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ORIGINAL ARTICLE

Clinical features and long-term outcomes of pediatric meningiomas

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Abstract

Objective Pediatric meningiomas are relatively rare and have atypical clinical features compared to adults. The purpose of this work is to report our 15-year experience in the management of pediatric meningiomas and assess their clinical characteristics, pathological features, and prognostic factors.

Methods A total of 40 children (age ≤ 15 years) who were diagnosed as pediatric meningiomas were enrolled in this study. Patient information including clinical presentation, gender, age at time of diagnosis, histopathological features, tumor location, tumor volume, treatment methods, and follow-up data were extracted and analyzed.

Results The mean age at diagnosis was 10.78 ± 3.50 years (range 2–15 years) in 40 patients with a male to female ratio of 1:1.11. Headache, epilepsy, visual disturbance, and limb weakness are common clinical manifestations. Two patients had multiple intracranial meningiomas. Fourteen (33.3%) of pediatric meningiomas were high grade meningiomas. Seven patients (17.5%) were treated with STR, while GTR was achieved in 33 patients (82.5%). The mean follow-up period was 82.1 months (range 9–173 months). Recurrence occurred in 9 patients (22.5%), and 5 patients (12.5%) passed away.

Conclusion The incidence of pediatric meningiomas increases with advancing age. In pediatric patients, the percentage of high-grade tumors is higher than adults. Younger children were more likely to have high-grade meningiomas, while patients with tumors located in skull base or parasagittal/falx tend to have low-grade meningiomas. The WHO grade III meningiomas were significantly correlated with poor prognosis. Adjuvant radiotherapy after surgery can improve prognosis and may be a potential treatment strategy in children with malignant meningiomas.

Keywords Pediatric meningiomas · Clinical features · WHO grade · Prognostic factors · Radiotherapy

Introduction

Meningiomas are one of most common primary tumors of the central nervous system (CNS) worldwide, comprising at least 20% of all brain tumors in adults [1, 2]. In sharp contrast, pediatric meningiomas are relatively rare and only constitute 0.4–4.6% of pediatric CNS neoplasms [3]. Less than 2.0% of all meningiomas occur in childhood and adolescence [4, 5]. Meningiomas are divided into three grades and 15 pathological subtypes according to the newest 2016 WHO classification criteria, and each of pathological subtypes has been found in pediatric meningiomas [2, 6].

Compared to adult meningiomas, pediatric meningiomas have different clinical characteristics, histopathological features, and prognosis, as described by previous literatures [7–11]. However, due to the rarity of pediatric meningiomas, the findings of these studies with small sample sizes were discrepant, and the clinical features of pediatric meningiomas remain uncertain. Herein, 40 children who were diagnosed and treated in our department were included in this retrospective study, and their clinical characteristics and follow-up outcome were analyzed in order to get a deeper understanding of pediatric meningiomas. To the best of our knowledge, this is one of the largest retrospective studies with the long-term follow-up.

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Methods

From 2003 February to 2017 October, 40 children (age ≤ 15 years) with sporadic pediatric meningiomas were operated in the neurosurgery department of Tongji Hospital, Wuhan, China. Two cases with incomplete data were excluded. Patients with neurofibromatosis type 2 (NF2) were not enrolled in this study, because the NF2-related meningiomas could have different biological behaviors compared to non-NF2 meningiomas. All children in this study had no known radiation exposure or associated family history of tumor. This study was approved by local ethical authorities of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, in accordance with the Helsinki Criteria. Written informed consent was obtained from each individual patient.

According to 2016 WHO grading criteria of CNS tumors, the diagnosis was independently confirmed by two neuropathologists through postoperative histopathological examination of tumor samples. Monoclonal antibody immunohistochemical staining was used to detect expression of vimentin (VIM), epithelial membrane antigen (EMA), glial fibrillary acidic protein (GFAP), S-100, and Ki-67.

Patient information including clinical presentation, gender, age at time of diagnosis, histopathological features, tumor location, tumor volume, treatment methods, and follow-up data were retrospectively reviewed. Tumor size was estimated from preoperative MRI. Tumor volume was calculated according to the following formula: tumor volume = (length × width × height × π)/6. Postoperative imaging examination and surgical records were used to determine the extent of resection according to the Simpson grading scale. Gross total resection (GTR) and subtotal resection (STR) were equivalent to Simpson grades I–II and III–V, respectively. Recurrence-free survival (RFS) was calculated from the date of first surgery to the time of tumor recurrence determined by postoperative follow-up MRI. Overall survival (OS) was defined as the time between the date of the first surgery and death. Patients alive are censored at last follow-up.

Independent *t* test and chi-square test (or Fisher's exact test) were used to compare continuous variables and categorical variables, respectively. Kaplan-Meyer method was conducted to estimate the survival curves, and log-rank test was used to compare the differences between groups. A p value < 0.05 was considered significantly different. R software (version 4.0.2) was used to perform all statistical analysis.

Results

A total of 42 meningiomas were operated in 40 patients. Two patients (5.0%) of 40 had multiple intracranial meningiomas. The clinical data are summarized in Table 1, and detail data are presented in supplementary material.

Demographic characteristics

The mean age at diagnosis was 10.78 ± 3.50 years (range 2–15 years) in 40 patients. Only 2 patients (5.0%) were aged 0–5 years, 15 patients (37.5%) were aged 6–10 years, and 23 patients (57.5%) were aged 11–15 years. Nineteen were male (47.5%), and 21 were female (52.5%) with a male to female ratio of 1:1.11. Female patients comprised 41.2% and 60.9% of patients aged 0–10 and aged 11–15, respectively.

Table 1 Summary of clinical characteristics for pediatric meningioma patients

Characteristics	Numbers (%)
Age (years)	
0–5	2 (5.0%)
6–10	15 (37.5%)
11–15	23 (57.5%)
Gender	
Male	19 (47.5%)
Female	21 (52.5%)
Location of tumor	
Skull base	6 (14.3%)
Intraventricular	11 (26.2%)
Convexity	15 (35.7%)
Parasagittal/falx	4 (9.5%)
Posterior fossa	4 (9.5%)
Optic nerve sheath	1 (2.4%)
Spinal	1 (2.4%)
Extent of surgery	
GTR	33 (82.5%)
STR	7 (17.5%)
Duration of symptoms	
≤ 1 months	20 (50.0%)
> 1 months	20 (50.0%)
WHO grade	
I	28 (66.7%)
II	9 (21.4%)
III	5 (11.9%)

Clinical manifestation, location, and volume of tumors

The location of these meningiomas was categorized as follows: skull base in 6 (14.3%), intraventricular in 11 (26.2%), convexity in 15 (35.7%), parasagittal/falx in 4(9.5%), posterior fossa in 4 (9.5%), optic nerve sheath in 1 (2.4%), and spinal (T12-L1) in 1 case (2.4%).

Figure 1A–B show sagittaland coronal MRI images for a 7-year-old girl with intraventricular meningioma(WHO grade I), and Fig. 1C–D show sagittal and coronal MRI images for a15-year-old boy with posterior fossa meningioma (WHO grade II).

Headache was the most common symptom and occurred in 24 patients (60.0%). Other symptoms included epilepsy ($n = 7$, 17.5%), visual disturbance ($n = 6$, 15.0%), limb weakness ($n = 4$, 10.0%), vomiting ($n = 2$, 5.0%), coma ($n = 2$, 5.0%), increased head circumference ($n = 1$, 2.5%), lumbago ($n = 1$, 2.5%), and hearing loss ($n = 1$, 2.5%). The duration of clinical symptoms which was defined as the time from the onset of symptoms to surgery ranged from 1 week to 7 years. The average volume of tumors is 43.54 cm^3. The volume of tumor of patients whose duration of clinical symptoms were < 1 month was smaller than patients with longer duration of clinical symptoms (≥ 1 month) (mean of volume 32.5 cm^3 vs. 53.5 cm^3, *t*-test, $p = 0.025$).

Histopathology

Twenty-eight WHO grade I meningiomas, 9 WHO grade II meningiomas, and 5 WHO III meningiomas were diagnosed through postoperative histopathological examination according to 2016 WHO grading criteria of CNS tumors. Histopathological subtypes included meningothelial ($n = 1$, 2.4%), fibroblastic ($n = 11$, 26.2%), angiomatous ($n = 2$, 4.8%), psammomatous ($n = 2$, 4.8%), transitional ($n = 12$, 28.6%), atypical ($n = 7$, 16.7%), chordoid ($n = 2$, 4.8%), papillary ($n = 2$, 4.8%), anaplastic ($n = 1$, 2.4%), and rhabdoid ($n = 2$, 4.8%). Characteristics associated with WHO grade are demonstrated in Table 2. Younger age was significantly associated with higher grade pediatric meningiomas (Pearson's chi-squared test, $p = 0.042$). Skull base or parasagittal/falx meningiomas were more likely to be low-grade meningiomas (Fisher's exact test, $p = 0.036$).

Immunohistochemistry was implemented in 17 patients. The positive rate of VIM is 100%. EMA and S-100 was positive in 14 samples and 6 samples, respectively. Samples of 5 patients were positive for GFAP. The average value of the KI-67 index was 4.4%.

Table 2 Correlation of clinical characteristics and tumor WHO grade in pediatric meningioma patients

	WHO I	WHO II/III	*p* value
Age (years)			0.042*
0–10	8	9	
11–15	19	4	
Gender			0.648
Male	14	5	
Female	13	8	
Tumor location			0.036*
Skull base or parasagittal/falx	11	1	
Others	17	13	
Volume of tumors			0.306
< 43.54 cm^3	16	11	
≥ 43.54 cm^3	12	3	
Extent of resection			
GTR	23	12	0.769
STR	5	2	

*$p < 0.05$

Treatment and prognosis

Survival data of 40 patients with pediatric meningiomas were available, and the mean follow-up period was 82.1 months (range 9–173 months). Tumor recurrence was observed in 9 patients (22.5%) by the time of last follow-up. All patients who relapsed received the same treatment procedure as previously. Five patients (12.5%) died of recurrence, and all of them were diagnosed as having WHO grade III meningiomas.

GTR was achieved in 35 meningiomas (83.3%), in which 2(5.7%) located in skull base. Seven meningiomas (16.7%) were treated with STR, and 4 of them (57.1%) were located in skull base. Tumor location was the only factor that has an extremely significant impact on extent of resection (Pearson's chi-squared test, $p < 0.001$).

Through Kaplan–Meier survival analysis, we revealed that patients with WHO grade III meningiomas tended to have a lower RFS (median RFS 12 months) and OS (median OS 31 months) (log-rank test, $p < 0.001$) (Fig. 2A, B), while the difference between grade I and II was not significant. The effects of other factors including age, gender, duration of symptoms, volume of tumor, extent of resection, and location of tumor on RFS and OS have not been demonstrated in this study.

Adjuvant radiotherapy was not performed in children with WHO grade I/II meningiomas, and only 2 patients with WHO grade III meningiomas were treated with Postoperative adjuvant radiotherapy. In comparison with patients without radiotherapy,

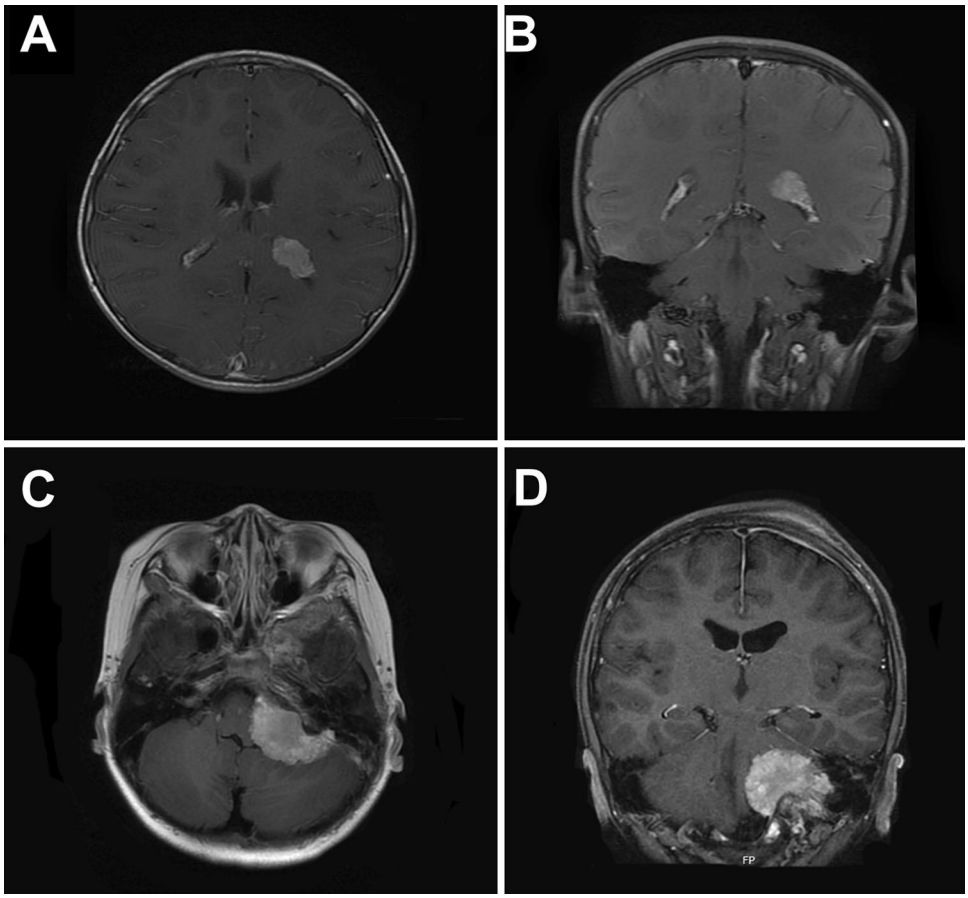

Fig. 1 **A**–**B** show sagittal and coronal MRI images for a 7-year-old girl with intraventricular meningioma (WHO grade I), and **C**–**D** show sagittal and coronal MRI images for a 15-year-old boy with posterior fossa meningioma (WHO grade II)

adjuvant radiotherapy improved prognosis of children with malignant meningiomas (WHO grade III) (median RFS 5.0 months vs. 51.5 months; median OS 22.0 months vs. 62.5 months), although the result was not significant potentially due to the low number of cases (Fig. 3A, B).

Discussion

Despite meningiomas can occur in any age group, pediatric meningiomas show unique clinical characteristics. Unlike adults, the prevalence of meningiomas was surprisingly low in pediatric population [12–15]. Even in children, the prevalence also increases with age. Only 5.0% of pediatric meningiomas occurred in children ≤ 5 years old, 37.5% of patients were aged from 6 to 10 years old, and 57.5% of patients were aged from 11 to 15 years old in our research. Similar findings have also been obtained by other authors [16–18]. Moreover, infantile meningiomas are extremely rare with only few cases reported in the previous literature [12, 19, 20], and no cases were observed in our series. Besides, obvious female predominance of adult meningiomas was not found in children [21–26]. In contrast to younger children, however, we

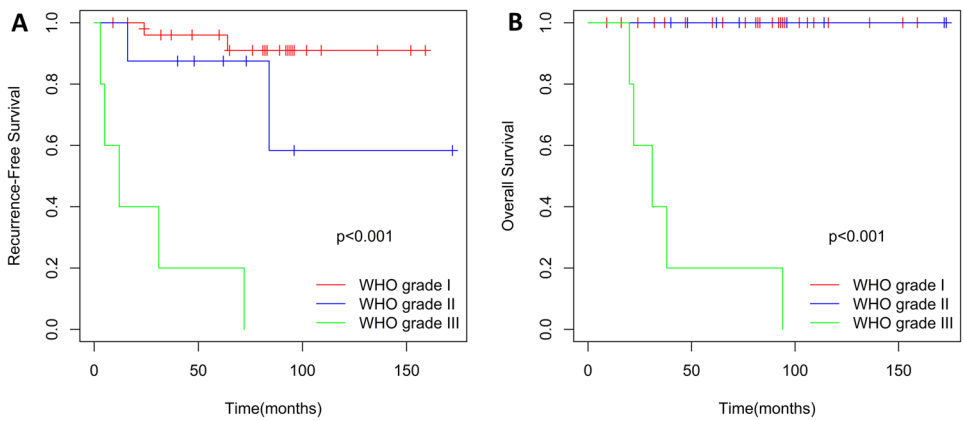

Fig. 2 Kaplan–Meier curves for recurrence-free survival (**A**) and overall survival (**B**) based on WHO grade

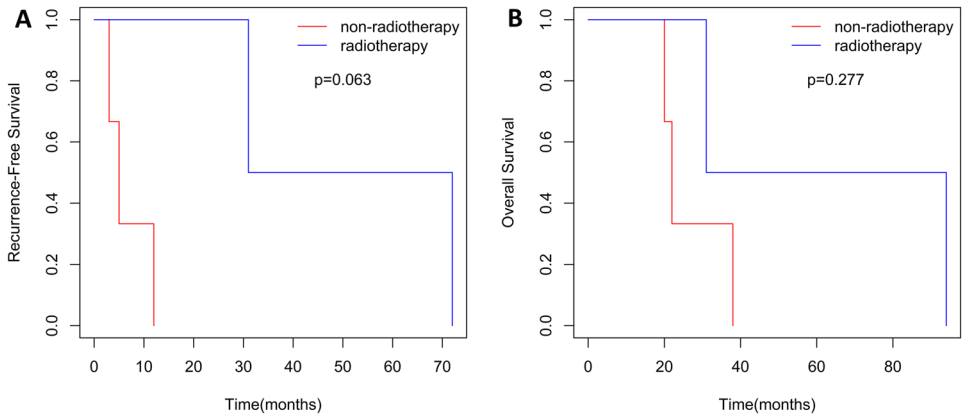

Fig. 3 Kaplan–Meier curves for recurrence-free survival (**A**) and overall survival (**B**) based on adjuvant radiotherapy after surgery or not in patients with WHO grade III meningiomas

found that proportion of female patients was slightly increased in older children (41.2% vs. 60.9%). This tendency was also seen in a recent study using the Surveillance, Epidemiology, and End Results (SEER) database and a meta-analysis [14, 15]. This phenomenon may represent a possible partial explanation for higher incidence with increasing age in pediatric meningiomas. The contrasting gender distribution among different age groups was thought to be likely due to the different sex hormone levels [24, 27].

In our study, headache, epilepsy, visual disturbance, and limb weakness are common clinical manifestations in pediatric meningiomas and this finding was also observed in other study [28, 29]. Clinical symptoms of patients with intracranial meningiomas are moderately associated with the tumor location. Symptoms related to raised intracranial pressure such as headache were more common in pediatric meningiomas, which may be attributed to higher incidence of intraventricular meningiomas in children. According to Liu et al., intraventricular meningiomas are more likely to result in raised intracranial pressure [19]. Our results show that the percentage of intraventricular meningiomas is second only to convexity meningiomas and is significantly higher than their adult counterparts with an incidence of around 0.5–4.5% [30]. Besides, 67% of children with visual disturbance have either skull base or optic nerve sheath meningiomas. In one case with hearing loss, the tumor is located in the cerebellopontine angle (CPA). In addition, tumors volume increases with longer duration of clinical symptoms, which is reported for the first time in this study. However, both of them were not correlated to prognosis.

Several studies have demonstrated a higher proportion of high-grade tumors in pediatric patients [17, 18, 31–33], which is also corroborated by our data. It is even more striking that more than 70% children were diagnosed as high-grade meningiomas in a recent series [34]. Younger children were also more likely to have WHO grade II/III meningiomas in agreement with the report of Grossbach et al. [18]. A number of studies have demonstrated that skull base meningiomas have a declined risk to be WHO grade II/III variants in adult patients [35–37]. Analogously, children with tumors located in skull base or parasagittal/falx tend to have low-grade meningiomas in this study. The difference of WHO grade distribution in different location may be ascribed to distinct meningeal embryogenesis and histological constitution of meninges [38–40]. As mentioned above in the results, the Kaplan–Meier survival analysis confirmed that the grade of tumor is an important prognostic factor of pediatric meningiomas. Nevertheless, tumor location did not significantly affect prognosis of pediatric patients, because only WHO grade III meningiomas were associated with lower RFS and OS, while there was little difference between WHO grades I and II. Moreover, due to the complexity of surgery, a lower rate of GTR achieved in skull base or parasagittal/falx meningiomas may be one of the reasons.

Although adjuvant radiotherapy is recognized to be effective to improve the long-term outcome of adults with meningiomas, it is uncertain for pediatric meningiomas due to the lack of evidence in children [3]. Li et al. think that radiation could result in DNA mutations and induce secondary tumors [41]. In our series, however, 2 patients with WHO grade III meningiomas adjuvant radiotherapy after STR or GTR had better RFS and OS compared three others without adjuvant radiotherapy after GTR (median RFS, 23.0 vs. 12.5 months; median OS, 68.5 vs. 34.5 months). Data of another retrospective study also support this view [42]. Therefore, adjuvant radiotherapy may serve as a potential treatment strategy to improve prognosis for children with malignant meningiomas.

The differences of clinical and histopathological features implied that genetic and epigenetic profiles are different between pediatric and adult meningiomas. However, there are very few literatures that have reported that molecular characteristics of pediatric meningiomas compared to adults. Loss of chromosome 10 is a marked feature in adult high-grade meningiomas, while it was

not founded in pediatric meningiomas in a recent study [43, 44]. As a predictor of poor prognosis in adult meningioma, hypomethylation of H3K27 was also not noted in children [43, 45]. Besides, according to Battu and his colleague, DNA sequencing in pediatric patients did not reveal mutations of KLF4, AKT1, SMO, TRAF7, and TERT which are very common in adult non-NF2 meningiomas [46, 47]. In short, at present, it is difficult to make treatment decisions and predict outcome of patients based on specific molecular features due to the rarity of cases. Hence, multi-center studies with large samples are necessary in future work.

Conclusion

Pediatric meningiomas are uncommon, and their incidence increases with advancing age. Female predominance of adult meningiomas was not observed in children, but the proportion of female patients was slightly increased in older children in contrast to younger children. In pediatric patients, the percentage of high-grade tumors is higher than adults. Besides, younger children were more likely to have high-grade meningiomas compared to older children. In contrast, children with tumors located in skull base or parasagittal/falx tend to have low-grade meningiomas. The WHO grade III meningiomas are significantly associated with lower RFS and OS. In terms of malignant meningiomas, adjuvant radiotherapy can improve prognosis and may be a potential treatment strategy in pediatric population.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00381-021-05296-4.

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Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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