Encephalopathy associated with occult neuroblastoma

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The authors report four cases of occult neuroblastoma in children with the striking clinical findings of opsoclonus, myoclonus, and ataxia. The diagnostic value of plain roentgenograms of the chest and abdomen or an intravenous pyelogram is emphasized. Assays for vanillyl mandelic acid and cystathionine may be of value. The clinical course and pathogenesis of encephalopathies due to neuroblastoma are discussed.

KEY WORDS • opsoclonus • myoclonus • ataxia • neuroblastoma

The combination of opsoclonus, myoclonus, and ataxia in small children suggests the presence of an occult neuroblastoma, and simple laboratory tests rather than sophisticated neuroradiological procedures may point directly to that diagnosis. Hospitalization for cerebral angiography or air encephalography, as in many cases of acute ataxia, may not be necessary.

We have evaluated four such children, each of whom had an occult neuroblastoma. Three of the children had normal cerebral angiograms or pneumoencephalograms before they were referred to us for evaluation. We are reporting these cases not only to emphasize the striking combination of findings but to point out the simple diagnostic tests available to facilitate early diagnosis of encephalopathies due to neuroblastoma.

Case Reports

Case 1

This 18-month-old girl was referred to us because of 10 weeks of progressive unsteady gait, “jerky” eye movements, and loose stools. Skull films and electroencephalogram obtained by her referring physician had been normal. The patient was alert and responsive. She sat with some swaying and was unable to stand. Cranial nerves were normal except for rapid bursts of conjugate ocular oscillations in all directions. The motor system was not remarkable except for moderate truncal and limb ataxia and occasional myoclonic jerks of the limbs. Responses to touch and pain were normal. Routine laboratory tests, skull films, and brain scan were normal. A 1 x 1 cm calcification was noted in the left posterior pelvis. Cerebrospinal fluid (CSF) was clear without cells, under normal pressure; the protein content was 16 mg% and the glucose 62 mg%. An intravenous pyelogram (IVP) and urinary vanillyl mandelic acid (VMA) were normal.

At laparotomy, a 4 x 5 cm mass bound to the sacral plexus was incompletely resected, and the histological diagnosis was ganglioneuroblastoma. The patient did well following surgery, and she received 3200 rads over a 3-week period followed by oral
cyclophosphamide (Cytoxan), 3 mg/kg/day. Six months following the onset of symptoms, she was readmitted for evaluation of an episodic jerking of the left arm. Skull films and cerebral angiography were normal. An electroencephalogram demonstrated mild asymmetrical slowing in the left occipital region. One year after the onset of symptoms, cyclophosphamide was discontinued. Three years following diagnosis of neuroblastoma, her general and neurological examinations are normal, and she shows no signs of recurrent tumor.

Case 2

This 1-year-old boy, while being treated for otitis media, had a generalized convulsion; within a few days he could no longer sit or walk unassisted, and had developed "fluttering" eye movements, tremors of the arms and legs, and difficulty swallowing liquids. Two weeks after the onset of symptoms he had another generalized fit and was seen by a neurosurgeon. Skull films, brain scan, electroencephalogram, and pneumoencephalogram were all normal. He was discharged with a diagnosis of "cerebellar inflammatory disease" and treated with additional antibiotics. He was referred to us 6 weeks after the onset of symptoms.

The general examination was normal except for diffuse rhonchi heard at auscultation of the chest. The cranial nerves were normal except for rapid, multidirectional conjugate eye movements. There was profound hypotonia and hypoactive deep tendon reflexes. The plantar responses were flexor. He was tremulous, had myoclonic jerks, and moderate limb and truncal ataxia, so that he was unable to sit, stand, or walk. His response to touch and pain was normal. Routine laboratory studies were unremarkable. Skull films, electroencephalogram, and brain scan were all normal. The CSF was clear and under normal pressure; there were two lymphocytes, a protein content of 12 mg%, and a glucose content of 57 mg%. Abdominal roentgenograms demonstrated a 4 x 5 cm right suprarenal mass with speckled calcifications and flattening of the upper calyx of the right kidney. The urinary VMA was 7.1 and 3.0 mg/24 hr preoperatively, and 0.4 mg/24 hr postoperatively (normal: to 3.0 mg/24 hr). Urinary homovanillic acid (HVA) and cystathionine were normal.

The right kidney and adrenal gland were removed, but the tumor mass could be only partially resected. Microscopic examination of the mass was interpreted as ganglioneuroblastoma. Postoperative radiation therapy included 1500 rads to the upper abdomen, 1000 rads to the pelvis, and 1500 rads to the mediastinum, over a period of 5 weeks. Maintenance chemotherapy with oral cyclophosphamide at 25 mg/day was then initiated. The myoclonus persisted, although it was less severe following administration of ACTH. Two subsequent courses of prednisone also diminished but did not abolish the opsoclonus, myoclonus, or ataxia. The child continues to have a marked neurological disability. There is no evidence of recurring tumor or metastasis 18 months after surgery.

Case 3

This 2-year-old boy was well until 10 days before admission when he showed repetitive jerking movements of the arms and legs and "rapid jiggling" eye movements. Because he could not sit, stand, or walk, he was referred to a neurosurgeon, who performed cerebral angiography and air encephalography, both of which were normal. The child was then referred to us for neurological evaluation.

The patient was lethargic. The cranial nerves were normal except for multidirectional, chaotic conjugate eye movements. The motor system was normal except for severe hypotonia and myoclonic jerks of the arms and legs, intensified by movement. The child had severe truncal and limb ataxia. He responded normally to touch and pain. Routine laboratory studies, skull films, brain scan, and electroencephalogram were normal. The CSF contained no cells, and the protein and glucose contents were 33 mg% and 72 mg% respectively; the CSF protein electrophoresis was normal. Cultures of CSF were sterile. A 2 x 4 cm right paravertebral mass was seen on chest and abdominal roentgenograms. There was calcification of the mass in the right paravertebral region extending to the region of the adrenal gland. Intravenous pyelogram, urinary VMA, HVA, and cystathionine were normal. At surgery, a 2 x 2 cm paravertebral thoracic mass was partially resected. The histological diagnosis was ganglioneuroblastoma.

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Following surgery, the patient received 2800 rads over a 4-week period directed to the mediastinum, upper abdomen, and adrenal gland. He received "pulse" cyclophosphamide, 10 mg/kg/day, for 10 days each month for 1 year. In an attempt to lessen opsoconus, myoclonus, and ataxia, he was given two separate courses of prednisone; improvement was questionable. One year after the initial symptoms, he still has moderate to severe truncal and limb ataxia, myoclonus, and opsoclonus; there is moderate psychomotor retardation but no evidence of tumor recurrence.

Case 4

Two months before admission, this 21-month-old boy developed an unsteady gait with frequent falls. Neurosurgical investigation included electroencephalogram, brain scan, lumbar puncture, cerebral angiogram, and air encephalography; all were normal. The ataxia increased, and he developed tremors, myoclonic jerks, and rapid involuntary eye movements. He was referred to us 10 weeks after the onset of symptoms.

The patient was irritable; he sat unsteadily in the tripod position, but could not stand or walk unassisted. Cranial nerves were normal except for rapid, agitated, multidirectional eye movements. Examination of the motor system revealed hypotonia, moderate truncal and limb ataxia, and frequent myoclonic jerks. The deep tendon reflexes were brisk and symmetrical; the plantar responses were bilaterally flexor. He responded to touch and pain normally. Routine laboratory studies were normal. The skull films and brain scan were normal. The CSF dynamics and cell count were normal; the protein content was 14 mg% and glucose 78 mg%. Poorly defined calcifications adjacent to the left L-1 and L-2 vertebral bodies were present on abdominal films. Intravenous pyelograms, urinary VMA, HVA, and cystathionine were normal. At laparotomy, left perirenal nodes were excised. A primary mass was not identified. Histological examination confirmed the preoperative diagnosis of neuroblastoma.

Following surgery, the patient received 2500 rads over a 3-week period directed to the left sympathetic ganglia, both adrenals, and the hilus of the left kidney. He was given "pulse" cyclophosphamide 10 mg/kg/day for 10 days of each month. Because of the persistent opsoconus, myoclonus, and ataxia 5 months after the onset of symptoms, prednisone was given and was followed by some lessening of these symptoms. The patient continues to have mild psychomotor retardation. There has been no evidence of tumor recurrence or metastasis 11 months after surgery.

Discussion

Neuroblastoma, a malignant tumor arising from embryonic sympathetic neuroblasts, occurs in the pediatric age group; more than half the patients reported are less than 3 years old. Catecholamines are often secreted by the tumor, and their metabolites, epinephrine, norepinephrine, VMA, and HVA, are detectable in the urine in approximately 90% of the patients. Cystathionine, a metabolite of methionine, present in normal liver, muscle, and brain but not in normal urine, is present in the urine in 50% of children with neuroblastoma.

Significant radiographic findings may include calcification within the tumor and in abdominal tumor displacement of the kidney without major distortion of the urinary collecting system. Paravertebral widening, seen on plain roentgenograms of the chest or abdomen, is reported to be typical of the tumor.

The association of opsoconus and occult neuroblastoma was first suggested by Solomon and Chutorian in 1968; other patients with opsoconus and occult neuroblastoma were reported shortly thereafter. Our patients (Table 1), like those reported by others, were young children who experienced the sudden onset of truncal ataxia without signs of increased intracranial pressure. At the same time or shortly thereafter, myoclonus of varying severity was observed in the limbs and, on occasion, myoclonic jerks of the trunk were seen. Eye movements typical of opsoconus were characterized by gross irregular, chaotic multidirectional conjugate jerks. This ocular agitation was present intermittently during wakefulness and with diminished amplitude during sleep.

Because of the opsoconus, myoclonus, and ataxia, occult neuroblastoma was suspected in each patient when admitted to our hospital. Tumor calcification was seen on the plain abdominal roentgenograms of all four children.
and in the chest films of two. Of the 24 patients reported with neuroblastoma-encephalopathy by others, radiographic findings consistent with neuroblastoma were observed in the chest films of 14 patients and on plain abdominal films of four (Table 1). Ten of 24 reported patients had x-ray evidence of tumor calcification. The location of the neuroblastoma in patients with encephalopathy was mediastinal in 16 of 28 patients (57%). However, in a survey of all the neuroblastomas from the California Tumor Registry over a 24-year period, only 16% were found in the mediastinum.

Determination of urinary VMA was elevated in one of our four patients, whereas it was abnormally elevated in nine of the 18 patients reported elsewhere in whom that assay had been performed.

The neurological signs of opsoclonus, myoclonus, and ataxia have preceded the detection of the neuroblastoma in all but two of the children reported; in the latter the neuroblastoma was found before the onset of neurological signs. It should be emphasized that several patients had neurological signs consistent with neuroblastoma-encephalopathy when initially seen, but the tumor was found only after repeated radiographic studies and urine assays for VMA had been carried out over a period of several months.

Treatment of the neuroblastoma usually includes the combination of surgical removal of the tumor followed by radiation therapy to the tumor site and sometimes chemotherapy. Symptomatic relief from opsoclonus and myoclonus has been reported following administration of ACTH or prednisone but the overall effectiveness and symptom control with steroids has varied from patient to patient. The post-treatment clinical course of children with neuroblastoma-encephalopathy has varied from complete disappearance of signs and symptoms to death. One of our four patients is asymptomatic; the remaining three have persistent mild-to-moderate opsoclonus, myoclonus, and ataxia, and are retarded in their development. Of our four patients plus the 24 reported elsewhere, three have died, 19 have some neurological sequelae, and six were normal at the time of the report. Ten of the 28 children reported are mentally retarded; two of these show no neurological abnormality.

The specific relationship of the neuroblastoma to the neurological signs of opsoclonus, myoclonus, and ataxia has remained unexplained. Some investigators

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**Table 1**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Tumor Histology</th>
<th>Tumor Site</th>
<th>Age/Onset Symptoms (mos)</th>
<th>VMA</th>
<th>Chest X-Ray</th>
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<tbody>
<tr>
<td>1</td>
<td>ganglio-</td>
<td>presacral</td>
<td>20</td>
<td>normal</td>
<td>neg</td>
</tr>
<tr>
<td></td>
<td>neuroblastoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>ganglio-</td>
<td>r. adrenal retroperitoneal nodes mediastinum</td>
<td>13</td>
<td>increased</td>
<td>pos</td>
</tr>
<tr>
<td></td>
<td>blastoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>ganglio-</td>
<td>mediastinum abdominal sympathetic chain</td>
<td>24</td>
<td>normal</td>
<td>pos</td>
</tr>
<tr>
<td></td>
<td>neuroblastoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>neuroblastoma</td>
<td>l. renal perirenal nodes primary unknown</td>
<td>18</td>
<td>normal</td>
<td>neg</td>
</tr>
<tr>
<td></td>
<td>reported cases:*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>neuroblastoma</td>
<td>mediastinal</td>
<td>av. age: 22.4 mos; range: 8 mos-5 yr</td>
<td>increased</td>
<td>in 9 of 18 assays</td>
</tr>
<tr>
<td></td>
<td>(19)</td>
<td>retroperitoneal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ganglio-</td>
<td>unknown primary</td>
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</tr>
<tr>
<td></td>
<td>neuroblastoma</td>
<td>(5)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*See refs 2-4, 5, 7, 10, 11, 14-20, 22, 24, 26, 27.
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TABLE 1 (continued)

<table>
<thead>
<tr>
<th>Abd.</th>
<th>Plain IVP</th>
<th>Treatment</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>pos</td>
<td>neg</td>
<td>incomplete excision; radiation therapy; Cytoxan</td>
<td>no evidence of tumor recurrence in 3 yrs; disappearance of symptoms within 8 mos of onset</td>
</tr>
<tr>
<td>pos</td>
<td>pos</td>
<td>incomplete excision including r. nephrectomy; radiation therapy; Cytoxan</td>
<td>no evidence of tumor recurrence in 18 mos; initial improvement, then variable course; continues to have opsoconus, myoclonus, ataxia</td>
</tr>
<tr>
<td>pos</td>
<td>neg</td>
<td>incomplete excision; radiation therapy; Cytoxan</td>
<td>slight improvement of neurological symptoms with steroids; continues to have moderate myoclonus, ataxia, developmental delay</td>
</tr>
<tr>
<td>pos</td>
<td>neg</td>
<td>incomplete excision; radiation therapy; Cytoxan</td>
<td>gradual improvement but continues to have mild myoclonus, ataxia, developmental delay</td>
</tr>
</tbody>
</table>

| 4    | 2         | the reported patients had a variety of therapeutic procedures; at the time of the report, 3 patients were dead, 16 had neurological sequelae, and 5 were normal |

have suggested that the tumor and neurological signs have an immunological etiology and cite as evidence a neuroblastoma-associated antigen to which both cell-mediated immunity and humeral antibody have been demonstrated. Furthermore, lymphocytes from patients with neuroblastoma, as well as from their mothers, have been shown to be cytotoxic to neuroblastoma cells in culture; this cytotoxic effect can be blocked by the serum of some patients with progressive disease or by the serum from their parents. Additional evidence for an immunological basis for the tumor is found in its spontaneous regression. Beckwith and Perrin reported an incidence of occult neuroblastoma cells in one of 200 autopsies of infants less than 3 months old; this is 40 times greater than the expected occurrence of the tumor in childhood.

Since most neuroblastomas are catecholamine- or cystathionine-liberating tumors, it is possible that these biogenic amines are toxic in some way to nerve tissue. It must be pointed out, however, that no relationship has thus far been found between the presence of these urinary metabolites and an increased incidence of neurological symptoms. Finally, although an oncogenic and neurotropic agent has been postulated, no such virus has yet been identified.

There is no definitive neuropathological study of this syndrome. Ross and Zeman, in their study of a patient with opsoconus, myoclonus, ataxia, and occult bronchogenic carcinoma, found a 10% to 20% loss of Purkinje cells, but thought this was non-specific and not adequate to explain the clinical signs. They also noted a mild chronic perivascular inflammation throughout the brain stem and basal leptomeninges that was suggestive of an immunological reaction. Histochemical changes of oxidative enzymes in the neuropil of the dentate nucleus were thought to be secondary to a destructive process of Purkinje cell synapses.

Conclusion

The unusual combination of opsoconus, myoclonus, and ataxia in a small child should alert the physician to the possibility of occult neuroblastoma. Diagnosis can often be made by simple radiographic studies of the chest, abdomen, or an intravenous pyelogram, rather than cerebral angiography or air encephalography. Urinary vanillyl mandelic
acid (VMA) may be of assistance in making the diagnosis. If no tumor is found in the presence of these clinical findings, the child should be carefully followed and reevaluated at periodic intervals with radiographic examinations of the chest and abdomen, intravenous pyelogram, and determination of urinary VMA.

References


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