

Syndrome of the month

Edited by D Donnai and R Winter

Sotos syndrome

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In 1964 Sotos *et al*¹ described five children with (1) large body size and early accelerated growth, (2) acromegaloid features, (3) advanced bone age, and (4) developmental delay and a non-progressive neurological disorder. Since this report over 200 further cases have been described, many with additional observations. Inclusion of new features into the clinical spectrum of Sotos syndrome has made it difficult to determine the minimal diagnostic criteria and the syndrome's phenotypic variation. Until reliable diagnostic criteria are available the incidence is likely to remain unknown.

Clinical features

GROWTH

The children tend to be large at birth, especially in length (table 1), and to show accelerated growth, particularly during the first five years.² Thereafter, growth usually continues parallel to, but above, the 97th centile for a variable period before gradually falling towards or below this centile (figs 1 and 2). Rarely, gigantic adult proportions may be attained but this group probably includes children with accelerated growth without advanced bone age and misdiagnosed cases. Typically, the head circumference, once perinatal moulding has settled, proceeds above the 98th centile³ (fig 3).

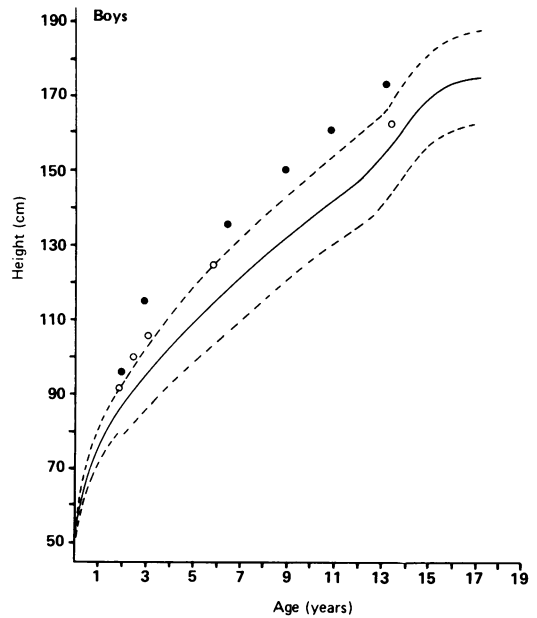


Figure 1 Height chart of two boys with Sotos syndrome.

Table 1 Series of 23 patients with Sotos syndrome in Cardiff study (unpublished data).

Birth measurements	No of patients	No of patients >97th centile
Length	15	13
Weight	23	5
OFC	12	7

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PERINATAL AND NEONATAL FEATURES

Following Sotos's original description, it was suggested that difficult deliveries of these large babies could be the cause of their developmental and neurological abnormalities. However, in our own series of 23 cases the incidence of forceps and caesarean deliveries was similar to the overall rate in the UK. Furthermore, there was no correlation between low Apgar scores and low DQ or IQ scores (Cole, unpublished data). There are two neonatal features, however, which might be ascribable to asphyxia and a difficult birth. Firstly, early feeding problems necessitating tube feeds were found in 35% of neonates (Cole, unpublished data) and, secondly, the high incidence of jaundice (40% of cases) could partly be explained by bruising at delivery.^{4 5}

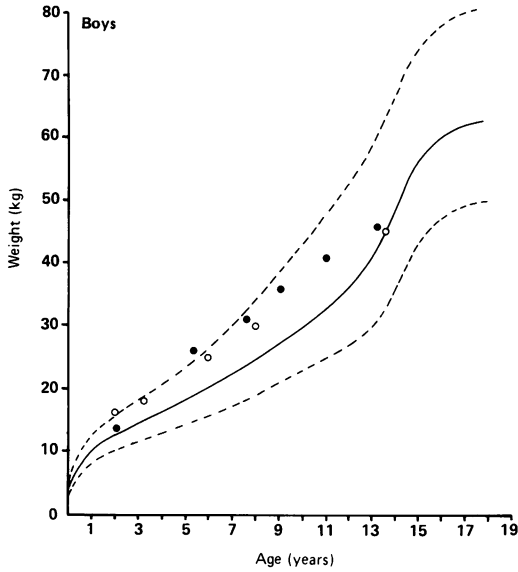


Figure 2 Weight chart of two boys with Sotos syndrome.



Figure 4 Patient 1 aged 18 months.

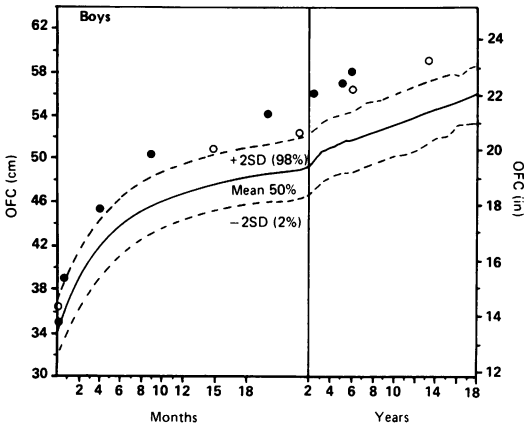


Figure 3 Head circumference chart of two boys with Sotos syndrome.

Table 2 Craniofacial features.

	Jaeken <i>et al</i> ^a (84 cases)
Dolichocephaly	84%
Hypertelorism	91%
Frontal bossing	96%
Highly arched palate	96%
Prognathism	83%
Antimongoloid slant	77%
Premature tooth eruption	57%
Macrocephaly >98%	100% (Cardiff study, unpublished data)



Figure 5 Patient 2 aged 4 1/2 years.

CRANIOFACIAL FEATURES

In infancy, the face and forehead are round and there is often striking frontal baldness (table 2) (figs 4 and 5). With time, the face becomes longer, the hair grows

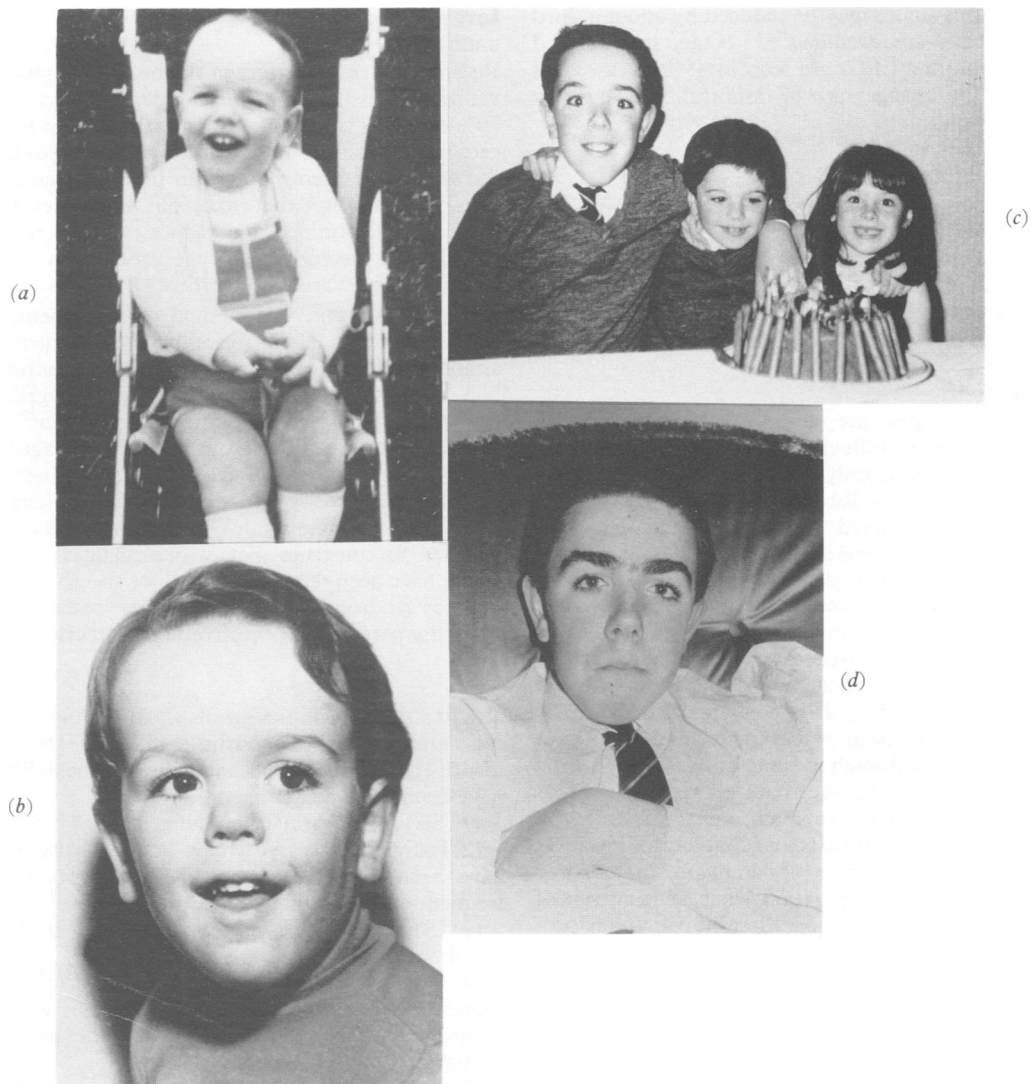


Figure 6 Patient 3 (a) aged 10 months, (b) aged 2½ years, (c) aged 9 years with sibs aged 7 and 5 years, (d) aged 13 years.

over the forehead, and prognathism and coarser facial features become more evident^{2,7} (fig 6). Paradoxically, the facial gestalt appears to become less obvious with advancing age but this is probably biased by lack of familiarity with the adult phenotype.

SKELETAL ANOMALIES

Hands and feet are often larger than expected for the patient's height.⁷ Joint laxity is a frequent finding with pes planus being particularly common. Other anomalies such as kyphoscoliosis and genu deformities are rarer.

NEUROLOGY

The major neurological deficit is a non-progressive incoordination often affecting gross movements more than fine control. Both tend to improve with age (Cole, unpublished data). Hypotonia, which is almost invariable during the first year of life, may persist, when it is often associated with unexpectedly brisk reflexes in the legs⁸ (Cole, unpublished data).

Cerebellar signs are rare although nystagmus has been reported.^{5,9,10} One case with clinical features suggestive of an unexplained peripheral neuropathy is known to the authors. Fits occur in up to 50% of cases

although this figure may be reduced by about a third if febrile fits are excluded^{11 12} (Cole, unpublished data). Abnormal EEGs are seen in 45% of cases but many of the changes are of doubtful clinical significance.⁶

OCULAR

Apart from strabismus (41%) (Cole, unpublished data) ocular problems are rare. Single cases of cataracts,¹³ and retinal¹⁴ and macular degeneration¹⁵ have been reported.

DEVELOPMENT

Motor milestones are usually delayed and are probably strongly influenced by early hypotonia. In general, the previously accepted view of global retardation has been disregarded and the IQ range of 18 to 119, as quoted by Smith,¹⁶ suggests that intelligence can be average or above. Many persons have only one or two specific learning deficits (poor language, numeracy, and social skills are common early features) and failure to recognise these isolated problems has led to inaccurate developmental assessments, particularly when motor and verbally based tests have been used.¹⁷ It is now apparent that early attention to these specific areas can result in significant improvements, although in some cases developmental improvement may be the 'natural' course of Sotos syndrome.^{9 18} These problems are consistent with immaturity or slow normal development, for instance, emotional immaturity is apparent in the anxiety caused by maternal separation when starting school owing to delay in the separation-individuation processes.¹⁹

The majority of patients at present recognised as having Sotos syndrome would be categorised as having a mild or borderline mental handicap. However, the developmental and behavioural problems in these children may be perceived as being more severe owing to enhanced expectations because of their size.

ADDITIONAL FEATURES

There seems to be an increased incidence of solid tumours in patients with Sotos syndrome but probably less than the 7% quoted by Wit *et al.*,² as biased reporting of two rare phenomena (childhood tumours and Sotos syndrome) is likely. Wilms' tumour is the only tumour type to have been described more than once,²⁰ although two different hepatic tumours have been recognised²¹ (Cole, unpublished data).

Japanese reviews have reported a high incidence of various congenital heart defects²² and urogenital anomalies.^{22 23} These features appear rarely in western published reports, thus raising the possibility of a separate syndrome in the Japanese patients.

Investigations

RADIOLOGY

Radiological investigation of the head has shown that ventricular dilatation of varying degrees is present in 70% to 100% of cases.^{2 24} Contrary to early reports, cerebral atrophy is rare. Anthropometric studies of the skull have been reported in four cases and some measurements are abnormal, but the series is too small to determine significance.²⁵ The reported incidence of advanced bone age varies from 74%⁶ to 100%.² This variability probably relates to the frequency, timing, and method of assessment. The figures could be falsely raised by ascertainment bias although 100% of cases probably do have an advanced bone age at some time. Often, bone age is described as dysharmonic, and Poznanski and Stephenson²⁴ stress the diagnostic significance of the phalangeal age being in advance of the carpal age. However, others have reported the reverse situation^{2 11} or even harmonically advanced bone age.⁵ X rays of the hand can also be used to construct metacarpophalangeal profiles, which have been reported to produce specific patterns in Sotos syndrome. If confirmed, these patterns could be used as part of more objective diagnostic criteria.²⁶⁻²⁸

BIOCHEMICAL AND ENDOCRINOLOGICAL STUDIES

No single test of diagnostic significance has been identified but occasional anomalies of the following have been documented.

- (1) Serum and urinary amino acids.^{29 30}
- (2) Individual cases with hypo- and hyperthyroidism have been documented but these findings are infrequent and reporting bias again is likely.³¹⁻³⁴
- (3) Abnormal glucose tolerance tests in family members (19%).⁶
- (4) Raised insulin-like growth factor 1^{35 36}; most values have been in the normal range but very few assays have been performed during the period of maximum growth.
- (5) Low insulin levels relative to age and plasma glucose (Cole, unpublished data).
- (6) Paradoxical rise of growth hormone (hGH) after glucose load, and suboptimal response of hGH to induced hypoglycaemia in the presence of a normal baseline.^{2 5} These hGH results, together with the clinical picture of excessive appetite and thirst, have been cited as evidence for abnormal hypothalamic function in Sotos syndrome. However, they are by no means constant findings.

CHROMOSOMES

There have been several reports in the last few years of children diagnosed as having Sotos syndrome with a fragile site at Xq27 on chromosomal analysis.³⁷⁻³⁹ Since these reports, many patients with Sotos syndrome have been karyotyped but do not show the

same fragile site. Therefore, it seems likely that the conditions are separate but owing to phenotypic overlap some patients with fragile X syndrome can be mistakenly diagnosed as having Sotos syndrome. A family with an unbalanced 12;13 translocation segregating with Sotos syndrome was reported by Blackston.⁴⁰ However, on review their phenotypes appear to be different from Sotos syndrome (Blackston, personal communication).

Differential diagnosis

The overgrowth syndromes that need to be differentiated from Sotos syndrome can be classified into two groups (table 3). The first group are relatively easily to distinguish because of other specific associated features, but the syndromes in the second group cause more difficulties. Developmentally delayed, rather clumsy, large children with macrocephaly are not uncommon. These features may even be familial. It is possible that some of these children represent one end of the spectrum of Sotos syndrome. Depending on the severity and age of presentation, other overgrowth syndromes, such as Weaver's syndrome, can also be difficult to separate from Sotos syndrome. Similarly, boys with fragile X, especially if prepubescent, can have phenotypic similarities to Sotos syndrome.

Natural history

Intellectual, behavioural, and coordination difficulties are very common and may seem to be more of a problem because of the child's size, but these features tend to improve with age.¹⁸ The facial gestalt undoubtedly alters with age.⁷ Typically, the face becomes longer and thinner and the prognathism is more pronounced (fig 6). At present, there are no frequent life threatening complications in Sotos syndrome. Occurrence of tumours is rare and one would predict a near normal life expectancy on the information currently available.

Table 3 Differential diagnosis.

Group 1	Group 2
1 Constitutional gigantism (alone)	1 Ruvalcaba-Myhre-Smith syndrome
2 Marfan syndrome	2 Weaver syndrome
3 Neurofibromatosis	3 Fragile X
4 Beckwith-Wiedemann syndrome	4 Constitutional giant with additional features
5 Marshall-Smith syndrome	5 Sporadic large stature with additional features
6 Simpson-Rosen-Golabi syndrome	
7 Adrenogenital and gonadal secreting tumours	
8 Klinefelter's syndrome	
9 Acromegaly	
10 San Filippo syndrome	

Aetiology

Sotos syndrome appears to be sporadic in most reports to date. However, familial cases including two three generation families⁴¹ (Child, personal communication) have been described. In familial cases the most likely mode of inheritance is autosomal dominant.^{4 18 22 30 41-45} Male to male transmission has been reported by Winship⁴² and Crammer and Niederdelman.⁴⁴ However, the patients in the latter report also had the basal cell naevus syndrome, which alone could explain all the clinical features, thus raising doubts over the diagnosis of Sotos syndrome. A slight excess of affected males has been documented.^{6 46} Apparent autosomal recessive inheritance has been reported in three families,⁴⁷⁻⁴⁹ but the clinical data in the abstract by Townes and Sheinen⁴⁸ are inadequate to confirm the diagnosis of Sotos syndrome. In 1974, Nevo *et al*⁵⁰ reported an inbred Arab family with three affected subjects and postulated an autosomal recessive pattern of inheritance for Sotos syndrome. However, the phenotype in this family was atypical and these cases are now generally regarded as having a separate syndrome.

Conclusions

As no diagnostic test is currently available for Sotos syndrome, it can often be difficult to arrive at a certain diagnosis, especially in more mildly affected cases. The four major characteristics originally described by Sotos *et al*¹ are not specific to the syndrome.

Recent reports suggest that the handicaps seen in Sotos syndrome are fewer than previously believed, and they do tend to improve with age. This tendency to 'normalisation' with increasing age makes identification of adults and possibly affected older relatives extremely difficult, which might explain the apparent rarity of affected relatives in an allegedly autosomal 'dominant' condition which has a near normal life expectancy. The variation in the observed phenotype and modes of inheritance suggests that the condition is likely to be heterogeneous in origin.

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