

Sotos syndrome and cutis laxa

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Abstract

Characteristics suggestive of connective tissue dysfunction have been described in Sotos syndrome and include joint hyperextensibility, pes planus, and a high arched palate. A variety of cutis laxa syndromes have also been described, some of them exhibiting mental retardation, but no reports have drawn an association with overgrowth or abnormal facies characteristic of Sotos syndrome. We report three patients with the anthropometric and dysmorphological appearance of classical Sotos syndrome in association with redundant skin folds, joint hypermobility, and, in two of the three, vesicoureteric reflux suggestive of a coexisting connective tissue disorder. All of the patients had a normal bone age suggesting that Sotos syndrome in its classically described form was not present and that this entity possibly reflects a related, perhaps allelic, condition.

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Sotos syndrome (cerebral gigantism, MIM 117550) is characterised by accelerated growth in childhood that usually normalises by adulthood, characteristic dysmorphism, and devel-

opmental delay.¹ An advanced bone age is often considered a prerequisite for the diagnosis.^{2,3} The disorder is dominantly transmitted with most cases being isolated instances within kindreds. Some variable characteristics of the phenotype are suggestive of a connective tissue defect, namely hyperextensibility of the joints, pes planus, and a high arched palate. We report three unrelated cases with a Sotos-like phenotype, marked joint hyperextensibility, cutis laxa, and vesicoureteric reflux. These patients show that the connective tissue dysfunction in this Sotos-like syndrome can be severe.

Case reports

CASE 1

Case 1, a male, was the second child of non-consanguineous parents, born after an unremarkable pregnancy and labour at 41 weeks' gestation. Birth weight was 4030 g (90th centile), length was 53 cm (90th centile), and head circumference was 40 cm (>97th centile). Immediately obvious at birth were facial jowls and wrinkles with folds of redundant skin elsewhere on the body (fig 1). The ears were overfolded and the helices were flattened bilaterally (fig 2). The hands and feet were disproportionately large. A left talipes equinovarus deformity was treated with a plaster cast. Initial poor feeding improved spontaneously after a week and the baby was



Figure 1 Facial features of case 1 in infancy.



Figure 2 The ears of case 1 showing overfolded and flattened helices.

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Figure 3 Case 1 in late infancy. The evolving facies of Sotos syndrome are evident (triangular face, broad forehead) together with loose folds of redundant skin.

discharged. Subsequent investigations included a normal karyotype and a negative qualitative test for urinary homocystine. Audiological assessment was normal.

Serial developmental assessments showed that gross motor, fine motor, and receptive language development was slightly delayed but expressive language development was particularly affected and lagged by six to 12 months over the first 36 months of life necessitating speech language therapy. Clinical reassessments showed the characteristic facies of Sotos

syndrome (fig 3), a high arched palate, pectus carinatum, and large hands and feet. Persisting connective tissue characteristics included joint hyperextensibility and lax skin although the laxity of the skin gradually diminished over the first decade of life. The head circumference tracked 2 cm above but parallel to the 97th centile from 2 months of age, while the height and weight followed the 97th centile then dropped to the 75th by 7 years of age. A bone age at 21 months was concordant with chronological age. No further bone ages or clinical assessments were performed as the child became lost to follow up.

CASE 2

Case 2, a female, was the second of three children born to a non-consanguineous couple after a pregnancy complicated by pre-eclampsia. There was no family history of genitourinary malformations or history of maternal diabetes in pregnancy. Birth weight was 4300 g (>97th centile). At 2 weeks of age her length was 57 cm (>97th centile) and head circumference was 37.5 cm (>97th centile). The child was hypotonic and fed poorly for the first seven days of life requiring gavage feeds. From birth there was pectus carinatum, the skin hung in loose, redundant folds, and joint hypermobility was present. The palate was high arched. These signs persisted as prominent features into the second decade of life (fig 4).

During follow up, the facies of Sotos syndrome was noted (fig 5) and the hands and feet were large with deep creases in the soles of the feet (fig 6). Serial bone ages (performed at 9 months and 6, 8, and 14 years) were commensurate with chronological age. A karyotype was 46,XX.

Developmental assessments showed mild delays in gross and fine motor skills but expressive language was more substantially

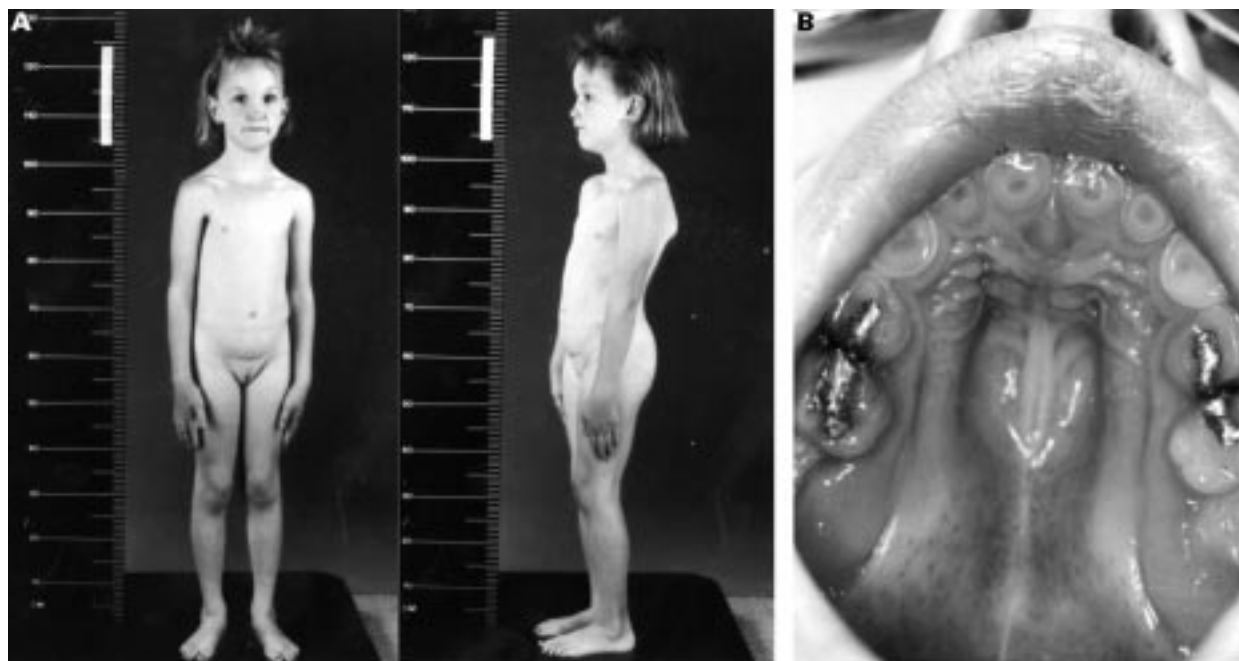


Figure 4 (A) Appearance of case 2 aged 4 years showing the facies of Sotos syndrome, large hands and feet, and genu valgum, and plantar valgus deformities reflecting her ligamentous laxity. (B) The palate is also high arched.



Figure 5 Persisting facies of Sotos syndrome at the age of 8.



Figure 6 Deep creases in the feet of case 2 reflecting the presence of cutis laxa.

delayed. Hypermetropia was diagnosed at 4 years requiring spectacles. A urinary tract infection at the age of 3 led to the discovery of vesicoureteric reflux with pronounced pelvicalyceal dilatation bilaterally. Bilateral ureteric reimplantations were performed at 5 years. Ligamentous laxity at the age of 6 led to an orthopaedic assessment where severe coxa valga with compensatory external tibial torsion was observed. Plantar valgus deformities led to the fitting of orthoses. Special schooling was necessary, with global cognitive development assessed at the 8 year level at 14 years of age.

CASE 3

Case 3, a male, was the third of three children of non-consanguineous parents with a negative family history for genitourinary malformations. The pregnancy was complicated by polyhydramnios and antenatal detection of urinary bladder dilatation and bilateral hydronephrosis. Delivery was induced at 36 weeks. Birth weight was 2760 g (50th centile) and length was 47.5 cm (50th centile). The head circumference was not recorded. At birth the face was noted to be triangular with a pointed chin and there were low set, posteriorly rotated ears, a depressed nasal bridge, and an upturned nose. The skin sat in multiple, loose folds. The anterior abdominal wall musculature was hypoplastic (fig 7). Postnatal urinary tract studies showed a megacystis with associated hydroureters and hydronephrosis (fig 8). Early neonatal life was complicated by feeding problems and neonatal jaundice requiring phototherapy. He was readmitted for failure to thrive aged 4 months and, although no firm diagnosis was made, thyroid function tests, serum lipid profile, intestinal biopsy, and serum copper were all normal. Persistent features consistent with Sotos syndrome have been noted over the subsequent 15 years, including frontal bossing (fig 9), high palate (fig 10), pectus carinatum, flat, small nails, and large hands and feet with deep creases on the palms and soles (fig 11). At 15 years of age his height was 175 cm (75th centile), the arm span was 192 cm, the head circumference was 58.8 cm (>98th centile), the hand length was 22 cm (>97th centile), and the foot length was 29 cm (>97th centile). Connective tissue laxity has been manifest throughout childhood as persisting vesicoureteric reflux necessitating ureteric reimplantation aged 2, bilateral inguinal herniae requiring operation aged 3 and 4, and bilateral pes planus requiring orthoses. Hypermetropia was diagnosed aged 5 and spectacles were prescribed. A gastroscopy performed aged 14 for persisting gastro-oesophageal reflux showed pronounced mucosal folds in the duodenum. An echocardiogram at 15 years showed mild diffuse dilatation of the ascending aorta above the sinotubular junction. A decision was made to begin prophylactic beta blocker therapy on an empirical basis.

He smiled at 4 weeks, sat alone at 12 months, crawled at 14 months, and walked at 2 years. An assessment at 42 months estimated language and fine motor skills at the 17-22 month level and gross motor function at the 16 month level using the Bayley Scales of Infant Development. Audiological testing was normal. A cerebral CT scan at 18 months showed mild dilatation of the lateral and third ventricles, but these changes had resolved on a follow up scan at 42 months. Bone age was repeatedly estimated at the ages of 4 months, 3½, 5½, and 9½ years and was commensurate with chronological age on each occasion. A karyotype from both skin and blood leucocytes was 46,XY.

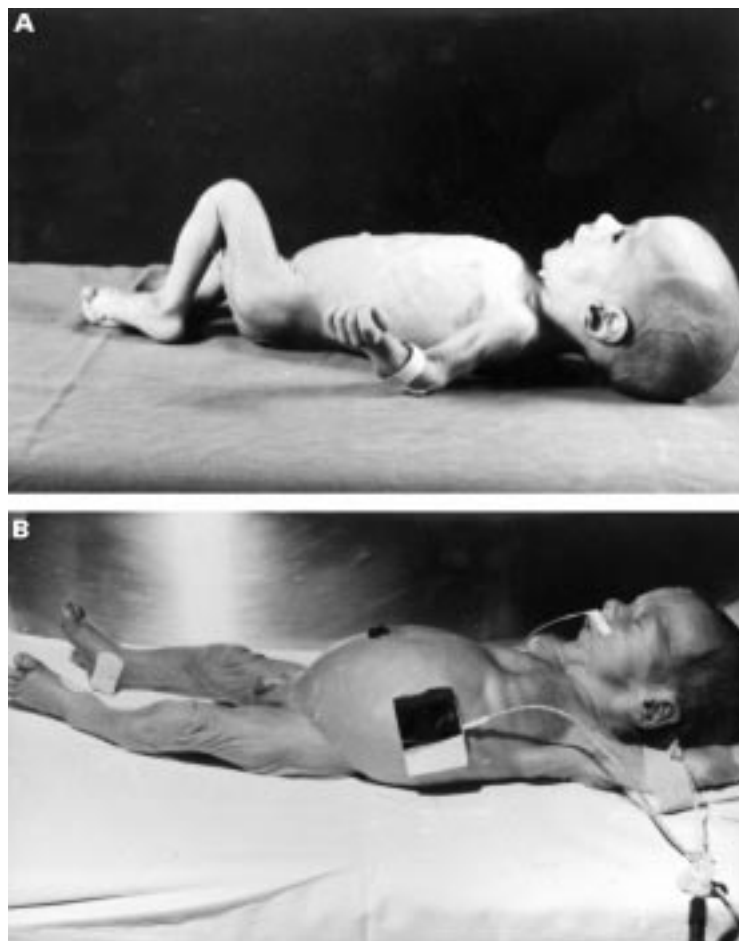


Figure 7 (A, B) Appearance of case 3 in the neonatal period. Loose redundant folds of skin are evident as is the high forehead and triangular shape to the face.

Discussion

Although the aetiology underlying Sotos syndrome is not established, the definition of the

phenotype, in particular the characteristic facies, and diagnostic criteria have become increasingly well delineated over the last decade.^{2,3} Various manifestations, such as pes planus, a high arched palate, and joint hyperextensibility have hinted that a connective tissue abnormality is part of the phenotype.¹ The pronounced nature of the connective tissue dysfunction described in the patients reported here, as illustrated by their facial appearance, redundant skin folds, joint hypermobility, vesicoureteric reflux of severe degree, and hypermetropia, all indicate that a more profound defect than that previously described in Sotos syndrome is present. The nature of these features is reminiscent of syndromes associated with cutis laxa, a heterogeneous group of disorders primarily affecting the skin but in some instances also the ligaments, viscera, and brain.⁴⁻⁷

These patients do not resemble any other previously described syndrome associated with cutis laxa or overgrowth. A diagnosis of Marfan syndrome could be entertained in these patients, especially in the light of the cardiac findings as found in patient 3, but the facies and developmental profile are more typical of Sotos syndrome and insufficient characteristics are present to fulfil the diagnostic criteria for Marfan syndrome.⁸ Recessively inherited entities have been described with developmental delay associated with cutis laxa and ligamentous laxity,⁹⁻¹¹ but overgrowth and Sotos-like dysmorphism are absent in these instances, and some syndromes have accessory features not present in our patients.^{7,12} Described dominantly inherited forms of cutis laxa are usually not associated with mental retardation or visceral anomalies⁴ and therefore are unlikely diagnoses in this instance.

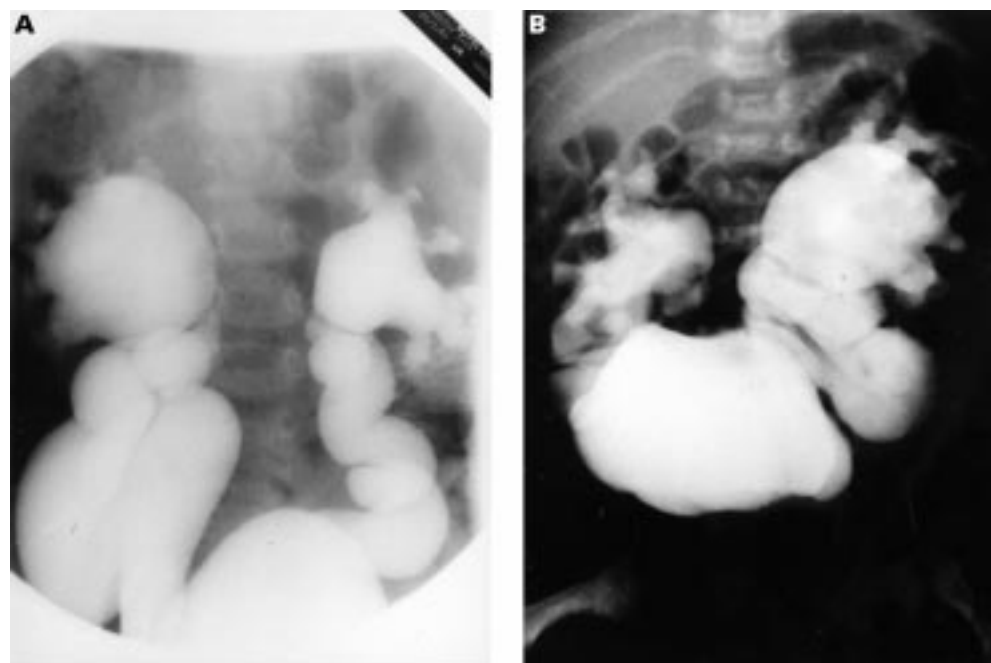


Figure 8 (A, B) Voiding cystourethrogram from case 3 performed in the neonatal period. Gross vesicoureteric reflux is shown together with the presence of a megacystis.

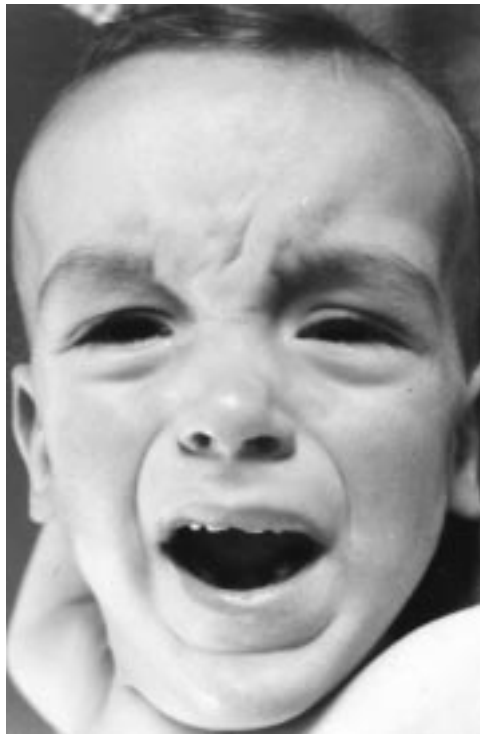


Figure 9 Facies of case 3 in early childhood. The typical features of Sotos syndrome are evident.



Figure 10 The high arched palate of case 3.

Cutis laxa can be associated with visceral abnormalities, particularly in the cardiorespiratory and gastrointestinal system, in conjunction with the skin findings.³ The redundant folds of duodenal mucosa observed at endoscopy and the diffuse dilatation of the ascending aorta in patient 3 are reminiscent of these reports.

The vesicoureteric reflux and urinary tract dilatation found in patients 2 and 3 were the

most prominent visceral manifestations of these patients' connective tissue defect. Vesicoureteric reflux has recently been recognised as a complication of Sotos syndrome in a sizeable minority of cases.^{13,14} Previous genitourinary involvement in syndromes associated with cutis laxa have included bladder diverticulae⁶ and bladder diverticulae in the presence of vesicoureteric reflux has been reported in Sotos syndrome.¹³ It has been suggested that such

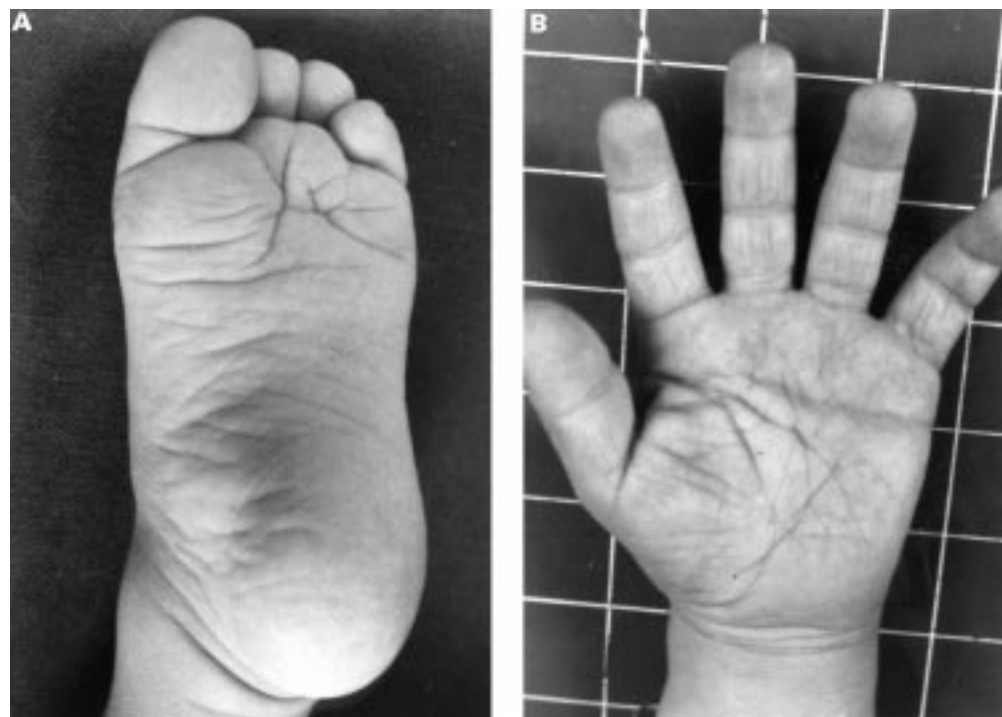


Figure 11 Large feet (A) and hands (B) with deep creases in case 3.

visceral defects may go undetected in this clinical context.¹⁴ The similarity of the genitourinary malformations found in cutis laxa and in these patients with Sotos syndrome with cutis laxa-like defects in their skin suggest that the presumptive defect in elastin function ascribed to cutis laxa¹⁵ may also be a contributor to the Sotos phenotype.

It has been suggested that a criterion for the diagnosis of Sotos syndrome is the documentation of an advanced bone age. Nevertheless in a study of a large cohort of Sotos syndrome patients, 17% registered a bone age less than the 90th centile and various reasons were outlined as to why the measurement of bone age should be used with caution as a diagnostic criterion.³ None of the three patients presented here had an advanced bone age, despite serial measurements in two of them and therefore the diagnosis of Sotos syndrome could be considered equivocal. Other elements of the phenotype in these patients, such as the slowed growth by the age of 7 in case 1, are also atypical of Sotos syndrome, but like the normal bone ages do not substantially threaten the diagnosis. The presence of the characteristic facies, macrocephaly, large hands and feet, growth trajectory, and delayed neurodevelopment of the Sotos phenotype effectively exclude the diagnosis of other described forms of overgrowth and imply that this entity is related to, if not allelic with, classical Sotos syndrome. Ultimately the characterisation of the molecular basis underlying many overgrowth disorders, including Sotos syndrome, should aid in distinguishing allelic variants from discrete disorders and allow more accurate delineation of their respective phenotypic spectra.

Note added in proof

Following the cardiac findings in case 3, cases 1 and 2 were recontacted and offered echocardiography. Case 1 showed dilatation of the

ascending aorta almost identical to that observed in case 3 and was accordingly started on beta blocker therapy. Case 2 showed no such dilatation but a minor “shelf” of tissue was seen at the level of the ligamentum arteriosum, which produced no obstruction to flow. In all three patients valvular function was normal. These observations underline the generalised nature of the connective tissue defect in these patients.

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