79-88, 145-165, 170-188]. Though ventricle was not the site of involvement in our case and the patient presented with only GTCS without any evidence of raised intracranial pressure.

In the literature, 0-41% of childhood meningioma is associated with neurofibromatosis (NF) [5]. Meningioma shows characteristic imaging features that include broad-based dural attachment, signal changes in the skull due to tumor infiltration, sharp demarcation between the tumor and the brain, mass effect on adjacent brain tissue and homogeneous enhancement of a contrast agent [11]. The site of origin provides a clear diagnosis in most cases, which often facilitate their diagnosis without the need of invasive diagnostic procedures.

The clinical outcome is available in only 267 cases, with a mean follow-up of 4.2 years. [14, 19-27, 91-99, 102-111] In 13% of these cases, tumor recurrence is described. [19-20, 97-108] Recurrence seems to be strictly related to incomplete resection and/or the histologic subtype of the meningioma: 54% of the recurring meningiomas were removed subtotally and 46% totally. Most of the latter were malignant or malignant variants; more precisely, 31% were anaplastic, 15% atypical, 10% papillary, and 10% sclerosing with brain invasion. The remainder were angiomatous (5%) and not invasive (26%). One of these latter cases was previously irradiated. One of our patients and another one reported in the literature [92] were affected by von Recklinghausen disease. Our patient had bilateral acoustic neurinoma 15 years after the operation without recurrence of meningioma, and the patient described in the literature had a recurrence of tumor. We found no other factors predisposing patients to the development of meningioma.

With regard to radiation-induced meningiomas, there are some differences when compared with both the spontaneous counterpart and radiation-induced meningiomas in adults. First, in paediatric post irradiation meningioma, there is a female to male ratio of 1.7:1. This female predominance is similar to that of meningiomas in adults, but it contrasts to the absence of a sex predominance observed in spontaneous paediatric meningiomas. Second, the rate of post irradiation meningiomas in children with aggressive behavior is similar to that in adults (15% vs 18.8%) but contrasts to the behavior of spontaneous meningiomas in children. Third, the latency period between irradiation and the diagnosis of meningioma tends to be shorter in paediatric patients than in adults. The latency period between RT and clinical onset of meningioma in the paediatric population is 9 years (2-15 years) versus 21.9 years in adults. The incidence of cystic changes is commonly seen in meningioma of children [12-19, 28-36, 44-49].

8. CONCLUSIONS

Meningiomas occur most commonly in the fifth decade of life, accounting for approximately 15-20% of primary intracranial tumors. Meningiomas in children and adolescents are rare tumors. In most large series, the incidence of meningiomas before the age of 16 years ranges from 0.4 to 4.6% of all primary brain tumors in this age group and 1.92% of total menigiomas. [1-9]

The female preponderance found in adult patients is not seen in children, the reported male- to-female ratio in children being 1.2:1.

Risk factors for the development of paediatric meningiomas include the diagnosis of NF-2 and a history of radiation therapy, the so-called radiation- induced meningiomas. [1, 11, 18-33, 44-57]

Meningiomas in children show some characteristic differences when compared with their adult counterparts. These include slight preponderance in male subjects, higher incidence of intraventricular and skull base location, and frequent cystic changes.

Paediatric meningiomas tend to present with features of raised intracranial pressure and seizure; they should be considered for early neurosurgical treatment and diligent follow-up.

Meningiomas in children have been considered by some to be more aggressive than their adult counterparts. [13–16] Total surgical excision should be performed wherever feasible, even if it requires staged resection. Advances in microneurosurgical and anesthesiological management have considerably reduced the operative morbidity and mortality.

There is a higher incidence of atypical and aggressive histological subtypes in the paediatric population. Children with complete resection of meningioma and a typical benign histology have a good prognosis like their adult counterparts.

As in adults, the great majority of meningiomas in younger patients are supratentorial. Histological types and features are similar to those observed in adults.

As meningiomas developing in the first two decades of life have a low recurrence rate after gross total resection, and the outcome and survival rate are excellent and very satisfactory.

In contrast to adults, the majority of survivors of child and adolescent meningioma had no or only mild long-term morbidity. However, 25% of patients had moderate=severe long-term neurologic morbidity. Given that the risk of morbidity is significantly increased in patients with relapsed disease and that, in the majority of patients, morbidity occurs as a consequence of the tumor itself, we conclude that aggressive surgery to achieve gross total resection is warranted. However, for children and adolescents with neurofibromatosis and for those with meningioma of the skull base, a more cautious surgical approach should be observed. Different series in the literature have shown a recurrence rate of approximately 13%. [22] Recurrence seems to be strictly related to incomplete resection and/or histologic subtype of the meningioma. Atypical, aggressive, and meningiomas with cortical invasion show a higher rate of recurrence.

Intraventricular meningioma is a rare neoplasm, more common in children and representing 0.5–3 % of all intracranial meningiomas [1-24]. Moreover, it's extremely rare to see a metastasis of meningioma cells (malignant meningioma), via cerebrospinal fluid (CSF) dissemination, involved in the diverse central nervous system (CNS) structures, such as cerebellum, multiple cranial nerves, spinal nerve roots and the cauda equina [2–4]. It is extremely rare to see cerebrospinal fluid dissemination of intraventricular meningioma, particularly with the development of acute, progressive brainstem / cerebellar dysfunction with an absence of mass formation in the corresponding anatomical sites.

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