

WL Yeung 楊慧蘭  
 CK Li 李志光  
 EAS Nelson 倪以信  
 KW Chik 戚其威  
 GM Joynt 喬伊諾  
 E Yuen 袁學遠  
 CK Yeung 楊重光

## Unusual neurological presentation of neuroblastoma

### 神經母細胞瘤的異常腦神經表現

.....  
 Acute cerebellar ataxia and opsomyoclonus are presenting signs of occult neuroblastoma for a substantial proportion of paediatric patients. Cerebellar ataxia may be due to antibodies against the neuroblastoma cross-reacting with cerebellar tissue. This report is of a 26-month-old boy who presented with encephalitis-like features of ataxia, seizures, decreased consciousness, and involuntary movements. Magnetic resonance imaging of the brain and spine were normal 2 weeks after presentation. The child did not have the classical signs of opsoclonus or myoclonus at any stage of the disease but was found to have occult neuroblastoma. The late demyelinating changes seen on magnetic resonance imaging of the brain support an immunological basis for the paraneoplastic manifestations of occult neuroblastoma in this child. Occult neuroblastoma should be considered as one of the differential diagnoses for children presenting with persisting encephalitis-like features in the presence of normal neuroimaging findings.

患上潛隱性神經母細胞瘤的兒科病人中，有部份患者出現急性小腦共濟失調和眼肌陣攣。小腦共濟失調可能是由神經母細胞瘤的抗體與小腦組織相互作用所引起。本報告報導一名26個月大的男孩，他呈現類似腦炎的病徵，包括共濟失調、癲癇、神智不清及不隨意動作笨拙。病人求診後兩週的腦及脊磁共振成像均屬正常。在整個發病期間，他並沒有眼陣攣和肌陣攣等潛隱性神經母細胞瘤的典型徵兆，但被證實患上此病。其後該男孩的腦磁共振成像上發現脫髓鞘，支持了神經母細胞瘤的副腫瘤綜合徵狀具有免疫學基礎。當兒童呈現持續的腦炎病徵，而神經圖像均屬正常時，應把潛隱性神經母細胞瘤列為鑒別診斷之一。

#### Key words:

Encephalitis;  
 Neuroblastoma;  
 Paraneoplastic syndrome

#### 關鍵詞：

腦炎；  
 神經母細胞瘤；  
 副腫瘤綜合徵狀

*Hong Kong Med J* 2003;9:142-4

The Chinese University of Hong Kong,  
 Prince of Wales Hospital, Shatin, Hong Kong:  
 Department of Paediatrics

WL Yeung, MB, ChB, MRCP

CK Li, MD, FRCPCH

EAS Nelson, MD, FRCP

KW Chik, MB, ChB, MRCP

Department of Anaesthesia and Intensive  
 Care

GM Joynt, MB, ChB, FFA(SA)

Department of Diagnostic and Organ  
 Imaging

E Yuen, MB, ChB, FRCP

Department of Surgery

CK Yeung, MD, FRCSEd

Correspondence to: Dr WL Yeung

#### Introduction

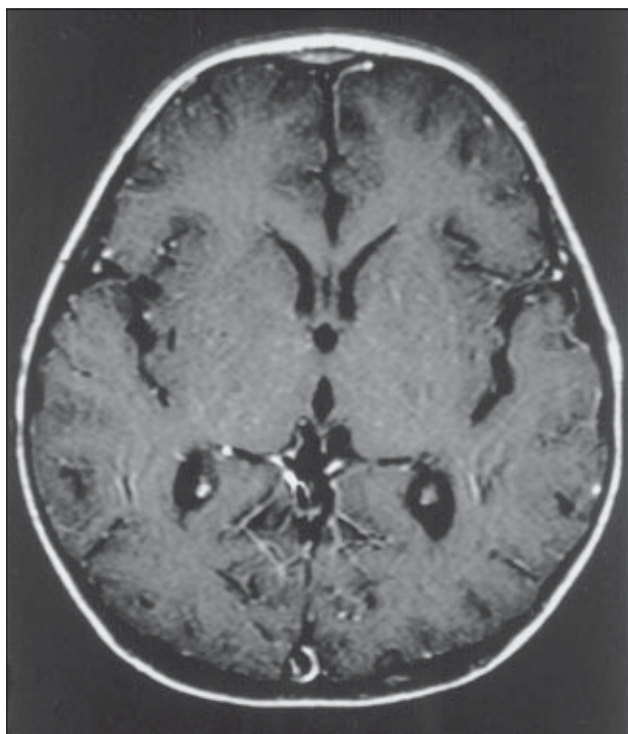
Acute cerebellar ataxia and opsomyoclonus, first reported as signs of occult neuroblastoma by Solomon and Chutorian,<sup>1</sup> are presenting features of neuroblastoma for a substantial proportion of paediatric patients.<sup>2,3</sup> This report is of a 26-month-old boy with occult neuroblastoma who presented with the encephalitis-like features of ataxia, seizures, decreased consciousness, and involuntary movements.

#### Case report

A previously healthy, 26-month-old boy presented to another hospital with a 2-day history of low-grade fever, followed by lower limb weakness, writhing hand movements, and irritability within 24 hours. On the morning prior to admission to hospital, his gait had become ataxic. Shortly after admission, the child had a generalised tonic-clonic seizure lasting for 5 minutes. The seizure was controlled by phenobarbitone and paraldehyde injection. Examination showed increased tone in both lower limbs with a power grade of 2/5. Knee and ankle reflexes were brisk and the plantar reflex was abnormal bilaterally. Blood electrolytes, glucose, haemoglobin, and cultures were normal; the white cell count (WCC) was  $17.7 \times 10^9/L$  (reference range,  $4.5-11.0 \times 10^9/L$ ) with 53% neutrophils and the erythrocyte sedimentation rate was 25 mm/h (reference range, 0-20 mm/h). Cerebrospinal fluid (CSF) examination showed a WCC of  $160 \times 10^6/L$  (reference level,  $<5 \times 10^6/L$ ), of which 84% were lymphocytes and 16% were neutrophils. The red blood cell (RBC) count in the CSF was  $20 \times 10^6/L$  (reference level,

$<2 \times 10^6/L$ ), protein level was 0.78 g/L (reference range, 0.2-0.4 g/L), and glucose level was 3.5 mmol/L (blood glucose level, 5.1 mmol/L) [reference range in CSF, 2.8-4.4 mmol/L; reference range in blood, 3.9-6.1 mmol/L]. Electroencephalography (EEG) and magnetic resonance imaging (MRI) studies of the brain were normal. Treatment at admission included ampicillin and ceftazidime for suspected bacterial meningitis. On day 2, the boy had repeated seizures and choreo-athetoid movements of all four limbs. A repeat EEG on day 3 showed diffuse slowing of brain waves. A repeat lumbar puncture on day 5 showed that the CSF WCC was still elevated at  $110 \times 10^6/L$ , with 97% lymphocytes and 3% neutrophils. The CSF protein level was 0.59 g/L and glucose level was 3.7 mmol/L (blood glucose level, 5.5 mmol/L). At this stage, acyclovir 500 mg/m<sup>2</sup> was given intravenously every 8 hours and continued for 21 days. A computed tomography (CT) brain scan on day 7 was normal.

On day 10 of the illness, the child was transferred to the Prince of Wales Hospital. At admission, he was comatose with no spontaneous eye movement. The doll's eye reflex was present and the corneal and gag reflexes were absent. There was hypotonia with brisk deep tendon reflexes, and down-going plantar reflexes. There was no response to painful stimuli but occasional movement of all four limbs was noted. A repeat CT scan of the brain was again normal, and a further lumbar puncture showed that the CSF WCC had returned to normal ( $6 \times 10^6/L$ ). The CSF RBC was  $1345 \times 10^6/L$ . Electroencephalography showed diffuse polymorphic slow delta waves with no epileptiform discharges, and the choreo-athetoid movements were not associated with any



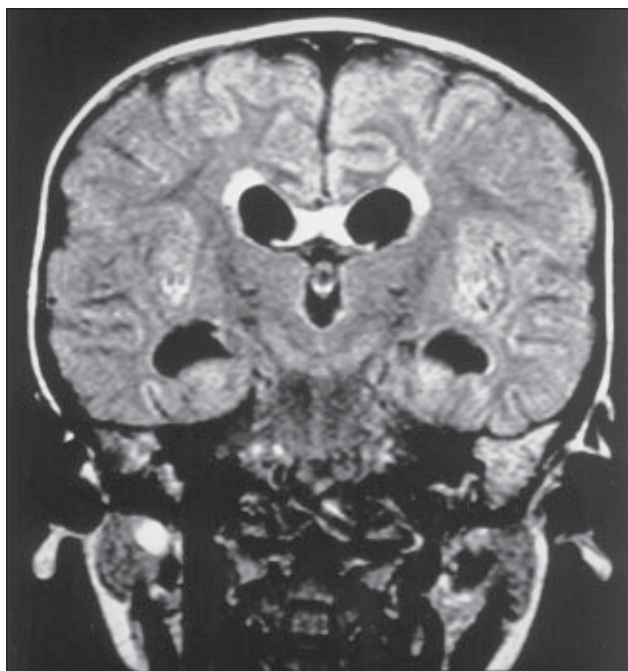
**Fig 1. Magnetic resonance imaging performed 2 weeks after initial presentation**  
Post-gadolinium T1-weighted axial image. No abnormal enhancement indicating a focal mass lesion was demonstrated

EEG changes. On day 13, abdominal palpation revealed some possible faecal masses and an ultrasound examination was performed. This revealed a left retroperitoneal mass measuring 5 x 4 x 4 cm. A needle biopsy of the mass suggested a diagnosis of neuroblastoma, which was confirmed after laparoscopic excision of the mass. During the operation, the tumour was found to be a well-encapsulated mass that could be completely mobilised and excised laparoscopically. Histology showed the tumour to be a differentiating subtype. Bone marrow examination showed no malignant infiltration and MRI scans of the brain (Fig 1) and spine were normal. Cerebrospinal fluid obtained for polymerase chain reaction detection of herpes simplex type 1 and 2 and enterovirus were negative. Viral titres for Japanese B, adenovirus, enterovirus, herpes simplex, influenza A and B, measles, mumps, mycoplasma, varicella zoster, rubella, and Epstein-Barr virus were not raised. Alpha-fetoprotein and lactate levels, thyroid function tests, anti-nuclear antibody, and anti-DNA immunofluorescent tests were all normal. Immunoglobulin (Ig) levels, including IgG, IgM, and IgA were normal but IgE was raised to 0.845 mg/L (reference range, 0.02-0.15 mg/L) [352 kIU/L; reference range, 8-64 kIU/L). Prior to surgery, the urine vanillylmandelic acid to creatinine ratio was 10  $\mu\text{mol}/\text{mmol}$  (reference level,  $<9 \mu\text{mol}/\text{mmol}$ ) but the dopamine to creatinine ratio was raised to 1394 nmol/mmol (reference level,  $<650 \text{ nmol}/\text{mmol}$ ). After surgery, the repeat dopamine to creatinine ratio had decreased to 947 nmol/mmol.

After excision of the tumour, the child had spontaneous eye opening for periods of 30 minutes to several hours. The corneal, gag, and cough reflexes remained absent and there was no reduction in the choreo-athetoid movements. A course of oral steroids 2 mg/kg/day for 1 week and intravenous Ig 1g/kg/day for 2 days were given but no improvements in involuntary movements were noted. No opsoclonus or myoclonus was noted at any stage during the illness. A follow-up CT scan of the abdomen was completed 1 month after surgery and showed recurrence of the tumour in the left adrenal bed. Open surgery proceeded but extensive tumour growth, with multiple tumour nodules, was found, and only tumour biopsy could be completed. Chemotherapy with carboplatin and etoposide was given for the residual intra-abdominal disease. A repeat MRI brain scan 2 months after diagnosis showed symmetrical, periventricular demyelination (Fig 2). The choreo-athetoid movements persisted until the child's death from septic shock, the consequence of a perforated duodenal ulcer that occurred while receiving chemotherapy 3 months after presentation. The family declined permission for postmortem examination.

## Discussion

Solomon and Chutorian<sup>1</sup> first described acute cerebellar ataxia and opsomyoclonus as signs of occult neuroblastoma in 1968. More than 50% of infants and children with opsoclonus ataxia have an underlying neuroblastoma.<sup>2,3</sup> Most patients present with signs of neurological irritability, ataxia,



**Fig 2. Magnetic resonance imaging performed 2 months after initial presentation**

Fluid attenuated inversion recovery coronal image shows prominent bilateral, symmetrical, confluent, periventricular white matter lesions, with sparing of the subcortical regions

myoclonus, and opsoclonus at a mean age of 2 years.<sup>4</sup> Cerebrospinal fluid pleocytosis may be noted but it is rare for the WCC to be above  $100 \times 10^6/L$ .<sup>5</sup> Computed tomography and MRI scans of the brain are typically normal. Urine for catecholamine metabolites can be raised or normal, and the neuroblastoma is usually identified by CT or MRI examination of the thorax or abdomen. Some patients may need a metaiodobenzylguanidine scan or Indium-111-pentetreotide scan to diagnose occult neuroblastoma.<sup>6</sup> Neurological abnormalities rarely improve with tumour resection, but symptoms are commonly alleviated after treatment with steroids or adrenocorticotropic hormone.<sup>7</sup> Relapse of symptoms has been reported when steroid treatment is tapered off or during a minor febrile illness.

One report of neurological improvement for a patient given intravenous Ig 1 g/kg for 2 days every 4 to 6 weeks has been published.<sup>8</sup> The prognosis for cure of neuroblastoma in patients presenting with opsoclonus-ataxia is excellent, with a 2-year survival rate of more than 90%.<sup>4,9</sup> After resection, the tumour recurrence rate is low. The reason for this very good prognosis is not clear but may relate to the unusual clinical findings prompting early diagnosis, or to underlying immunological effects. It is postulated that the cerebellar ataxia in neuroblastoma is due to antibodies against the neuroblastoma cross-reacting with cerebellar and possibly other CNS tissue.<sup>4</sup> Patients with neuroblastoma and paraneoplastic opsoclonus-myoclonus are more likely to have antineuronal antibodies.<sup>10</sup> The demyelinating changes seen on the repeat MRI brain scan 3 months after presentation in this patient (Fig 2) suggest non-specific, immune-mediated damage of the white matter.

This patient presented with encephalitis-like clinical features, with ataxia, seizures, decreased consciousness, and involuntary movements. Although the subsequent diagnosis was a paraneoplastic syndrome of occult neuroblastoma, the typical features of opsoclonus-myoclonus were absent. Seizures and involuntary movements, in the presence of CSF pleocytosis ( $WCC > 100 \times 10^6/L$ ) might suggest a diagnosis of encephalitis or meningitis. However, the absence of any visible lesion on neuroimaging should suggest the possibility of metabolic encephalopathy, including that resulting from neuroblastoma.

The presentation of this case, rapidly progressing from muscular weakness to profound coma, has not been previously reported, and this contributed to the delayed diagnosis of neuroblastoma. In contrast to previously reported cases, the presence of seizures, involuntary movements, and significant cerebrospinal pleocytosis was unusual for this condition. The classically described signs of opsomyoclonus were not detected.

## Conclusion

Although this is a single case report, it nevertheless suggests that occult neuroblastoma be considered in children presenting with persisting encephalitis-like features, in the presence of normal neuroimaging findings. The later demyelinating changes seen in the MRI brain scan of this patient have not been previously reported in patients with neuroblastoma who have paraneoplastic syndrome. This finding supports an immunological basis for the paraneoplastic manifestations.

## References

1. Solomon GE, Chutorian AM. Opsoclonus and occult neuroblastoma. *N Engl J Med* 1968;279:475-7.
2. Baker ME, Kirks DR, Korobkin M, Bowie JD, Filston HC. The association of neuroblastoma and myoclonic encephalopathy: an imaging approach. *Pediatr Radiol* 1985;15:184-90.
3. Bolshausen E, Deonna T, Hirt HR. Myoclonic encephalopathy of infants or "dancing eyes syndrome". Report of 7 cases with long-term follow-up and review of the literature (cases with and without neuroblastoma). *Helv Paediatr Acta* 1979;34:119-33.
4. Telander RL, Smithson WA, Groover RV. Clinical outcome in children with acute cerebellar encephalopathy and neuroblastoma. *J Pediatr Surg* 1989;24:11-14.
5. Mitchell WG, Snodgrass SR. Opsoclonus-ataxia due to childhood neural crest tumors: a chronic neurologic syndrome. *J Child Neurol* 1990;5:153-8.
6. Posada JC, Tardo C. Neuroblastoma detected by somatostatin receptor scintigraphy in a case of opsoclonus-myoclonus-ataxia syndrome. *J Child Neurol* 1998;13:345-6.
7. Nickerson BG, Hutter JJ Jr. Opsomyoclonus and neuroblastoma. Response to ACTH. *Clin Pediatr (Phila)* 1979;18:446-8.
8. Petruzzi MJ, de Alarcon PA. Neuroblastoma-associated opsoclonus-myoclonus treated with intravenously administered immune globulin G. *J Pediatr* 1995;127:328-9.
9. Altman AJ, Baehner RL. Favorable prognosis for survival in children with coincident opso-myoclonus and neuroblastoma. *Cancer* 1976;37:846-52.
10. Antunes NL, Khakoo Y, Matthay KK, et al. Antineuronal antibodies in patients with neuroblastoma and paraneoplastic opsoclonus-myoclonus. *J Pediatr Hematol Oncol* 2000;22:315-20.