NEUROPATHOLOGICAL CONFERENCE

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A 22-year-old Female with Visual Disturbances and Raised Intracranial Pressure

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PATIENT DESCRIPTION

Clinical presentation

This 22-year-old right-handed female was referred for neuro-ophthalmologic evaluation by her optometrist. The patient, a successful graduate student, had no history of previous illness and no family history of neurological disorders. She had been well until six weeks prior to admission, when she started experiencing progressive visual disturbances. She described sudden episodes of blurred vision, occurring in particular when moving from the sitting to the standing position. She described a sensation of "a black veil falling in front of her eyes", followed by the progressive recovery of normal vision. She denied having headaches, diplopia or other associated symptoms. In the days preceding her admission, the episodes had become much more frequent, occurring ten to fifteen times daily.

On examination, she was an alert, well-oriented female in no apparent distress. Examination of the chest, abdomen, and skin was unremarkable. Fundoscopy revealed bilateral papilledema. Apart from bilaterally enlarged blind spots (confirmed by formal visual field testing), the neurologic examination was normal.

Dr D. Charest: The main presenting symptom was visual, similar to the monocular "amaurosis fugax" associated with significant obstructive cerebrovascular disease. In this case, the visual symptoms were stereotyped and binocular. Although non-specific, this presentation has been associated with papilledema. Headaches were not present, as can be the case in 10% of patients with papilledema secondary to increased intracranial pressure.[1-3]

Physical examination confirmed papilledema without any other neurological deficits apart from the bilaterally enlarged blind spots. In particular, no cranial nerve abnormalities or cerebellar signs were observed.

Clinically, the patient presents with elevated intracranial pressure without localizing signs. This type of presentation can be seen with pseudotumor cerebri, venous occlusion, or midline space-occupying lesions (supra or infratentorial) causing hydrocephalus. In a young female, pseudotumor must be considered. This patient was not obese and was not under any medication (including oral contraceptives) often associated with pseudotumor or venous occlusion. If one considers a space-occupying process, the relatively rapid clinical course (six weeks) points toward a malignant lesion or a more benign entity with the recent onset of obstructive hydrocephalus. A posterior fossa lesion large enough to obstruct the fourth ventricle will often be accompanied by headache, nausea and ataxia, not present in this case. Midline supratentorial mass lesions causing hydrocephalus without focal signs will be found in the third ventricle (anterior or posterior): colloid cysts and lesions of the pineal region, for example.

In summary, the clinical picture points toward a supratentorial midline mass lesion with hydrocephalus. Pseudotumor or venous occlusion cannot be ruled out on the sole basis of clinical presentation.

IMAGING

Brain CT scan shows dilated lateral ventricles with a large intraventricular mass containing small calcifications and hypodense areas suggestive of cystic degeneration.

The lesion is better appreciated on MRI (Figure 1). Obstructive hydrocephalus of the lateral ventricles, more apparent on the right, is caused by a large (4.7 x 4.7 x 3.8 cms), lobulated mass extending from the inferior surface of the corpus callosum to the foramina of Monro and the dorsal thalami. The tumour is attached to the septum pellucidum and appears predominantly solid, with some cystic areas. The solid part of the mass is isointense on T1 and proton density, and T2 images. The cystic areas are hypointense on T1; hyperintense on T2 studies. After administration of contrast (gadolinium), the solid portion of the lesion enhances homogeneously. MR angiography shows an inferior displacement of the deep venous system, a patent sagittal sinus with a symmetrical pattern of parasagittal bridging veins.

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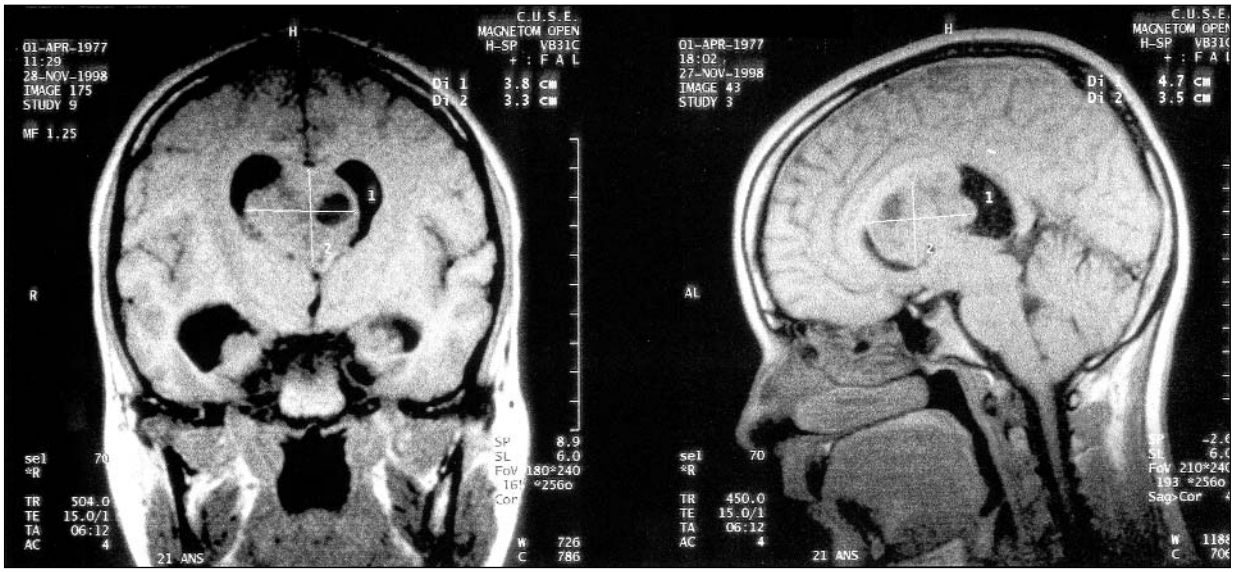

Figure 1: *MRI (T1) image without gadolinium. Note the large intraventricular lesion, cystic areas and obstructed foramina of Monro.*

A surgical procedure was performed three days after the patient's admission.

DIFFERENTIAL DIAGNOSIS

The imaging narrows the differential diagnosis to the discussion of an intraventricular tumour in a young adult. MRI shows a homogeneous mass arising from the septum pellucidum. The tumour enhances slightly with gadolinium and there were focal calcifications (on CT scan) and cystic changes.

Oligodendrogliomas are frequently calcified. This tumour is rarely seen in the ventricles. The radiological appearance can be similar to central neurocytoma but enhancement is usually more pronounced.[4]

Subependymal giant cell astrocytomas are often calcified and usually seen in the first two decades of life in the context of tuberous sclerosis. However, in one third of cases, this tumour can be the initial manifestation of this phakomatosis.[5] Therefore, the absence of the other stigmata of the disease in this case does not allow us to rule out this diagnosis. These lesions are usually attached to the lateral wall of the ventricle; in this case, the lesion originates from the septum pellucidum.

Subependymomas are also slow-growing intraventricular lesions. Most of the reported cases are incidental findings at autopsy. It is unusual (but possible) for this tumour to become this large. Imaging characteristics are also similar to oligodendrogliomas and central neurocytomas.[6] However, calcifications are unusual and this lesion usually presents at a more advanced age.

Central neurocytomas are also seen in young adults. First described in 1982 by Hassoun et al,[7] their imaging characteristics are similar to the findings in our case: moderate enhancement, cystic areas, calcifications.[8] Often originating from the region of the septum pellucidum, they will become symptomatic when obstructive hydrocephalus is present. Central neurocytomas are typically intraventricular, although lesions in the third and fourth ventricle, the brain parenchyma or spinal cord have been reported.[9-12]

Astrocytomas can also be observed in the lateral ventricles. However, they will usually appear as exophytic lesions originating from the peri-ventricular parenchyma.

Ependymomas, papillomas of the choroid plexus and meningiomas usually enhance strongly with contrast and are located more posteriorly in the lateral ventricles.

Dr D. Charest: Differential diagnosis and surgical options

The treatment offered to this patient must meet three objectives:

- tissue sampling for histological diagnosis
- relief of hydrocephalus, responsible for the patient's symptoms
- long-term control or cure of the intraventricular tumour.

A conservative approach such as biopsy and shunting alone is not an acceptable option in a young patient with a suspected benign lesion. Although endoscopy could be used alone or in conjunction with another approach,[13] it may not allow the safe resection of a large tumour. In order to approach a lesion in the central or anterior part of the lateral ventricles, two techniques must be considered: the trans-frontal or interhemispheric trans-callosal approaches.[14]

The trans-frontal/trans-cortical approach to the lateral ventricle has been described extensively.[15-17] The degree of ventricular dilatation present in this case would facilitate the approach through a corticotomy in the second frontal gyrus. However, the resection of a lesion of this size could be difficult, as the angles of vision are not as versatile as with the transcallosal approach. The cortical incision may also create a potentially epileptogenic scar.

The interhemispheric trans-callosal approach would be my choice in this case. It will allow visualization of the anterior and

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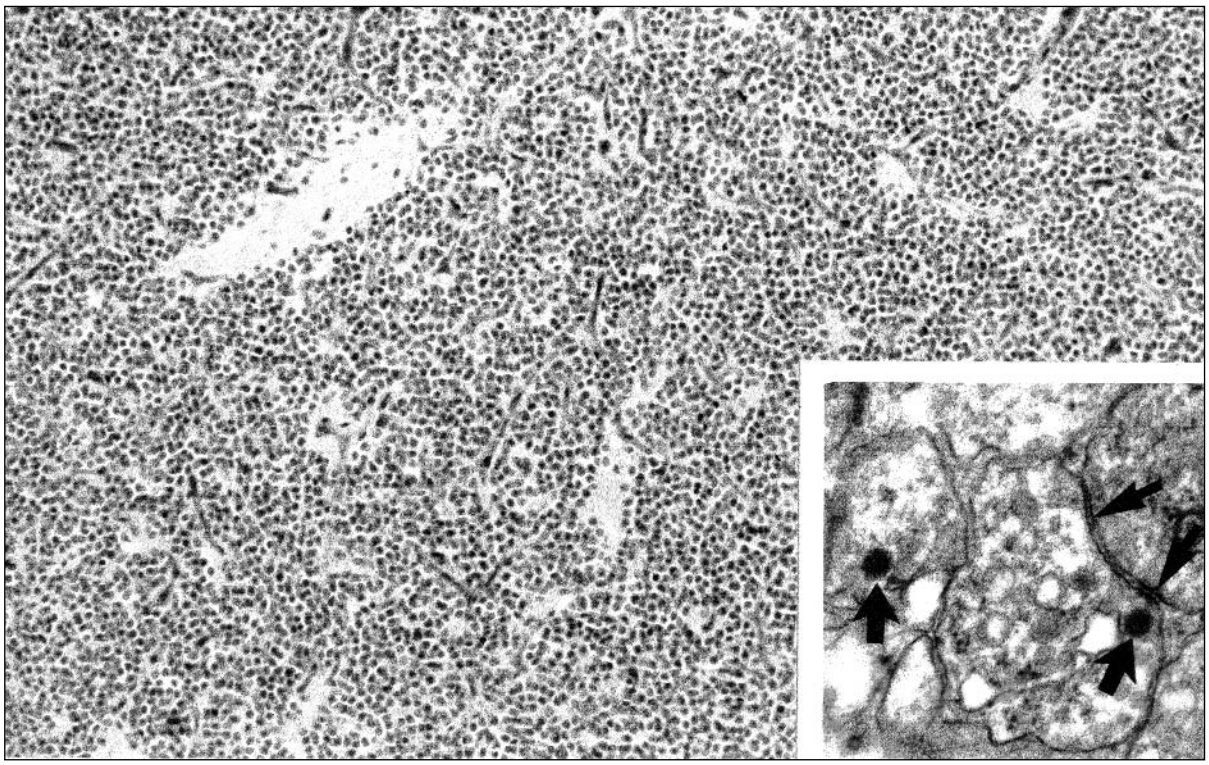

Figure 2: *Histology: small monotonous cells with uniform nuclei in a rich network of fine capillaries. Inset (electron microscopy): dense core granules (short arrows), synapse-like membrane thickening (long arrows).*

central region of the lateral ventricle without the inconvenience of a cortical incision. The craniotomy is usually done on the non-dominant side, although the anatomical disposition of the parasagittal bridging veins can sometimes dictate a left-sided approach. The size of the callosal incision should be kept at a minimum (2.5 to 3 cm) in order to avoid a postoperative disconnection syndrome.[18]

Pre-operative diagnosis: histologically benign tumour of the lateral ventricles arising from the septum pellucidum: central neurocytoma (probable), subependymal astrocytoma or oligodendroglioma.

Discussion and diagnosis

Dr Couillard: A transcallosal approach from the right was performed. The bone flap crossed the midline and was centered on the coronal suture. Only a small anterior bridging vein needed to be sectioned in order to gain access to the interhemispheric fissure. After a three centimetre long incision of the body of the corpus callosum, we came in contact with the lesion. The mass was moderately vascular, and could be debulked with the ultrasonic aspirator. The attachment of the tumour to the septum pellucidum was resected, and both foramina of Monro were patent at the end of the procedure. Postoperatively, the patient did well, with no postoperative deficits and could resume her studies after six weeks of convalescence. The papilledema subsided and the size of the ventricles decreased on subsequent imaging. Postoperative imaging showed a small amount of residual tumour in the superior lateral angle of the right lateral ventricle. The size of this residual tumour gradually increased in the following months, leading to re-operation six months later. At the time of the second procedure, gross total resection could be achieved. One year later, the patient remains neurologically intact and imaging shows no evidence of tumour recurrence.

Neuropathology (Dr. J.B. Lamarche): The frozen section diagnosis was a uniform small round cell tumour consistent with either an oligodendroglioma or a neurocytoma. Several large fragments of neoplastic tissue were available for the histological studies.

The tumour was composed of sheets of densely packed small monotonous cells with uniform round nuclei containing finely speckled chromatin and small nucleoli and little visible or clear cytoplasm. The tumour contained a rich network of fine capillaries and numerous fibrillar islands often centered on a blood vessel (Figure 2). In some areas, there was a perivascular arrangement of neoplastic cells suggesting ependymal pseudorosettes. In some fragments, there were occasional foci of tumour cells with perinuclear halos reminiscent of oligodendroglial differentiation. There was no pleomorphism, vascular proliferation or necrosis but a few mitotic figures were noted. Immunohistochemical study showed positive immunoreactivity for both synaptophysin and neuron-specific enolase in the fibrillar zones. Ultrastructural findings included a dense feltwork of cytoplasmic process containing microtubules, a small number of dense core granules, clear vesicles and occasional synapse-like membrane thickening (Figure 2, inset). The proliferation potential was assessed on MIB-1

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immunostained sections, 1000 cells being counted. The MIB-1 labelling index was found to be 5.5%.

The histological, immunohistochemical and ultrastructural findings were typical of a central neurocytoma.

Central neurocytoma is a well-defined clinicopathological entity recognized by the new WHO classification of tumours of the nervous system.[19,20] The neuronal nature of this neoplasm was demonstrated by Hassoun et al in 1982[7] in two young adults who developed a heavily calcified intraventricular tumour composed of small round cells resembling oligodendrocytes. Because of the mature character of some of their ultrastructural features, which distinguish this tumour from neuroblastoma, the authors proposed the term central neurocytoma for these rare tumours (less than 200 cases having been published). Its incidence ranged from 0.25% to 0.5% of all intracranial tumours in two large surgical biopsy series.[21,22] Young adults are most often affected but cases have been reported in patients ranging in age from six and 64 years. Clinical manifestations occur at a mean age of 20 years and most often consist of symptoms of increased intracranial pressure in relation to hydrocephalus. Central neurocytoma usually develops in the lateral and/or the third ventricle, the anterior portion of one lateral ventricle in relation to the foramina of Monro being the most frequent site. Its histogenesis is hypothetical: some authors favour an origin from small grey nuclei of the septum pellucidum, others from remnants of the subependymal plate of the lateral ventricles.[9] The tumour, grossly greyish, finely granular and often calcified is generally only locally attached to the ventricular wall at its site of origin. Most of these neoplastic lesions were previously misinterpreted as oligodendroglioma or ependymoma, the main differential diagnosis of this tumour along with neuroblastoma. Verification of the diagnosis usually requires positive immunoreactivity with synaptophysin and neuron-specific enolase or electron microscopical evidence of neuronal differentiation.

The prognosis in neurocytoma especially of those of younger than 50 years is excellent, intraventricular spread being rare. When residual neoplasm remains, regrowth is possible but clinical recurrence only comes about slowly. There has been an increasing number of reports of cases of neurocytoma with poor outcome and the term atypical central neurocytoma or proliferating neurocytoma, has been proposed for such tumors.[14,22,23] Atypical features including cellular pleomorphism, vascular endothelial proliferation, necrosis and the proliferative potential as assessed by the MIB-1 labelling index have been studied and compared with clinical outcome.[24,25] The proliferation potential has been found to be the most useful predictor of clinical outcome, histologic atypia alone not being considered significant in term of prognosis. A labelling index of more than 2% carries a poor outcome.[24] The risk of relapse among a series of 36 patients with a labelling index of less than 2% was 22%. This risk increases to 63% with an index greater than 2% over an observation time of 150 months.[24] In our case, there was no necrosis, vascular proliferation or cellular pleomorphism and only a few mitosis were identified. However, the MIB-1 labelling index was greater than 2%. In retrospect, this high proliferation potential could explain the early tumour recurrence observed in our patient.

Final diagnosis

Central neurocytoma with a high proliferative index (>2 %) and an early recurrence.

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