The femoral hypoplasia-unusual facies syndrome

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SUMMARY A series of thirteen persons with bilateral femoral hypoplasia are presented. Six of these had facial features compatible with a diagnosis of femoral hypoplasia-unusual facies syndrome. One was attributable to severe fetal constraint secondary to oligohydramnios, three were associated with maternal diabetes, and two were idiopathic. All thirteen cases were sporadic.

In 1975, Daentl *et al*¹ described the femoral hypoplasia-unusual facies syndrome, claiming it to be a separate entity with a characteristic facial appearance: a short nose with a broad tip, a long philtrum, a thin upper lip, and upward slanting palpebral fissures. Other features of their four cases were micrognathia, with cleft palate in some, and club foot deformity. Diabetes was not present in the mothers or their relatives. The authors reproduced a published case previously considered to be a case of caudal regression on the basis of a history of diabetes in the mother. Pitt *et al*² reported a further patient and summarised 16 reported cases. There has been a report by Lampert³ of an affected male whose daughter had a similar spectrum of anomalies, raising the possibility that this syndrome results occasionally from a single dominant gene. Lord and Beighton⁴ examined seven patients with bilateral femoral hypoplasia, but did not find significant alteration of facial features, and called into question the existence of this syndrome as a distinct entity. Recently, Johnson *et al*⁵ reported three children with typical features of the syndrome all born to diabetic mothers, drawing attention again to the importance of maternal diabetes mellitus.

The experience of The Hospital for Sick Children, Great Ormond Street, London, is presented, on the basis of which we discuss diagnostic criteria, pathogenesis, aetiology, and risks of recurrence.

Methods

A search was made, using the hospital records stored on computer by diagnostic code, for cases of femoral hypoplasia, dysplasia, or aplasia. As expected the majority were cases of isolated unilateral proximal

femoral focal deficiency and were excluded. Among 156 records examined, 14 had bilateral femoral involvement. Two had grossly abnormal tibiae and were not included. In one of these the mother was diabetic. Twelve families were approached through their general practitioners and nine responded. During the course of the study four further children were referred for assessment and are included, making a total of 13 cases. They are presented under the following headings.

(1) Femoral hypoplasia-unusual facies syndrome.

- (A) Fetal constraint: deformation (one case).
- (B) Maternal diabetes: disruption (three cases).
- (C) Undetermined aetiology (two cases).

(2) Femoral hypoplasia with normal face.

- (A) Fetal constraint: deformation (one case).
- (B) Maternal diabetes: disruption (one case).
- (C) Undetermined aetiology (five cases).

Case reports

(1A) FETAL CONSTRAINT SEQUENCE

Case 1 (male)

Six weeks after her last period in September 1979, the mother of case 1 had a brief blood loss. Episodes of blood loss on rising and after prolonged standing continued for 6 weeks. A pregnancy test at 10 weeks by dates was positive. At 24 weeks by dates she first became aware of continual wetting of her underwear. The wetting became more severe but was thought to be stress incontinence and she remained ambulant. Her underwear was never stained and did not smell suggesting that this was, in fact, a loss of liquor. In the third trimester, loss was so severe she found it necessary to wear a disposable nappy. Spontaneous labour began 10 days after term by dates and 37 weeks by scan. Breech presentation and cephalopelvic disproportion made necessary delivery by

caesarian section. A striking deficiency of liquor was noted, and the male infant was compressed into a 'Buddha' pose, with the left side of the chin on the chest. The placenta was pale, weighed 550 g, and had three cord vessels. Resuscitation was not required and respiratory distress did not develop. Several abnormalities were noted: plagiocephaly, micrognathia more marked on the left, a posterior cleft palate, severe bilateral talipes equinovarus, a fixed flexion deformity at both elbows and both knees, and rhizomelic shortening of the legs.

He gained weight on bottle feeding but took food slowly. By 20 days when he was discharged, he had gained 100 g over his birth weight of 2.43 kg and had developed a soft systolic murmur at the left sternal edge. He was readmitted at 3 months with a history of deteriorating feeding owing to breathlessness and was found to have evidence of mild pulmonary stenosis.

Examination at 8 months revealed an alert child with plagiocephaly, micrognathia worse on the left, mild left torticollis, and posterior cleft palate. He had a long philtrum and normal palpebral fissures (fig 1a). The tendency of his lower legs, with marked talipes equinovarus, to return to the 'in utero' position was noted. The femora were short with pits on the lateral aspect of each thigh, overlying the point of angulation of the bowed femora (fig 1b). A pseudarthrosis was evident on the left, no proximal deficiency was noted, and the pelvis and lower spine were normal. There was dislocation of both radial heads and a left inguinal hernia. A grade 3/6 harsh midsystolic murmur, maximal in the pulmonary area, radiated to the back with a normally split second sound. Echocardiography supported the view that the atrial and ventricular septa were intact and the valves were normal. A mild degree of pulmonary artery stenosis was considered the only likely structural defect.

(1B) MATERNAL DIABETES DISRUPTION

Case 2 (female)

Case 2 was the only child of non-consanguineous parents. The mother had been diabetic since the age of 13 and was on insulin. Her blood sugars had been monitored during pregnancy but control was not good and at 32 weeks she was admitted to hospital to improve diabetic management. The child was born at 36 weeks by emergency caesarian section, because of maternal pre-eclamptic toxemia, and weighed 2.67 kg. A small jaw and cleft palate with bilateral short femora were noted (fig 2a, b, and c). The pelvis was not involved. There was soft tissue syndactyly of the fourth and fifth toe of the right foot.

(a)

FIG 1a Case 1. Deformation due to oligohydramnios. There is torticollis, a small mandible, posterior cleft palate, severe talipes, and left inguinal hernia. The philtrum is long and the femora are short and bowed, leading to a diagnosis of femoral hypoplasia-unusual facies syndrome.

(b)

FIG 1b Case 1. The pelvis and sacrum are normal. The femora are short, more on the left, with lateral bowing on the right and a pseudarthrosis on the left. Both femoral heads appear dislocated due to failure of ossification of the upper femur in the presence of coxa vara. Subsequent films show the capital epiphyses ossifying in the acetabula. The skeletal features are considered to be unusual manifestations of deformation with both thighs being compressed end to end from an early stage.

FIG 2 Case 2. (a, b, c) Femoral hypoplasia-unusual facies syndrome associated with poorly controlled maternal diabetes. Note the very long philtrum, short nose, small jaw, posterior cleft palate, and severe shortening of the thighs with lateral dimpling.

Case 3 (female)

Case 3 was born by caesarian section at 39 weeks because of gestational diabetes, breech presentation, and disproportion. Her birth weight was 2.5 kg. The pregnancy itself was uneventful. The mother had suffered gestational diabetes during this and the previous pregnancy, for which simple dietary measures were prescribed. At birth the clinical features were low set ears, a short neck, small jaw, short upturned nose, and a long philtrum (fig 3a). Both legs showed shortening of the upper segments

FIG 3 Case 3. Typical facial features again associated with maternal diabetes.

with bowing. There was a bifid first toe on the right and preaxial polydactyly of the left foot with bilateral talipes. X-rays showed bowing of the femora with dislocation of the hip joints and extensive hemivertebrae in the dorsolumbar spine. The ribs were deformed with irregular widening.

Case 4 (male)

Case 4 was born on 22.9.75 at 36 weeks' gestation and weighed 3.24 kg. The mother had suffered a threatened miscarriage at 10 weeks with bleeding for 3 days. This settled on bed rest. No abnormality was recognised until 6 weeks when bilateral bowing of the femora was noted. He required bilateral orchidopexy and developed mild asthma, but was developmentally normal. His mother was 34 years old at his birth and his father was 30 years old. There were two other children who had normal limb development. During the previous pregnancy, the mother was found to be prediabetic and subsequently became insulin dependent. Control was good initially, but became difficult during the early stages of this third pregnancy, with a three-fold increase in insulin requirement. At 6 months' gestation she suffered an episode of diabetic coma.

The proband had bowing of both thighs with lateral dimpling (fig 4a). X-ray showed proximal hypoplasia with sclerosis and lateral bowing of the upper shaft (fig 4b). The pelvis, back, and heart were normal and his facial appearance (fig 4c) was unremarkable with palpebral fissures of normal site and size. However, his philtrum was relatively long at 1.8 cm compared to a nose length of 3.9 cm, a

FIG 4 Case 4. (a, b, c) Third case of maternal diabetes. The long philtrum, short bowed femora, and lateral dimpling of the thighs are less striking but still easily recognised.

ratio of 0.46 (upper limit of normal range, based on 22 age matched controls, being 0.36).

(1C) UNCERTAIN AETIOLOGY

Case 5 (female)

Case 5 was born at 39 weeks' gestation and weighed 2.2 kg. There was no relevant family history and a later born sib was normal. The mother was a 26 year

old teacher. The pregnancy, the mother's first, had been uneventful. Fetal movement was reduced and at delivery there was little liquor, though no leakage had been noted.

Fig 5a shows the facial features evident at birth, micrognathia and long philtrum. There was a wide posterior cleft palate. The legs were short with dimpling of both lateral thighs over angulated

FIG 5 Case 5. (a, b, c) Femoral hypoplasia-unusual facies syndrome of uncertain aetiology. In the neonatal period the micrognathia is striking, together with short thighs due to severe sclerosis and shortening and lateral bowing of both femora. The photograph at a later age shows the 'typical' face with short pinched nose with a broad tip, long philtrum, and thin upper lip. There is a mild degree of upward slanting of the left palpebral fissure.

femora. X-ray examination (fig 5b) revealed hypoplasia of the mid shaft of both femora. The pelvis, tibiae, and fibulae were not involved. Fig 5c shows her physical appearance at 3 years: pinched nose, thin upper lip with rather long philtrum, and persistent severe proximal limb shortening. Intellectual development had progressed normally and she was mobile.

Case 6 (male)

Case 6 was born at 33 weeks and weighed 1.5 kg. The mother was 32 years old and had a history of fits but was not on drug therapy. The father was 34 years old. His father and other family members were short but had normal body proportions. The mother reported heavy loss of fresh blood over 13 days at 8 to 10 weeks' gestation. Extended breech presentation made forceps extraction necessary. Bilateral femoral hypoplasia with hip dislocation, micrognathia, and a posterior cleft palate were noted, together with a right inguinal hernia. Fig 6a shows the facial appearance at 15 months of age. The micrognathia remained evident, with a long philtrum. Fig 6b and c show the clinical and radiological appearance of the

lower limbs. There was symmetrical hypoplasia of the femora with lateral bowing. The tibiae, fibulae, and sacrum were normal.

(2A) FETAL CONSTRAINT SEQUENCE

Case 7 (male)

Case 7 was born in 1971. His father was 27 and his mother 24 years of age. His mother had had a miscarriage at 6 weeks the previous year. They subsequently had two normal children. The early stages of this pregnancy were uneventful and movement was felt at 18 weeks. Extended breech presentation persisted until delivery at 41 weeks by caesarian section after a 24 hour labour. After birth the thighs were noted to be short and bowed laterally, with limited abduction at the hips but normal joints. X-ray examination revealed lateral bowing with sclerosis of the shaft. Fig 7a, b, and c show the progressive resolution of the femoral abnormality. At examination at the age of 11 years, slight valgus deformity at the right knee and inturning of the feet during walking were the only abnormalities. Intellectual development and facial morphology were normal (fig 7d).

FIG 6 Case 6. (a, b, c) Again, short nose, long smooth philtrum, small jaw, and short laterally bowed femora without a recognised cause. The radiograph shows the typical point of angulation between the proximal and middle thirds.

FIG 7 Case 7. (a, b, c, d) Normal face in a child with a history of fetal compression. The sclerosis and mild lateral bowing of both femora is, again, regarded as a minor degree of deformation. The resolution of the bowing and normal later growth (b, c) are in keeping with this explanation.

(2B) MATERNAL DIABETES DISRUPTION

Case 8 (female)

Case 8 was born in March 1951, the third child of a 33 year old mother and a 28 year old father. The mother had four healthy children by her previous marriage. The father had a congenitally small left arm. Otherwise, there was no family history of malformation. The mother fainted frequently in the first trimester of this pregnancy. A diagnosis of epilepsy was considered, but in the postnatal period polyuria, polydipsia, and glycosuria were recognised and a diagnosis of diabetes mellitus was made. Control with oral hypoglycaemic agents and diet was considered adequate. In the following decade coronary artery disease developed and the mother died in 1970 at the age of 52 years. The mother's father and sister also suffered maturity onset diabetes.

Case 8 was found at birth to have short malformed lower limbs. When seen at this hospital at the age of 1 year she was noted to have a marked proximal deficiency of both femora. The distal fifth of the left

femur and the distal three-fifths of the right were visible on x-ray. A capital epiphysis on the right was located in the acetabulum. One metatarsal and toe on the right and two metatarsals and toes on the left were absent. Following prolonged traction and left knee arthrodesis she became mobile on artificial limbs. Apart from her limb malformations she was healthy. She was found during her first pregnancy to have a small distorted pelvis necessitating elective caesarian section. This child and her two subsequent offspring are normally developed. The youngest, aged 10 months, required surgery in infancy for pyloric stenosis.

On review at the age of 32 years case 8 was found to have normal facies apart from a rather short philtrum.

(2C) UNCERTAIN AETIOLOGY

Case 9 (male)

Case 9 was born in 1975. His mother, who later developed severe rheumatoid arthritis, had had one

previous pregnancy 7 years earlier resulting in a normal female. The pregnancy with case 9 was unremarkable. At birth severe malformations were evident involving both lower limbs, but worse on the left. At review at the age of 7 years, the following anomalies were found: sacral agenesis, a soft tissue web in the left groin associated with coxa vara, and proximal femoral deficiency. The left femur was 11 cm shorter than the right and there was fixed flexion at the knee. The left fibula was absent (fig 8a). There was bilateral posterior dislocation of the radial heads. His record showed that bilateral orchidopexy and adenoidectomy had been performed in 1981 and 1982, respectively.

Although listed in the 'normal face' category fig 8b and c shows that micrognathia was evident at 7 years, associated with a cleft uvula. The facial appearance was otherwise unremarkable.

Case 10 (female)

Case 10 was born in 1972, the second child of a 28 year old mother and 29 year old father. During the pregnancy, persistence of breech position was noted. The mother commented at the time on a lesser degree of movement than during her previous pregnancy, and the fetal head remained in the right hypochondrium. Loss of liquor began at 34 weeks and persisted in small quantities until delivery at term. An attempt at manual version failed. The mother was not diabetic and has not since become so.

On examination at the age of 7 years, case 10 was

found to be of normal facial appearance and normal intelligence. Her thighs were short and bowed with bilateral femoral hypoplasia evident on x-ray. The femoral head on the left articulated with the ilium. On the right the distal femoral and proximal tibial epiphyses were abnormal. In addition she had amelia of the left upper limb, the right upper limb being normal.

Case 11 (female)

Case 11 was born in 1967, the only child of a 25 year old mother and 28 year old father. The mother suffered a heavy but brief blood loss at 2 months' gestation. There was persistent breech presentation and little recognisable intrauterine movement. Delivery was at 39 weeks with forceps assistance after a 29 hour labour. The proband weighed 2.73 kg and was initially thought only to have 'club feet', but was then diagnosed as having dislocated hips and placed in an abduction splint. On examination the femoral heads were in the acetabulae, but both femora were found to be short. There was lateral bowing with overlying dimpling. Early photographs suggested a long philtrum but subsequent examination revealed the reverse, with a short philtrum and long nose.

Cases 12 and 13 (male, female)

Cases 12 and 13 had unremarkable antenatal histories. In each case the facial appearance was normal, while proximal femoral hypoplasia resulted in severe proximal shortening of the lower limbs. Case 13

FIG 8 Case 9. (a, b, c) Asymmetrical femoral hypoplasia together with sacral agenesis. The face is listed as 'normal' in that the nose and philtrum are unremarkable, though micrognathia is evident with an associated cleft uvula. Some degree of micrognathia is often associated with sacral agenesis or 'caudal regression', but does not constitute a diagnosis of femoral hypoplasia-unusual facies syndrome.

had the additional features of absence of the right fibula and a left pseudarthrosis.

Discussion

Our findings suggest that the femoral hypoplasia-unusual facies syndrome is a recognisable entity. It is of interest that Lord and Beighton,⁴ who questioned the existence of this syndrome, did not refer to the patient reported by Bailey and Beighton in 1970,⁶ who was described as having cleft palate and bilateral femoral dysgenesis. This young lady, from the published photograph, had very similar physical features to one of the cases reported by Daentl *et al.*¹ This difference of terminology probably accounts for the absence of this case, and the two reported by Burck *et al.*,⁷ from the review of Pitt *et al.*² Also omitted was the report by Graviss *et al.*,⁸ under the title 'Proximal femoral focal deficiency associated with the Robin anomalad'. The term 'proximal femoral focal deficiency' is well established in orthopaedics and it is reasonable to retain this in cases of isolated femoral defect. Similarly, the term femoral hypoplasia has now gained acceptance, even though 'dysgenesis' or 'dysplasia' might be considered preferable terms.

Femoral hypoplasia-unusual facies syndrome must remain a descriptive term as it would appear that cases with very similar clinical and radiological features may have differing causes. We report one child where severe intrauterine compression owing to oligohydramnios appeared to be the sole cause of the syndrome, though this is probably a rare explanation. Our finding of four cases associated with maternal diabetes, on the other hand, suggests that this is a frequent cause of the syndrome. This finding adds weight to the view that femoral hypoplasia-unusual facies syndrome is part of the spectrum of diabetic embryopathy or, to use the more recent terminology, maternal diabetes disruption. This would make the femoral hypoplasia-unusual facies syndrome and sacral agenesis differing manifestations of the caudal regression syndrome.⁹ The features of case 9 confirmed this relationship since this child had sacral agenesis and vertebral anomalies together with severe femoral and lower limb involvement, a small mandible, and a cleft uvula.

Graviss *et al.*⁸ suggested that the 'unusual face' was merely the typical face of Robin anomalad, now Robin sequence. The basis of this sequence is a small mandible. This causes the tongue to be posteriorly placed and often to interfere with closure of the palatal shelves. The mandible may fail to grow due to a genetic defect in the first branchial arch, or due to disruption by, for example, maternal

diabetes. Growth of the mandible may be prevented by extreme flexion of the neck, such as can occur with oligohydramnios, so that some cases of Robin sequence are due to deformation. A short nose and long philtrum may be associated with Robin sequence but are distinct from it. They imply disturbance of growth of the frontonasal and maxillary processes, particularly the medial nasal process of the former. Case 5 illustrates how a small mandible may be impressive in the neonate but, with the passage of time, abnormal development of the midface to produce the long philtrum and pinched nose accounts for the 'unusual face'.

The murmur of pulmonary stenosis and the episode of right heart failure in case 1 may have resulted from a degree of lung hypoplasia owing to the prolonged loss of liquor. None of the five children with the classical femoral hypoplasia-unusual facies syndrome had heart murmurs. Taking from published reports only those with a typical face, normal spine and sacrum, and bilateral femoral involvement there is also no case of heart malformation, whereas cardiac defects are common in association with sacral agenesis and those 'mixed' cases with spinal and femoral involvement. In the diabetic cases this may reflect a different timing of the insult.

The striking analogy between these clinical observations and experiments on chickens is worthy of note. Landauer^{10,11} in the 1940s showed that injection of insulin into the yolk sac could produce a syndrome of short upper beak with proximal limb defects closely analogous to the femoral hypoplasia-unusual facies syndrome (fig 9). If the injection was performed earlier, rumplessness was produced. This was characterised by absence of the sacrum, similar to that seen in the more classical caudal regression syndrome. Landauer postulated that the disturbance of glucose metabolism affected metabolic pathways common to proximal limb bud and facial development. The defect could, in addition, be more easily provoked in some strains than others. Chickens could be bred which were particularly sensitive to the insulin injection and in these supplementation of the diet with nicotinamide greatly reduced the frequency of malformation. It is plausible to suggest that, as the chicken, disturbance of glucose pathways in early development may produce the features of this syndrome, but that some genetic predisposition is also essential.

In a review of the subject, Landauer¹² repeated his belief that insulin had direct teratogenic effects in the chicken. In humans, however, the relationship between poor control and frequency of malformations suggests that instability of glucose homeostasis is more detrimental than the presence of exogenous insulin. Case 8 is important in this regard. The

FIG 9 Experiments by Landauer^{10 11} which showed that the timing of an injection of insulin into the yolk sac determined whether rumplessness or short upper beak were produced. These patterns of malformation are very similar to the sacral agenesis and femoral hypoplasia-unusual facies syndromes seen in man.

mother had symptomatic diabetes mellitus during pregnancy, but was not diagnosed or treated until after delivery of the proband. The rarity of limb malformations in the offspring of diabetic mothers suggests that, as in the chicken, there is genetic variation in susceptibility. The protective effect of nicotinamide in chickens prone to malformation raises the intriguing question of whether similar supplements might be beneficial for diabetic women. To establish a protective effect would require a study of such proportions, however, that effort would be better devoted to improving the provision of good antenatal care for women at risk.

Though probably not completely analogous, the experiments in the developing chicken lend support to the belief that in pregnancies at risk from maternal diabetes, the involvement of the proximal femora

and maxilla, rather than the sacrum and vertebral column, is determined by the later timing of an abnormal fluctuation in glucose homeostasis. The low prevalence of these skeletal anomalies among the offspring of diabetic mothers implies, in addition, genetic variation in susceptibility, as was seen in the chicken. The pattern of malformation suggests that the proximal lower limb buds and the first and second branchial arches share in common developmental pathways liable to disturbance. In cases attributed to deformation or disruption, the risk of recurrence will be substantial in cases of maternal uterine anomaly, such as bicornuate uterus, and with persistently bad diabetic control in a mother.

There were no familial instances in the 13 cases reported, but on the basis of Lampert's report³ it is likely that, in some cases at least, the condition is

autosomal dominant. The possibility of fresh mutation accounting for some or all of the six patients of unknown aetiology remains a possibility, but in general the recurrence risk in the offspring of this group is likely to be small. It is possible that the risk will be greater to the offspring of those, such as cases 2 and 3, who have the full syndrome with facial involvement.

In summary, it is postulated that bilateral femoral hypoplasia, with or without an unusual face, is a heterogeneous condition with three aetiological categories identified to date. The descriptive term 'femoral hypoplasia-unusual facies syndrome' is valid and is of clinical value.

Reproduction of fig 9, with permission, from the review by Hadorn E. *Developmental genetics and lethal factors*. London: Methuen, 1961: 241 (translated by U Mittwoch).

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