

SYNDROME OF THE MONTH

Weaver syndrome

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In 1974 Weaver *et al*¹ described two unrelated children with accelerated growth, advanced bone age, and a characteristic facial appearance. The condition subsequently became known as the Weaver-Smith syndrome (WSS). Since the original report, approximately 30 further cases have been described. It is still debatable if the syndromes of Marshall-Smith (MSS) and Weaver-Smith (WSS) are one²⁻⁴ or separate entities,^{5,6} but at present most authors believe they are different conditions.⁷ Here we briefly include details on four new cases of Weaver-Smith syndrome and review the published reports.

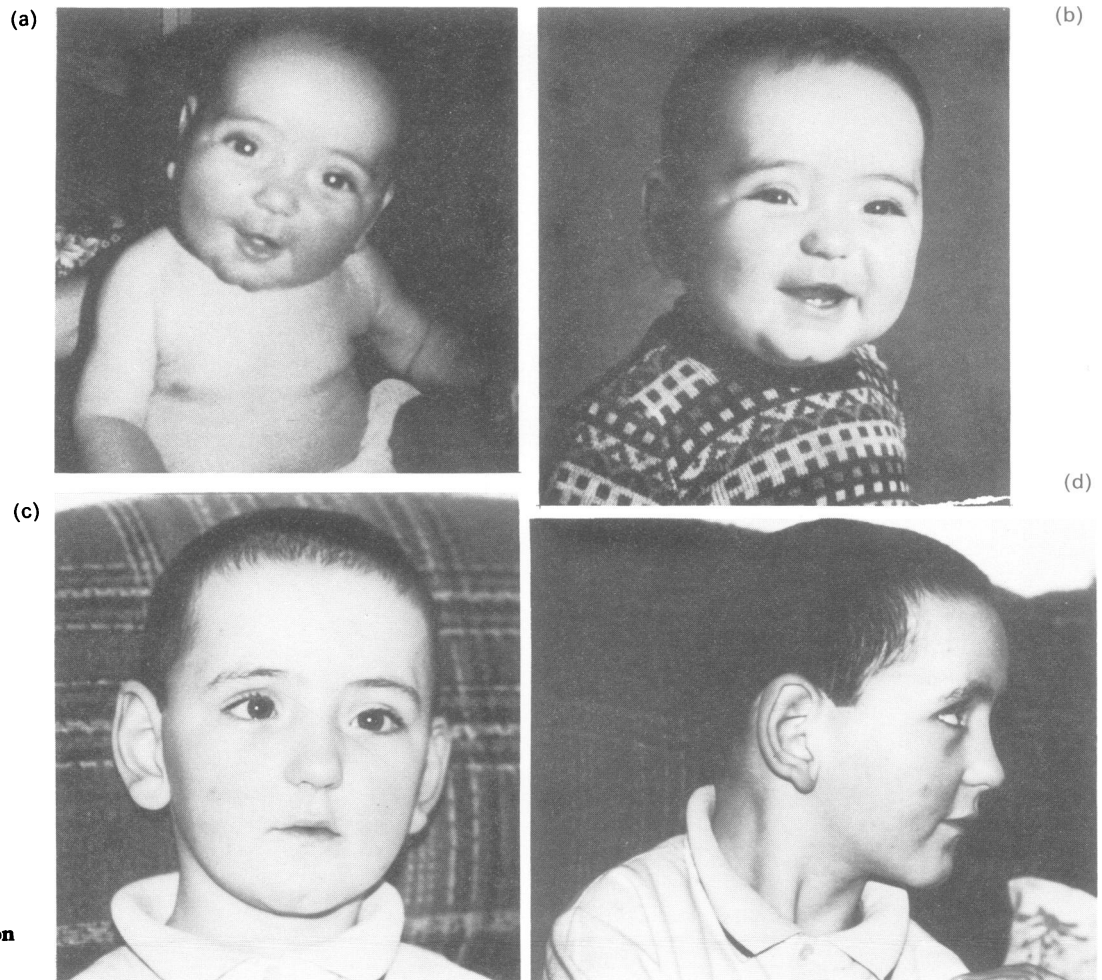
Case reports (figs 1-6)

Clinical details of four new cases of WSS are summarised in table 1. All are male and were

born at 40 to 41 weeks' gestation. Cases 1, 2, and 3 were born by caesarean section because of fetal distress, but there were no serious neonatal complications. Paternal ages were 33, 26, 35, and 32 years and maternal ages 39, 25, 28, and 23 years, respectively.

Review of clinical features**GROWTH**

In WSS there is increased prenatal (table 2) and postnatal weight (fig 3). Birth length and OFC seem to be similarly affected (figs 4 and 5), but there are fewer data on these particular parameters. On reviewing 25 published cases^{1,2,4,7,9-18} and the four new cases in this report, birth length and OFC are increased above the 97th centile in 15/18 and 8/15 children, respectively. Postnatal height and OFC



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Figure 1 Case 1 at ages (a) 4 months, (b) 12 months, (c and d) 5 years.

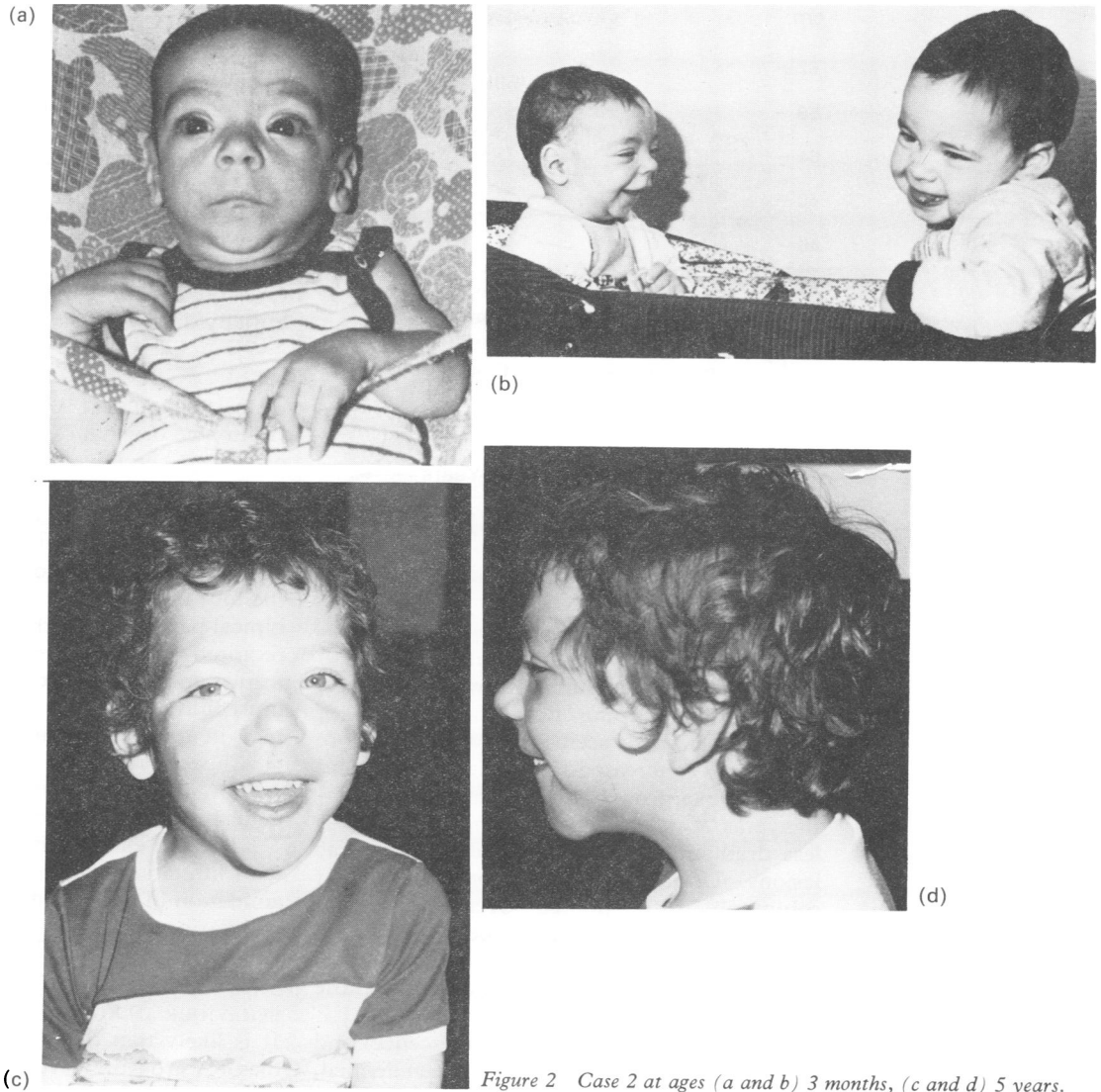


Figure 2 Case 2 at ages (a and b) 3 months, (c and d) 5 years.

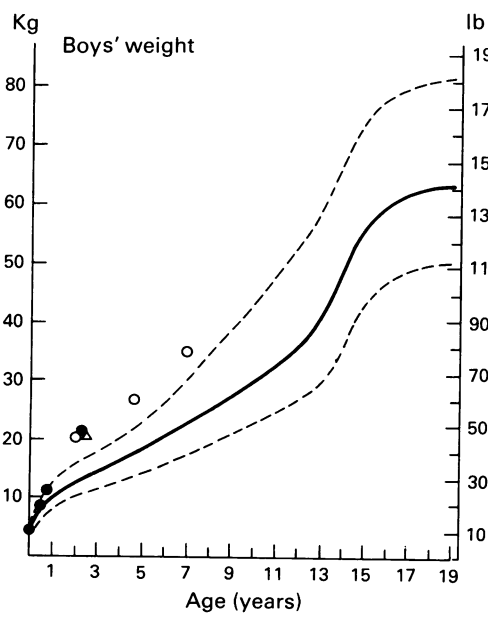


Figure 3 Weight chart cases 1-4.

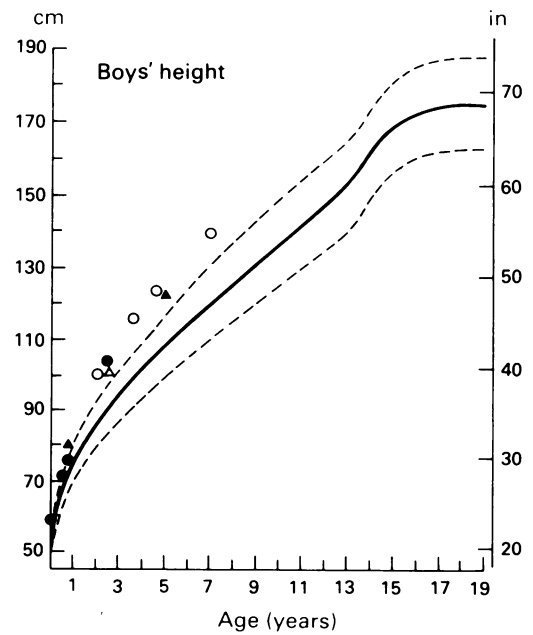


Figure 4 Height chart cases 1-4.

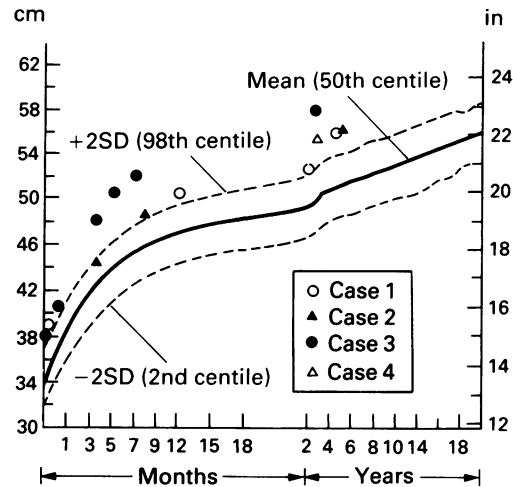


Figure 5 Occipitofrontal circumference charts cases 1-4.

also appear to be increased (usually >97th centile), but in the authors' own experience, which is in keeping with the findings of Majewski *et al*,⁹ it seems that weight is more significantly increased than height (figs 3 and 4). The overgrowth in the cases of Bosch-Banyeras *et al*² and Weisswichert *et al*¹² was less dramatic, but both children had cardiac lesions. Unlike Sotos syndrome, the most commonly differentiated overgrowth condition, OFC in WSS does not appear to be >97th centile in all cases. Five patients out of 29 have post-infancy OFC values between the 50th and 97th centiles.

The growth pattern in adolescence and through to adulthood has not yet been defined, but the adult cases reported to date have achieved heights of 209.5 cm (+5.2 SD),⁷ 187 cm (+3.5 SD),¹⁸ and 161 cm (50th centile).¹⁶ However, the diagnosis of WSS in the latter case cannot be confirmed on the information provided. These limited data would seem to suggest that adult height in WSS may be greatly increased; however, these reported cases were diagnosed as adults when tall stature may have biased ascertainment.

CRANIOFACIAL FEATURES (TABLE 1)

In infancy the face is round with retrognathia and a small but very prominent chin, which often has a central dimple (figs 1 and 2). In childhood, the face becomes longer and less distinctive,¹⁸ although the latter may reflect lack of experience in assessing patients with WSS in older age groups. In mid-childhood there are similarities between the facial gestalt of Sotos syndrome and WSS (figs 1d and 2c). Cases 1, 2, and 4 in the present series were initially diagnosed as having Sotos syndrome.

LIMB AND SKELETAL ANOMALIES

In the two original cases,¹ prominent fingertip pads (fig 6) and deep set nails were described. These features can also be seen on examination of the toes (fig 6). Camptodactyly, although common (11/16, Ardinger *et al*⁷) is by no means a consistent finding and was seen in only one of the four present cases. Cases 1, 2, and 3 had a typical pattern of overriding toes (fig 6) which required surgical correction in case 2. This feature may just reflect crowding of the toes, but could be analogous to the camptodactyly seen in the hands. Similar toe abnormalities have been identified in previous case reports^{1,2,4,7,11,20} in addition to a variety of foot deformities, such as pes cavus¹⁵ and club feet.⁷

Knee and elbow joints are often rather large with limitation of extension. Radiological examination of these joints may show metaphyseal flaring.

BEHAVIOUR AND DEVELOPMENT

It is likely that there has been ascertainment bias towards the severe end of the developmental spectrum in the early descriptions. All seven cases of WSS reported by Ardinger *et al*⁷ were developmentally delayed on early assessments, although one patient subsequently achieved an IQ score of 100 and one other patient was described as being within the low average range. Cases 1 and 2 of the present series fall into the category of borderline or mild mental handicap and together with case 4 show marked early motor and speech delay.

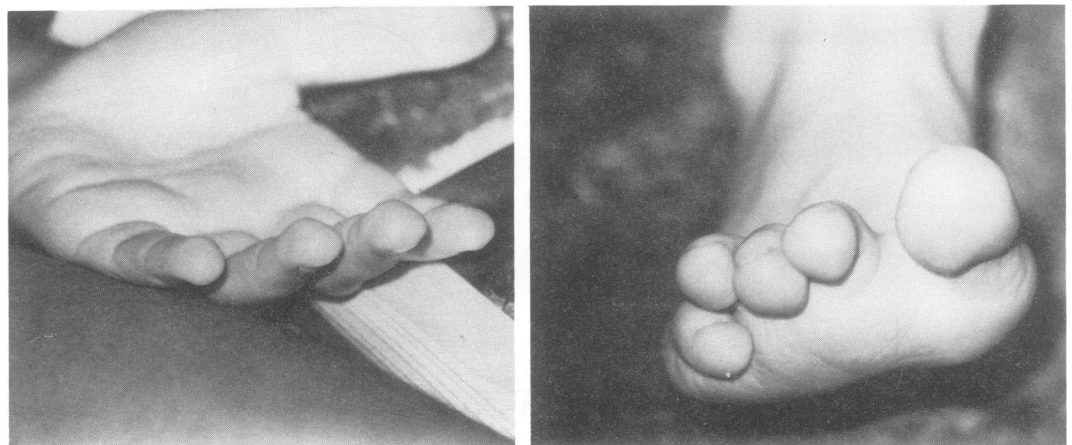


Figure 6 Case 1 showing prominent finger tip pads, prominent pads on toes, and overriding 4th toe.

Table 1 Clinical summary: four new cases of Weaver-Smith syndrome

	Case 1	Case 2	Case 3	Case 4	Ref 7
Age	4y 11m	5y 1m	7m	1y 10m	
Birth weight (g)	5500	4200	4500	4200	
(SD)	(+3.8)	(+1.3)	(+2.3)	(+1.3)	
Birth length (cm)		61	56.6		
(SD)		(+5.7)	(+3.4)		
Birth OFC (cm)	39		38		
(SD)	(+1.5)		(+1.0)		
Broad forehead	+	+	+	+	18/19
Round face in infancy	+	+	+	+	
Micrognathia	+	+	+	+	17/19
Prominent philtrum	+	+	+	+	10/14
Large ears	+	+	+	+	15/17
(length cm)	(7.1)	(6.7)		(6.8)	
Hypertelorism (ICD cm)	(3.5)	(3.9)		(3.5)	19/19
Large hands	+	+	+	+	
Deep set nails	+	-	+	+	9/10
Prominent finger/toe pads	+	-	+	+	6/9
Overriding toes	+	+	+	-	
Syndactyly	-	+	-	-	
Genital anomalies	+	+	+	-	
Tone	Normal	Reduced	Normal	Reduced	↑10/18 ↓5/18
Reflexes	Normal	Brisk	Brisk	Brisk	

Table 2 Comparative birth measurements in three overgrowth syndromes.

	Weaver	Sotos ⁸	Marshall ^{5*}
Weight > 97th centile	14/29	6/41	1/11 > 90 cen
Weight < 50th centile	3/29	4/41	6/11
Length > 97th centile	15/18	23/27	5/10 > 90 cen
OFC > 97th centile	8/15	12/27	3/7 > 90 cen

*Cut off at 90th centile.

These deficits are now improving. At present, case 3 appears to be developing normally (table 3).

Speech in WSS is not only delayed, but is also often described as slurred or dysarthric and the tone of the voice is rather hoarse and low pitched.

Behavioural problems are common in WSS and poor concentration and temper tantrums may be particularly difficult to manage. These problems are present in the three older children in this report (cases 1, 2, and 4). It is possible that these features reflect the patient's frustration, particularly when communication is a problem, rather than an intrinsic component of the syndrome. Similar behavioural problems have been recognised in children with Sotos syndrome.

NEUROLOGICAL FEATURES

Tone appears to be altered in most cases and was described as increased in 10 out of 18, and decreased in five out of 18 by Ardinger *et al.*⁷ Hypotonia alone would obviously influence early motor development and articulation.

Table 3 Early developmental milestones (months).

	Case 1	Case 2	Case 3	Case 4
Sitting unaided	9	9	7	9
Walking unaided	17	17	14	20
First words	-	13	16	22
2 word sentences	48	30	27	-

There are suggestions in published case reports that muscle tone may increase with time. In the series of patients reported by Ardinger *et al.*,⁷ those patients with hypotonia were aged 0 to 24 months while the hypertonic patients were aged between 5 and 39 years. Lower limb reflexes in cases 2, 3, and 4 of the current report are rather brisk, although the plantar response is still flexor. Case 7 described by Ardinger *et al.*⁷ had a progressive spasticity resulting in the patient becoming wheelchair bound in adulthood. Myelography in this patient showed what was described as 'questionable' spinal stenosis. Mohonen and Menezes¹⁹ reported a case of Weaver syndrome with instability of the cervical spine and speculated that this might explain progressive spasticity. Case 2 of the present series has fusion of the second and third cervical vertebrae but no other axial anomaly. It is speculative whether progressive involvement of the spinal cord, on a background of 'central hypotonia', is the underlying cause of these lower limb signs.

ADDITIONAL FEATURES

Weaver *et al.*,¹ in their original paper, reported the presence of short penile length in both their patients. This feature does not appear to be a common finding in subsequent cases, although cryptorchidism has been reported.^{11 12 16} Inguinal and umbilical herniae are common, the latter present in cases 2 and 3 of the current series. In addition, case 2 had a very high left testis and cases 1 and 3 had hydroceles in infancy.

Hirsutism, which is more usually associated with MSS,⁵ has been reported by Jalaguier *et al.*⁴ in a patient where the diagnosis of either WSS syndrome or MSS syndrome is questioned. However, this feature has also been documented by Stoll *et al.*¹⁶ in a patient where the diagnosis of WSS seems certain.

Other overgrowth syndromes such as Sotos syndrome, Beckwith syndrome, and hemihypertrophy have been associated with an increased incidence of tumour formation.²⁰ To date, only one case of a neuroblastoma has been reported in WSS syndrome.¹⁹

Cardiac lesions have been recorded in four out of nine patients in a review of WSS by Fitch.⁶ None is present in the four new patients in this report.

Investigations

RADIOLOGICAL

The bone age in all cases of WSS appears to be advanced, although Stoll *et al.*¹⁶ reported a 6 year old child with a normal bone age, but which had been significantly advanced at 18 months of age. The bone age probably is dysharmonic, with the ossification of the carpal bones being more advanced than that seen in the phalangeal bones (table 4). However, it should be remembered that carpal assessments are highly variable and may not always be accurate.

Widened metaphyses, involving the femur or humerus or both, were documented in three

of the present cases and in 16 out of 18 cases in the review by Ardinger *et al.*⁷

ENDOCRINOLOGICAL

Endocrinological investigations to date have been normal in most cases.^{1,7,9-12} Amir *et al.*¹⁴ described a case with acquired hypothyroidism, but thyroid function tests are usually normal in WSS.¹⁵⁻¹⁷ Stoll *et al.*¹⁶ reported a low basal and stimulated level of human growth hormone (hGH) in a 6 year old boy and his apparently affected mother, who also was found to have hyperprolactinaemia. However, normal hGH levels have been reported by several authors and Amir *et al.*¹⁴ showed a normal 24 hour hGH pattern in the patient they reported.

Although endocrinological abnormalities have only been documented in three cases of WSS, it is interesting to note that the same abnormalities, that is, hypothyroidism²² and low basal and induced levels of hGH (Hindmarsh, personal communication), have also been described occasionally in Sotos syndrome.

CYTOGENETIC

Chromosomal analyses were reported in 12 out of the 29 cases included in this review and all were normal. Only two patients (cases 1 and 2 in the present paper) appear to have had fragile X studies; both were normal.

Differential diagnosis

There are several conditions which may be associated with overgrowth and these are listed in the differential diagnosis of WSS (table 5). However, most can be excluded by the absence of an advanced bone age and their differing facial phenotypes. The three conditions most likely to cause confusion with WSS are Sotos syndrome, Ruvalcaba-Myhre-Smith syndrome, and MSS.

In Sotos syndrome, the infants are less likely to have an increased birth weight and in childhood tend to be tall and thin.²³ They also have

Table 4 Bone age assessments (years).

	Case 1	Case 2	Case 3	Case 4
Chronological age	5.4	6.4	0.9	1.6
Tanner-Whitehouse (TW2) bone age	8.2	8.8	1.9	2.0
Carpal bone age	11.6	9.4	4.4	2.6

Table 5 Differential diagnosis of Weaver-Smith syndrome.

Sotos
Marshall-Smith
Simpson-Golabi-Behmel
Beckwith-Wiedemann
Perlman
Proteus
Sanfilippo
Marfan
Neurofibromatosis type 1
Fragile X
Klinefelter
Trisomy 8 mosaicism
Benign familial macrocephaly

a longer face and jaw compared to the rounder, fuller face, retrognathia, and well defined, small, dimpled jaw of WSS. The facial gestalt currently perceived as typical for WSS may be age dependent and limited to the first couple of years of life. As our experience of WSS in adolescence and adulthood increases, it may be that an 'older phenotype' becomes more obvious. For example, the gestalt of case 1 (fig 1b) at the age of 1 year is very similar to the appearance of the two original cases of WSS at a similar age.¹ However, the gestalt of case 1 at the age of 5 years (fig 1d) has clearly changed.

Patients with Ruvalcaba-Myhre-Smith syndrome,²⁴ like Sotos syndrome, also have rather longer faces and can be further differentiated by the presence of pigmentation on the genitalia, colonic polyps, and a positive family history.

The main diagnostic controversy is the differentiation of WSS from MSS. However, comparison of the phenotypes of these two conditions shows that children with MSS have much thinner faces and a rather gaunt appearance accentuated by proptosis, anteverted nares, small facial bones, and long, thin extremities. They also have poor weight gain, both pre- and postnatally, feeding difficulties with aspiration, recurrent pneumonia, and early death, usually within the first two years of life. Both conditions are associated with a significantly advanced bone age but characteristically MSS patients have broad middle phalangeal bones. This feature has also been described in the case who probably has WSS² and therefore could be an occasional feature in Weaver syndrome.

Several authors²⁻⁴ have described families or individual patients with features of both WSS and MSS and have suggested that the two syndromes are morphological variants of the same condition. This argument is addressed in some depth by Fitch.^{5,6} The present authors are of the opinion that the two conditions are separate and that the cases of Bosch-Banyeras *et al.*² and Jalaguier *et al.*⁴ are more typical of WSS. The lack of postnatal overgrowth in the former patient could be accounted for by the documented but undefined 'cardiopathy'. The patient described by Shimura *et al.*³ is not typical of either WSS or MSS. The case reported by Tsukahara *et al.*²⁵ as WSS has been reclassified by Stoll *et al.*¹⁶ as Simpson-Golabi-Behmel syndrome. The second patient with suspected WSS described by Majewski *et al.*⁹ is believed by the authors to be more typical of benign familial macrocephaly, and this diagnosis ought to be considered within the differential diagnosis of WSS.

Inheritance

In this review of 25 published cases and four new cases, nine are female and 20 are male. Most reports to date suggest sporadic occurrence of this condition, but there have been three families where autosomal recessive inheritance has been postulated. In the family described by Roussounis and Crawford,²⁶ the surviving sib has since been reviewed and

chromosome analysis showed the karyotype 46,XX, 5p-; the concurrence of this recognised chromosomal syndrome and WSS would seem unlikely (R Mueller, personal communication). Teebi *et al*²⁷ described a consanguineous Bedouin family with two sibs manifesting features similar to those of WSS. However, on review of the clinical data, neither case would appear to be typical of the syndrome. For example, the younger sib does not exhibit accelerated growth and has delayed bone maturation at the age of 13 months. Jalaguier *et al*⁴ reported two sibs with clinical features of both Weaver syndrome and Marshall-Smith syndrome. Unfortunately, a photograph of the older sib is not provided. Data on the surviving sib are typical of Weaver-Smith syndrome. Clinical data on the parents are insufficient to rule out mild expression of the WSS phenotype. Therefore, either dominant or recessive inheritance of Weaver syndrome might be exhibited by this family, but this is impossible to confirm.

There are a further three published pedigrees which are compatible with either autosomal dominant inheritance with sex limited expression or X linked recessive inheritance. As previously stated, patient 2 described by Majewski *et al*⁹ was felt by the authors possibly to be more typical of benign familial macrocephaly. The other two families are described by Ardinger *et al*⁷ (case 1) and Stoll *et al*.¹⁶ In both these reports, it is not possible on the information provided to confirm or refute the suggestion that the two mothers show a mild expression of WSS while their affected sons show the full clinical picture.

Natural history

It is difficult to assess the risk of early childhood mortality in WSS while the controversy concerning separation of WSS and MSS remains. The two patients described by Jalaguier *et al*⁴ died in infancy and the authors believe that at least the second sib had WSS. Beyond early childhood years, life expectancy is probably normal, at least into early adulthood. Little else is known about the natural history of Weaver syndrome as only two adults have been fully documented.^{7,18} Both were tall with adult heights +5.2 SD and +3.5 SD. Therefore, it is possible that final height in WSS may be greater than in other overgrowth syndromes. The facial characteristics appear to change markedly through childhood and adolescence.¹⁸ There was no evidence of intellectual regression in any of the reported cases.

Conclusions

Weaver-Smith syndrome is a rare overgrowth syndrome identified by the presence of advanced bone age, metaphyseal flaring of the long bones, developmental delay, and characteristic facies (macrocephaly, broad forehead, a rounded face in infancy, long, prominent philtrum, small but distinctive chin, and large

ears). It should be remembered that cases reported at present probably lie at the more severe end of the spectrum. Without reviewing photographs of children at different ages, WSS may be difficult to differentiate from Sotos syndrome. In the absence of a diagnostic marker, the controversy regarding its separation from MSS, and indeed Sotos syndrome, is likely to remain. Recurrence risks are still unclear, but the majority of cases to date have been isolated.

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