Sotos' Syndrome of Cerebral Gigantism

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Excessive secretion of growth hormone after epiphysial fusion will produce the clinical features of acromegaly, which is not in itself associated with increased stature. Before closure of the epiphyses this situation will lead to gigantism, which is confined almost exclusively to the adolescent age-group in its first appearance. Though concomitant enlargement of some of the extremities is not uncommon in true or even constitutional gigantism, it is almost unknown in pre-adolescent children. Recently Sotos *et al.* (1964) described a condition characterized by excessively rapid growth dating from infancy, acromegalic features, and a non-progressive neurological dysfunction manifested by clumsiness and a dull intelligence. The affected patients bore a remarkable resemblance to each other. The authors coined the term 'cerebral gigantism' for this syndrome. Other relatively constant clinical features noted in their cases included dolicocephaly, with macrocrania, hypertelorism, a high arched palate, accelerated skeletal maturation, and the absence of obvious endocrine dysfunction. Pneumoencephalography in such cases usually reveals dilated cerebral ventricles without an obstructive lesion. Convulsions are frequent in this syndrome but electroencephalography shows only non-specific abnormalities.

A patient conforming closely to the criteria of Sotos and co-workers had been described earlier (Mikulowski, Stopyrowa, and Medvey, 1962). 41 examples of this syndrome are now known, and details of 2 further cases with full endocrinological findings are presented in this paper.

Case Reports

Case 1. The patient was the only child of unrelated 19-year-old parents. The mother's general health had been good, and the only drugs taken during the pregnancy were promethazine and iron. Labour was

induced surgically for moderate pre-eclamptic toxæmia at 37 weeks' gestation. She was delivered normally by the vertex, the birthweight being 2466 g. (1 SD below the mean). Length and head circumference were not recorded at birth, but she seemed long and had long fingers and toes, a possible diagnosis of Marfan's syndrome being entertained at this time. Initially, she fed poorly and was moderately jaundiced, the serum bilirubin reaching 19 mg./100 ml. on the sixth day.

At 2 weeks of age, she developed bronchopneumonia with cyanosis and convulsions which responded to antibiotics, anticonvulsants, and oxygen. Four weeks later, she was readmitted with vomiting which subsided after administration of methylscopolamine nitrate, though the cause was not ascertained. Scattered cavernous haemangiomas were noticed at this time and several fresh lesions appeared over the next 6 months. The patient was admitted on two further occasions on account of febrile convulsions secondary to otitis media.

On examination at the age of 14 months her acromegalic features and increased stature were obvious (Fig. 1). She had a dolicocephalic skull, a prominent forehead with recession of the hair line (Fig. 2), plethoric cheeks, prognathism, a high arched palate, and large hands and feet. There was a marked kyphosis. The feet were extremely flat, and there was limitation of abduction at both hips. Multiple haemangiomas, many of them fading, ranging in size from 2 mm. to 4 cm. in diameter, covered part of the trunk and buttocks. The subcutaneous tissues seemed generally thickened. She exceeded the 97th centile for height (Fig. 3) and weight (Fig. 4), and had 12 teeth.

She was noticed to rock herself frequently, scream for no apparent cause, and drool incessantly. At this age, she could sit without support, stand with support only, and speak six meaningful words. Neurological examination failed to reveal any specific deficiency though she was notably clumsy. The skull circumference was 50.8 cm. (Fig. 5), with a cephalic index of 0.73.

There was some facial resemblance to the mother and both had reddish-gold hair. The only relevant disease in the family was diabetes mellitus in a maternal great aunt. The father was 174 cm. and the mother 165 cm. tall.

FIG. 1.—Case 1 aged 16 months with normal child of 2 years.

FIG. 3.—Height chart of Cases 1 and 2.

FIG. 2.—Profile of Case 1 to compare with Fig. 8.

FIG. 4.—Weight chart of Cases 1 and 2.

FIG. 5.—Head circumference chart of Cases 1 and 2.

FIG. 6.—Pneumoencephalograph of Case 1 showing ventricular dilatation.

The following were within normal limits: serum electrolytes and urea, calcium, phosphorus, alkaline phosphatase, serum proteins, and electrophoresis. The urine contained no excess of amino acids. Wassermann reaction was negative. Chromosomal analysis showed a normal female karyotype.

Endocrine investigations. These did not reveal any abnormalities apart from the skeletal age of which the phalangeal development at 3 years was considerably in advance of the chronological age. Carpal bone age was at 2 years less advanced. The protein bound iodine (PBI) was $5.4 \mu\text{g./100 ml.}$, and the serum cholesterol 209 mg./100 ml. Fasting plasma 17-hydroxy-

corticoids were $12 \mu\text{g./100 ml.}$, rising to $70 \mu\text{g./100 ml.}$ after 10 units of lysine-8-vasopressin intramuscularly. The 24-hour urinary excretion of 17-ketosteroids was 0.2 mg. and that of the 17-hydroxycorticosteroids 8.4 mg.

Growth hormone and plasma cortisol response to insulin and carbohydrate loading are shown in Table I. The peak glucose level attained was lower than might be expected. The 5-hour level was considerably below the fasting level.

CNS investigations. CSF was normal in all respects. An EEG showed an excess of slow wave activity compatible with a diffuse disturbance of cerebral function. Skull x-rays showed a normal sella turcica, but the sutures seemed widened.

A left carotid angiogram showed no vascular lesion, but ventriculograms with myodil instillation showed moderate uniform dilatation of both lateral ventricles, with comparatively greater enlargement of the third ventricle (Fig. 6). Myodil flowed down the basal cisterns and cervical canal, but air could not be made to enter the cortical subarachnoid spaces. The carotid angiogram, however, showed that the vessels of the cortex were not in as close apposition to the inner diploid of the skull as would normally be expected, suggesting an excess of CSF in the subarachnoid spaces and thus ruling out any marked degree of internal hydrocephalus.

Cortical biopsies from the left and right parieto-occipital region, obtained during ventriculography, showed some blood vessels in the white matter surrounded by lipophages. Staining for myelin and fibrous gliosis revealed no abnormality (Dr. L. Crome).

Psychological evaluation showed her developmental quotient to be 70 (Griffiths Mental Developmental Scale). Her performance was uneven, being most retarded in the locomotor and hearing-speech areas. She performed enthusiastically with the test materials, and showed relatively greater insight into function than might have been expected. The general pattern was unlike that of global retardation, and the frequent hospital admissions were thought to have retarded learning. It was thought that her ultimate intellectual function might well be less impaired than suggested by the initial test.

Case 2. The patient was the 6th child of a 40-year-old mother but the second child of the present union. All of the previous 5 children are normal. The father was aged 54 years at the time of conception. No member of either family has exceeded 173 cm. in height.

The pregnancy and delivery were normal, the birth-weight being 3002 g., slightly less than the mean for 38 weeks' gestation. Respirations were established immediately. Her unusual appearance was noted by the attending obstetrician at this time. She was moderately jaundiced for the first 5 days of life. Feeding was slow up until her first hospital admission at the age of 5 weeks, though her weight gain was normal.

FIG. 7.—Case 2, aged 16 months, showing typical facies, heavy build, and large hands.

FIG. 8.—Profile of Case 2 aged 16 months.

Her initial admission was occasioned by a moderately severe right upper lobe pneumonia which responded satisfactorily to antibiotics. At that time, she was noted to have mild inspiratory stridor, long digits, a high arched palate, small mandible, and dolicocephalic skull. Her extreme length was noted on this and many subsequent occasions (Fig. 3), though the weight increments were not commensurate until the age of 12 months (Fig. 4). Additionally, a congenital dislocation of the left hip was discovered, which was successfully treated with a van Rosen splint.

There were many episodes of otitis media and respiratory infections over the first year of life, and at the age of 11 months she had her first generalized convulsion. Locomotor development had been delayed; she sat with support at 8 months, rolled from prone to supine at 9 months, and sat without support rather poorly at 11 months. She began to crawl at 14 months, and at 16 months could only just stand with support. She had 8 teeth by the age of 8 months.

She was admitted at 16 months of age for investigation of increased stature. On examination, she was a large child with a moderate thoracic kyphosis, a broad chest, and increased limb musculature (Fig. 7). The supine length was 85 cm. and the span 86 cm. The skull circumference was 50.8 cm. and bossed in the frontal region (Fig. 8). The hair line was set far back and the hair itself was a reddish-gold colour. She had a marked facial plethora. Hypertelorism was pronounced and was confirmed radiologically (Hansman, 1966); the interorbital distance of 2.47 cm. being considerably in excess of the upper limit of normal for the age. The palate was high and arched, with the teeth morphologically normal though extremely carious. The mandible was now prognathic. Hand size was increased, as was that of the feet which showed marked pes planus. The skin had a rubbery texture. The cardiovascular, respiratory, and alimentary systems were normal. No specific neurological deficit could be found.

She drooled constantly and exhibited aggressive tendencies which alarmed the mother.

Plasma electrolytes and urea, serum calcium, inorganic phosphate, proteins, transaminases, and cholesterol were normal, as were two urinary amino-acid chromatograms.

Endocrine investigations. PBI 4.7 $\mu\text{g.}/100$ ml. at 16 months and 5.8 $\mu\text{g.}/100$ ml. at 2 years and 2 months. T_3 resin uptakes were 25% (16 months) and 28% (2 years and 2 months). Thyroidal ^{131}I uptake was 12% at 2 hours and 15% at 4 hours.

Synacthen test—resting plasma cortisol 25 $\mu\text{g.}/100$ ml. and 58 $\mu\text{g.}/100$ ml. 30 minutes later.

17-oxosteroid excretion 0.2 mg./24 hours and 17-oxogenic steroid excretion 1.0 mg./24 hours. Administration of metyrapone 500 mg. 4-hourly produced an apparently impaired response, the 17-oxogenic steroids rising to 1.5 mg./24 hours. An insulin sensitivity test (Table II) produced a normal cortisol response, however, though the plasma growth hormone did not rise.

TABLE I
Insulin and Glucose Tolerance Tests in Case 1

Value	Time (min.) After Insulin						Time (min.) After Oral Glucose						
	0	20	30	40	60	80	0	30	60	120	180	240	300
Blood glucose (mg./100 ml.) ..	52	<10	19	27	49	47	91	107	91	98	72	67	72
Plasma growth hormone (ng./ml.) ..	2.0	2.5	14.5	9.5	5.0	3.5	2.0	2.0	2.5	3.0	2.5	2.0	2.0
Plasma 'cortisol' (μg./100 ml.) ..	39	—	37	—	29	24	—	—	—	—	—	—	—

TABLE IIA
Insulin and Oral Glucose Tolerance Tests in Case 2 at 16 Months

Value	Time (min.) After Insulin						Time (min.) After Oral Glucose						
	0	20	30	40	60	80	0	20	30	60	90	120	150
Blood glucose (mg./100 ml.) ..	95	40	40	—	90	—	55	136	155	189	82	64	59
Plasma growth hormone (ng./ml.) ..	2.5	2.5	2.5	—	2.5	—	—	—	—	—	—	—	—
Plasma 'cortisol' (μg./100 ml.) ..	38	37	45	—	55	—	—	—	—	—	—	—	—

TABLE IIB
Insulin and Intravenous Glucose Tolerance Tests in Case 2 at 2 years 2 months

Value	Time (min.) After Insulin						Time (min.) After Intravenous Glucose*						
	0	20	30	40	60	80	0	3	15	30	60	120	1180
Blood glucose (mg./100 ml.) ..	59	28	—	29	29	39	75	215	170	120	75	80	80
Plasma growth hormone (ng./ml.) ..	3.0	4.0	—	3.5	2.5	3.0	—	—	—	—	—	—	—

* Rate of clearance (k) glucose, 1.82% per minute.

The carpal bone age at 16 months was compatible with chronological age, but the phalangeal development was at the 2½-year-old level.

Carbohydrate tolerance tests. These are given in Table I and are shown to be normal.

CNS investigations. The CSF was normal. Two EEGs were within normal limits for the age.

An air encephalogram at this time showed generalized dilatation of the lateral and third ventricles, with no evidence of displacement. The fourth ventricle and aqueduct were central. The basal, pontine, and chiasmatic cisterns were well demonstrated and no abnormalities were seen. The pituitary fossa was of normal size.

Psychological evaluation showed her developmental quotient to be 86 (Griffiths Mental Developmental Scale). Retardation was most marked in the locomotor area and in hearing and speech. She enjoyed the manipulative tests and performed best in this sphere.

Clinical features of the Syndrome

The main clinical features are summarized in Table III. Complete information is not obtainable for all cases reported. Only those findings known to be definitely present or absent are there-

fore included in this Table. For the purpose of clarification some of these are discussed below.

Neonatal features. The birthweight tends to be high, with a mean of 4002 g. for 39 patients, 1 SD above the mean for full-term infants in the United Kingdom. The affected patients tend to be born near or beyond term. Only 3 patients are recorded as being less than 38 weeks' gestation, including Feingold's (1966) remarkable patient of 26 weeks' gestation who weighed 1728 g. at birth. Hypoxia at the time of birth and respiratory problems during the first week of life are not infrequent and may play a part in the aetiology of the cortical atrophy found in some cases. Several patients were cyanosed after birth (Sotos *et al.*, 1964; Turner and Sloan, 1965; Sizonenko *et al.*, 1968) or required immediate resuscitation. The feeding problems encountered in some infants seem to be related to poor sucking and slowness in feeding rather than to failure to gain weight normally.

Developmental features. Though many patients

TABLE III
Analysis of Findings in 43 Cases of Sotos' Syndrome

Feature	Case 1	Case 2	Observed Frequency
Neonatal			
Sex	F	F	26 M 17 F
Birthweight (g.) ..	2466	3002	Mean 4002 (39 cases)
Birth length (cm.) ..	?	?	Mean 55.4 (21 cases)
Gestation (wk.) ..	37	38	Mean 39 (17 cases)
Respiratory problems	+	—	10/30
Jaundice	+	+	7/22
Feeding problems ..	+	+	7/14
Developmental			
Early dentition ..	+	+	7/9
Delayed walking ..	+	+	22/31
Delayed speech ..	+	+	18/25
Aggressiveness ..	—	+	5/7
IQ or DQ <90 or severely retarded	+	+	34/42
Cranio-facial			
Macrocrania for age	+	+	41/41
Dolicocephaly ..	+	+	23/26
Hypertelorism ..	+	+	22/30
Antimongoloid slant of palpebral fissures	+	—	10/18
High arched palate ..	+	+	28/32
Prognathism	+	+	24/28
Facial plethora ..	+	+	4/4
Marked macro-glossia	—	—	Twice reported
Skeletal			
Kyphosis or scoliosis	+	+	8/24
Spina bifida occulta	—	—	Twice reported
Large hands and feet	+	+	23/27
Syndactyly of toes ..	—	—	8/30
CNS			
Convulsions	+	+	13/39
Clumsiness	+	+	26/26
Drooling	+	+	4/7
Investigations			
Abnormal EEG	+	—	14/36
Abnormal AEG	+	+	23/27
Normal pituitary fossa	+	+	36/40
Growth hormone normal	+	+	23/33
Elevated 17-ketosteroids ..	—	—	Frequent finding
Advanced bone age	+	+	33/39

Source of material for Table III

Cohen, 1 case; Hook and Reynolds 6 cases; Kjellman, 1 case; Kowlessar, 1 case; Ludwig, Chaykin, and Escueta, 1 case; Marie *et al.*, 4 cases; Mikulowski, 1 case; Milunsky, 2 cases; Poznanski and Stephenson, 10 cases; Sizonenko *et al.*, 6 cases; Sotos *et al.*, 5 cases; Turner and Sloan, 2 cases; and Feingold, 1 case.

sat unsupported at the normal age, delay in walking is frequent, and few have walked before the age of 15 months. Invariably there is no specific explanation for this on neurological examination apart from the generalized clumsiness noted in all cases. Delay in speaking is usual; many cases are unable to say more than a few words by the

age of 2½ years. The IQ or DQ is less than 90 in most cases, but the retardation is not necessarily severe. 5 children have been in the 80-90 range and 8 patients in excess of 90 have been reported. 2 patients reported by Sizonenko *et al.* (1968) were considered mentally normal, and IQ's of 110 (Cohen, 1964), 115, and 109 (Hook and Reynolds, 1967) have been reported.

Cranio-facial features. As can be seen from Tables I and II and from the illustrations in this report, the patients tend to resemble each other in appearance. Prognathism is not a feature at birth and tends to become more prominent with age. The facial plethora in our cases was striking but only Milunsky, Cowie and Donoghue (1967) have commented on this previously. A further case observed elsewhere by one of us also had this feature.

Skeletal features. Apart from the enlarged hands and feet, the most frequent finding is that of kyphosis or kypho-scoliosis. Kyphosis is, interestingly, a frequent finding in acromegaly (Kellgren, Ball, and Tutton, 1952). The acceleration of skeletal maturation typically affects the phalangeal centres more than the carpal centres (Poznanski and Stephenson, 1967). This disparity was found in both our cases.

Central nervous system features. Convulsions have occurred in a third of the reported cases, but the EEG findings have often been normal, while the abnormal EEG findings, typically diffuse and non-specific, have not been confined to those patients having convulsions.

The typical clumsiness of these patients seems partially to be related to the difficulty of the developing locomotor system in coping with the unusual size. The gait is deliberate and limb movements ponderous. Continuous drooling together with the facial plethora, frequent respiratory infections, kypho-scoliosis, and relative insensitivity to pain, suggested a similarity to some of the features of familial dysautonomia. An intradermal histamine test on Case 2 gave a normal response, and no pupillary constriction was observed on administration of methacholine eye drops.

Marked aggressiveness, a feature of Case 2, has been commented upon previously (Kjellman, 1965; Milunsky *et al.*, 1967).

The pneumoencephalograms in affected patients have generally shown a non-specific ventricular dilatation without a block (Poznanski and Stephenson, 1967). Cortical atrophy is not uncommon. Three

cases have had a cavum septum pellucidum demonstrated (Marie *et al.*, 1965; Poznanski and Stephenson, 1967).

Dermatoglyphic features. Professor L. S. Penrose analysed the dermatoglyphs of our patients and compared them with those of the two cases published by Milunsky *et al.* (1967). The unusual features noted by these authors included a thenar exit of the A-line, an increased a-b ridge distance, and a high a-b ridge count. Case 1 in this report had a normal exit of the A-line, a low a-b ridge count (66), and a total ridge count of 141. Case 2 had a thenar exit of the A-line on the left hand, a normal a-b ridge count (88), and a rather high total ridge count of 174. Of two further cases to which the authors had access, one had a thenar exit of the A-line on one hand and a total ridge count of 172, and the other had only an increased a-b distance. The general dermatoglyphic patterns in these cases are not therefore particularly unusual, with the exception of a relatively increased a-b distance and a considerable increase in the mean ridge breadth. The latter would be expected in gigantism (L. S. Penrose, 1968, personal communication), but interestingly this parameter measured 0.434 mm. in Case 1 and 0.400 mm. in Case 2, being appropriate to controls of 5 and 4 years, respectively; the prints were taken when the height age was 3 years for Case 1 and 2½ years for Case 2. These findings suggest that the hands in these cases were disproportionately large, even when taking into account the excessive stature.

Discussion

The two cases reported here bear a striking resemblance to each other and conform closely with the criteria proposed by Sotos and his co-workers (1964). Other causes of large stature in this age-group, such as Marfan's syndrome, neurofibromatosis, McCune-Albright's syndrome, familial gigantism, and various virilizing conditions, could be readily excluded on clinical and laboratory grounds. Patients suffering from these disorders do not resemble each other, and, with the exception of Marfan's syndrome, enlargement of the extremities is not found.

That the rapid growth is not mediated by excessive growth hormone secretion is probably borne out by the normal levels found in Case 1 and the sub-normal levels of Case 2. Similar findings have been reported by all other authors where this had been measured (Hook and Reynolds, 1967; Milunsky *et al.*, 1967; Stephenson, Mellinger, and Manson 1968). Likewise it is probably not due to a hyper-

sensitivity to this hormone, as there is a normal rise in plasma non-esterified fatty acids after its exogenous administration (Stephenson *et al.*, 1968). The 24-hour total secretion of growth hormone might conceivably be greater in these cases than in the normal, but this is impossible to demonstrate at this time. Against this theory, however, is the acceleration of skeletal maturation and the absence of visceromegaly. In a number of reported cases the gigantism has been present at birth, as instanced by two cases being 63.5 cm. in length at this time (Turner and Sloan, 1965; Hook and Reynolds, 1967). Possibly a separate growth factor, fetal or maternal, may operate over the initial period of high growth velocity occurring over the last trimester of intrauterine life and for the first three months of life. Intrauterine growth retardation was not observed in 16 cases of isolated growth hormone deficiency recently described (Goodman, Grumbach, and Kaplan, 1968), and none of these exhibited growth failure before the age of 4 months. The continuance of the excessive growth beyond this time cannot, however, be explained by such a factor.

The acceleration of skeletal maturation has been ascribed to the increase of urinary 17-ketosteroids seen in some cases (Kowlessar, 1965; Stephenson *et al.*, 1968) where these have been considerably in excess of the normal for either chronological or height age. But most cases, including ours, show no such increase. Case 1 in this report, however, showed a disproportionate increase in urinary 17-hydroxycorticosteroids, noted also in Kowlessar's case.

The hypothalamic region, being a link between the higher cerebral centres and the endocrine glands, has been incriminated as the main seat of pathology in this syndrome. Only the non-specific enlargement of the third ventricle found in many cases might support this. Lesions in this region are known to be associated with early increase in stature and enlargement of the extremities in at least three other conditions. The diencephalic syndrome of emaciation may initially show this pattern, but this is not maintained because of extension of the neoplasm into the anterior hypothalamus (Russell, 1951; Gamstorp, Kjellman, and Palmgren, 1967). Likewise, this situation is found in generalized lipodystrophy (Berardinelli, 1954; Seip, 1959), though the total absence of body fat is obviously the most striking feature.

Increased stature is also found in the syndrome of exomphalos with macroglossia (Wiedemann, 1964; Beckwith *et al.*, 1964; Irving, 1967), and increased bone age, prognathism, and high arched palate

are further clinical features shared with Sotos' syndrome. Features absent, however, from Sotos' syndrome include relative microcephaly, exomphalos, neonatal hypoglycaemia, and a tendency to familial incidence.

As far as we are aware, there has been no report of cerebral biopsy or post-mortem study of the brain in Sotos' syndrome. The cortical biopsy in Case 1, performed at the time of ventriculography for which a burr hole was required, showed only a non-specific abnormality. The absence of demonstrable endocrine abnormalities, the resemblance of the patients to each other, sometimes at birth, and the neurological features suggest a congenital malformation syndrome.

Summary

Two cases of Sotos' syndrome are described and the 43 recorded cases reviewed. The condition is characterized by: (1) high birthweight for gestational maturity, (2) an unusual appearance with macrocrania, dolicocephaly, hypertelorism, prognathism, a high arched palate, and facial plethora, (3) accelerated growth and accelerated skeletal maturation from early infancy, with some features of acromegaly (4) clumsiness without neurological deficit, (5) normal endocrine functions. The aetiology remains obscure.

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