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Headaches in Children With Craniopharyngioma

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Abstract

Craniopharyngioma frequently involves intracranial pain-sensitive structures. We retrospectively studied prevalence, associated risk factors, and outcome of headaches in children with craniopharyngioma. Fisher exact test and multivariate analysis were used to study association of study variables. Of the 51 craniopharyngioma patients treated at our institution from January 1994 to December 2005, 40 (78%) reported headaches (35 [68%] before tumor diagnosis). Migraine headaches were diagnosed in 32 (63%) and tension-type headaches in 11 patients (22%). The median follow-up period was 2.7 years. At the last follow-up, 38 (75%) were headache free. Presence of hydrocephalus, distortion of circle of Willis, and large tumor volume were associated with headache, and the last 2 variables were also associated with more severe and frequent headaches. Radiation treatment and insertion of Ommaya reservoir were associated with reduced headache frequency. In conclusion, headaches are common in patients with craniopharyngioma and are likely related to tumor size and volume. In most patients, headaches improve with successful tumor treatment.

Keywords

brain tumor; craniopharyngioma; headache; migraine; hydrocephalus

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Author contributions

RBK wrote the first manuscript and its revisions. This study was conceived by RBK and LEK, who is also the senior author. AOT is the study statistician. All other authors were involved in the care of these patients and helped develop study variables. They also helped in the editing of the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Institutional Review Board of the St. Jude Children's Research Hospital approved this retrospective study. Data collection started after the IRB approval was obtained.

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Headaches are common in brain tumor patients, occurring in up to 50% of adults and 60% of children.^{1,2} Headaches are usually associated with other neurologic signs and symptoms at presentation but can be the only symptom in some brain tumor patients.³ Headaches in brain tumor patients may resemble migraine variants or more commonly be tension-type headaches, as defined by the International Headache Society.^{1,3} Location of the tumor may affect headache frequency; for example, patients with infratentorial tumors have a high frequency of headaches.⁴

The pathophysiology of headaches in brain tumor patients is not completely understood. Traction of pain-sensitive intracranial structures from the expanding tumor mass and hydrocephalus are the most common causes of headaches.⁵ Potential pain-sensitive intracranial structures include basal arteries, venous sinuses, and basal meninges.⁶ Craniopharyngioma is primarily a childhood brain tumor involving the parasellar region, which is close to these pain-sensitive structures, and may frequently involve the structures themselves. Little is known about the incidence, risk factors, and outcomes of headaches in children with craniopharyngioma. Two studies reported a prevalence of 39% and 56% in long-term survivors of craniopharyngioma, but did not address headache type and related disability.^{7,8} We conducted a retrospective study of the incidence, severity, and types of headaches in children with craniopharyngioma and determined the risk factors associated with increased frequency and intensity of headaches.

Methods

This retrospective study was approved by the institutional review board of St. Jude Children's Research Hospital. Records were reviewed of patients with a diagnosis of craniopharyngioma who were treated from January 1994 to December 2005, and were identified from the institutional database. All patients were routinely seen by a neurologist per the radiation oncology study protocol. Study variables (Table 1) were determined before reviewing charts and collecting data. Magnetic resonance imaging (MRI) scans of the brain of all patients were reviewed by a single investigator (RBK). Tumor volume was calculated by obtaining maximum diameter measurements in 3 different planes; circle of Willis distortion was defined as any deviation of basal arteries from the normal position because of the tumor; and Meckel cave involvement was present if the tumor encroached over it. The distortion of cavernous sinus anatomy because of the tumor was also noted. Headache severity scale was constructed based on the presence of headache and need to lie down during a headache (no need to lie down $\frac{1}{4}$ 0, need to lie down $\leq 50\%$ of the time $\frac{1}{4}$ 1, and need to lie down $>50\%$ of the time $\frac{1}{4}$ 2); number of headache days in the past 30 days (no headache $\frac{1}{4}$ 0, headache for 1–5 days $\frac{1}{4}$ 1, headache for 6–10 days $\frac{1}{4}$ 2, headache for 11–15 days $\frac{1}{4}$ 3, and headache for 16–30 days $\frac{1}{4}$ 4); presence of vomiting during a headache (none $\frac{1}{4}$ 0, $\leq 50\%$ of the time $\frac{1}{4}$ 1, $>50\%$ of the time $\frac{1}{4}$ 2); and presence of photo and phonophobia (absent $\frac{1}{4}$ 0, present $\frac{1}{4}$ 1). Total scores of headache severity were categorized as follows: 1–4, mild headache; 5–8, moderate headache; and 9–10, severe headache. Headache type was defined according to the criteria established by the International Headache Society.⁹

Statistics

Fisher exact test was used to study univariable association with presence of headache. An extended multivariate model based on generalized estimating equations was used to determine the associations between the presence of headaches and potential risk factors (age at diagnosis, log-transformed tumor volume, Sella expansion, circle of Willis distortion, Meckel cave involvement, distortion of cavernous sinus anatomy, brainstem displacement, Ommaya reservoir, and ventriculoperitoneal shunt) and all possible 2-way interactions. If patients experienced headaches at any time during the follow-up period, they were coded as having a headache. The generalized estimating equation model took into account multiple visits per patient, but did not incorporate the time between visits. All variables were coded in a time-varying manner to determine their pattern of change between visits. A backward stepwise elimination was used to determine the final multivariate model.

A similar generalized estimating equation model was used to determine the associations between the above-mentioned variables and severity and frequency of headaches. For the 109 visits from 51 patients, headache severity was categorized as none ($n = 54$), mild ($n = 21$), moderate ($n = 18$), and severe ($n = 16$) (see Methods for severity scale). An ordinal logistic regression approach was used to analyze the relationships between the covariates and the severity score aggregated to a 4-point scale. A generalized estimating equation approach with a multinomial cumulative logit model was used to account for intra-patient correlations induced by multiple observations per patient. A stepwise backward elimination procedure was used to generate the best-fitting parsimonious model. Headache frequency within and across patients was compressed into 4 ordinal categories: no headache days/month $\frac{1}{4}$ 0; 1 to 14 headache days/month $\frac{1}{4}$ 1; 15 to 29 headache days/month $\frac{1}{4}$ 2; and 30 headache days/month $\frac{1}{4}$ 3. These categories were set based on the observation that the headache frequency variable was polarized at 0 and 30 in our data. Of the 109 visits included in this dataset, 54 were coded as 0, 18 were coded as 1, 16 were coded as 2, and 21 were coded as 3. The generalized estimating equation model took into account the multiple visits per patient but did not incorporate the time between visits.

Results

Patient Characteristics

A total of 51 patients with craniopharyngioma (109 clinic encounters) were identified. Of the 51 patients, 50 went to the neurology clinic at least twice and 1 was seen once (9 years after tumor diagnosis). All patients were seen in their last follow-up by a neurologist, and 6 patients were not seen by a neurologist at their first visit as the hospital did not have a neurologist at that time. Table 1 gives the clinical characteristics of patients. There were 24 (47%) males, and the median age at tumor diagnosis was 7.06 years (range $\frac{1}{4}$ 0.36–17.58 years). Thirty-six patients had partial resection of the tumor. Conformal radiation was administered to 43 patients, and P32 instillation was additionally given to 2 patients. Hydrocephalus was present at diagnosis in 18 patients, and 19 patients received a ventriculoperitoneal shunt. An Ommaya reservoir was placed in the tumor cyst in 25 patients.

Headache Severity and Type

Headaches started at a median time of 61 days (range 0–2518 days) before tumor diagnosis in 35 patients, and 5 patients developed headaches in the posttreatment period. Median follow-up was 2.7 years (range 0.4–13.4 years). The median number of headache days each month before tumor diagnosis was 25 (range 0–30 days), and 32 patients had more than 15 days of headache each month. Headaches before tumor diagnosis were categorized as severe in 16, moderate in 12, and mild in 7 patients. At the last follow-up, only 1 patient still had severe headaches, 4 had moderate headaches, and 46 had mild or no headaches. At the last follow-up, 38 (74.5%) patients had no headaches, 7 had 1–5 headache days/month, 2 had 6–14 headache days/month, and 4 had 15 or more headache days/month.

Headache type included migraine without aura in 30, migraines with aura in 2, and tension-type headaches in 11 patients; 3 patients with tension-type headaches experienced migraine headaches as well. Most common treatments to control the headaches were acetaminophen (n = 28) and ibuprofen (n = 5). Preventive therapy was required in 10 patients (topiramate, n = 6; valproic acid, n = 3; and gabapentin, n = 1), and 9 responded to preventive therapy.

Association of Study Variables With Headache

The Fisher exact test showed that only the presence of hydrocephalus ($P = .004$), and compression of cavernous sinus ($P = .059$) were significantly associated with presence of headache (Table 2). On multivariable analyses, presence of hydrocephalus, distortion of the circle of Willis by the tumor, and larger tumor volume were associated with the presence of headaches and with more severe headaches (Table 3). The final model suggested that posttreatment headache frequency was reduced by radiation treatment and insertion of the Ommaya reservoir and increased by the presence of hydrocephalus, distortion of the circle of Willis, and presence of tension-type headaches (Table 3).

Discussion

To our knowledge, this is the first detailed retrospective study of headaches in children with craniopharyngioma. All patients in this cohort were seen by a neurologist. A headache incidence rate of 69% before tumor diagnosis in this study is consistent with the reported rate of 60% in children with brain tumors,² but much higher than that reported in normal children.^{10,11} Of the 35 children with headaches before tumor diagnosis, 29 (83%) could be classified as having the chronic daily headache syndrome, per the criteria of the International Headache Society. Migraine headaches were much more frequent than tension-type headaches in our study, contrary to earlier reports that tension-type headaches are more common in brain tumor patients.^{1,3} This may be due to direct involvement of pain-sensitive structures in craniopharyngioma or because the encroaching tumor triggers the trigeminal-vascular cascade.

We did not record the pediatric headache disability scale during clinic visits. Instead, we constructed a severity scale based on the frequency of headaches, need to lie down during a headache, and presence of vomiting, photophobia, and phonophobia. This is not a validated scale and at best provides an estimate of headache severity. Questions related to the

disability scale were routinely asked during clinic visits from August 2001 onward, but for the 17 patient visits before that time period some information had to be extracted from the notes of a non-neurologist. All these 17 patients had at least 1 follow-up visit after August 2001. Thus, disability data should be interpreted with caution, as some measures were indirectly evaluated and the scale itself has never been validated. However, this scale provides a comparison of headaches over time. With tumor treatment, and preventive pharmacologic therapy when needed, headaches improved by the last follow-up and only 10% of children still experienced moderate or severe headaches. The headache-free status improved from 33% to 75% at the last follow-up.

Compression of the cavernous sinus by the tumor volume on univariable analyses and presence of hydrocephalus on multivariable analyses correlated with presence of headache. Presence of distortion of the circle of Willis by tumor and larger total tumor volume also indicated an association with headache. Presence of hydrocephalus and distortion of the circle of Willis also correlated with increased headache severity, whereas presence of larger tumor volume showed a trend toward correlation with increased headache severity. These variables directly or indirectly reflect tumor size, which in turn suggests traction on basal pain-sensitive structures as the underlying cause of headaches in these patients.

In most patients, headaches improved after surgical resection or radiation treatment. Approximately 25% of patients continued to experience headaches after tumor treatment, and 10% had moderate to severe headaches. All the 5 children with moderate to severe headaches were using acetaminophen and ibuprofen daily, which may have caused analgesia-overuse headaches as well, and 2 of them were not on preventive therapy. Radiation treatment and Ommaya reservoir correlated with reduced posttreatment headaches and indicates reduction in tumor volume and reduced traction on basal pain-sensitive structures. Interestingly, presence of tension-type headaches predicted a higher frequency of posttreatment headaches, which may be related to increased analgesia use by these patients.

Craniopharyngioma is an uncommon childhood tumor with an estimated annual incidence of 1.13 per million people.¹² Although the sample size in our study is smaller than those in other studies on childhood headaches, it is a relatively large cohort considering the low annual incidence of craniopharyngioma. It is the largest study on headaches in children with craniopharyngioma to date, and also the first to assess risk factors and headache outcomes. Thus, our study provides important information for neurologists and other physicians who provide care to children with craniopharyngioma.

In conclusion, headaches with migraine features are a very common presenting symptom of children with craniopharyngioma, and neuroimaging is recommended in children who have new or recurring migraine or tension-type headaches. As headache severity and frequency are likely related to tumor size, efforts need to be directed at safely reducing tumor size in children with craniopharyngioma.

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Table 1

Demographics and Clinical Characteristics of Patients(n = 51).

Variable	Number (%)
Gender	
Male	24 (47)
Female	27 (53)
Median age at diagnosis (range), y	7.06 (0.36–17.58)
Surgical resection	36 (71)
Radiation treatment	43 (84)
Presence of headaches	40 (78)
Before tumor diagnosis	35 (69)
Posttreatment	5 (10)
Median follow-up (range), y	2.7 (0.4–13.4)
Median headache days before diagnosis (range)	61 (0–2518)
Patients with headaches at last follow-up	13 (25)
Headache type	
Migraine without aura	30 (59)
Migraine with aura	2 (4)
Tension type	11 (22)
Headache severity at diagnosis	
Severe	16 (31)
Moderate	12 (24)
Mild or none	23 (45)
Headache severity at last follow-up	
Severe	1 (2)
Moderate	4 (8)
Mild or none	46 (90)
Frequency of headaches at last follow-up	38 (74)
1–5 days/month	7 (14)
6–14 days/month	2 (4)
2–15 days/month	4 (8)

Table 2

Study Variables and Their Association With the Presence of Headache by Fisher Exact Test.

Variable	Frequency	P
Sella expansion	11	1.000
Hydrocephalus	18	.004
Circle of Willis ^a	38	.105
Cavernous sinusa	8	.059
Meckel cave ^b	3	.533
Brainstem ^c	10	.424
Ommaya reservoir ^d	25	1.000
Ventriculoperitoneal shunt ^e	18	.287

^a Distortion or compression by tumor.^b Encroachment by tumor mass.^c Expansion of tumor cyst anterior to brainstem.^d Insertion of Ommaya reservoir in tumor cyst.^e Insertion of ventriculoperitoneal shunt.

Table 3

Multivariable Analyses of Positive Associations of Study Variables for Presence of Headache, Its Severity, and Frequency.

Study variable	Headache		Headache severity		Headache frequency ^d	
	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)
Hydrocephalus	.02	4.44 (1.3, 14.9)	.01	3.5 (1.3, 9.2)	.09	2.32 (0.87, 6.21)
Circle of Willis ^b	.06	2.16 (0.96, 4.8)	.03	2.5 (1.1, 5.6)	.06	2.52 (0.95, 6.65)
Tumor volume ^c	.06	1.6 (0.97, 2.7)	.07	1.5 (0.97, 2.3)	NA	NA
Ommaya reservoir ^d	NA	NA	NA	NA	.08	0.44 (0.18–1.12)
Radiation treatment	NA	NA	NA	NA	<.0001	0.075 (0.026–0.213)
Tension-type headache	NA	NA	NA	NA	.0001	7.54 (2.71–20.99)

Abbreviations: CI, confidence interval; NA, not applicable as not included the general estimation equation model.

^a Headache days each month.

^b Expansion or distortion by tumor mass.

^c Larger tumor volume.

^d Presence of Ommaya reservoir.