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Choroid plexus tumors in childhood

Histopathologic study and clinico-pathological correlation

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Abstract. Choroid plexus tumors are rare and account for only 2.3% (8/352) of primary childhood intracranial neoplasms in our series. Most of our patients were under 2 years of age. The tumors had a predilection for the lateral ventricle. Calcification was found in half of these tumors, and ossification was seen in 1 case. Histological features of malignancy including invasion, loss of differentiation, and severe nuclear pleomorphism pointed to a poor prognosis. Such features were found in 2 cases. Neither a large number of mitoses nor necrosis was a constant feature in cases of malignancy. Transthyretin, a marker for choroid plexus tumors, was positive in all cases. However, negative S-100 or positive carcinoembryonic antigen was not necessarily associated with a more aggressive histological pattern. All the papillomas could be totally resected without recurrence, and all the patients with carcinoma died within a few months.

Key words: Choroid plexus tumor – Immunohistochemistry – Childhood

Choroid plexus tumors (CPTs) are rare and account for only 1.5–4% of all intracranial tumors in children [6–8, 15, 19]. They occur even less frequently in adults, amounting to only 0.3–0.8% of intracranial tumors in such patients [6, 8, 15, 19, 21]. This article deals with our experience relating to CPTs in children over a period of 14 years. Detailed histological and immunohistochemical studies were performed and evaluated using the clinical data available for each case.

Materials and methods

Eight CPTs, including 6 choroid plexus papillomas (CPPs) and 2 choroid plexus carcinomas (CPCs), were diagnosed in a series of 352 pathologically proven childhood brain tumors in the Veterans General Hospital-Taipei from 1977 to 1990. Their clinical manifestations, treatment, and follow-up data were reviewed from the medical records.

All the tissue sections were re-cut from the paraffin blocks. Hematoxylin and eosin (H&E) stain as well as periodic acid-Schiff reaction with and without diastase pretreatment were performed for morphological evaluation. Immunostains for glial fibrillary acidic protein [GFAP, dilution 1:450, peroxidase-antiperoxidase (PAP), Dako, Glostrup, Denmark], S-100 protein (1:300, PAP, Dako), cytokeratin [CKER, AE1/AE3, 1:120, avidin biotin peroxidase complex (ABC), Signet Lab., Oedham, Mass.], vimentin (VIM, 1:10, ABC, Dako), carcinoembryonic antigen (CEA, 1:600, PAP, Dako) and transthyretin (TTR, prealbumin, 1:500, PAP, Dako) were performed with appropriate positive and negative controls. Since TTR was sensitive to heat and would attenuate or lose its immunoreactivity [11], we air-dried the slides for TTR overnight and incubated them at 37 °C for 2 h instead of incubating the slides at 55 °C for less than 2 h as for the other immunostains. The staining intensity was estimated based on the proportion of cells stained and the intensity of their staining: +/−: less than 1% cells stained intensely/moderately or some cells stained weakly; 1+: less than 10% cells stained intensely/moderately or many cells stained weakly; 2+: 10–50% cells stained intensely or many cells stained moderately; 3+: 50–80% cells stained intensely; and 4+: more than 80% cells stained intensely.

Results

There were 6 CPPs and 2 CPCs (Table 1). The age of the patients ranged from 6 months to 13 years. Six were male and 2 were female. Among the 6 CPPs, 3 were located in the lateral ventricle, 1 was located in the lateral and the III ventricles, 1 in the III ventricle and 1 in the IV ventricle. Of the 2 CPCs, 1 was located in the lateral ventricle and 1 in the cerebellopontine (c-p) angle. Hydrocephalus was present in all patients, and the most common symptoms and signs were related to increased intracranial pressure. Total resection of the tumor was performed in all cases of CPP. The follow-up time ranged from 4 to 13 years. All patients were alive without local recurrence or subarachnoid seeding. The 2 CPCs could only be partially resected because of infiltrative growth and the high vascularity of these tumors. These 2 patients died 1 and 3 months after the operation, respectively.

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Table 1. Clinical findings of choroid plexus tumor. CPP, Choroid plexus papilloma; lat, lateral ventricle; TR, total resection; III, III ventricle; IV, IV ventricle; CPC, choroid plexus carcinoma; PR, partial resection; c-p, cerebellopontine angle; L, left; R, right

	Age/sex	Site	Size	Symptoms and signs	Hydro-cephalus	Therapy	Outcome	Follow-up
CPP								
1.	6 months/F	lat L	4 cm	Irritability, hyperreflexia	+	TR	Alive	5 years
2.	1 year 3 months/M	lat R	6 cm	Consciousness change, enlarged head	+	TR	Alive	5 years
3.	2 years/M	lat L	3 cm	Lower limb weakness, drowisness, ataxia	+	TR	Alive	9 years
4.	11 months/F	lat R & III	5 cm	Failure to thrive, enlarged head	+	TR	Alive	4 years
5.	1 year/M	III	4 cm	Nausea, vomiting, enlarged head, ataxia	+	TR	Alive	6 years
6.	13 years/M	IV	4 cm	Vomiting, papilledema, truncal ataxia	+	TR	Alive	13 years
CPC								
7.	2 years/M	lat R	5 cm	Convulsion, semicoma, papilledema	+	PR	Dead	1 month
8.	6 years/M	c-p R	4 cm	Vomiting, truncal ataxia	+	PR	Dead	3 months

Table 2. Histopathological findings of CPT. PB, Psammoma bodies; AC, amorphous calcification; Oss, ossification; Hem, hemorrhage; Ple, nuclear pleomorphism; Mit, mitoses/10 HPF; Nec, necrosis; 1+, mild; 2+, moderate; 3+, severe

	Pattern			Calcification		Oss	Hem	Ple	Mit	Nec
	Papillary	Acinar	Solid	PB	AC					
CPP										
1.	+	–	–	–	–	–	–	1+	3	–
2.	+	–	–	–	–	–	+	2+	–	–
3.	+	Focal	–	3+	–	–	–	–	–	–
4.	+	–	–	2+	1+	–	–	–	–	–
5.	+	–	–	1+	1+	–	–	–	–	–
6.	+	–	–	1+	–	+	–	–	Rare	–
CPC										
7.	+	–	+	–	–	–	+	2–3+	Rare	Focal
8.	+	–	+	–	–	–	–	3+	>10	–

Histologically, the CPPs were composed of papillary fronds covered with a single layer of well-differentiated cuboidal to columnar epithelium with round to oval, basally situated nuclei. Mitotic figures were absent or rare (<1/40 HPF) in all except 1 case, in which mitotic activity reached 3/10 HPF. The stroma was composed of fibrovascular connective tissue (Fig. 1). An acinar pattern was seen in 1 CPP. Both CPCs, in addition to a papillary pattern, showed loss of differentiation with a solid growth pattern and severe nuclear pleomorphism. Endothelial proliferation was prominent in their stroma (Fig. 2). A large number of mitoses and spotty necrosis were also found in the CPCs (Table 2). Calcification in the form of psammoma bodies and amorphous calcification was found in 4 of 8 CPTs (Fig. 3). Ossification was noted in 1 of 8 CPTs (Fig. 4). Hemorrhage could be observed in 1 of 6 CPPs and 1 of 2 CPCs.

The results of immunohistochemical staining are listed in Table 3. Five CPTs were positive for GFAP. Although the staining for S-100 was usually strong in CPPs and negative or weak in CPCs, it was negative or weak in 2 CPPs. The staining for CKER and VIM was generally weaker in CPCs than CPPs, although staining in some CPPs was negative or weak. All CPTs were positive for TTR (Figs. 5, 6) and negative for CEA.

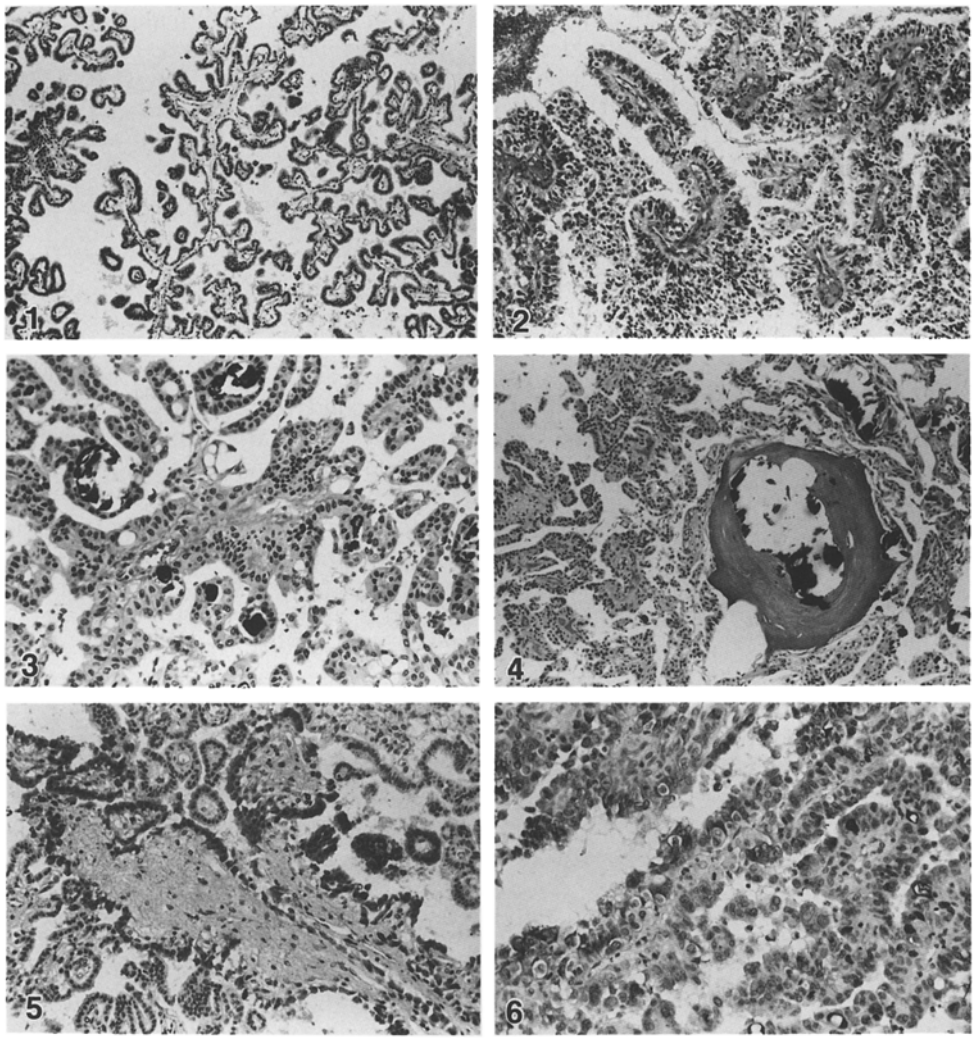

Fig. 1. Choroid plexus papilloma (CPP) showing papillary fronds covered with well-differentiated cuboidal to columnar epithelium and fibrovascular connective tissue stroma. H&E, ×47

Fig. 2. Choroid plexus carcinoma (CPC) showing loss of differentiation with solid pattern, severe nuclear pleomorphism and endothelial proliferation in the stroma. H&E, ×78

Fig. 3. CPP with psammoma bodies. H&E, ×130

Fig. 4. CPP with ossification. H&E, ×62

Fig. 5. CPP showing transthyretin (TTR) immunoreactivity. Anti-TTR immunoperoxidase, ×98

Fig. 6. CPC showing TTR immunoreactivity. Anti-TTR immunoperoxidase, ×130

Table 3. Immunohistological findings of CPT. GFAP, Glial fibrillary acidic protein; S-100, S-100 protein; CKER, cytokeratin (AE1/AE3); VIM, vimentin; CEA, carcinoembryonic antigen; TTR, transthyretin (prealbumin). +/−, <1% cells stained intensely/moderately or some cells stained weakly; 1+, <10% cells stained intensely/moderately or many cells stained weakly; 2+, 10–50% cells stained intensely or many cells stained moderately; 3+, 50–80% cells stained intensely; 4+, >80% cells stained intensely

	GFAP	S-100	CKER	VIM	CEA	TTR
CPP						
1.	1+	4+	1+	+/−	−	2+
2.	−	−	−	1+	−	3+
3.	1+	1+	1+	2+	−	3+
4.	−	4+	+/−	−	−	3+
5.	2+	4+	2+	4+	−	2+
6.	2+	4+	3+	4+	−	1+
CPC						
7.	1+	+/−	−	+/−	−	2+
8.	−	−	1+	1+	−	3+

Discussion

The incidence of CPTs in our series of 352 pathologically proven primary intracranial neoplasms in infancy and childhood was 2.3% (8/352), and most (6/8) cases were under 2 years of age. Both findings are compatible with previous reports [6–8, 15, 19, 21]. CPT has a predilection for the lateral ventricle in children and for the IV ventricle in adults [8, 15, 21]. Indeed, of our 6 patients 2 years old or younger, 4 had tumors in the lateral ventricle, 1 in the lateral and the III ventricles, and 1 in the III ventricle alone. The 6-year-old and 13-year-old patients had tumors in the c-p angle and the IV ventricle, respectively. CPT in either the III ventricle or the c-p angle is rare. Only 25 cases of the former had been reported up to 1981 [20], and up to 1987, only 20 cases of the latter [3, 21].

The most common symptoms and signs in our patients were related to increased intracranial pressure due to coexisting hydrocephalus, which can be the result of hypersecretion of cerebrospinal fluid (CSF) or obstruction of

CSF pathways [14, 20]. Tumor hemorrhage, desquamation of necrotic tumor, and metastases along the CSF pathways have also been implicated as causes of hydrocephalus in these patients [6, 14].

Calcification, in the form of psammoma body or amorphous calcification, is common [14] and occurred in 4 of our 8 cases. Ossification, present in 1 of our cases, however, is an exceedingly rare occurrence – only 3 cases had been reported up to 1985 [2].

Two (25%) CPTs in our series were CPCs; the reported incidence of malignant CPT falls between 10% and 30% [19]. In general, we followed the criteria defined by Russell and Rubinstein [18] and Lewis [12] for the diagnosis of CPC, including invasion of adjacent neural tissue, loss of regular papillary architecture (loss of differentiation), and cytological evidence of malignancy or anaplasia.

The differential diagnosis should include papillary ependymoma and metastatic papillary carcinoma especially from the lung [5]. By classic histological criteria CPT is usually easily distinguished from papillary ependymomas by virtue of its delicate fibrovascular stroma, in contrast to the presence of fibrillary neuroglial stroma in papillary ependymomas [5, 17]. The distinction of CPT from metastatic carcinoma still requires extensive clinical evaluation [4, 18], although the presence of GFAP in the tumor cells would virtually exclude the diagnosis of metastatic carcinoma [18], and TTR appears to be a promising marker for choroid plexus neoplasm [11]. In children the question of secondary carcinoma can be ignored, as this phenomenon has not yet been described [12].

GFAP was focally identified in 5 of our 8 CPTs. It has been suggested by Rubinstein and Brucher [17] that GFAP positivity is an indication of focal glial, presumably ependymal, divergent differentiation of the choroid plexus epithelium.

TTR (prealbumin), a transport protein for thyroxine and retinol, is synthesized in liver, retinal pigment epithelium and choroid plexus epithelium [1, 10, 11]. At the present time, it is claimed to be a specific marker for CPT [11]. Although TTR expression in CPT is inconsistent in the literature [13, 16], Herbert et al. [11] have reported that TTR antigenicity in tissue sections is sensitive to heat and to the method of fixation and embedding; after appropriate methodological modifications, they found consistently positive TTR immunostaining in primary choroid plexus neoplasm. Following the recommendation of incubating the slides at 37 °C [11], we were also able to enhance the TTR staining. Indeed, all our CPPs and CPCs demonstrated TTR antigenicity.

According to previous reports, CPP contains more S-100-positive tumor cells than CPC does, and the absence of S-100 is claimed to be associated with malignancy [4, 13]. In our cases, although S-100 staining was strong in 4 of 6 CPPs and negative or weak in CPCs, staining in 2 of 6 CPPs was also either negative or weak. Absence of or only weak staining with S-100 is, therefore, not necessarily associated with malignancy.

Previous reports have shown a high incidence of CEA positivity in CPC [4, 7, 13] and an absence [7, 13, 16] or low incidence [4] of CEA positivity in CPP, suggesting that the presence of CEA is indicative of malignancy and associated with a worse prognosis [4]. However, our findings showed that there was no staining with CEA in any of the CPTs, including the malignant ones. A recently reported large series of CPCs, which also showed a low incidence (2/22) of CEA positivity, suggested that its presence denotes the possibility of a metastatic carcinoma [16].

There have been different opinions on the correlation between morphological features and prognosis. Some authors [14, 16] did not find features such as increased cellular density, nuclear pleomorphism, blurred papillary structure, presence of occasional mitotic figures, microscopic infiltration, and ependymal differentiation to be correlated with prognosis. Several authors [9, 19] also stated that the likelihood of recurrence or tumoral seeding does not appear to be strictly related to histological malignancy. However, others [14, 16, 18] found that tumors with histological features such as invasion, complex growth pattern, nuclear pleomorphism, mitotic activity and necrosis imply a poor prognosis.

In our cases, invasion, loss of differentiation, severe nuclear pleomorphism, mitoses and necrosis were associated with malignancy and poor prognosis. Among all these features, invasion, loss of differentiation and severe nuclear pleomorphism appeared to be the most important. A large number of mitoses and necrosis did not appear to be essential for the diagnosis of malignancy, since they might not be present in individual cases (Table 2).

Our study strongly indicates that the histopathological features of CPT correlate well with its prognosis. All our CPPs could be totally resected and showed neither signs of subarachnoid seeding nor recurrence; however, all the patients with CPC died within a few months. Because of the poor outcome of CPC, accurate pathological diagnosis is mandatory for further adjuvant management.

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