Case Report

Camptodactyly in Sotos syndrome

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We describe a girl with Sotos syndrome presenting at two and a half years age with developmental delay. She has camptodactyly which has not previously been reported in Sotos syndrome but is a common finding in Weaver syndrome. Both these conditions have been reported to have NSD1 gene mutations. This report is consistent with the conditions being allelic.

Key words: Camptodactyly, Sotos syndrome, Weaver syndrome

Introduction

Sotos syndrome is a dysmorphic syndrome characterized by early overgrowth, developmental delay, advanced bone age and characteristic craniofacial appearance.[1] Sotos syndrome results from mutation involving the nuclear receptor SET-domain-containing protein (NSD1) gene, located on chromosome 5q.[2] The mutational mechanism can be a point mutation in the NSD1 gene or a microdeletion that includes NSD1. Fluorescence *in situ* hybridization (FISH) did not detect microdeletion of 5q35 in this patient. NSD1 gene mutations are also found in Weaver syndrome where camptodactyly is a common feature. This report describes camptodactyly for the first time in a girl with Sotos syndrome and provides further evidence that Sotos and Weaver syndrome are allelic disorders.

Case Report

We describe a two and half years old girl born of non-consanguineous Tamilian parents. Polyhydramnios was noted in the antenatal period at 35 weeks gestation. She was born by Caesarean section, was cyanosed at birth and required oxygen. Birth weight was 3.75 kg. Milestones were delayed with head holding at 6 months, walking at 2 years and delayed speech. Family history was unremarkable.

At two and a half years she weighed 15 kg, height was 97 cm and head circumference was 52.5 cm (all above 90th centile). She had a high forehead with frontal bossing, dolichocephaly, large ears, pre-auricular pits, down-slanting palpebral fissures, high arched palate, pointed chin and pectus carinatum [Figure 1]. She had three café au lait spots distributed on the chest and trunk, large hands and camptodactyly of the left hand [Figure 2]. She had generalized hypotonia. There was a continuous murmur on auscultation of the precordium. The rest of the physical examination was normal. An echocardiogram showed patent ductus arteriosus. The bone age was advanced. Imaging of the brain and routine karyotyping were normal. FISH studies carried out using probe RP11-265K23 did not reveal a microdeletion of the 5q35 region.

A clinical diagnosis of Sotos syndrome was made based on the criteria comprising of rapid early growth, advanced bone age, developmental delay and characteristic facial appearance. Camptodactyly in Sotos syndrome has not been previously described in literature to the best of our knowledge. Weaver syndrome another overgrowth syndrome has camptodactyly as an important feature. Clinical and molecular overlaps in overgrowth syndromes have been previously described.[3] Point mutations in the NSD1 gene have been described in both these syndromes.[4,5] A high frequency of congenital heart defects has been reported in patients with intragenic mutations of the NSD1 gene and phenotypic overlap with other overgrowth syndromes, in particular with Weaver syndrome is seen.[6] Though this Sotos patient is likely

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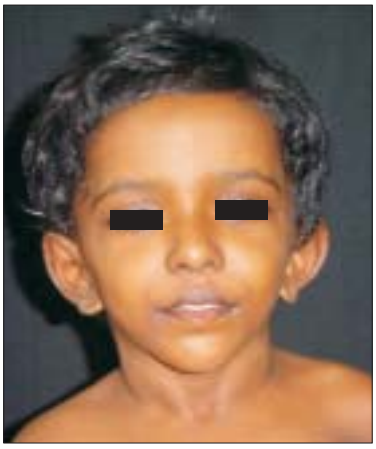

Figure 1: Face showing the facial features of Sotos syndrome

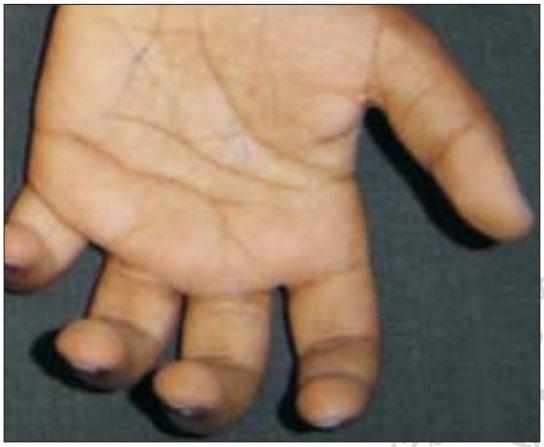

Figure 2: Left hand showing camptodactly

to have a point mutation of the NSD1 gene, this could not be confirmed due to lack of facilities.

Discussion

Sotos syndrome was first recognized as a distinct clinical syndrome in New England in 1964. The diagnosis is based on the clinical criteria of rapid early growth (pre and post natal), advanced bone age, developmental delay and characteristic facial appearance.[1] The disorder is dominantly inherited. Most cases are sporadic and represent new dominant mutation. Growth is rapid in the first years of life but final height may not be excessive. Intellectually, the IQ ranges from 21 to 103 with a mean of 74 and almost half of affected children achieve normal schooling. Behavioral issues are common and are one of the key areas that can influence the outcome. Hypotonia is usually present from birth and although this improves during childhood, subtle evidence may remain even in adults. Congenital heart disease is not very common in this condition and overall incidence of cardiac defects is approximately 8%.[7] An association of Sotos syndrome with tumor development was documented over 30 years ago and has been a point of debate ever since. Gorlin *et al.* estimated a risk of 3.9% of benign or malignant tumors in Sotos syndrome.[8] Handicaps in Sotos syndrome are fewer than previously believed and tend to improve with age.[1]

In patients with Sotos syndrome harboring a chromosomal translocation Kurotaki *et al.* isolated the nuclear receptor SET-domain-containing protein (NSD1) gene from the 5q35 breakpoint.[2] The results indicated that haploinsufficiency of NSD1 is the major cause of Sotos syndrome.

Kurotaki *et al.* added noted a large difference between Japanese and non-Japanese patients in the frequency of microdeletions, which occurred in 49 (52%) of the 95 Japanese but in only 1 (6%) of the 17 non-Japanese.[9] There was a strong correlation between presence of an NSD1 alteration and clinical phenotype, in that 28 of 37 (76%) patients with typical Sotos or Sotos-like phenotype had NSD1 mutations or deletions.

Rio *et al.* studied NSD1 gene in a series of typical Sotos patients (23/39), Sotos-like patients (lacking one major criteria, 10/39) and Weaver patients (6/39).[4] They identified NSD1 intragenic mutations in 3/6 Weaver patients. In their study they conclude that NSD1 mutations account for most cases of Sotos syndrome and a significant number of Weaver syndrome cases.[4]

Comparing the clinical phenotype of children carrying either a deletion or a mutation, Rio *et al.* failed to detect distinctive features except for the severity of mental retardation. They reported, 4/6 children carrying a NSD1 deletion were extremely severely mentally retarded with no language at all, major delay in motor milestones and autistic features. By contrast, in patients carrying NSD1 mutations, mental retardation was usually mild to moderate with verbal skills being more affected.[5]

The major differential diagnoses for Sotos syndrome are other conditions with overgrowth including Beckwith-Weidemann, Weaver, Nevo and Simpson Golabi Behmel syndromes. The typical facial gestalt of Sotos syndrome clinches the diagnosis. However NSD1 gene mutations

have been found in Beckwith-Weidemann syndrome, Weaver syndrome and the 11p15 abnormalities seen in Beckwith-Wiedemann syndrome have been found in some cases of Sotos syndrome.[3]

Camptodactly has not been previously described in literature to the best of our knowledge with Sotos syndrome but is seen in Weaver syndrome where NSD1 mutations have been described. We describe camptodactyly in Sotos syndrome for the first time. Phenotypic variations are seen in genetic syndromes. These could be due to, allelic heterogeneity, effect of other modifying genes ethnic background and nutritional status adding to the overall expression of a syndrome.

Microdeletions of chromosome 5 were not detected in our case suggesting a likely point mutation in the NSD1 gene and further evidence of that Weaver and Sotos syndrome are allelic. Further delineation of the phenotype with molecular studies will provide correct genotype-phenotype correlations.

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