Clinical Reports

Paraneoplastic papilloedema in neuroblastoma

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Summary: We report a case of bilateral papilloedema in an adult male with neuroblastoma, in the absence of hypertension or detectable intracranial disease. This complication has not previously been described in the English-speaking literature. Possible mechanisms are discussed.

Introduction

Non-metastatic neurological disease complicating neuroblastoma is well recognized. The phenomenon of occult tumour presenting with opsoclonus and/or cerebellar ataxia has been extensively reviewed^{1,2} since first described by Solomon and Chutorian in 1968.³ Myasthenia gravis has also been reported.⁴ We describe a case of neuroblastoma with gross papilloedema in the absence of intracranial disease and speculate as to the relationship between this and other non-metastatic neurological complications of this tumour.

Case report

The patient, a 21 year old white male, presented with a 4-week history of lassitude and frontal headache. Physical examination revealed pallor and marked bilateral papilloedema with fundal haemorrhages (Figure 1). The patient was normotensive. Full blood count demonstrated moderate pancytopenia (haemoglobin 10.0 g/dl) and a biochemical screen showed mild hypercalcaemia of 2.82 mmol/l.

Bone marrow biopsy showed diffuse infiltration with metastatic small cell tumour growing in sheets. Poorly-formed rosettes were detected with a focal fibrillary background and neurone-specific enolase immunohistochemistry was strongly positive (Figure 2). A diagnosis of metastatic neuroblastoma was made and computed tomographic (CT) scan of the abdomen

confirmed the presence of a poorly-vascular mass in the region of the left adrenal.

The patient was seen by an ophthalmologist who found him to have normal pupillary reflexes and visual acuity. The visual fields were normal apart from a slight increase in the blind spots and marked papilloedema was demonstrated. Because of the patient's critical condition fluoroscein angiography was not performed.

In view of the florid papilloedema, intracerebral metastases were suspected. CT scan of the head revealed normal eyes, orbits and optic nerves. There was no evidence of ventricular dilatation, mid-line shift or a space-occupying lesion in the brain. A lumbar puncture was performed. Cerebrospinal fluid (CSF) pressure, cell count and protein content were normal. In view of the very low cell count no more sophisticated cytological analysis was performed.

A fluorimetric assay for total urinary catecholamines was within normal limits, as were urinary metanephrines and vanillylmandelic acid excretion. At no stage was the patient's blood pressure elevated. A short course of treatment with dexamethasone 4 mg t.d.s. was begun and a chemotherapy regimen alternating courses of cyclophosphamide, doxorubicin and VP16-213 with cisplatin, vinblastine and bleomycin was instituted. Over a period of 5 months, six courses were administered during which time the fundoscopic appearances gradually returned to normal (Figure 1). A repeat bone marrow biopsy after six courses of chemotherapy demonstrated differentiation of the tumour to ganglioneuroblastoma (Figure 3). Further treatment comprising combination chemotherapy and possible removal of the abdominal tumour is now planned.

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Figure 1 Right and left fundi before (above) and after (below) treatment with dexamethasone and combination chemotherapy.

Discussion

Despite considerable investigation and speculation over the past decade, the exact mechanism of papilloedema remains uncertain. While there is a large body of research suggesting that the primary defect is one of axoplasmic transport⁵ there are authorities who feel that ischaemia and failure of autoregulation in retinal arterioles have a role to play.^{6,7} The pathophysiology of opsoclonus is also unclear. While post-mortem studies have demonstrated cerebellar demyelination, gliosis and loss of Purkinje cells, the exact mechanisms of such damage are uncertain.⁸

Neuroblastomas are known to be secretory tumours and it has been postulated that some cases of opsoclonus may be due to the effects on the cerebellum of a toxic metabolite secreted by the tumour.⁹ It has been shown by Hayreh *et al.*¹⁰ that toxic metabolites can also cause axoplasmic flow stasis and resultant papilloedema in cases of methanol poisoning. Such mechanisms may underlie the papilloedema seen in our

case and the opsoclonus described in other patients.

It has also been suggested that opsoclonus may be due to a vigorous immune response to the neuroblastoma cross-reacting with cerebellar tissues.⁹ This view is supported by the observation that patients who demonstrate opsoclonus have a better than expected survival¹¹ due to a higher incidence of differentiation to ganglioneuroblastoma. Interestingly, therapy in the patient described here produced such an histological change (Figure 3). We feel it is possible that a common mechanism underlies the papilloedema seen in our patient and previously described cases of opsoclonus complicating neuroblastoma.

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Figure 2 Initial bone marrow biopsy. (a) Marrow is largely replaced by an infiltrate of small round cells which focally show a fibrillary stroma (arrow) characteristic of neuroblastoma (haematoxylin and eosin, $\times 160$). (b) Clusters of malignant cells within the marrow (arrows) are highlighted by staining for an antibody against neurone-specific enolase, a marker of neuroendocrine cells. A positive result is indicated by dark cytoplasmic staining (peroxidase anti-peroxidase technique $\times 160$).

Figure 3 Post therapy bone marrow biopsy. (a) Maturation of neuroblastoma to ganglioneuroblastoma is illustrated by the presence of ganglion cells (G) and extensive neural processes (N) forming nerve-like structures. Like the neuroblastoma cells these more mature tissues are strongly neurone-specific enolase positive (peroxidase anti-peroxidase technique with anti-neurone specific enolase, $\times 160$). (b) Membrane bound neurosecretory granules within the cytoplasm of neuroblastoma cell (electron micrograph $\times 4300$; bar = 5 μ m).

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