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The association of acute cerebellar encephalopathy and neuroblastoma

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Acute cerebellar encephalopathy is a rare neurological disorder associated with neuroblastoma and is characterized by ataxia, somatic myoclonus and opsoclonus. The pathogenesis which underlies the relationship between the two conditions is obscure.

One patient with neuroblastoma and acute cerebellar encephalopathy is reported. The occurrence of neuroblastoma and acute cerebellar encephalopathy in this case may be coincidental but, on the basis of frequent recent reports of this association, a possible relationship between these two entities is entertained. It is therefore recommended that all patients with acute cerebellar encephalopathy be surveyed for unapparent neuroblastoma. The search should include chest and skeletal X-rays, intravenous urogram, inferior venocavogram, quantitative determination of urinary VMA and HVA, cystathionine and bone marrow examination for malignant cells.

After acute leukemia and brain tumors, the most common malignancy in children is neuroblastoma. The incidence is highest during the first two years of life and falls rapidly thereafter. Neuroblastomas originate from primitive sympathetic neuroblasts of the neural crest. The wide distribution of these cells in the embryo helps to explain the variable clinical behavior of the tumor.

There is no specific symptomatology or characteristic manner of onset to distinguish neuroblastoma. Initial symptoms, often vague, include fever, lymphadenopathy, pain, gastrointestinal disturbances, failure to thrive and bone pain. Acute cerebellar encephalopathy is a rare neurological disorder associated with neuroblastoma and is characterized by ataxia, somatic myoclonus and opsoclonus.

This report emphasizes the frequent association between acute cerebellar ataxia and neuroblastoma.1,2

Case Report

A two-year-old black boy with a normal birth and early development was admitted to Henry Ford Hospital for evaluation of cerebellar ataxia.

One month prior to this admission the patient was treated for an acute asthma attack at another hospital with epinephrine and aminophylline. These symptoms regressed spontaneously two days later. He
was well until nine days prior to this admission, when he was again treated for an acute asthma attack with epinephrine and aminophylline. The next morning, his mother noted irritability, trembling of the head, trunk and extremities, unsteady gait, and dancing movements of the eyes. This progressed within one or two days to complete inability to stand alone or walk. There was no history of trauma, drug ingestion, neonatal difficulties or previous seizure.

On physical examination, the patient was irritable, having constant generalized myoclonus with opsoclonus and tremor of the eyelids. He was unable to sit or stand without support. Deep tendon reflexes, plantar responses and cranial nerve functions were within normal limits. Examination of the abdomen disclosed a 10 cm hard, nontender mass in his left lower abdomen.

Initial laboratory data revealed normal complete blood count, urinalysis, blood urea nitrogen, serum calcium, phosphorus and magnesium. Serum protein electrophoresis as well as serum immunoglobulins were normal. Cerebrospinal fluid pressure, chemistry and bacteriological studies were within normal limits. Lead level in blood was at the upper limit of normal. Urine showed small amounts of morphine, heroin and phenothizine. His blood, however, was only positive for phenothizine. Subsequent examination revealed no further traces of these materials in blood and urine. The virus neutralizing antibody titer showed no rise. Measurements or urinary catecholamines revealed normal values (von mandolic acid 3.31/μg/mg and homo vanillic acid was negative). Bone marrow was within normal limits. EEG, brain scan, chest x-ray, skull series and metastatic bone survey were all negative. An intravenous pyelogram showed anterior and lateral displacement of the left ureter by a large, left retroperitoneal, infra-renal mass.

On his third hospital day, surgical exploration was undertaken and a partially differentiated neuroblastoma arising from the left lumbar sympathetic chains was removed en-bloc, together with several retroperitoneal lymph nodes. The tumor mass, however, was entering multiple left spinal neural foramina and complete resection was not technically possible.

Post-operatively, the patient was given a total dose of 2952 rads of Cobalt 60 to the tumor bed as identified by metallic clips placed at the time of operation and the radiation was carried across the midline to include the entire width of the spine at this level. He was also started on Vincristine and Cytoxan cyclic chemotherapy. (VCR 1.5 mg/m² by I. V. push alternating with Cytoxan 300 mg/m² weekly.)

After surgery, radiation and chemotherapy, there was gradual improvement in the patient’s neurologic status, his opsoclonus had disappeared, but there were occasional occular flutters with very slight occasional ataxia. He was able to walk on crutches and stand up with assistance.

Followup 35 months later showed the patient with very minimal ataxia. He has gained weight remarkably and his neurologic as well as mental status have improved considerably, and he has been able to walk reasonably well. There is no evidence of recurrence or metastatic disease.

Discussion

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ataxia and neuroblastoma in children has recently been reported with increasing frequency.\textsuperscript{1–3} The pathogenesis of the relationship between the two conditions is not known. One of the theories to explain this relationship includes viral infection. One could speculate that a neurotropic virus may produce both an encephalopathy and neoplasia. No documental evidence in support of this theory could be found.

A second consideration might suggest that the neuroblastoma liberates an antigen which forms antibodies and these antigen-antibodies produce an immune response which could damage the nervous system.

The third possible mechanism might be the liberation of some metabolites, such as catecholamines in excess amounts or cystathionine which in turn damages the cerebellum by virtue of its toxic chemical properties.

Finally, and least important of all, is the presence of some undefined carcinogen in the patient’s system which could cause encephalopathy. More extensive research work is needed before a definite conclusion regarding this relationship can be found.

In our case, no rise in virus neutralizing antibody titer was found. His urinary catecholamines were normal. We are, therefore, unable to give any support in favor of the above theories. Since the patient started his cerebellar ataxia following epinephrine injection, it is conceivable that his tumor has hormone properties at times. However, we do not have any evidence to support this.

The next important question in a child with cerebellar ataxia is to find the etiology. The diagnostic consideration in these circumstances include drug intoxication, encephalitis and brain tumor. When evidence of positive traces of narcotics were found in our patient we became concerned about the possibility of withdrawal syndrome, but subsequent study did not confirm this.

As far as encephalitis is concerned, we investigated this patient for this possibility. He had an afebrile hospital course. His cerebrospinal fluid findings were not suggestive and there was no history of exposure. With a negative brain scan and skull series, the probability of brain tumor as the cause of this patient’s ataxia can also be ruled out.

From a practical standpoint, patients who present with neurologic syndrome or ataxia should be surveyed carefully for an inapparent neuroblastoma. The clinical and laboratory survey should include chest and skeletal x-rays, intravenous urogram, inferior venecavogram, quantitative determination of urinary VMA catecholamines and homovanillic acid, cystathionine and a bone marrow examination for malignant cells. Awareness of the association between acute cerebellar encephalopathy and neuroblastoma should lead to an immediate diagnostic investigation for such a tumor. An unusual feature of neuroblastoma presenting with acute cerebellar ataxia is the high incidence of intrathoracic tumor as well as normal urinary catecholamine excretion. Tumors arising from spinal nerve roots and ganglia show normal urinary catecholamine excretion. Cystathionine, if present in the urine, might be indicative of active metastatic liver disease. The course of acute cerebellar encephalopathy is usually protracted by exacerbators and remissions. Mental retardation may occur if therapy is delayed. Early detection may contribute greatly to a favorable prognosis.
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References

