Papillomas and carcinomas of the choroid plexus in children

Philippe Pencalet, M.D., Christian Sainte-Rose, M.D., Arielle Lellouch-Tubiana, M.D., Chantal Kalifa, M.D., Francis Brunelle, M.D., Spiros Sgouros, M.D., F.R.C.S., Philippe Meyer, M.D., Giuseppe Cinalli, M.D., Michel Zerah, M.D., Alain Pierre-Kahn, M.D., and Dominique Renier, M.D.

Services de Neurochirurgie Pédiatrique, Anatomie Pathologique, Radiologie Pédiatrique, and Anesthésie-Réanimation, Hôpital Necker-Enfants Malades, Paris, France; and Service d'Oncologie Pédiatrique, Institut Gustave Roussy, Villejuif, France

Object. Choroid plexus tumors are rare intraventricular tumors (1% of all intracranial tumors) that occur mainly in children. The physiopathological characteristics of associated hydrocephalus, surgical management, and oncological issues related to these tumors remain a matter of debate. To understand more about these tumors, the authors have reviewed their experience with the management of 38 children with choroid plexus tumors.

Methods. There were 25 cases of papilloma and 13 of carcinoma. The mean age of the patients at presentation was 22.5 months and one-half of the patients were younger than 2 years of age. Hydrocephalus was present in 33 patients and poorly correlated with the size, site, and pathological characteristics of the tumor. In nine children, a ventriculoperitoneal shunt was required after tumor excision, calling into question the notion that cerebrospinal fluid oversecretion is the only cause of hydrocephalus.

Complete excision was achieved in 96% of the cases of papilloma and 61.5% of the cases of carcinoma. These surgical procedures were complicated by the risks of perioperative hemorrhage, which proved to be fatal in two cases, and postoperative brain collapse, which led to subdural fluid collections requiring subdural shunt placement in six patients. Preoperative embolization was partially successful in four cases and significantly assisted surgery. Preoperative controlled drainage of excessively dilated ventricles and intraoperative gluing of the cortical incision have been used to address the problem of postoperative brain collapse.

Patients with carcinomas were treated postoperatively by chemotherapy alone (seven cases), radiotherapy (one case), or chemotherapy plus radiotherapy (one case). The overall 5-year survival rate was 100% for patients with papillomas and 40% for those with carcinomas.

Conclusions. Total surgical excision is curative in cases of papillomas. For carcinomas, the most effective treatment remains total surgical excision; however, adjuvant treatment in the form of chemotherapy in patients younger than 3 years, supplemented by radiation therapy in older children, can moderately reduce the risk of recurrence.
Tumors of the choroid plexus are rare neoplasms of neuroectodermal origin, accounting for less than 1% of all intracranial tumors.[6,7,28,41,61] These tumors are primarily found in children, but they can be observed as well as in adults and infants,[11,23,33,36,55,62] and prenatal occurrence has been reported.[2] In children, tumors of the choroid plexus are located most often in the lateral ventricle, but they can also be found in the third ventricle and in the posterior fossa.[6,8,10,11,13,20,21,27,29,42,56,60]

Of particular surgical interest in cases of choroid plexus tumors are: 1) the associated hydrocephalus, its pathophysiological characteristics, and the way it interferes with removal of the tumor:[15,17,22,26,30,37,40,50,53,57,59] and 2) the increased vascularity of these tumors, which makes surgery challenging, particularly in cases of carcinoma because the patients tend to be of young age.[7,24,41,47,51,54,58,62] Although papillomas are usually cured by surgery, carcinomas have a tendency to recur. The type of adjuvant treatment necessary remains open to discussion.[3,4,14,38,44,48,54]

**CLINICAL MATERIAL AND METHODS**

Between 1971 and 1996, 38 children (24 boys and 14 girls) were treated at Hôpital Necker-Enfants Malades, Paris for choroid plexus tumors, including papillomas and carcinomas. The children were aged 2 months to 15 years (median 22.5 months). One-half of them were younger than 2 years of age at presentation. Radiological diagnosis was made by means of ventriculography and angiography in six patients, all of whom were treated before 1977, and by computerized tomography (CT) or magnetic resonance (MR) imaging in 32 cases.

All histological slides in these cases were reviewed by the same pathologist. Histological diagnosis was assessed according to the World Health Organization (WHO) criteria[32] for choroid plexus tumors. Choroid plexus papillomas were composed of a single layer of cuboidal-to-columnar cells, resting on a basement membrane overlying papillary and vascularized connective tissue. Carcinomas were diagnosed when there was evidence of anaplasia such as increased mitotic activity, nuclear atypia, loss of papillary differentiation, and necrosis. Immunoreactivity of tumor cells for cytokeratin was required for diagnosis.[43] In some instances, choroid plexus carcinomas were difficult to distinguish from papillary forms of ependymomas. Immunocytochemical analysis was helpful in these cases, with ependymomas generally displaying a widespread positive reaction for glial fibrillary acidic protein and a negative reaction for cytokeratin, in contrast to choroid plexus tumors.[31,45] Following the criteria outlined, the tumors were classified as benign choroid plexus papilloma (25 cases) or malignant choroid plexus carcinoma (13 cases). However, it is probable that in choroid plexus tumors the distinction between benign and malignant is not as simple as that described in the WHO classification. Mixed forms of papilloma, combining well-differentiated papillary structures and anaplastic areas are not rare.[14] Such a form was observed in this study and was categorized as carcinoma. In the early years of this study, two patients with papillomas that exhibited mitotic features were categorized as having papillomas.

**RESULTS**

The patients' presenting symptoms are outlined in Table 1. Signs of raised intracranial pressure were a common feature. Duration of symptoms before diagnosis varied from 1 day to 4 years in cases of
papilloma (median 4 weeks) and from 3 days to 1 year in cases of carcinoma (median 5 weeks). Children younger than 5 years of age had a shorter mean duration of symptoms before diagnosis (8.4 compared with 48.1 weeks).

Radiological Examination

In 27 cases (71%) the tumor arose from the lateral ventricle (in 15 cases from the right side and in 12 from the left), in three cases (8%) from the third ventricle, in five cases (13%) from the fourth ventricle, and in three cases (8%) the tumor was located extraventricularly, at the cerebellopontine angle. The mean size of the tumor in its largest diameter was 4.5 cm (range 1-8 cm).

The typical appearance of the tumor on neuroradiological examinations (CT or MR imaging) was that of a hyperdense, contrast-enhancing lesion developing in the lateral or third ventricle in relation to the choroid plexus (Fig. 1 left). Diagnosis can be difficult when the lesion is outside the lateral ventricles. Hydrocephalus was seen in all but five cases (Fig. 1 right). CT scans revealed calcifications in four patients (10.5%). Preoperative angiography was performed in 25 cases.
Fig. 1. Left: Contrast-enhanced T₁-weighted MR images showing a choroid plexus papilloma that developed in the third ventricle. The vascular tumor pedicle arising from the choroid plexus and the associated hydrocephalus are typically observed in cases of these lesions. Right: An MR image showing a choroid plexus carcinoma of the lateral ventricle without hydrocephalus. In children such appearances can be similar to those of an ependymoma or an intraventricular meningioma.

In recent years, preoperative angiography was combined with a trial of embolization, in an attempt to reduce perioperative hemorrhage in seven patients who had tumors that developed in the lateral ventricle (five carcinomas and two papillomas). This proved partially successful in three cases of carcinoma (Fig. 2), and in one case of papilloma. Despite the partial embolization, obliteration of the major arterial pedicle(s) made surgery easier and safer in cases in which the tumor volume made control of these arteries impossible at the beginning of surgery. In all cases, the tumors were vascularized by choroidal arteries that extended from the posterior cerebral artery. In addition, in one case, a carcinoma was also fed by cortical branches and in another case by the anterior choroidal artery. Unsuccessful embolization in choroid plexus tumors can be explained by the difficulty entering the posterior choroidal artery because of its recurrent course from the posterior cerebral artery and by the absence of increased flow such as that which exists in arteriovenous malformations.
In the last patient admitted to the series (a 4-year-old boy with a carcinoma) the first operation, which was performed after partial embolization of the posterolateral choroidal artery, had to be abandoned because of profound intraoperative hemorrhage resulting from 10 hours of dissection and hemostasis. One month after the unsuccessful surgery, percutaneous stereotactic intratumoral embolization was performed using a technique similar to the one described by Casasco and colleagues.[9] The tumor was tapped stereotactically. After an initial injection of diluted contrast medium, bidirectional fluoroscopy revealed the local parenchymography followed by local and regional venous drainage without extravasation and allowed us to determine that the volume required to enhance the whole lesion was 0.5 ml. An equal volume of a mixture of a sclerosant agent (ethoxyscerol) plus contrast medium was then injected. Total excision of the tumor, which had been partially devascularized, was then achieved 5 days after embolization (Fig. 3).

In patients with carcinomas, postoperative MR examination of the spinal cord did not reveal any metastatic lesion. The only metastasis observed at presentation was located in the ambient cistern.

**Surgical Management**

The surgical approach was chosen according to tumor location. Removal of the tumor was total in 96% of cases of papilloma (24 of 25 patients). In one child who had a fourth ventricular papilloma, tumor adherence to the floor of the fourth ventricle was encountered, which necessitated subtotal excision.
Total excision was achieved in 61.5% of cases of carcinoma (eight of 13 patients). Three of these children underwent two-stage surgery; the first operation was stopped because of excessive bleeding in a young patient. Total removal of the tumor achieved a few weeks later in a second operation. As already mentioned, one of these children was surgically treated after direct stereotactic embolization of the lesion. Of the remaining five children, two died as a result of excessive blood loss and cardiorespiratory arrest at the time of surgery and two died in the 1st postoperative month following a protracted period of intensive care; in the other patient, only a partial excision was performed because of tumor adherence to the midline structures and excessive perioperative bleeding. This hemorrhage, observed only in large lesions located in the lateral ventricle, had two possible origins: the tumor itself, when it was not possible to control arterial feeding vessels prior to tumor debulking, or an injury of the deep drainage veins on the midline, responsible for a sudden hemorrhage at the latest stage of surgery in an infant who had already received significant blood transfusion.

Management of Cerebrospinal Fluid-Related Complication

Before surgery, eight patients were treated by external ventricular drainage and one by endoscopic ventriculocisternostomy in a tumor of the fourth ventricle. In one patient in whom external ventricular drainage was used, increased production of cerebrospinal fluid (CSF) to 800 ml/24 hours was recorded. He had a papilloma of the third ventricle and 5 months after total removal, placement of a ventriculoperitoneal shunt was required for slowly progressive hydrocephalus. Nine patients (24%) required ventriculoperitoneal shunt placement after surgery (six children papillomas and three with carcinomas). In one patient a shunt was placed after partial resection. Despite complete tumor removal, in seven patients (five with papillomas and two with carcinomas), hydrocephalus continued to progress and required insertion of a shunt after an interval ranging from 1 to 5 months (median 10 weeks). Preoperative duration of symptoms was significantly longer in patients who required postoperative shunt insertion (30 weeks compared with 11 weeks; Student's t-test, p = 0.01). In the patients who required a permanent shunt, the tumor was located in lateral ventricles in six cases and in the third ventricle in three cases. One child developed metastasis in the posterior fossa, which impaired the CSF hydrodynamics; this patient required shunt placement 3 years after tumor removal.

After surgery, six children (two with papillomas and four with carcinomas; 18% of the survivors group) developed subdural fluid collections that required subduroperitoneal shunts. All of these patients displayed marked ventricular dilation at the time of tumor surgery, had not undergone ventricular drainage, and had been surgically treated from the lateral ventricle via a transcortical (transfrontal, transtemporal, or parietooccipital) approach. Of the six, three (one with a papilloma and two with carcinomas) had had their corticotomy sealed with biological glue (Tisseel, Immuno AG, Vienna, Austria)[25] and three (one with papilloma and two with carcinomas) had not. In the former three patients, sealing of the corticotomy allowed successful drainage of the subdural fluid collection and reexpansion of the thin cortical mantle (Fig. 4).
Fig. 4. Neurological images obtained in a case in which closure of the corticotomy was accomplished with biological glue. Left: The risk of a permanent communication between the ventricles and the subdural spaces is maximum in cases in which there is a thin cortical mantle. Center: Closing the corticotomy with biological glue isolates the ventricular system from the subdural space, allowing the cortical mantle to reexpand. Right: This technique allows efficient drainage of a postoperative cerebral fluid collection if needed.

In the latter three patients, who were treated in the beginning of our experience, persistent direct communication of the subdural spaces with the ventricular system, resulted in poor resolution of the fluid collection despite shunt placement (Fig. 5).

Fig. 5. Neuroimaging study showing that subduroperitoneal fluid diversion with a simple tube is insufficient to drain a pericerebral fluid collection when a large communication between the ventricles and the subdural spaces exists. Inevitable enlargement of these subdural pericerebral collections is usually associated with poor patient outcome.
Adjuvant Treatment in Cases of Choroid Plexus Carcinomas

Of the nine patients with carcinoma who survived surgery, seven received postoperative chemotherapy alone, one received radiotherapy only (55 Gy), and one received both chemotherapy and radiotherapy. Before 1990, chemotherapy was mainly based on nitrosoureas. The four children treated since 1990 received the "BB-SFOP" protocol, a 16-month-long multiagent chemotherapeutic protocol used in young children who harbor malignant brain tumors. A biopsy specimen was obtained in one patient at another institution; the diagnosis was malignant ependymoma, for which he received two courses of etoposide plus carboplatin. After experiencing clinical deterioration, he was surgically treated on our service but died perioperatively. Postoperative histological examination showed a choroid plexus carcinoma. Two patients who had papillomas that exhibited mitotic features were treated in the early years of this series with postoperative radiotherapy.

Recurrence of Tumor

None of the children with papillomas experienced tumor recurrence, including the patient who underwent subtotal tumor removal.

Of the eight patients whose carcinomas were completely excised, six experienced no recurrence after a median follow-up period of 3.6 years. The two patients who developed recurrence had been treated after the initial operation by chemotherapy alone (vincristine/N-(chloroethyl)-N'-cyclohexyl-N-nitrosourea or BB-SFOP, respectively). Unsuccessful treatment of recurrence included radiotherapy and chemotherapy. Surgery was not performed for tumor recurrence. The child who underwent incomplete excision of a carcinoma died of progressive residual disease 7 months later despite receiving adjuvant radiotherapy and chemotherapy.

Tumor Metastases

Among the cases of carcinomas, three patients experienced metastases. In one patient, a lesion in the ambient cistern was seen at presentation. In the other two patients, multiple metastases were observed in supratentorial, infratentorial, and spinal locations during the follow-up examination. In one patient, tumor spread was discovered on routine MR imaging performed 18 months after surgery; in the other one, leg pain, occurring 1 year after tumor removal, was the reason for neuroradiological examination.

Clinical Outcome

The overall 5-year survival rate was 100% for children with papillomas and 40% for those with carcinomas. The outcome of the patients is depicted in Fig. 6. Outcome was much better for patients with papillomas than for those with carcinomas.
Postoperative seizures appeared in two cases. Three children who had experienced seizures preoperatively did not have seizures after surgery. Hemiparesis had been present preoperatively in five patients; in four it persisted postoperatively and in one it regressed completely. Hemianopsia was seen in two patients postoperatively (both were surgically treated for tumors of the lateral ventricle and their corticotomies were parietooccipital and transparietal, respectively). Persistent strabismus was seen in four cases. The three children with subdural fluid collections who had closure of the corticotomy achieved a relatively good outcome, whereas the three who did not, had a poor outcome. None of the latter three patients were cured of their subdural collections, and permanent shunts were required.

**DISCUSSION**

Choroid plexus tumors are commonly seen in very young children. As seen in this and other series, the majority of patients are younger than 3 years of age at presentation.[7] This makes management of their disease challenging. The main treatment remains surgical excision, which is associated with certain problems related to the young age of the patients. Several issues merit detailed discussion.

**Surgical Management of Tumor Vascularity**

Choroid plexus tumors tend to be large, fragile, and very vascular. This presents a particular challenge to the neurosurgeon, who is often performing surgery on a baby with a small total circulating blood volume, risking intraoperative death from uncontrollable hemorrhage.[6,24,39,61] This complication seems to occur more commonly in cases of carcinomas than in cases of papillomas. The most important surgical issue is the identification and obliteration of the feeding vessels, which are commonly found in the pedicle of origin.[24,39,51] This does not always prove successful because often the large size of the tumor prevents access to the vascular pedicle, which usually is deeply situated, away from a direct approach.[63] Not uncommonly, the surgeon has to remove the tumor in a piecemeal fashion, a maneuver invariably followed by profound hemorrhage. For this reason, there has been a move toward preoperative embolization. Hypertrophy of one of the choroidal arteries is a usual angiographic feature[51] and tumor blush is commonly seen, occasionally with several minor feeding vessels.
contributing. Although preoperative embolization would appear to be easy, in clinical practice success has been the exception rather than the rule. Failure to cannulate the feeding vessels is the main reason for this.

In one of the cases in this series, percutaneous stereotactic embolization performed by means of a sclerosant agent was used to counteract tumor vascularity.[9,18] During the first operation, profound bleeding prevented any surgical manipulation. Following several hours of dissection and hemostasis, the operation had to be abandoned. Percutaneous stereotactic direct injection of a sclerosant agent reduced vascularity sufficiently to make a second operation feasible after 5 days. After the second operation, the tumor resection was complete and the patient was neurologically intact. To our knowledge, this technique has not been used before in children, but could be an alternative mode of action in those difficult cases.

Management of CSF-Related Complications

Not uncommonly, the predominant symptoms of intracranial hypertension, in relation to acute hydrocephalus, demand controlled CSF diversion for a short duration (a few days) prior to performing surgery for excision of the tumor. The objective of such a staged treatment would be to improve the situation of the brain by relieving raised intracranial pressure, in preparation for a major intervention, while at the same time the advantage of ventriculomegaly is maintained. In the presence of dilated ventricles, excision of a choroid plexus papilloma is easier because the tumor is floating inside the ventricular cavity. If this advantage is lost and the ventricles are dramatically reduced in size, the operation is significantly complicated.

Previously attention focused on the relationship between cerebral mantle thickness and the risk for chronic subdural fluid collection.[7] Preoperative controlled CSF diversion allows the cerebral mantle to expand. An important detail of surgical technique is the closure of the corticotomy with biological glue at the end of the procedure.[25] This is better achieved when the cerebral mantle is expanded. Closure of the corticotomy will isolate the ventricular system from the subdural space, thus significantly decreasing the chances of postoperative subdural hygromas that require subduroperitoneal diversion. In the presence of such a communication, any diversion of the subdural space is likely to be insufficient. As already mentioned, these permanent subdural fluid collections were associated in our experience with poor patient outcome.

Pathophysiological Characteristics of Hydrocephalus

Hydrocephalus remains the main presenting feature of choroid plexus tumors and is responsible for several problems that can adversely influence outcome. Considerable speculation has been made as to the cause of hydrocephalus in these patients. Overproduction of CSF is universally regarded as a very important factor.[17,30,34,35,42,52,57] It has been consistently observed and documented[15,19] that a choroid plexus tumor produces amounts of CSF that are well in excess of the average level of 450 ml during a 24-hour period; in one case in our series the tumor produced 800 ml of CSF over a 24-hour period. Therefore, especially in very young children, it is thought that CSF overproduction induces increased intracranial pressure to maintain balance with CSF absorption, resulting in communicating hydrocephalus. In addition, occasionally the tumor mass is found to obstruct the ventricular system (commonly, the foramen of Monro or the sylvian aqueduct), causing obstructive hydrocephalus.[53]

It is has been observed that hydrocephalus can persist even after successful excision of the choroid
plexus.[26,40,47,51] In this series, nine children required ventricular shunts several months after tumor removal. Similar findings have been reported in other series as well.[7,24,47,51] It would be expected that, after removal of the source of excess CSF production, normal CSF dynamics would be restored.[15,22,29,30,39,59,61] We would postulate that in these circumstances, the cause for the communicating hydrocephalus that is observed is functional obstruction at the level of the arachnoid granulations. The choroid plexus tumor is a site where the blood-brain barrier has broken down, as evidenced by the pronounced tumor blush seen on angiograms. This site of disrupted blood-brain barrier is freely exposed to the ventricular cavity. It is conceivable that the tumor is releasing protein material, particularly fibrin. This would circulate along the normal CSF pathway and eventually reach the arachnoid granulations. Chronic deposition of protein in the subarachnoid spaces and/or in the arachnoid granulations would result in increased CSF outflow resistance and communicating hydrocephalus, in a fashion analogous to hydrocephalus seen after subarachnoid hemorrhage or head injury. Other authors have postulated that a similar obstruction at the level of the arachnoid granulations could be due to particles of tumor residue[34,57] or blood diffusing during the operation.[1,49] No factors have been identified that could predict a late occurrence of hydrocephalus except a correlation, found in this series, between the preoperative duration of the symptoms and the postoperative occurrence of hydrocephalus. In particular, preoperative CSF xanthochromia and protein content have not been found to correlate, but CSF fibrin content was not specifically analyzed.[16,24] This late occurrence of hydrocephalus should always be borne in mind when following the case of a child who had an otherwise successful surgical treatment of a choroid plexus papilloma.

**Postoperative Adjuvant Treatment**

Choroid plexus papillomas are benign tumors, and it is widely accepted that their complete excision is curative.[16,46] The situation is different for choroid plexus carcinomas.[5] They are malignant tumors of neuroectodermal origin, with a known propensity for recurrence. Despite some reports,[4] adjuvant treatment has not been shown to be very effective in these tumors. In older children, radiotherapy can be effective against recurrence. Unfortunately, radiotherapy is not an option in the majority of cases because of the young age of the patients and the size of the field to be irradiated.[48] Although it contributes to long-term survival,[3,14,38,48] chemotherapy cannot prevent recurrence. It appears that total surgical excision is the main predictor of long-term survival and achieving total excision should be the goal of any treatment strategy.[12,16,48,54]

**CONCLUSIONS**

Benign papillomas of the choroid plexus are cured by surgical excision. For carcinomas of the choroid plexus, maximum surgical resection offers the best chance for long-term survival. At the end of surgery, it is important to isolate the ventricular system from the subdural space by closing the corticotomy with biological glue. Particular attention should be paid to tumor vascularity and preoperative embolization should be attempted. It should be emphasized that complete tumor excision does not remove the risk of later development of hydrocephalus.

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Address reprint requests to: Christian Sainte-Rose, M.D., Service de Neurochirurgie Pédiatrique, Hôpital Necker-Enfants Malades, 149, rue de Sèvres, 75015, Paris, France.