Neuroblastoma in a patient with Sotos' syndrome

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Abstract

Sotos' syndrome, or cerebral gigantism, is a disorder of growth regulation. Tumours have occasionally been reported in children with Sotos' syndrome, but it is uncertain whether this is a coincidence, or whether it is aetiologically related to the underlying disorder of growth. We report a 15 month old child with a paraspinal neuroblastoma and Sotos' syndrome and suggest that children with this condition may be at higher risk for developing tumours than the general population.

Sotos' syndrome was first described in 1964 in five unrelated children who had large body size for age with advanced bone age and similar facial features (large jaw, large forehead with frontal bossing, temporal hair recession, hypertelorism, and downward slanting palpebral fissures).¹ Subsequent reports have confirmed the characteristic phenotype, and added to it other consistent features, such as developmental delay, clumsiness and other neurological abnormalities, enlarged ventricles on x ray, and early eruption of deciduous teeth.²⁻⁴ The cause of this primordial overgrowth syndrome is not known; serum growth hormone and somatomedin C levels are normal, and no histological or laboratory evidence of pituitary or hypothalamic dysfunction has been found.^{5,6} Most cases of Sotos' syndrome are sporadic, although other genetic patterns have appeared in isolated families. The relationship between Sotos'

syndrome and neoplasia is uncertain; however, a disproportionate number of patients reported with this diagnosis have also had malignancies.

Case report

A 15 month old child presented to the Variety Club Children's Hospital at the University of Minnesota with a one month history of loss of developmental milestones and the development of abnormal eye and limb movements. She was born with a birth weight of 3892 g at 36 weeks of gestation to a 27 year old, G3P3 mother and a 41 year old father. Her growth chart is illustrated in fig 1. Her first teeth erupted at four

Figure 1 Growth curves for the patient. Both height and weight follow a curve well over the 95th centile.

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months and she had learned to walk and say two or three words by 13 months of age. Over the month before admission she had lost the ability to walk, fell frequently while standing, and used only one word. She had two normal sibs and her father had cataplexy.

On examination her height was 90.5 cm, her weight 15.4 kg, and her head circumference 50.5 cm, all well above the 98th centile. She had a large dolichocephalic head with frontal bossing, a frontal upsweep, and temporal recession of the hairline (fig 2). She also had a plethoric facies, a small nose, and a prominent chin. Her hand length was 11.4 cm, foot length 15.7 cm (both hand and foot length above the 97th centile, both approximately 50th centile for 42 months), and arm span 90.5 cm. A right transverse palmar crease was present. Genitalia were normal for a prepubertal female, and no abnormalities of the heart, abdomen, or skin were noted. She manifested opsoclonus, frequent myoclonic movements of the extremities, and ataxia of the trunk and limbs.

A cranial MRI scan showed mildly enlarged ventricles, and her bone age was increased at 2.5 years (SD for chronological age, 5.2 months). Serum growth hormone levels ranged between 1.9 and 4.4 µg/l on several samples (normal 0 to 10 µg/l), and the serum somatomedin C level was 5.8 nmol/l (normal for age 0.1 to 2.0 years, 3.4 to 15.8 nmol/l). Her 24 hour excretion of HVA and VMA was raised for her age, but normal when standardised to her creatinine excretion or her size. A CT scan of the abdomen showed a large paraspinal mass extending from T12 to

L3, with compression of the dural sac from L1 to L3 owing to invasion of the spinal canal.

She underwent gross total resection of her tumour without difficulty; the left L2 nerve was invaded with tumour and was sacrificed. Subsequent studies for tumour staging (lumbar puncture, bone marrow biopsy/aspiration) were negative, and she is at present being followed without further adjuvant therapy for stage II neuroblastoma. The abnormal limb and eye movements were felt to represent the opsoclonus-myoclonus syndrome (or acute myoclonic encephalopathy of infancy), which is known to be associated with neuroblastomas⁷; they have shown some improvement with oral steroid therapy.

Discussion

Several types of neoplasms have been reported in patients with Sotos' syndrome, including hepatocarcinoma, Wilms' tumour, vaginal carcinoma, parotid tumour, cavernous haemangiomas, osteochondroma, neuroectodermal tumour, and giant cell granuloma of the mandible.⁵⁻⁸⁻¹³ Ours is the first reported case of neuroblastoma occurring with Sotos' syndrome. In their 1984 review, Maldonado *et al*⁹ found eight patients with tumours among the 132 cases of Sotos' syndrome reported before 1981, and felt that this was highly suggestive of an increased cancer risk in these patients.

Several other syndromes feature somatic overgrowth and malignancy. Beckwith-Wiedemann syndrome and Perlman's syndrome both include macrosomia and a predisposition to Wilms' tumour among their clinical characteristics. Neurofibromatosis is a disorder of neural growth regulation in which there is clearly an increased risk of tumour development, particularly in neural tissues. Ruvalcaba-Myhre-Smith syndrome features early macrosomia, hypotonia, characteristic ocular findings, and intestinal polyposis similar to that in Peutz-Jeghers syndrome. Sotos' syndrome, in contrast to these syndromes, does not yet appear to be related to a specific tumour type, but rather to solid tumours of ectodermal or mesodermal origin in general.

Macrosomia occurring in the absence of a specific syndrome has also been proposed as a risk factor for childhood cancer. One recent study showed an association between high birth weight (>4000 g) and childhood cancers.¹⁴ Neuroblastoma was one of the types of malignancy associated with this higher risk. Although a second study focusing on neuroblastoma alone failed to confirm this association,¹⁵ it would be valuable to consider whether any of the reported high birth weight infants who developed neuroblastoma had clinically unrecognised Sotos' syndrome or some other disorder of growth regulation.

As more is learned in the coming years about the relationship at the molecular level between normal

Figure 2 Frontal view of the patient's face. Note the prominent forehead, frontal upsweep and temporal recession of the hairline, relatively small nose, and plethoric facies.

growth regulation, disordered growth regulation, and oncogenesis, conditions such as Sotos' syndrome will be better understood. Until that time, physicians should be alert to the possibility of this diagnosis in macrosomic infants with advanced bone age, and aware of the increased risk of neoplasia in these patients.

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