Aarskog's syndrome

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SUMMARY Six children with Aarskog's facial-digital-genital syndrome are described, and the genetics of the condition discussed. We suggest that this anomaly may be fairly common and that a syndrome identification centre could lead to earlier diagnosis of children with this and other syndromes.

In 1970 Aarskog,¹ in Norway, described a syndrome associating short stature with certain anomalies of the face, hands, feet, and genitalia in 7 males from two generations of the same family. He favoured transmission as an X-linked trait, noting that the carrier women in the pedigree tended to be short. All 7 were of normal intelligence. Since 1970 there have been several reports from transAtlantic sources,²⁻⁷ describing similarly affected kindreds with full expression of features in males, and occasional minimal expression in the females. An account of the syndrome had already been given from the USA, for in 1967 Hanley *et al.*⁸ described 2 brothers with osteochondritis dissecans and associated malformations who undoubtedly had Aarskog's syndrome. It has been suggested that an alternative descriptive term might be the facial-digital-genital syndrome.

We now report 6 boys with the syndrome, 3 of them brothers; this is the first description of this malformation from the UK. The eldest of the affected 3 brothers will first be described in detail. The anomalies he shows together with those found in his 2 brothers and the other 3 children are listed in the Table.

Case reports

Case 1 (Fig. 1), the second child born to unrelated parents, was delivered in 1967 at 33 weeks' gestation weighing 1.80 kg. At birth he was noted to have an odd facial appearance and abnormalities of the hands and feet. Further anomalies were noticed during his first 3 years, but the following observations were made when he was 10 years old. His height was then 131 cm (10-25th centile), weight 32.9 kg (75-90th centile), and head circumference 51 cm (10th centile). His forehead was broad with a prominent

Fig. 1 Facial features of Case 1.

metopic suture, and his hairline showed a pronounced widow's peak. There was primary telecanthus,* the inner canthal distance being 36 mm, the outer canthal distance 82 mm, and the interpupillary distance 58 mm. The Mustardé index†⁵ was 62%. He had slight right ptosis and was hypermetropic and astigmatic. His nose was short and

* Increased distance between the inner canthi, affecting only the soft tissues.

† The ratio of the inner canthal to interpupillary distance (normal less than 55%).

Table

Features	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Birthweight (kg)	1.80	2.50	2.64	3.00	2.94	1.85
Gestational age (weeks)	33	40	38	41	38	31
Height centile	10-25	3-10	<3	3-10	10-25	<3
Bone age	Normal	1 year retarded	Normal	1 year retarded	Normal	Not known
Prominent forehead	+	+	+	+	+	+
Metopic suture prominent	+	+	Not known	+	+	+
Widow's peak	+	+	+	+	+	+
Telecanthus	+	+	+	+	+	+
Ptosis	+	—	—	+	—	—
Broad nasal bridge	+	+	+	+	+	+
Short stubby nose	+	+	+	+	+	+
Flared anteverted nostrils	+	+	+	+	+	+
Long prominent philtrum	+	+	+	+	+	+
Thin upper lip	+	+	+	+	+	+
Pouting lower lip	+	+	+	+	+	+
Linear groove below lower lip	+	+	+	+	+	+
High narrow palate	+	+	—	+	+	+
Prominent point to chin (not prognathism)	+	+	+	+	+	—
Ears: thickened down-turned helices and fleshy lobes	+	+	+	+	+	+
Long neck and sloping shoulders	+	+	+	—	—	Not known
Long narrow chest	+	+	+	+	+	+
Pectus excavatum	+	+	+	+	+	+
Midline depression (xiphisternum to umbilicus)	+	+	+	+	+	—
'Button' umbilicus	+	+	+	+	+	+
'Shawl' scrotum	+	+	+	+	+	+
Prominent median raphe	+	+	+	+	+	+
Inguinal herniae	+	+	+	+	—	+
Position of testes	Both retractile	Left retractile	Right and left orchidopexy	Both retractile	Both retractile	Both retractile
Clinodactyly 5th fingers with single or abnormal creases	+	+	+	+	+	+
Simian crease	+	Broken	Broken	+	+	—
Interdigital webbing (mild syndactyly)	+	+	+	+	+	+
Hyperextensible fingers	—	+	+	+	+	—
Genu recurvatum	—	+	—	+	+	+
Metatarsus varus	+	+	+	+	+	+
Bulbous toes	+	+	+	+	+	—
IQ or DQ	IQ 83	Normal	Normal	Normal	Normal	Low normal

stubby with anteverted nostrils, the nasal bridge being broad and prominent. The philtrum was long and the mouth wide, with a thin upper lip and a horizontal skin crease immediately below the lower lip. There was dental malocclusion with overbite. The palate was high and narrow. The ears had a thickened down-turned helix and a large fleshy lobe. He had a long neck with sloping shoulders and prominent sterno-clavicular joints. There was a minor degree of pectus excavatum in a long tubular chest, and a shallow midline depression continued from the xiphisternum to the umbilicus; the umbilicus was prominent and stood out like a button. The scrotum continued ventrally around the base of the penis giving a hooded appearance (shawl scrotum), and there was a pronounced median raphe simulating a bifid scrotum. Inguinal scars denoted previous repair of bilateral inguinal herniae (Fig. 2). Both testes were retractile.

In the hands, the 5th digit showed clinodactyly and was short with a single ventral crease, although it had 3 interarticulating phalanges. There was webbing between the fingers, and abduction of the

Fig. 2 Cases 1, 3, and 2 (left to right) showing midline depression of chest, prominent umbilicus, shawl scrotum, inguinal herniorrhaphy scars.

thumb was limited by interdigital webbing (Fig. 3). Each palm had a single, broken simian crease. The feet were short, flat, and broad with a pronounced degree of metatarsus varus. There was

Fig. 3 Right hands of Cases 1, 3, and 2 (left to right) showing interdigital webbing.

webbing of the toes, and the distal portions of the 1st and 2nd toes were bulbous, the 2nd toe inclining away from the first.

IQ was 83 on the Wechsler scale. Chromosome studies using Giemsa banding showed a normal male pattern. A vertebral x-ray showed no abnormality, and the bone age was normal.

His two brothers Case 2 (Fig. 4) and Case 3 (Fig. 5) have almost identical anomalies (Table).

Fig. 4 Facial features of Case 2.

Fig. 5 Facial features of Case 3.

The mother of these 3 children (Cases 1, 2, and 3) showed some of their features. Her height was 153 cm (3rd centile). Her eyes were prominent but there was no primary telecanthus. She had a broad thin upper lip and fleshy ear lobes. Her nose and palate were normal. There was clinodactyly of the 5th fingers and both these digits were short

with single ventral creases; there was a fixed flexion deformity of the 5th metacarpo-phalangeal joints. Her 1st and 2nd toes were bulbous terminally. She has 3 brothers; one brother has hands and feet similar to hers, and looks very much like one of her affected sons.

Her first child was found to have a widow's peak, fleshy ear lobes, clinodactyly of the 5th fingers, and slight bilateral metatarsus varus, but no other features of Aarskog's syndrome. His young sister also has a widow's peak and fleshy ear lobes, but none of the other striking features present in her 3 affected brothers. The father showed no features of the syndrome.

Identification of Aarskog's syndrome in this family soon led to the recognition of the syndrome in the following 3 boys. They are not related to each other.

Case 4 (Fig. 6) had been examined at birth by one of us (TM) and because of 'a strange facies' and other dysmorphic features, has been followed up

Fig. 6 Facial features of Case 4.

Fig. 7 Case 4. Feet showing metatarsus varus.

ever since. His height and weight have remained at between the 3rd and 10th centiles. He has normal intelligence although his school reported that he has learning problems, especially with mathematics. This child is remarkable in showing almost all the components of Aarskog's syndrome so far described (Table). His mother is short (height 156.3 cm). She shows a slight widow's peak, prominence of the chin, camptodactyly of the 5th fingers with a single crease on the right side, hyperextensibility of the metacarpo-phalangeal joints, short broad feet with metatarsus varus and bulbous ends to the toes similar to those of her son (Fig. 7). Her other child, a daughter, shows no sign of the condition.

Case 5 was first seen at age 2 months in the orthopaedic clinic because of his metatarsus varus, and the syndrome was recognised at age 2½ years. His features are listed in the Table. His mother is of normal height (167 cm) and shows no obvious features of Aarskog's syndrome.

Case 6 was diagnosed when being investigated for short stature at age 16 months. His features are shown in the Table. His mother's height is only 155 cm, but she has no sign of the condition. An elder brother is normal but a maternal first cousin, a boy, unknown to us, may be affected.

Genetics

This condition appears to be controlled by a single gene, but whether this is autosomal or X-linked is not clear. As all the initial cases were boys and their mothers sometimes showed minor features, an X-linked gene seems likely to be responsible. In 1975 Berman *et al.*⁹ reviewed families with good pedigree data and found evidence for transmission through females and some, but not all, of these women showed features of the condition. Two women had affected sons by two different marriages. This

suggested either an X-linked gene with partial expression in carrier females, or an autosomal gene with sex limitation leading to much greater expression in males. To distinguish between these two possibilities, sons of affected males were studied. Four affected men had 7 unaffected sons, strongly supporting X-linked rather than autosomal control. However, since then Welsh (G Welsh, personal communication) and Harris¹⁰ have described an affected father and son, so that an autosomal dominant gene with sex limitation of expression has to be considered. The matter will become clearer when more families have been studied, although a later review¹¹ again favours the X-linked hypothesis.

Discussion

The finding of this malformation syndrome in 4 unrelated families (6 cases) in the south of England suggests that the condition is not as rare as may appear from the scanty reports in the British journals. The problem for the paediatrician today is familiarisation with the ever increasing number of new syndromes. We believe that there is a good case for setting up a national reference centre of syndromes. Had such a centre existed 8 years ago, the syndrome in the original family might have been recognised, and almost certainly a diagnosis would have been made in Case 4 shortly after birth. His parents have had 8 years of anxiety about their son's condition. Furthermore, when they sought genetic advice some years ago before embarking on a further pregnancy, they were told, incorrectly as we now know, that the chance of recurrence of the syndrome in another child was small.

Affected children not detected at birth are commonly referred to an orthopaedic surgeon because of metatarsus varus or other limb abnormalities; general surgeons may be consulted about inguinal herniae or cryptorchidism: eye problems are common and may lead to an ophthalmic consultation, or the child may be referred to a paediatrician because of shortness of stature. A national reference centre would surely heighten the awareness of all clinicians and lead to a speedier diagnosis of some of the more obscure syndromes, and to a greater understanding of their genetic implications.

Case 4 was presented to the Paediatric Section of the Royal Society of Medicine on the 27 October 1978.

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