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Review Article

High-grade (WHO Grades II and III) Cranial Meningiomas in Paediatric Practice: A Review

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Abstract

Background and Objective: Although the clinico-histologic features, radiological findings and management of benign paediatric cranial meningioma are well documented, the biological nature of its high-grade counterparts remains uncertain. Of late, numerous studies on atypical and malignant morphologies of this tumour have been published. This review focuses on the clinical course, treatment, biological behaviour and prognostication of these high-grade lesions.

Material and Method: Retrospective observations and analysis of the literature (in English) were made on high-grade paediatric cranial meningiomas published between 1991 and November 2016. Using Medline and PubMed database, a search was conducted using the search terms: "paediatric", "malignant", "meningioma", "radiology", "therapy", and "prognosis".

The core material consisted of 24 case-reports and 6 published series on paediatric anaplastic cranial meningiomas and their variants (WHO Grade III) and 17 case studies on the WHO Grade II categories. Forty-four publications on the malignant potentials and risk factors of cranial meningiomas in the paediatric and adult population are also included.

Results: Forty patients in the WHO Grade III group had anaplastic lesions. Eleven had died, including 3 with papillary meningiomas and 2 who harboured the rhabdoid forms. Research is directed at the causative factors in transformation of benign meningiomas to malignancy. This is mediated through a complex interacting process with chromosome instability caused by epigenetic factors as the most relevant.

The WHO Grade II group consisted of both clear cell and chordoid meningiomas. The latter are commoner, usually affecting young adults. Of 8 children with chordoid meningiomas, one died from disseminated metastases despite radical excision and radiotherapy. Where surgical removal of a meningioma is incomplete its recurrence invariably turns into a higher grade. Such biological behaviour typifies those meningiomas manifesting as part of Neurofibromatosis 2.

Conclusion: For high-grade meningiomas radical excision to ensure a prolonged recurrence free survival period is the aim. Surgical approaches are dictated by lesional locations: skull base and intraventricular tumours are at risk for incomplete removal. Adjuvant radiotherapy is only offered to children with recurrent disease.

Keywords: *Childhood; Malignant; Cranial Meningiomas; Imaging; Surgery; Prognosis*

Abbreviations

WHO: World Health Organization; RIM: Radiation Induced Meningiomas; CT: Computed Tomography; DSA: Digital Subtraction Angiography; NF2: Neurofibromatosis 2; MRI: Magnetic Resonance Imaging; ADC: Apparent Diffusion Coefficient; SEGA: Subependymal Giant Cell Astrocytomas; GTR: Gross Total Resection; CCM: Clear Cell Meningiomas

Introduction

Cranial meningiomas are uncommonly encountered in children and adolescents. Cushing and Eisenhardt described an incidence of 1.9% in children among 313 patients with meningiomas in their famed 1938 monograph [1]. A more recent surgical series documented

an incidence of 1.08% among children and adolescents operated on over a 15-year period (1985 - 2000) [2]. Thus, the overall prevalence of paediatric cranial meningioma has not changed in over 50 years.

Most meningiomas (80%) affecting adults are benign and are categorised as WHO Grade I [3]. In a recent series on 38 patients of paediatric and adolescent age, [4] 27 (63%) were histologically classified as WHO Grade I, 9 belonged to WHO Grade II and the remaining 2 (4.8%) were Grade III. In another publication [5] with 31 cases, 8 (26%) were Grade II and 3 (9%) belonged to the anaplastic category (Grade III). Wang X., *et al*. in 2012 published the largest collection of WHO Grade III childhood meningiomas [6]. Of their 8 cases, 4 were anaplastic while 3 belonged to the papillary category, the last being a rhabdoid form of the tumour. Malignant meningiomas in this age group are therefore uncommon. Since our insight into their biological behaviour is still limited, they pose a challenge in management. The study of these malignant variants and those in WHO Grade II category forms the basis of this review.

Materials and Methods

A search of the MEDLINE and PubMed databases was performed on paediatric cranial meningiomas in the English language from 1991 to November 2016. The following keywords were used: "paediatric", "meningioma", "malignant", "radiology", "therapy", and "prognosis". Of the 95 articles found in the primary search, 85 met the criteria; 5 review papers in the latter were used as sources of reference.

Results and Discussion

The core material consisted of 40 cases of paediatric anaplastic cranial meningioma and its variants (WHO Grade III). There were 17 other studies belonging to WHO Grade II category. Eight chordoid and 6 clear cell meningiomas, together with 3 case-reports on the atypical subset, formed the balance of this Grade II group. Forty-four publications on the biological behaviour of adult and paediatric cranial meningiomas focusing on potentials for malignancy, surgical risks, histo-morphologic and genomic profiles in predicting post-therapy recurrences were also included.

WHO Grade III Cranial Meningiomas

(Anaplastic meningiomas, papillary and rhabdoid forms; meningeal sarcomas)

The following discussion aims at distinguishing the features between the above-mentioned 3 main variants of WHO Grade III meningiomas. Meningeal sarcoma is added on account of its unrelentingly adverse clinical course. In adults, the anaplastic meningiomas are defined by a histological picture of frank malignancy typified by the presence of 20 or more mitosis per ten high power fields [7]. The classic anaplastic tumours have a recurrence rate of 50% to 94% [7] and a 5-year disease free survival rate of 34% to 53% [8]. This anaplastic category also includes the subgroups of papillary meningioma and meningeal sarcomas. Researchers in genetics have identified frequent loss of chromosome 9p and amplification of 17q23 among anaplastic meningiomas [9]. Conceivably, the progress from low-grade to anaplasia over time is an expression of the tumour's chromosomal instability, possibly driven by other epigenetic factors [9].

A common variant of anaplastic meningioma is the papillary form. Histologically, it is defined by a characteristic peri-vascular and pseudo-rosette pattern interspersed with meningothelial cells [3]. At immunohistochemistry, a raised MIB-1 labelling index is the most crucial factor indicative of an increased risk of recurrence [3]. In accordance with the observations by Kros JM., *et al*. the tumour had a tendency to metastasise [10]. They stated that papillary meningiomas mostly involved adult males with a median age of 34-years (range 28-40 years). Contrarily, Riemenscheider M., *et al*. [3] considered the tumour to be commoner in children. However, a literature search has shown a limited number of detailed reports in children. For example, over a period of 16 years, among 23 children examined at the Philadelphia Children's Hospital, only a single case treated with surgical excision and adjuvant radiotherapy was ever encountered [11]. The most comprehensive series stemmed from Wang XQ., *et al.* [6] who presented 3 patients in whom 1 (a 5-year-old girl) had succumbed to widespread metastases. This had given credence to the postulation that one of the ultimate clinical outcomes of this tumour is metastatic disseminations [12]. This paper illustrated an adolescent female harbouring a rare cystic papillary meningioma in the lateral ventricle that revealed classical peri-vascular, pseudo-papillary pattern at histology. The final stage of her condition was characterised by subarachnoid space dissemination. Another report was on a 3-year–old boy who had a posterior fossa lesion treated with gross total resection. But

he suffered a recurrence with ensuing disseminated intracranial and spinal leptomeningeal metastases. The tumour's histo-morphology showed papillary architecture, becoming more distinctive in the recurrences [13]. Yet in another case report of a 13-year-old boy with a left posterior fossa tentorial papillary meningioma, the authors emphasised on the tumours infrequency in children [14]. Finally, in discussing the clinical condition of a 16-year-old boy with a similar papillary tumour, the authors [15] referred to a series dating back to 1975. Based on this source, they quoted an incidence of 47% in children. There was a 5-year survival rate of only 40%, these figures relating to both adults and children [15].

Among children the commonest form of intracranial sarcoma is rhabdomyosarcoma. In clinical practice this tumour is so rarely seen there is a lack of consensual treatment regime. The usual victims are children of pre-school age [16,17]. The lesion can be cruelly devastating to those affected. Of the 3 children with middle cranial fossa rhabdomyosarcoma, 2 died within 1 year following gross total resection and the third succumbed to aggressive tumour recurrence after 3 years [18]. In summary, irrespective of age, all forms of intracranial sarcomas are grossly malignant: the 5-year progression free and overall survival rates are stated to be 21% and 44% respectively [19].

Although of similar malignant potentials with anaplastic forms, rhabdoid meningioma (WHO Grade III) has only been recently regarded as a distinct entity [20]. But there are exceptions to its usual aggressive clinical course [21]. These investigators showed that up to 50% in their cohort lacked anaplastic features. At least 22 of their 44 cases were found to have a low percentage (< 20%) of rhabdoid cells: in consequence, they were categorised as WHO Grade I tumours [21]. A ground-breaking study described the gradual transformation of benign cellularity of a WHO Grade I meningioma to one of rhabdoid malignancy [20]. These researchers advocated the concept of a gradual "take over" of the histo-morphology of a benign meningioma by rhabdoid cells. In time the lesion assumed the clinical aggressiveness of a rhabdoid lesion when the transformation neared completion.

Since the classic paper by Kepes., *et al*. [20] and his group, there have been other publications in support of their arguments that rhabdoid meningiomas predominantly occurred in recurrent meningiomas that were originally benign. Significantly these recurrences had been subjected to resections on multiple occasions [22]. Moreover, the rhabdoid histo-morphology was only detectable in these recurrences. For the past two decades research on rhabdoid meningiomas had focused on adult patients, as the condition primarily affects the middle-aged and geriatric population. In their series of 15 adult patients, 13 (87%) had suffered at least one recurrence and 8 died from the disease in a median time to death of 5.8 years [22].

It is only of late that case reports on paediatric cranial rhabdoid meningiomas have appeared in the literature [23]. These authors noted the tumour cells had a characteristic globoid appearance with eosinophilic cytoplasm and peripheral nucleic. The rhabdoid morphology dominated the histologic picture typified by abundant cytoplasm and occasional intranuclear pseudo inclusions. Contrary to adults the disease occurs infrequently in children and adolescents and only 11 cases had been reported since 2010 [24]. Of the 11 cases in this survey, there was only 1 recurrence at 4 months post-surgery. Only 1 patient death was recorded 25 years post-surgery. Although the case series was small in number, the authors [24] suggested that the outcome among children with rhabdoid meningiomas seemed better than those of the adults. Yet on the odd occasion the tumour's presentation bordered on baffling. It involved a 9-year-old boy with intermittent symptoms of a chronic infection probably associated with a vasculitic process. Ultimately, it was discovered that an atypical meningioma that transformed into a rhabdoid form had caused his illness. He recovered following its excision. It was argued the presence of pyrogenic cytokines within the tumour cells enabled production of the enzymes IL-6 and TNF that caused his symptoms [25].

Clinical Presentations

The Main Features

The initial presentations of High-Grade meningiomas are no different from those of the benign category. Thus, headache is a common manifestation of obstructive hydrocephalus irrespective of WHO grades, either benign [26] or malignant [27]. Nausea and vomiting due to raised intracranial pressure are equally common. There can be visual disturbance due to cranial nerve involvement [5]. A clonic, tonic seizure, a sign of cortical irritation, has been encountered in a child with rhabdoid meningioma [28]. Occasionally a malignant lesion causes asymmetrical enlargement of the head from tumour pressure of the skull vault [29]. At other times the child has a non-tender boggy,

swelling of the scalp tissues [28,30,31]. A tense frontal fontanelle, poor control of the head and prominence of the scalp veins, are signs of intracranial hypertension [32]. Parents may also notice an unusual increase in head circumference. Occasional seizure and gait disturbance is not an uncommon manifestation: this was illustrated in a 4-year-old girl harbouring a giant (7.8 cm diameter) meningioma in the atrium of her left lateral ventricle [33]. Infrequently, there is an exacerbation of a chronic headache that was an expression of an acute intra-tumoural haemorrhage [16]. The main complaint can be a failure to thrive as in the case of a 14-yer-old boy with a fourth ventricular clear cell meningioma [34]. Or the prime clinical scenario is an arrest in psychomotor development [32]. And in the odd presentation of headache accompanied by involuntary eye flickering in an 8-year-old boy, imaging revealed a 7 cm diameter parasagittal tumour that was confirmed as an atypical meningioma at histopathology [35]. Therefore, one must be alert to non-specific symptoms that can delay diagnosis for children too young to express their distress [33].

Other Crucial Factors

In any work-up on a child or adolescent with clinical suspicion of a cranial meningioma, obtaining an accurate history is essential. Although childhood meningiomas as a manifestation of Neurofibromatosis 2 (NF2) are uncommon compared to their adult counterparts, emphasis should be placed on the high incidence of aggressive behaviour in this subset of meningiomas [36]. According to Evans DGR., *et al*. [37] meningiomas are present in 53% of patients with NF2. Moreover, in NF2, meningiomas can be multiple with some situated in the skull base and parasellar regions [6]. These NF2 associated cranial lesions are genotypically and phenotypically aggressive with high percentages of anaplasia (11%), recurrences (39%) and patient death (17%) [36]. With the high incidence of undiagnosed NF2 in the paediatric population, a thorough search for other stigma is indicated [36]: a familial history is the starting point. Physical examination focuses on skin lesions such as intra-cutaneous nodules and slit lamp examination of the lenses for juvenile cataracts. Audio-vestibular testing and a full contrast enhanced MRI study of the cranio-spinal axis for a second lesion complete the basic investigations [38].

In recent times a growing number of adolescents and young adults with documented histories of radiotherapy for past brain tumours are presenting with a second neoplasm, which in the main are cranial meningiomas. Radiation induced meningiomas (RIM) are the by-products of our success in the treatment of childhood brain cancers. Soffer., *et al.* [39] introduced the concept that exposure to therapeutic irradiation at a very young age predisposed to induction of malignant meningiomas rather than benign ones. It follows that such RIMs were inclined to be biologically aggressive. In another paper that analysed 440 cases from the literature, Caroli *et al.* in 2006 [40] strengthened these arguments by concluding that malignant forms of meningiomas in children are common among RIMs. In addition, the detailed case studies by Muller HL., *et al.* [41] have given credibility to Caroli's [40] observations. Thus, of their 5 cases, 2 were in the WHO Grade III category, the third was Grade II while the other 2 were Grade I. Caroli [40] and colleagues pointed out the younger the child to receive a high-dose irradiation the shorter the latency period for the formation of RIM, an experience shared with another group [42]. They described an 11-year-old boy who developed multiple fronto-basal atypical meningiomas 14 months after treatment of a posterior fossa medulloblastoma with craniospinal irradiation.

Radiological Findings

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 researchers [43] had attempted to use Computed Tomography (CT) findings to characterise malignant cranial meningiomas. Such endeavour has since been revisited [44]. Thus, presence of intra-tumoural low densities, a sign of necrosis, is suggestive of malignancy. Similarly, skull vault erosion by a heterogeneously enhancing mushroom-shaped tumour with fringed margins is strongly indicative [44]. 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 4 showed skull vault and scalp erosions on CT or Magnetic Resonance Imaging (MRI) [28,30,31,45].

Since a paper by Mattei T., *et al*. [46] in 2005, it has become routine practice to correlate histologically benign and malignant meningiomas with the extent of peritumoural 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 [28,52], while others had survived with the aid of surgery and radiotherapy [51]. 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 [24]. In consequence, his tumour 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 advent of 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 tumours 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 tumour 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 Diffusion Weighted MRI in recent years makes it possible to differentiate WHO Grade I meningiomas from those in the higher grades. Recent papers by Surov., *et al*. [55] and Nagar., *et al*. [56] have shown, in adult patients, that WHO Grade II and III tumours 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 water and space that in turn is manifested as reduced ADC values. Benign tumours retain their intracellular water; in consequence, their ADC values remain high [57]. The use of diffusivity of water in tumour 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 tumours 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.

Cerebral Angiography

The versatility of contrast enhanced MR angiogram has made it almost redundant to employ cerebral DSA as a surgical road map in children. But in situations where the tumour is at the skull base or shown to be highly vascular on contrast enhanced MRI, then a pre-operative embolisation of the arterial feeders may be indicated. 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 embolisation was performed prior to complete excision of the tumour [5].

Surgery

The main aim of surgery is complete resection of the tumour [5,60]. This surgical principal stems from the fact that recurrences invariably arise from the residual disease [6,60]. Recurrent tumour tends to become one of a higher grade [6,40,60]. Recurrence of a benign meningioma that eventually transformed into a malignant rhabdoid meningioma had also been documented [61]. Unfortunately, tumour location dictates the surgical approach. It might not be possible and prudent to completely excise a parasellar meningioma with bilateral cavernous sinus extensions. A subtotal resection was therefore performed to preserve cranial nerve function [62].

A child's frailty and limited physical reserves are factors that contribute to potential complications in paediatric neurosurgery [60,62]. To take an extreme example, blood loss in surgery of an intraventricular meningioma can amount to between 600 to 2,000 ml [26]. Yet by

meticulous dissection a vascular anaplastic intra-parenchyma meningioma near to the convexity was completely excised without resorting to pre-operative embolisation [51]. Although pre-operative embolisation has its value, there are risks and limitations to this technique [59]. The child's tiny vessels pose challenges in selective catheterisation. Thus, the fine ethmoidal arteries along the anterior cranial fossa are not suited for embolisation [59]. There is also the limited amount of intravascular contrast an interventionist can use. It is debatable to use this procedure in young children with potential complications of stroke and intra-tumoural haemorrhage [59]. In another series of 8 patients with skull base/cerebello-pontine angle lesions, none was subjected to pre-operative embolisation [6]. However, when performed efficiently, embolisation can reduce the amount of intra-operative blood loss [63].

Paediatric skull base surgery demands a surgeon's vigilance. The surgical approach should consider the un-erupted dentitions, the developing basicranium and the potential for long-term effect to the cranio-facial anatomy of these children [62]. There is the shallowness of the anterior cranial fossa and developing paranasal sinuses to contend with when a frontal surgical approach is used [64].

WHO Grade II meningiomas

(Atypical cranial meningiomas and 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: in retrospect, 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]. 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 [60]. In most large paediatric series, the incidence of atypical meningiomas ranges from 9.1% [66] to 26% [67]. 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 [68].

Chordoid Meningioma is a malignant variant of meningioma with an incidence of 0.5% of all meningiomas in adults. The tumour 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] only 2 of 42 patients affected were children. In another series of 12 children with WHO Grade II cranial meningiomas [6] 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 tumours 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 tumour's histological pattern and CT features were analysed in detail. The basic histo-morphologic structure consisted of a meningothelial cellular pattern mixed with tumour 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]. It remains essentially a tumour of the adult population. In accordance with a survey by a Canadian group in 2014 [72], 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 me-

ningioma [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 tumour 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]. 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 tumour and radiotherapy to the whole of the neural axis [76]. 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]. It was uncertain her past history of surgical excision and irradiation of an abdominal Wilms tumour 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 [78] in which the age group comes closest to that of children, gross total resection (GTR) is considered the strongest predictor of tumour control while tumours 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 has been 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 tumour 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 tumours 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].

Cytologically, CCM possesses whorled syncytial architecture with bland-looking nuclei. 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]. Immunohistochemical analysis will reveal positivity in the vimentin and epithelial membrane antigens while S-100 staining is negative. Ki-67 proliferative index can be elevated to 10% in some cases but may not necessarily correlate with tumour aggressiveness [79]. While describing CCM's rather innocuous histological appearance, one group [81] 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 tumour 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 tumour 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].

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 [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 tumour at the cerebello-pontine angle on MRI were strongly indicative of Castleman's syndrome. Excision of the tumour 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 [79]. The uniqueness of childhood and adolescent CCM is that in only 4 instances were the tumours situated in the supra tentorial compartment. The CP angle is site of origin in up to 48% of cases [79]. 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 [6]. 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 had been fully 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 tumour's WHO Grade II classification [79]. This research group had identified a mutation of the SMARCE1 gene that could implicate in establishing peculiar clear cell histology of CCM.

Treatment and Prognostication

Complete tumour extirpation is paramount in preventing recurrence for patients in all age groups. In children and adolescents, the extent of surgical resection is the prime prognostic indicator. Through the application of immunohistochemistry certain biomarkers are created to predict the clinical course of malignant diseases. Thus, the MIB-1 labelling Index can identify the likelihood of recurrence in high-grade tumours. A negative progesterone index in combination with a positive Bcl-2 immunoreaction might be predictive of tumour recurrence [6]. The use of adjuvant radiotherapy in a clinical setting of recurrent/residual disease for children with surgically inaccessible skull base locations such as the suprasellar and petro-sphenoid regions has been highlighted [62]. There are risk factors in patients suffering meningiomas associated with NF2. A close watch should be paid for those with this clinical history. That patients with NF2 have an increased incidence of malignant transformation in recurrences is well documented. They belong to a special risks category and need life-long follow-up [84].

Chemotherapy had not been absolutely safe or effective in treating paediatric high-grade meningiomas. Nonetheless, one report of an anaplastic lesion with extensive lymph node metastasis in the upper neck in an 8-year-old boy did slow the lesion's progress following a course of chemotherapy specific for soft tissue sarcomas [49]. In a novel form of molecular targeted therapy, a 6-year-old girl with wide spread leptomeningeal metastasis caused by a cranial rhabdoid meningioma, had her disease arrested after treatment with BRAF inhibitor. The attending oncologists had used comprehensive genome profiling and found genomic alterations in the form of activating BRAF mutation (V600E) [85].

Conclusion

Although the follow-up periods (ranging from 3 to 60 months) of patients in the case-reports and published series in this review are short, they have disclosed rare insights into the biological behaviour of high-grade cranial meningiomas in the children and adolescents. The clinico-pathologic and radiological findings are crucial in their diagnostic work up and therapeutic strategies. Current trends focus on the genomic influence on cranial meningiomas with chromosome instability, being associated with high-grade meningiomas. There are other genetic mutations that inform us more on their histological phenotypes and clinical outcome. This enables us to counsel those affected more constructively.

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Conflict of Interest

The author has no conflict of interest to disclose.

Dedication

To Shirley, my wife and my rock

Bibliography

1. Cushing H and L. Eisenhardt. "Meningiomas: Their Classification, Regional Behavour, Life History and Surgical End Results". Charles C. Thomas Springfield (1938).

2. Amirjamshidi A., *et al*. "Meningiomas of the Central Nervous System Occurring Below the Age of 17: Report of 24 Cases Not Associated with Neurofibromatosis and Review of Literature". *Childs Nervous System* 16.7 (2000): 406-416.

3. Riemenschneider MJ., *et al*. "Histological Classification and Molecular Genetics of Meningiomas". *Lancet Neurology* 5.12 (2006): 1045-1054.

4. Menon G., *et al*. "Childhood and Adolescent Meningiomas: A Report of 38 Cases and Review of Literature". *Acta Neurochirurgica* 151.3 (2009): 239-244.

5. Ravindranath K., *et al*. "Management of Pediatric Intracranial Meningiomas: An Analysis of 31 Cases and Review of Literature". *Childs Nervous System* 29.4 (2013): 573-582.

6. Wang XQ., *et al*. "Clinical Features and Treatment of World Health Organization Grade II and III Meningiomas in Childhood: Report of 23 Cases". *Journal of Neurosurgery. Pediatrics* 10.5 (2012): 423-433.

7. Backer-Grondahl T., *et al*. "The Histopathological Spectrum of Human Meningiomas". International Journal of *Clinical and Experimental Pathology* 5.3 (2012): 231-242.

8. Lim YS., *et al*. "Long Term Clinical Outcomes of Malignant Meningiomas". *Brain Tumor Research and Treatment* 1.2 (2013): 85-90.

9. Bi WL., *et al*. "Genomic Landscape of Intracranial Meningiomas". *Journal of Neurosurgery* 125.3 (2016): 525-535.

10. Kros JM., *et al*. "Papillary Meningioma with Pleural Metastasis: Case Report and Literature Review". *Acta Neurologica Scandinavica* 102.3 (2000): 200-202.

11. Perilongo G., *et al*. "Childhood Meningiomas. Experience in the Modern Imaging Era". *Pediatric Neurosurgery* 18.1 (1992): 16-23.

12. Zhi L., *et al*. "Cystic Papillary Meningioma with Subarachnoid Dissemination: A Case Report and Review of the Literature". *Pathology, Research and Practice* 205.8 (2009): 582-587.

13. Bouvier CMD., *et al*. "Cerebellar Papillary Meningioma in a 3-Year-Old Boy: The Usefulness of Electron Microscopy for Diagnosis". *American Journal of Surgical Pathology* 23.7 (1999): 844-848.

14. Miyajima Y., *et al*. "Tentorial Papillary Meningioma in a Child: Case Report and Review of the Literature". *Clinical Neuropathology* 26.1 (2007): 17-20.

15. Avninder S., *et al*. "Papillary Meningioma: A Rare but Distinct Variant of Malignant Meningioma". *Diagnostic Pathology* 2 (2007): 3.

16. Guilcher GM., *et al*. "Successful Treatment of a Child with a Primary Intracranial Rhabdomyosarcoma with Chemotherapy and Radiation Therapy". *Journal of Neuro-Oncology* 86.1 (2008): 79-82.

17. Lee JY., *et al*. "Primary Meningeal Rhabdomyosarcoma Associated with Chronic Subdural Effusion: Case Report". *Journal of Neurosurgery. Pediatrics* 5.2 (2010): 167-171.

18. Mandonnet E., *et al*. "Spectrum of Skull Base Tumors in Children and Adolescents: A Series of 42 Patients and Review of the Literature". *Childs Nervous System* 24.6 (2008): 699-706.

19. Maher OM., *et al*. "Primary Intracranial Soft Tissue Sarcomas in Children, Adolescents, and Young Adults: Single Institution Experience and Review of the Literature". *Journal of Neuro-Oncology* 127.1 (2016): 155-163.

20. Kepes JJ., *et al*. "Rhabdoid Transformation of Tumor Cells in Meningiomas: A Histologic Indication of Increased Proliferative Activity: Report of Four Cases". *American Journal of Surgical Pathology* 22.2 (1998): 231-238.

21. Vaubel RA., *et al*. "Meningiomas with Rhabdoid Features Lacking Other Histologic Features of Malignancy: A Study of 44 Cases and Review of the Literature". *Journal of Neuropathology and Experimental Neurology* 75.1 (2016): 44-52.

22. Perry A., *et al*. ""Rhabdoid" Meningioma: An Aggressive Variant". *American Journal of Surgical Pathology* 22.12 (1998): 1482-1490.

23. Martinez-Lage JF., *et al*. "Rhabdoid Meningioma: A New Subtype of Malignant Meningioma Also Apt to Occur in Children". *Childs Nervous System* 22.3 (2006): 325-329.

24. Buccoliero AM., *et al*. "Pediatric Rhabdoid Meningioma: A Morphological, Immunohistochemical, Ultrastructural and Molecular Case Study". *Neuropathology* 31.1 (2011): 59-65.

25. Rittierodt M., *et al*. "Evidence of Recurrent Atypical Meningioma with Rhabdoid Transformation and Expression of Pyrogenic Cytokines in a Child Presenting with a Marked Acute-Phase Response: Case Report and Review of the Literature". *Journal of Neuroimmunology* 120.1-2 (2001): 129-137.

26. Dash C., *et al*. "Pediatric Intraventricular Meningioma: A Series of Six Cases". *Journal of Pediatric Neurosciences* 11.3 (2016): 193-196.

27. Greenberg SB., *et al*. "Malignant Meningioma in a Child: CT and MR Findings". *AJR: American Journal of Roentgenology* 160.5 (1993): 1111-1112.

28. Kheshaifati H., *et al*. "Rhabdoid Meningioma with Lung Metastasis in a Paediatric Patient: A Case Report and Literature Review". *Journal of Health Specialties* 4.4 (2016): 301-305.

29. Ghosh R., *et al*. "Recurrent Skull Base Rhabdoid Meningioma in an Adolescent Patient". *Neurology India* 64.6 (2016): 1365-1369.

30. Kotil, K. "Extensive Invasion of Malignant Meningioma on the Scalp Case Report and Review of the Literature". *Istanbul Medical Journal* 11 (2010): 77-79.

31. Ludemann WO., *et al*. "Seeding of Malignant Meningioma Along a Surgical Trajectory on the Scalp. Case Report and Review of the Literature". *Journal of Neurosurgery* 97.3 (2002): 683-686.

32. Tomita T and Grahovac G. "Cerebellopontine Angle Tumors in Infants and Children". *Childs Nervous System* 31.10 (2015): 1739-1750.

33. Ciurea AV., *et al*. "Intraventricular Meningioma in 4 Years Old Child: Case Presentation". *Romanian Neurosurgery* 18.3 (2011): 306-309.

34. Burgan OT., *et al*. "Clear Cell Meningioma of the Fourth Ventricle in a Child: A Case Report and Literature Review". *Pediatric Neurosurgery* 46.6 (2010): 462-465.

35. Doxtader EE., *et al*. "Aggressive Pediatric Meningioma with Soft Tissue and Lymph Node Metastases: A Case Report". *Pediatric and Developmental Pathology* 12.3 (2009): 244-248.

36. Perry A., *et al*. "Aggressive Phenotypic and Genotypic Features in Pediatric and Nf2-Associated Meningiomas: A Clinicopathologic Study of 53 Cases". *Journal of Neuropathology and Experimental Neurology* 60.10 (2001): 994-1003.

37. Evans DGR., *et al*. "A Clinical Study of Type 2 Neurofibromatosis". *Quarterly Journal of Medicine* 84.304 (1992): 603-618.

38. Goutagny S and Kalamarides M. "Meningiomas and Neurofibromatosis". *Journal of Neuro-Oncology* 99.3 (2010): 341-347.

39. Soffer D., Gomori JM., Siegal T., Shalit MN. "Intracranial Meningiomas after High-Dose Irradiation". *Cancer* 63.8 (1989): 1514-1519.

40. Caroli E., *et al*. "Intracranial Meningiomas in Children: Report of 27 New Cases and Critical Analysis of 440 Cases Reported in the Literature". *Journal of Child Neurology* 21.1 (2006): 31-36.

41. Muller H. and Gebhardt U. "Meningioma as Second Malignant Neoplasm after Oncological Treatment During Childhood". *Strahlentherapie und Onkologie* 188.5 (2012): 438-441.

42. Choudhary A., *et al*. "Radiation Induced Meningioma with a Short Latent Period Following High Dose Cranial Irradiation - Case Report and Literature Review". *Journal of Neuro-Oncology* 77.1 (2006): 73-77.

43. New PFJ., *et al*. "Malignant Meningiomas: CT and Histologic Criteria, Including a New CT Sign". AJNR: American *Journal of Neuroradiology* 3.3 (1982): 267-276.

44. AL-Shalchy AK. "Malignant Features of Meningioma CT Scan Study". *Journal of the Faculty of Medicine, Baghdad* 52.3 (2010): 267-268.

45. Buschmann U., *et al*. "Uncommon Case of a Cystic Papillary Meningioma in an Adolescent". *Childs Nervous System* 21.4 (2005): 322-326.

46. Mattei TA., *et al*. "Edema and Malignancy in Meningiomas". *Clinics* 60.3 (2005): 201-206.

47. Gao X., *et al*. "Childhood and Juvenile Meningiomas". *Childs Nervous System* 25.12 (2009): 1571-1580.

48. Guner M., *et al*. "Childhood Malignant Meningioma". *Turkish Neurosurgery* 6.3-4 (1996): 79-82.

49. Lucchesi M., *et al*. "A Successful Case of an Anaplastic Meningioma Treated with Chemotherapy for Soft Tissue Sarcomas". *CNS Oncology* 5.3 (2016): 131-136.

50. Morina A., *et al*. "Rhabdoid Meningioma in an Eight-Year-Old Child". *Medical Archives* 64.2 (2010): 123-124.

51. Nayil K., *et al*. "Intraparenchymal Anaplastic Meningioma in a Child: A Rare Entity". *Asian Journal of Neurosurgery* 10.2 (2015): 111-113.

52. Bayram I., *et al*. "Malignant Meningioma in a 3-Year-Old Girl". *American Journal of Clinical Oncology* 29.3 (2006): 320-321.

53. Fan MC., *et al*. "Malignant Meningioma of the Cerebellopontine Angle in a 2-Year-Old Girl: A Case Report and Literature Review". *Chinese Journal of Cancer* 32.7 (2013): 415-417.

54. Darling CF., *et al*. "MR of Pediatric Intracranial Meningiomas". *American Journal of Neuroradiology* 15.3 (1994): 435-444.

55. Surov A., *et al*. "Use of Diffusion Weighted Imaging in Differentiating between Malignant and Benign Meningiomas. A Multicenter Analysis". *World Neurosurgery* 88 (2016): 598-602.

56. Nagar VA., *et al*. "Diffusion-Weighted MR Imaging: Diagnosing Atypical or Malignant Meningiomas and Detecting Tumor Dedifferentiation". *American Journal of Neuroradiology* 29.6 (2008): 1147-1152.

57. Filippi CG., *et al*. "Appearance of Meningiomas on Diffusion-Weighted Images: Correlating Diffusion Constants with Histopathologic Findings". *American Journal of Neuroradiology* 22.1 (2001): 65-72.

58. Pond JB., *et al*. "Chordoid Meningioma: Differentiating a Rare World Health Organization Grade II Tumor from Other Meningioma Histologic Subtypes Using MRI". *American Journal of Neuroradiology* 36.7 (2015): 1253-1258.

59. Wang HH., *et al*. "Preoperative Embolization of Hypervascular Pediatric Brain Tumors: Evaluation of Technical Safety and Outcome". *Childs Nervous System* 29.11 (2013): 2043-2049.

60. Jaiswal S., *et al*. "A Clinicopathological and Neuroradiological Study of Paediatric Meningioma from a Single Centre". *Journal of Clinical Neuroscience* 18.8 (2011): 1084-1089.

61. Cai C., *et al*. "Rhabdoid Meningioma in a Child: Report of a Case and Literatures Review". *Chinese Journal of Clinical Oncology* 5.1 (2008): 67-71.

62. Hayhurst C., *et al*. "Skull Base Surgery for Tumors in Children: Long-Term Clinical and Functional Outcome". *Journal of Neurosurgery. Pediatrics* 11.5 (2013): 496-503.

63. Gump WC. "Meningiomas of the Pediatric Skull Base: A Review". *Journal of Neurological Surgery-Part B* 76.1 (2015): 66-73.

64. Tsai EC., *et al*. "Tumors of the Skull Base in Children: Review of Tumor Types and Management Strategies". *Neurosurgical Focus* 12.5 (2002): e1.

65. Symons P., *et al*. "Brain-Invasive Meningioma in a 16-Month-Old Boy". *Pathology* 33.2 (2001): 252-256.

66. Arivazhagan A., *et al*. "Pediatric Intracranial Meningiomas--Do They Differ from Their Counterparts in Adults?" *Pediatric Neurosurgery* 44.1 (2008): 43-48.

67. Santos MV., *et al*. "Pediatric Meningiomas: A Single-Center Experience with 15 Consecutive Cases and Review of the Literature". *Childs Nervous System* 28.11 (2012): 1887-1896.

68. Germano IM., *et al*. "Intracranial Meningiomas of the First Two Decades of Life". *Journal of Neurosurgery* 80.3 (1994): 447-453.

69. Baum J., *et al*. "Chordoid Meningioma: A Short Series of Five Cases at a Single Institution and Literature Review". *Austin Neurosurgery: Open Access* 2.2 (2015): 1032.

70. Couce ME., *et al*. "Chordoid Meningioma: A Clinicopathologic Study of 42 Cases". *American Journal of Surgical Pathology* 24.7 (2000): 899-905.

71. Kepes JJ., *et al*. ""Chordoid" Meningeal Tumors in Young Individuals with Peritumoral Lymphoplasmacellular Infiltrates Causing Systemic Manifestations of the Castleman Syndrome". *Cancer* 62.2 (1988): 391-406.

72. Di Ieva A., *et al*. "Chordoid Meningiomas: Incidence and Clinicopathological Features of a Case Series over 18 Years". *Neuropathology* 35.2 (2015): 137-147.

73. Kobata H., *et al*. "Chordoid Meningioma in a Child. Case Report". *Journal of Neurosurgery* 88.2 (1998): 319-323.

74. Lee J., *et al*. "Chordoid Meningioma in a Pediatric Patient with Tuberous Sclerosis Complex". *The Korean Journal of Pathology* 48.4 (2014): 302-306.

75. Nambiar A., *et al*. "Intraventricular Chordoid Meningioma in a Child: Fever of Unknown Origin, Clinical Course, and Response to Treatment". *Journal of Neurosurgery. Pediatrics* 10.6 (2012): 478-481.

76. Mullassery D., *et al*. "Malignant Disseminated Chordoid Meningioma in a 12-Year-Old Child: A Role for Early Cranial and Spinal Radiation Treatment after Subtotal Resection". *Childs Nervous System* 22.10 (2006): 1344-1350.

77. Glasier CM., *et al*. "Meningiomas in Children: MR and Histopathologic Findings". *American Journal of Neuroradiology* 14.1 (1993): 237-241.

78. Choy W., *et al*. "Predictors of Recurrence in the Management of Chordoid Meningioma". *Journal of Neuro-Oncology* 126.1 (2016): 107-116.

79. Raffalli-Ebezant H., *et al*. "Pediatric Intracranial Clear Cell Meningioma Associated with a Germline Mutation of Smarce1: A Novel Case". *Childs Nervous System* 31.3 (2015): 441-447.

80. Zorludemir S., *et al*. "Clear Cell Meningioma: A Clinicopathlogic Study of a Potentially Aggressive Variant of Meningioma". *American Journal of Surgical Pathology* 19.5 (1995): 493-505.

81. Kumar R., *et al*. "Clear Cell Meningioma in a Child: A Case Report and Review of the Literature". *Asian Journal of Neurosurgery* 10.1 (2015): 53.

82. Sato T., *et al*. "Clear Cell Meningioma Causing Castleman Syndrome in a Child". *Journal of Neurosurgery, Pediatrics* 5.6 (2010): 622-625.

83. Lee W., *et al*. "MR Imaging Features of Clear-Cell Meningioma with Diffuse Leptomeningeal Seeding". *American Journal of Neuroradiology* 21.1 (2000): 130-132.

84. Kotecha RS., *et al*. "Meningiomas in Children and Adolescents: A Meta-Analysis of Individual Patient Data". *Lancet Oncology* 12.13 (2011): 1229-1239.

85. Mordechai O., *et al*. "Metastatic Rhabdoid Meningioma with Braf V600e Mutation and Good Response to Personalized Therapy: Case Report and Review of the Literature". *Pediatric Hematology and Oncology* 32.3 (2015): 207-211.

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