Title

Surgical outcomes in choroid plexus papillomas: an institutional experience

Journal

Journal of Neuro-Oncology, 113(1)

ISSN

0167-594X

Authors

Safaee, Michael

Clark, Aaron J

Bloch, Orin

et al.

Publication Date

2013-05-01

DOI

10.1007/s11060-013-1097-3

Peer reviewed

J Neurooncol (2013) 113:117–125
DOI 10.1007/s11060-013-1097-3

CLINICAL STUDY

Surgical outcomes in choroid plexus papillomas: an institutional experience

Michael Safaee · Aaron J. Clark · Orin Bloch · Michael C. Oh · Anahat Singh · Kurtis I. Auguste · Nalin Gupta · Michael W. McDermott · Manish K. Aghi · Mitchel S. Berger · Andrew T. Parsa

Received: 1 December 2012 / Accepted: 22 February 2013 / Published online: 7 March 2013

Abstract Choroid plexus papillomas (CPPs) are rare, indolent lesions that comprise less than 0.5 % of intracranial tumors. We sought to assess the long-term outcomes and associated surgical complications at our institution. A review of the University of California, San Francisco (UCSF) Brain Tumor Research Center (BTRC) database was performed to identify a cohort of patients treated for CPP from 1997 to 2011. Patients were grouped based on tumor location and extent of resection. Outcomes including progression-free survival and surgical complications were assessed. We identified 24 patients (16 female, 8 male) ranging in age from 6 months to 55 years (median 29 years) treated at our institution. Tumors were found in the following locations: 16 (67 %) fourth ventricle/cerebellopontine angle; 7 (29 %) lateral ventricle; 1 (4 %) third ventricle. Gross total resection (GTR) was achieved in 20 patients (83 %) with subtotal resection (STR) in 4 (17 %). Median follow-up time was 2.8 years with 3 recurrences identified at 1.6, 3.3, and 8.5 years. Extent of resection and tumor location were not associated with recurrence. There was one new permanent neurologic deficit detected after surgery. All patients were alive at most recent follow-up. Attempted gross total resection is the standard treatment for CPPs and generally associated with excellent outcomes. Since recurrences are rare, even among patients who undergo STR, radiation may be reserved for cases of tumor progression. This modern experience at a tertiary care center performed exclusively during the MRI-era demonstrates that CPPs can be safely removed with minimal morbidity and good tumor control.

Keywords Choroid plexus papilloma · Surgical resection · Complications · Tumor recurrence

M. Safaee · A. J. Clark · O. Bloch · M. C. Oh · A. Singh · K. I. Auguste · N. Gupta · M. W. McDermott · M. K. Aghi · M. S. Berger · A. T. Parsa (✉)
Department of Neurological Surgery, University of California at San Francisco, 505 Parnassus Ave, San Francisco, CA 94117, USA
e-mail: parsaa@neurosurg.ucsf.edu

K. I. Auguste · N. Gupta
Department of Pediatrics, University of California at San Francisco, San Francisco, CA, USA

Introduction

Choroid plexus papillomas (CPPs) are rare, indolent neuroepithelial tumors arising from the choroid plexus. They are generally found within the ventricles and comprise less than 0.5 % of intracranial tumors [1]. Patients typically present with signs and symptoms of increased intracranial pressure, however some CPPs are incidentally found. These tumors are more common in children and can often prove challenging due to their deep intraventricular location and high vascularity. The differential diagnosis generally includes ependymoma, intraventricular meningioma, and metastatic carcinoma.

The preferred treatment of these lesions is gross total resection, which is generally associated with excellent outcomes [2, 3]. In cases of subtotal resection, the role of adjuvant radiation is not clear, but often reserved for tumor progression documented by imaging. A meta-analysis of 566 choroid plexus tumors found no difference in survival among patients with recurrent CPPs compared to those with stable disease [3]. We retrospectively reviewed our institutional experience of 24 patients with CPPs treated from 1997–2011 to evaluate tumor control, surgical complications, and the potential effects of tumor size and location on these outcomes.

Methods

Previously treated patients were identified through a query of the UCSF Brain Tumor Research Center (BTRC) database. Each patient's medical history, physical exam, radiographic studies, and pathology reports were reviewed. All research activities were approved by the UCSF institutional review board for human research (CHR #10-04026). Extent of resection was determined by review of postoperative imaging. The absence of any residual enhancing tumor was defined as gross total resection (GTR); patients with any amount of residual disease were classified as subtotal resection (STR). Tumor size was defined by the maximum diameter in any dimension on the preoperative MRI. Tumors were dichotomized into those less than 3 cm or greater than or equal to 3 cm in any dimension. Tumor location was classified as supratentorial (lateral ventricle or third ventricle) or infratentorial (fourth ventricle or cerebellopontine angle).

Surgical complications were classified as major or minor. Major complications included new permanent neurologic deficits or change in functional status. Transient complications that resolved over time were classified as minor and included transient cranial neuropathies, deep venous thrombosis (DVT), temporary postoperative seizures, or wound healing complications including infection, cerebrospinal fluid (CSF) leak, and pseudomeningocele. Statistical analysis was performed using SPSS version 20 (IBM). Categorical variables were compared using the Chi squared or Fisher's exact test if cells contained less than 5 expected values. Independent samples t test was used to compare continuous variables. Statistical significance was defined as $p < 0.05$.

Results

Clinical characteristics

This case series includes 24 patients treated from 1997–2011. Patients ranged from 6 months to 55 years of age (mean 28 years, median 29 years), with 16 females and 8 males. There were 17 adult (age > 18 years) and 7 pediatric (age < 18 years) patients in this cohort. Among 12 patients in which symptom duration was reported, the mean time was 7 months. The remaining tumors were either incidentally found ($n = 8$) or presented with symptoms of undocumented duration ($n = 4$). Tumors were distributed as follows: 16 (67 %) fourth ventricle/cerebellopontine angle (CPA); 7 (29 %) lateral ventricle; 1 (4 %) third ventricle. Among tumors in the lateral ventricle, 5 (71 %) were right-sided and 2 (29 %) left-sided. The mean maximum diameter was 3.0 cm with a median of 3.2 cm; among supratentorial tumors the mean was 3.1 cm compared to 3.0 cm in infratententorial lesions ($p = 0.89$). The most common presenting symptoms were headache (12 patients, 52 %) and nausea/vomiting (8 patients, 33 %). A total of 9 patients (39 %) had hydrocephalus on preoperative imaging. A review of pathology reports found that 2 tumors (8 %) were atypical CPPs (WHO grade II) with the remainder of tumors demonstrating benign (WHO grade I) pathology. Patient characteristics and clinical outcomes are summarized in Table 1.

To further analyze our cohort, we grouped patients by extent of resection (Table 2). When stratifying by extent of resection, there were 20 patients in the GTR group and 4 in the STR group. The mean age among patients who underwent GTR was 26 years compared to 34 years among those with STR ($p = 0.38$). Tumor sizes were similar, with mean maximum diameters of 2.9 cm and 3.7 cm in the GTR and STR groups, respectively ($p = 0.49$). There was a higher proportion of infratentorial tumors in the STR group (100 %) compared to the GTR group (60 %), although this difference was not statistically significant ($p = 0.26$). Patients who underwent STR had significantly longer follow-up (10.6 versus 3.2 years) compared to those with GTR ($p < 0.001$). When stratifying tumors by location (supratentorial versus infratentorial), there was a significant difference in age at diagnosis, with a mean of 14 years in the supratentorial group compared to 34 years in the infratentorial group ($p = 0.002$). There were no differences in gender, tumor size, or extent of resection (Table 3).

Surgical outcomes

All 24 patients underwent surgical resection at the time of initial presentation. GTR was achieved in 20 patients (83 %) with STR in the remaining 4 (17 %). Neuronavigation was used in the surgical resection of 14 patients but was not associated with extent of resection ($p = 1.00$) or major surgical complications ($p = 1.00$). Five patients (21 %) required CSF diversion for persistent hydrocephalus after initial resection. There was no association between the need for a postoperative shunt and tumor location ($p = 1.00$) or extent of resection ($p = 1.00$). No patients received up-front radiation following initial resection.

A single significant postoperative complication occurred in a 41 year old female who presented with headaches and ataxia; she was found to have a 3.3 cm heterogeneously enhancing mass in the fourth ventricle and underwent GTR of a CPP. Postoperatively the patient was found to have altered mental status and dysarthria attributed to cerebellar swelling and lower cranial nerve dysfunction; these symptoms had completely resolved by time of discharge. At her most recent follow-up, 33 months after surgery, her

Table 1 Summary of patient characteristics and treatment outcomes

Age/ gender	Presenting symptoms	Tumor location	Tumor pathology	Extent of resection	Time to recurrence (months)	Treatment at recurrence	Length of follow-up (months)
20 F	2 months of worsening headache	4V	CPP MIB-1: 7 %	GTR	41	STR + 54 Gy fractionated IMRT	67
33 F	NR	4V	CPP	STR	103	1st recurrence: STR + 36 Gy fractionated radiotherapy 2nd recurrence 9 months later: 32 Gy GKRS	125
42 F	24 months of intermittent nausea/vomiting	4V	CPP MIB-1 < 1 %	STR	–	–	176
44 M	NR	4V	CPP	GTR	–	–	23
16 M	6 months of worsening headache, nausea/vomiting, vertigo, and acute complex partial seizure	LV	CPP No mitotic activity	GTR	–	–	8
9 F	Incidental finding on dental X-ray	LV	CPP	GTR	–	–	17
11mo F	2 weeks of progressive lethargy and nausea/vomiting	LV	CPP MIB-1: 1 %	GTR	–	–	149
21 M	1 month of headache and nausea/ vomiting	4V	CPP MIB-1 < 1 %	STR	–	–	147
30 F	4 months of progressively worsening headaches	4V	CPP No mitotic activity	GTR	–	–	2
38 M	Incidental finding during brain MRI for melanoma staging	4V	CPP	GTR	–	–	34
11mo F	2 weeks of irritability, nausea/ vomiting	LV	CPP MIB-1: 2 %	GTR	–	–	39
16mo F	1 week of lethargy and decreased ambulation	LV	CPP MIB-1: 5 %	GTR	–	–	86
39 F	12 months of worsening headaches, presented after generalized tonic–clonic seizure	CPA	CPP No mitotic activity	STR	–	–	63
39 F	24 months of worsening headache and altered mental status	4V	Atypical CPP MIB-1: 4 %	GTR	–	–	93
26 M	Incidental finding on MRI as a control subject in neuropsychological study	4V	CPP	GTR	–	–	49
6mo M	Presented with lethargy and concern over enlarging head circumference	LV	CPP	GTR	–	–	73
28 F	Incidental finding on head CT after automobile accident	4V	CPP MIB-1 < 4 %	GTR	–	–	24
41 F	Long history of migraines and gait instability	4V	CPP No mitotic activity	GTR	–	–	33
46 F	Incidental finding during workup for stroke/TIA	4V	CPP	GTR	–	–	7
42 M	2 months of headache, hearing loss, and hoarse voice	CPA	Atypical CPP MIB-1: 8 %	GTR	20	STR + 25 Gy hypofractionated CyberKnife radiosurgery	34
26 F	Incidental finding after syncopal event	LV	CPP No mitotic activity	GTR	–	–	13
16 F	Incidental finding on MRI after workup for Kallmann syndrome	4V	CPP	GTR	–	–	13
55 M	10 months of worsening headaches	3V	CPP MIB-1 < 2 %	GTR	–	–	13
38 F	Incidental finding on head CT	4V	CPP	GTR	–	–	10

Age listed in years unless otherwise specified, *NR* not recorded/data unavailable, - not applicable, *LV* lateral ventricle, *3 V* third ventricle, *4 V* fourth ventricle, *CPA* cerebellopontine angle, *GTR* gross total resection, *STR* subtotal resection, *IMRT* Intensity-modulated radiation therapy, *GKRS* Gamma Knife radiosurgery

Table 2 Summary of clinical characteristics by extent of resection

	GTR (%)	STR (%)	Significance (p value)
Number of cases	20 (83)	4 (17)	
Patient age (years)			
Mean	26	34	0.38*
Median	27	36	
Range	0.5–55	21–42	
Gender			
Male	7 (35)	1 (25)	1.00†
Female	13 (65)	3 (75)	
Max diameter (cm)			
Mean	2.9	3.7	0.49*
Median	3.0	3.7	
Tumor location			
Supratentorial	8 (40)	0 (0)	0.26†
Infratentorial	12 (60)	4 (100)	
Postoperative shunt	4 (20)	1 (25)	1.00†
Tumor recurrence	2 (10)	1 (25)	0.44†
Major complications	1 (5)	0 (0)	1.00†
Follow-up (years)	3.2	10.6	<0.001*

*Independent samples t test

†Fisher's exact test

Table 3 Summary of clinical characteristics by tumor location

	Supratentorial (%)	Infratentorial (%)	Significance (p value)
Number of cases	8 (23)	16 (67)	
Patient age (years)			
Mean	14	34	0.002*
Median	5	38	
Range	0.5–55	16–46	
Gender			
Male	3 (38)	5 (31)	1.00†
Female	5 (62)	11 (69)	
Max diameter (cm)			
Mean	3.1	3.0	0.89*
Median	3.3	2.9	
Extent of resection			
GTR	8 (100)	12 (75)	0.26†
STR	0 (0)	4 (25)	
Postoperative shunt	2 (25)	3 (19)	1.00†
Tumor recurrence	0 (0)	3 (19)	0.53†
Major complications	0 (0)	1 (6)	1.00†
Follow-up (years)	4.1	4.6	0.78*

*Independent samples t test

†Fisher's exact test

disease was stable with no signs of recurrence but she had persistent left sixth and seventh cranial nerve palsies, as well as bilateral dysmetria. Six minor complications were identified and included the following: transient left vocal cord paralysis, DVT, single postoperative seizure, pseudomeningocele, transient occulomotor nerve palsy, and a single acute psychotic episode, likely secondary to steroid use.

Tumor control

Clinical follow-up time ranged from 1 month to 14.6 years (mean 4.5 years, median 2.8 years); all patients were alive at last follow-up. Seven patients were lost to follow-up, two less than 1 year from the time of surgery. Eight patients (33 %) were treated within the past 5 years. Surveillance imaging varied by provider, but in general patients received MRI scans every 6–12 months after surgery until their disease was stable for 2–3 years, at which point they received annual scans.

Three recurrences were identified at 1.6, 3.3, and 8.5 years. Of the tumors that recurred, two were benign CPPs (WHO grade I) and the other an atypical CPP (WHO grade II). Since the sample size was limited, we were unable to observe an association with increased recurrence in patients with atypical CPPs ($p = 0.24$). Furthermore, although two recurrences occurred in patients with GTR, there was no association between recurrence and extent of resection ($p = 0.44$) or tumor location (0.53). There was no association between large tumors ($\geq$3 cm) and recurrence ($p = 0.48$), however the mean tumor size of recurrent tumors was 4 cm compared to 2.9 cm among stable lesions ($p = 0.40$). The mean age at diagnosis was 32 years for patients with recurrent tumors compared to 27 years among patients with stable disease ($p = 0.62$). MIB-1 values were available for 10 tumors; the average value was 7.3 % among those that recurred compared to 2.6 % among those that remained stable ($p = 0.006$). The presence or absence of mitotic figures was documented in 8 patients; they were only present in atypical CPPs ($p = 0.04$), but had no association with tumor recurrence ($p = 0.25$).

The first recurrence occurred in a 20 year old female with a fourth ventricular CPP that was multilobulated with both solid and cystic components on MRI (Fig. 1a, b). She underwent GTR (Fig. 1c, d) and remained stable for 3.3 years until she developed 2 months of diminished hearing and worsening headaches. An MRI demonstrated recurrent disease in the fourth ventricle and left CPA, with similar radiographic characteristics as the primary tumor

(Fig. 1d, e). She underwent STR of the recurrent lesion with fractionated intensity-modulated radiation therapy (IMRT, 54 Gy in 1.8 Gy fractions). At her most recent follow-up, 5.6 years after initial diagnosis, her disease was stable with no major complications or permanent neurologic deficits. The second patient was 42 year old male initially diagnosed with an atypical CPP of the CPA treated with GTR. The patient remained at his baseline for 1.6 years until local tumor recurrence was detected on a routine follow-up MRI. Our institutional tumor board recommend radiosurgery or prolonged fractionated radiotherapy, however the patient chose radiosurgery due to geographic limitations. He underwent STR with hypofractionated CyberKnife radiosurgery (25 Gy delivered to the 80 % isodose line over 5 days) for the recurrent tumor and recovered from both procedures with no major complications. His tumor was stable at last follow-up, 2.8 years after the initial diagnosis. A third recurrence was identified in a patient initially treated at an outside institution. The primary tumor was a fourth ventricular CPP treated by STR that remained stable until progression 8 years after surgery. At progression, the tumor was disseminated with drop metastases to the spine at L5-S1. The patient was treated with STR and fractionated radiotherapy (36 Gy total) to the brain and spine. The tumor progressed locally 9 months after the second surgery and was treated with Gamma Knife radiosurgery (32 Gy total) at our institution. The patient's disease is now stable 10.4 years after initial diagnosis.

Post-resection CSF diversion

We sought to identify factors that predicted the need for permanent CSF diversion. The average tumor size of patients presenting with hydrocephalus was 4.2 cm compared to 2.3 cm among those without hydrocephalus ($p = 0.008$). There was no association between tumor location and hydrocephalus ($p = 0.18$) or tumor location and the need for CSF diversion ($p = 1.00$). As predicted, we observed a strong trend among patients with preoperative hydrocephalus and the need for permanent CSF diversion ($p = 0.056$). The average time from tumor resection to shunt placement was 15 days (range 9–30 days). Only 1 pediatric patient (15 %) required shunting compared to 7 adults (24 %), but this difference was not statistically significant ($p = 1.00$). The average age of patients requiring shunts was 32.3 years compared to 26.3 years among those who did not ($p = 0.48$).

Discussion

CPPs are rare, indolent neoplasms that are usually treated by surgical resection alone. GTR is the objective, but is not always possible when the tumor is in close proximity to critical brainstem structures and cranial nerves, or invades the adjacent parenchyma. Although there are reports of radiation therapy for residual tumor [4, 5] or as a neoadjuvant treatment to shrink large lesions preoperatively [6], the indolent nature of these lesions suggests that observation of residual disease may be most appropriate. Most authors agree that radiation should be reserved for recurrent or malignant lesions, even in cases of STR, and certainly not in children less than 3 years of age [2, 7–9]. This is supported by our data, which demonstrated stable disease in all but one patient who underwent STR alone, with a mean follow-up time of over 10 years. Since recurrence is likely driven by the tumor's unique biology rather than extent of resection, we recommend maximal safe resection, with radiation reserved for documented growth, not residual disease.

Due to the scarcity of these tumors, the literature consists mainly of case reports and small institutional series.

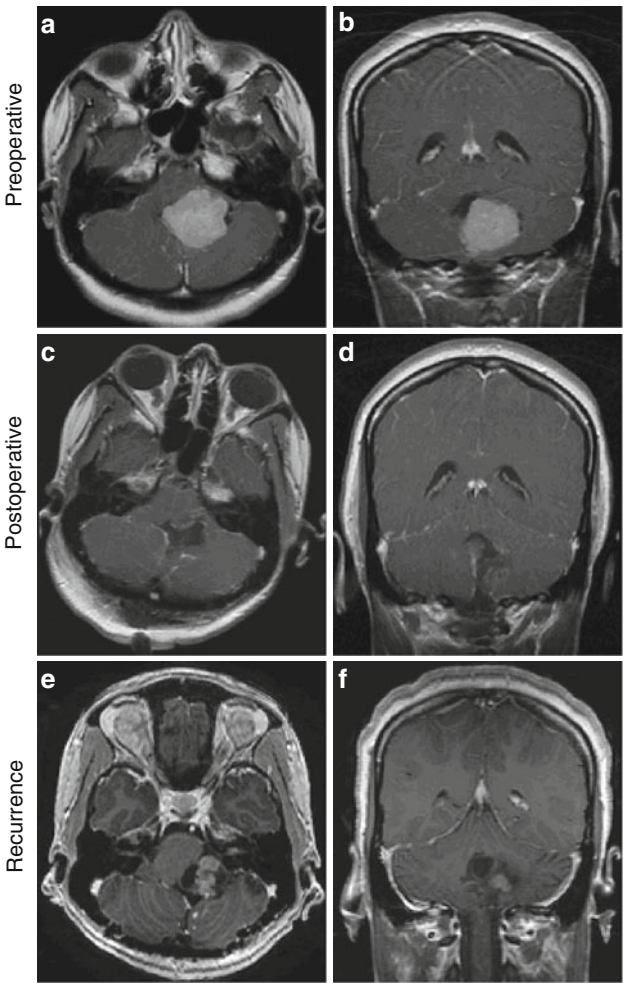

Fig. 1 Radiographic features of a choroid plexus papilloma at diagnosis, post-resection, and recurrence

Table 4 Summary of modern surgical series for choroid plexus papillomas

Years	Author	Study period	Number of patients	Age	Follow-up	Tumor control	Comments
2010	El-Gaidi and Eissa	2005–2008	3 CPP	9.5 mo (median) 7.2 mo (mean)	12 mo (median) 9.3 mo (mean)	100 % for CPP (0/3 recur)	3 GTR, 2 pts required shunts 1 death at 6 months due to shunt infection
			2 ACPP	11mo (mean)	18 mo (mean) range: 1–24 mo	100 % for ACPP (0/2 recur)	2 GTR, 1 pt required shunt 1 death at 12 months due to shunt infection
2010	Menon et al.	1998–2010	12 CPP	18.3 yrs (mean) range: 6 mo–50 yrs	5.4 yrs (mean) range: 1–10 yrs	92 % for CPP (1/12 recur at 9 yrs in pt who initially underwent total resection)	11/12 complete resection None received adjuvant therapy
			4 ACPP	22.1 yrs (mean) range: 9 mo–43 yrs	2 6mo (mean) range: 18–44 mo	50 % for ACPP (2/4 recur at 4 and 6 yrs in pts who underwent STR and NTR, respectively)	0/4 complete resection At recurrence, all ACPPs treated with surgery and chemotherapy 6 pts required shunts 4 pts developed motor deficits
2010	Tena-Suck et al.	1993–2005	24 CPP	31.5 yrs (mean)	12 mo (mean) range: 6–19.5 mo	42 % for CPP (14/24 recur)	10 GTR, 14 STR 20 pts required shunts Complications: 2 hemorrhages, 5 herniations, 1 infarction, 8 deaths
			4 ACPP	35 yrs (mean) range : 15–70 yrs (all patients)	8.5 mo (mean) range: 7–10.5 mo	0 % for ACPP (4/4 recur) Time to recurrence not reported	2 GTR, 2 STR 4 pts required shunts Complications: 3 hemorrhages, 1 infarct, 1 death
2005	Kumar et al.	1991–2001	8	13 mo (median) 2.5 yrs (mean) range: 2 mo–12 yrs	6 mo (median) 1.5 yrs (mean) range: 6 mo–5 yrs	100 % (0/7 recur)	7 GTR, 1 NTR 3 pts required shunts 1 intraoperative death
2004	Krishnan et al.	1974–2000	41	36 yrs (median) 36. yrs (mean) range: 6mo–74 yrs	6.5 yrs (median) 6.6 yrs (mean) range: 4 mo–28 yrs	76 % (10/41 recur at median time of 3.4 yrs)	23 GTR, 18 STR 5 tumors with atypical features EOR associated with tumor control (100 % 5 year local control among GTR vs. 68 % in STR) Over half of recurrences occurred < 14 months after initial surgery Temporary swallowing dysfunction in 22 % of pts 2 deaths at 3.5 and 1.3 years (both underwent STR)
2001	Due-Tønnessen et al.	1975–1998	13	1.2 yrs (median) 3.3 yrs (mean)	12.1 yrs (median) 11.1 yrs (mean) range: 0–24 yrs	100 % (0/11 recur)	11 GTR, 2 STR 5 pts required shunts 2 deaths from intraoperative hemorrhage Authors used Collin's law for follow-up MRI (scan every 3–6 months for duration equal to 9 months + age at surgery)
2001	Levy et al.	1985–1995	12	10.5 mo (median) 22.4 mo (mean) range: 2–9 6mo	7.7 yrs (median) 7.7 yrs (mean) range: 2.8–13.6 yrs	100 % (0/12 recur)	11 GTR, 1 STR 7 pts required shunts Developmental delay in 6 pts (2 mild, 1 moderate, 2 moderate/severe, 1 severe) 1 pt with seizure disorder due to surgery
2000	Nagib et al.	1988–2000	7	11mo (median) 2.3yrs (mean) range: 9wks–8yrs	4yrs (median) 5.8yrs (mean) range: 4mo–13.5yrs	100 % (0/7 recur)	7 GTR 2 pts required shunts 3 pts in special education No new postoperative deficits

Table 4 continued

Years	Author	Study period	Number of patients	Age	Follow-up	Tumor control	Comments
1998	Pencalet et al.	1971–1996	25 CPP	22.5 mo (median) range: 2 mo–15 yrs	NR	100 % (0/5 recur at 5 yrs)	24 GTR, 1 STR 17 pts required shunts 4 deaths: 2 related to operative blood loss, 2 occurred during first month of ICU hospitalization
1998	Talacchi et al.	1972–1996	12	39.5 yrs (median) 41.6 yrs (mean) range: 19–61 yrs	4.6 yrs (median) 7.3 yrs (mean) range: 3 mo–1 7yrs	80 % (2/10 both recur at 5 yrs)	4 GTR, 2 GTR + RT, 4 STR, 4 STR + RT 4 pts required shunts 6 deaths: 2 perioperative, 1 from lung cancer, 1 from aspiration pneumonia, 2 from tumor recurrence
1996	Tacconi et al.	1955–1992	32	30 yrs (median) range: 5 mo–72 yrs	13 yrs (median) range: 1.5–36 yrs	91 % (3/32 recur at median time of 10 yrs)	31 GTR, 1 STR + RT At last follow-up: 17 pts neurologically intact, 3 disabled, 1 with mild psycho-motor retardation, 8 deaths (2 unrelated to tumor), 6 shunts (all within 3 months of surgery), 1 death in elderly pt after surgery for recurrence Improved outcomes when comparing pre- to post-microsurgical era
1991	Knierim et al.	1980–1988	7	13 mo (median) 40 mo (mean) range: 3.5 mo–20 yrs	1.5 yrs (median) 2.1 yrs (mean)	100 % (0/7 recur)	EOR not specified 3 pts required shunts 1 pt required endocrine replacement No pts received RT

CPP choroid plexus papilloma, *ACPP* atypical choroid plexus papilloma (officially recognized by WHO in 2007), *GTR* gross total resection, *NTR* near total resection, *STR* subtotal resection, *RT* radiotherapy, *NR* not reported, *pt(s)* patient(s), *wks* weeks, *mo* months, *yrs* years

We performed a literature review to identify major surgical series published during the course of our data collection (Table 4). Our study compares favorably with respect to the number of patients included, however it is also important to note that the WHO has only officially recognized the diagnosis of atypical choroid plexus papilloma since 2007. Our study is unique because it is a modern series (1997–2011) consisting exclusively of patients treated in the MRI-era, and explicitly describes the association of extent of resection with respect to progression-free survival and surgical complications. The largest single institutional series to date consisted of 41 patients treated over a 26 year period [2]. The authors showed that extent of resection was associated with increased local tumor control, which has been confirmed in other institutional series and meta-analyses [3, 5, 8, 9]. The authors also reported a 22 % incidence of temporary swallowing dysfunction that required percutaneous endoscopic gastrostomy tubes, tracheostomy, or both, with no difference in the incidence when comparing patients who received GTR to STR [2]. Additionally, with respect to prognostic factors, we identified an association between MIB-1 index and tumor recurrence, which is supported by previously published data [10].

Major complications in our series were rare, which can be attributed to the fact that this is a modern series treated at a tertiary care center. The only significant complication occurred in a case of GTR. We are cautious to make any assumptions given the modest size of this study and it is unclear if aggressive surgical resection was a principle factor in the development of this major complication. As a result, we recommend limiting the resection to avoid neurologic injury. Overall, the incidence of complications observed in our study compares favorably with other published studies [5, 7, 9, 11], particularly those including patients treated in the pre-microsurgical era [6, 12, 13], in which perioperative mortality was high, especially in children [14–19]. Compared to published series from the modern microsurgical era, our observed morbidity and mortality were very minimal, once again confirming that these tumors can be safely resected in both children and adults [2, 3, 5, 9, 11]. Additionally, there was no association between surgical complications and tumor size. Although some studies have

described neurocognitive sequelae related to surgery for CPP [19, 20], both involved pediatric populations. Unfortunately, this data was not available for our population. Furthermore, our cohort is not large enough to make any significant conclusions with respect to differential outcomes in children compared to adults. The excellent outcomes in our study may be attributable to the relatively high proportion of adult patients, however a large prospective study would be best suited to identify potential discrepancies in outcomes between adult and pediatric patients. Lastly, since the current literature lacks standardized complication profile reporting, more rigorous reporting standards should be stressed in future studies analyzing surgical outcomes in CPPs.

There are several limitations to the present study. Small sample size limits the statistical power of our analysis, but is an unfortunate and inevitable consequence of studying such a rare tumor. Regardless, our study size compares favorably to other modern series and is among the largest analyses performed exclusively in the MRI-era (Table 4). Although our mean follow-up time of 4.5 years is modest, the largest single institution series found that most tumors recurred within the first 14 months after surgery [2]. Additionally, since our patient base consists mostly of referrals for tertiary care, it is not uncommon for individuals to seek follow-up care locally in order to avoid travelling long distances to our institution. Only two patients were lost to follow-up less than 1 year from the date of surgery. Furthermore, since this is a contemporary series, 8 patients (33 %) were treated in the past 5 years and therefore have limited follow-up duration. It is important to note that our average duration of follow-up for patients with STR was 10.7 years, which compares favorably to previous reports in the literature. With respect to surveillance imaging, practices varied by provider. Although Collin's law is often utilized in scheduling follow-up imaging for pediatric patients (surveillance imaging every 3–6 months for a duration equal to the patient's age at surgery plus 9 months), guidelines for adults are less established. Our experience has been to obtain MRI scans every 6–12 months, regardless of extent of resection, until the patient's disease has been stable for 2–3 years, at which point scans can be performed every 1–2 years.

There are inherent limitations to a retrospective analysis including recall bias, inability to control for confounders (no randomization or blinding), and difficulty establishing cause and effect [21]. Unfortunately, randomized prospective studies are impractical for surgical diseases, particularly those as rare as CPP. Combining pediatric and adult tumors, as well as different histologic groups, may be considered a limitation, however it allows for a more thorough analysis of these tumors in a heterogeneous population. Despite these limitations, our data is pertinent given the rarity of this tumor. Furthermore, we have demonstrated that these tumors can be safely removed, regardless of location, and likely do not require up-front radiation, even in cases of STR. Since some CPPs still recur despite GTR, future studies should build upon previously published genetic analysis of these tumors in order to identify markers that can refine our current grading scheme and provide improved insight towards predicting which tumors will recur [22–26]. Platelet-derived growth factor receptor (PDGFR) has been implicated in choroid plexus tumors, particularly carcinomas [27]. Imatinib, a tyrosine kinase inhibitor that targets PDGFR, was shown to decrease proliferation in the immortalized choroid plexus epithelial line Z310, suggesting it may play a role in future treatments [27]. The transcription factor TWIST1 is upregulated in CPPs compared to normal choroid plexus and is also found in the Z310 cell line [28]; decreasing its expression can decrease both infiltrative capacity and proliferative rate [29]. Current data suggests that activated Notch3 may function as an oncogene in the developing brain, driving choroid plexus tumor formation in utero [30]. The tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) pathway is involved in ligand-induced apoptosis and was found to be methylated in a large proportion of CPPs [31]. In choroid plexus carcinomas, extensive analysis has shown that *TP53* status can predict survival; those with wild-type *TP53* and low total structural variation (TSV) have a favorable prognosis and do not require radiation therapy, while those with *TP53*-mutated tumors should be treated more aggressively [22]. Given the rarity of these lesions and complex molecular pathways involved in tumorigenesis, large multi-institutional collaborative efforts will be needed to produce meaningful progress in the treatment of this disease.

Conclusions

Our data demonstrates that while transient perioperative complications are common, the overwhelming majority of patients fully recover with no long-term neurologic deficits. These tumors can be safely removed with good tumor control, even in cases of subtotal resection. Given the rarity of these tumors, future studies should focus on collaborative efforts among multiple institutions in order to use genetic analysis to refine our current classification system and improve our ability to predict long-term tumor control based on the tumor's biology, not surgical management.

Acknowledgments Mr. Safaee was supported by a grant from the Doris Duke Charitable Foundation. Dr. Parsa was partially funded by the Reza and Georgianna Khatib Endowed Chair in Skull Base Tumor Surgery.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Paulus W, Bradner S (2007) WHO Classification of Tumours of the Central Nervous System. IARC Press, Lyon
2. Krishnan S, Brown PD, Scheithauer BW, Ebersold MJ, Hammack JE, Buckner JC (2004) Choroid plexus papillomas: a single institutional experience. J Neurooncol 68:49–55
3. Wolff JE, Sajedi M, Brant R, Coppes MJ, Egeler RM (2002) Choroid plexus tumours. Br J Cancer 87:1086–1091. doi:10.1038/sj.bjc.6600609
4. Palazzi M, Di Marco A, Campostrini F, Grandinetti A, Bontempini L (1989) The role of radiotherapy in the management of choroid plexus neoplasms. Tumori 75:463–469
5. Tacconi L, Delfini R, Cantore G (1996) Choroid plexus papillomas: consideration of a surgical series of 33 cases. Acta Neurochir (Wien) 138:802–810
6. Hawkins JC 3rd (1980) Treatment of choroid plexus papillomas in children: a brief analysis of twenty years' experience. Neurosurgery 6:380–384
7. Talacchi A, De Micheli E, Lombardo C, Turazzi S, Bricolo A (1999) Choroid plexus papilloma of the cerebellopontine angle: a twelve patient series. Surg Neurol 51:621–629
8. McGirr SJ, Ebersold MJ, Scheithauer BW, Quast LM, Shaw EG (1988) Choroid plexus papillomas: long-term follow-up results in a surgically treated series. J Neurosurg 69:843–849. doi:10.3171/jns.1988.69.6.0843
9. Menon G, Nair SN, Baldawa SS, Rao RB, Krishnakumar KP, Gopalakrishnan CV (2010) Choroid plexus tumors: an institutional series of 25 patients. Neurol India 58:429–435
10. Kato T, Fujita M, Sawamura Y, Tada M, Abe H, Nagashima K, Nakamura N (1996) Clinicopathological study of choroid plexus tumors: immunohistochemical features and evaluation of proliferative potential by PCNA and Ki-67 immunostaining. Noshuyo Byori 13:99–105
11. Tena-Suck ML, Salinas-Lara C, Rembao-Bojorquez D, Castillejos M (2010) Clinicopathologic and immunohistochemical study of choroid plexus tumors: single-institution experience in Mexican population. J Neurooncol 98:357–365
12. Guidetti B, Spallone A (1981) The surgical treatment of choroid plexus papillomas: the results of 27 years experience. Neurosurg Rev 4:129–137
13. Wilkins H, Rutledge BJ (1961) Papillomas of the choroid plexus. J Neurosurg 18:14–18. doi:10.3171/jns.1961.18.1.0014
14. Pencalet P, Sainte-Rose C, Lellouch-Tubiana A, Kalifa C, Brunelle F, Sgouros S, Meyer P, Cinalli G, Zerah M, Pierre-Kahn A, Renier D (1998) Papillomas and carcinomas of the choroid plexus in children. J Neurosurg 88:521–528. doi:10.3171/jns.1998.88.3.0521
15. Piastra M, Di Rocco C, Tempera A, Caresta E, Zorzi G, Tosi F, Massimi L, Pietrini D (2007) Massive blood transfusion in choroid plexus tumor surgery: 10-years' experience. J Clin Anesth 19:192–197. doi:10.1016/j.jclinane.2006.10.010
16. Kumar R, Singh S (2005) Childhood choroid plexus papillomas: operative complications. Childs Nerv Syst 21:138–143. doi:10.1007/s00381-004-0993-4
17. Due-Tonnessen B, Helseth E, Skullerud K, Lundar T (2001) Choroid plexus tumors in children and young adults: report of 16 consecutive cases. Childs Nerv Syst 17:252–256
18. El-Gaidi MA, Eissa EM (2010) Infantile intracranial neoplasms: characteristics and surgical outcomes of a contemporary series of 21 cases in an Egyptian referral center. Pediatr Neurosurg 46:272–282. doi:10.1159/000321540
19. Nagib MG, O'Fallon MT (2000) Lateral ventricle choroid plexus papilloma in childhood: management and complications. Surg Neurol 54:366–372
20. Levy ML, Goldfarb A, Hyder DJ, Gonzales-Gomez I, Nelson M, Gilles FH, McComb JG (2001) Choroid plexus tumors in children: significance of stromal invasion. Neurosurgery 48:303–309
21. Hess DR (2004) Retrospective studies and chart reviews. Respiratory care 49:1171–1174
22. Tabori U, Shlien A, Baskin B, Levitt S, Ray P, Alon N, Hawkins C, Bouffet E, Pienkowska M, Lafay-Cousin L, Gozali A, Zhukova N, Shane L, Gonzalez I, Finlay J, Malkin D (2010) TP53 alterations determine clinical subgroups and survival of patients with choroid plexus tumors. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 28:1995–2001. doi:10.1200/JCO.2009.26.8169
23. Custodio G, Taques GR, Figueiredo BC, Gugelmin ES, Oliveira Figueiredo MM, Watanabe F, Pontarolo R, Lalli E, Torres LF (2011) Increased incidence of choroid plexus carcinoma due to the germline TP53 R337H mutation in southern Brazil. PLoS ONE 6:e18015. doi:10.1371/journal.pone.0018015
24. Rickert CH, Wiestler OD, Paulus W (2002) Chromosomal imbalances in choroid plexus tumors. Am J Pathol 160:1105–1113. doi:10.1016/S0002-9440(10)64931-0
25. Losi-Guembarovski R, Kuasne H, Guembarovski AL, Rainho CA, Colus IM (2007) DNA methylation patterns of the CDH1, RARB, and SFN genes in choroid plexus tumors. Cancer Genet Cytogenet 179:140–145. doi:10.1016/j.cancergencyto.2007.05.029
26. Safaee M, Oh MC, Bloch O, Sun MZ, Kaur G, Auguste KI, Tihan T, Parsa AT (2012) Choroid plexus papillomas: advances in molecular biology and understanding of tumorigenesis. Neuro-oncology. doi:10.1093/neuonc/nos289
27. Koos B, Paulsson J, Jarvius M, Sanchez BC, Wrede B, Mertsch S, Jeibmann A, Kruse A, Peters O, Wolff JE, Galla HJ, Soderberg O, Paulus W, Ostman A, Hasselblatt M (2009) Platelet-derived growth factor receptor expression and activation in choroid plexus tumors. Am J Pathol 175:1631–1637. doi:10.2353/ajpath.2009.081022
28. Hasselblatt M, Bohm C, Tatenhorst L, Dinh V, Newrzella D, Keyvani K, Jeibmann A, Buerger H, Rickert CH, Paulus W (2006) Identification of novel diagnostic markers for choroid plexus tumors: a microarray-based approach. American J Surg Pathol 30:66–74
29. Hasselblatt M, Mertsch S, Koos B, Riesmeier B, Stegemann H, Jeibmann A, Tomm M, Schmitz N, Wrede B, Wolff JE, Zheng W, Paulus W (2009) TWIST-1 is overexpressed in neoplastic choroid plexus epithelial cells and promotes proliferation and invasion. Cancer Res 69:2219–2223. doi:10.1158/0008-5472.CAN-08-3176
30. Dang L, Fan X, Chaudhry A, Wang M, Gaiano N, Eberhart CG (2006) Notch3 signaling initiates choroid plexus tumor formation. Oncogene 25:487–491. doi:10.1038/sj.onc.1209074
31. Michalowski MB, de Fraipont F, Michelland S, Entz-Werle N, Grill J, Pasquier B, Favrot MC, Plantaz D (2006) Methylation of RASSF1A and TRAIL pathway-related genes is frequent in childhood intracranial ependymomas and benign choroid plexus papilloma. Cancer Genet Cytogenet 166:74–81. doi:10.1016/j.cancergencyto.2005.09.004