Osteoporosis-pseudoglioma syndrome with congenital heart disease: a new association

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SUMMARY We report a sibship of two brothers and one sister with the osteoporosis-pseudoglioma syndrome and congenital heart disease. They presented in infancy with visual impairment and psychomotor retardation. Major features included bilateral cataracts, generalised osteopenia, severe platyspondyly, borderline mental retardation, muscular hypotonia, joint laxity, and ventricular septal defect. Parental consanguinity and affected sibs of both sexes strongly suggested autosomal recessive inheritance. Analysis of the present and previously reported cases showed a wide range of interfamilial variability which may point to the existence of multiple allelism or genetic heterogeneity in this syndrome.

The osteoporosis-pseudoglioma syndrome is a rare genetic disorder comprising early generalised osteoporosis, visual impairment, muscular hypotonia, and joint laxity. Probably the first instance of the condition was reported in 1931 by Pellathy.¹ Since then another 29 patients from 10 families have been described.²⁻¹⁴ Some of these families^{2,3} were later described in more detail.^{5,6} Of the 11 reported families, eight were from Mediterranean countries. We report here an Arab family with three affected sibs with the osteoporosis-pseudoglioma syndrome and congenital heart disease and some other previously unrecognised findings.

Case reports

CASE 1

The proband was a five year old disabled boy when examined in August 1985. He was referred because of visual impairment and psychomotor retardation and had a brother and a sister with the same condition. Their parents were phenotypically normal first cousins from Oman. Both were 30 years old and had an older daughter and son who were reported to be normal. No-one in the last four generations of the family had a similar problem. The proband and his affected brother and sister were all born normally at term after uneventful pregnancies with unremarkable neonatal histories, though floppiness was noticed in the first few months of life.

The proband had a visual problem suspected at the age of four months and bilateral cataracts were diagnosed and operated upon when he was six months old. Subsequently, little improvement in his vision was noticed but in the last two years further deterioration has occurred. He sat at the age of 18 months and could crawl at 20 months. However, he can not walk, can only stand with support, and moves around on his bottom because of inability to bear his weight. Recently, he had a fractured femur after a fall from bed.

On examination he had stunted growth with height 91 cm, weight 10 kg, and head circumference (OFC) 50 cm. He had normal craniofacial features, yellow teeth, short, collapsed spine, barrel shaped chest with sternal bulge, protuberant abdomen with no hepatosplenomegaly, and hyperextensible joints more pronounced in the hands and feet. Muscles were generally hypotonic with a mild degree of wasting in both upper and lower limbs but no limitation of movement. Neurological examination showed no abnormality. IQ using the Griffiths mental developmental scale was 60. Cardiovascular examination revealed a pansystolic murmur heard maximally at the lower sternal edge suggestive of ventricular septal defect, thought to be a large one on ECG and echocardiography. Hearing and speech were normal. Eye examination showed blue sclerae, normal sized globes, nystagmus, bilateral cataracts (needing to be reoperated), cloudy vitreoretinal structures, and very poor vision.

Skeletal radiographs showed generalised severe

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FIG 1 (a) Case 1. Radiograph showing severe osteopenia, coarse trabecular structure of both femora with thin cortex, and wide femoral necks. (b) Radiograph of the right femur showing a recent supracondylar fracture.

osteopenia, coarse trabecular structure of long bones, thin cortex, and wide femoral necks (fig 1a). The left capital humeral epiphyses showed subluxation with evidence of recent supracondylar fracture of the right femur (fig 1b). Skull bones were flattened and thin with early closure of cranial sutures and no wormian bones (fig 2). The spine showed biconcave end plates and severe platyspondyly starting in the thoracic region (fig 3). Chest x ray showed cardiomegaly resulting from congenital heart disease. The bone age was normal.

Haematological and biochemical investigations showed a mild degree of iron deficiency anaemia and normal calcium, phosphorus, magnesium, and urinary excretion of calcium. Serum alkaline phosphatase was moderately raised. Creatine kinase (CK) levels and plasma and urine amino acid analysis were normal. Routine urine analysis was normal. Urine screening for reducing substances and mucopolysaccharides was negative.

CASE 2

A brother of case 1, also disabled, was examined at the age of three years. His psychomotor development was slightly delayed. He began to cruise and walk with support at the age of 18 months but he is now unable to do this and moves around on his

bottom. At the age of two years, a cataract in the right eye was diagnosed and surgery performed.

On examination he showed short stature with height 85 cm, weight 10 kg, and OFC 48 cm. Features were similar to those of his brother with VSD (diagnosed clinically) but with normal coloured teeth, a slightly better muscle tone, and an IQ of 70. Eye examination also showed blue sclerae, normal sized globes, and bilateral cataract (the right eye showing recurrent cataract). Vitreoretinal structures were cloudy and vision was very poor. Skeletal radiographic findings were similar to case 1 but less severe (figs 2, 3, and 4). The same investigations as performed in case 1 showed similar findings.

CASE 3

A sister of cases 1 and 2 presented at 15 months of age. She showed slightly delayed psychomotor milestones. She sat at nine months, crawled at one year, and now can stand with support only.

On examination her height was 72 cm, weight 8.5 kg, and OFC 43.5 cm. Features were similar to cases 1 and 2 with a VSD (diagnosed clinically) and an IQ of 75 to 80. Radiological manifestations were milder (fig 3). Eye examination showed whitish sclerae, normal sized globes, and bilateral cataract with poor vision.

(a)

(b)

FIG 2 Skull radiographs showing thin skull bones with early closure of cranial sutures in (a) case 1 and (b) case 2.

FIG 4 Case 2. Chest radiograph showing cardiomegaly.

Routine investigations showed a moderately raised alkaline phosphatase as in cases 1 and 2.

Further studies on the three affected sibs were not possible because the family decided to return to their home country. The findings in the three patients are summarised in the table.

Discussion

Osteoporosis-pseudoglioma syndrome (OPS) is a well delineated autosomal recessive disorder.¹⁵ As

(a)

(b)

(c)

FIG 3 Lateral spine radiographs showing severe progressive osteopenia, platyspondyly, and biconcave end plates in (a) case 1, (b) case 2, and (c) case 3.

TABLE Findings in the three patients affected with osteoporosis-pseudoglioma syndrome.

Findings	Case 1	Case 2	Case 3
Sex	M	M	F
Age (y)	5	3	1½
Eye findings			
Poor vision	++	++	+
Cataract	+	+	+
Vitreous clouding	+	+	?
Nystagmus	+	-	-
Blue sclerae	+	+	-
Radiological findings			
Osteoporosis	++	+	+
Platyspondyly and biconcave end plates	++	++	+
Flattened skull bones	+	+	+
Early closure of cranial sutures	+	+	?
Fractures	+	-	-
General findings			
Short stature	+	+	+
Borderline intelligence/mild MR	+	+	-
Microcephaly (-2 SD)	-	+	+
Muscular hypotonia	+	+	+
Hyperextensible joints	+	+	+
Short spine	++	+	+
Barrel shaped chest	+	+	+
Discoloured teeth	+	-	-
Alkaline phosphatase abnormality	+	+	+
Congenital heart disease (VSD)	+	+	+

the name implies, OPS has two major components: the x ray evidence of osteoporosis and the 'pseudogliomatous' changes in the eyes. These two components have been considered to be the minimal diagnostic criteria for OPS.¹³ Minor components which are not consistently reported include short stature, mental retardation, muscular hypotonia, joint laxity, and other anomalies.

The manifestations of OPS are in general highly variable. In all reported cases, radiographs showed generalised osteopenia with decreased bone density, coarse trabecular structure, and thin cortex. These findings are of variable severity with or without fractures and deformities. Vertebral anomalies, which include variable degrees of platyspondyly, concave end plates, and kyphoscoliosis are present in most cases. Wormian bones have been reported in some cases.^{8-10 12}

Our cases have a severe degree of osteoporosis more noticeable in the oldest, with fractures but with no deformities of long bones. They also showed progressive and severe platyspondyly with biconcave end plates of a severity never reported previously in children with OPS.

Our cases showed no wormian bones but they did have early closure of the cranial sutures, a new finding in OPS patients which may explain the microcephaly in some cases. Recently¹³ it was suggested that microcephaly is relative rather than absolute in relation to height, but in one of our cases it seems absolute.

Eye findings in OPS are highly variable and non-specific, though visual impairment appears to be a constant manifestation. Out of 32 cases reported so far, only one case has had normal vision.⁹ Some cases have congenital blindness and others have blindness of later onset. The eye manifestations may include microphthalmia, anterior chamber anomalies, cataracts, vitreoretinal anomalies, or phthisis bulbi. Our patients had poor vision, cataracts, and vitreoretinal clouding but no microphthalmia. Two of our cases had blue sclerae, a previously unrecognised finding in OPS patients reported so far.

Short stature is a common manifestation in OPS patients of various ages with or without skeletal deformities. Our cases are short with a short trunk relative to the lower limbs, as has been described previously in OPS.^{4 9}

Intelligence is normal in most cases and mental retardation when present is of mild to borderline degree.^{1 8 9} Our cases show mild to borderline mental retardation which might be attributed in part to their poor vision and lack of external stimulation.

Muscular hypotonia and joint laxity have been recorded in about half of OPS patients¹³ and are thus probably integral components.⁸

Results of blood chemistry have usually been normal except for hypercalciuria and slight hydroxyprolinuria in one patient studied.⁴ Increased bone resorption and depressed bone formation with normal width of osteoid tissue were also reported by the same authors. Our cases had moderately raised alkaline phosphatase levels indicating an active process in the bone which includes increased breakdown. Such a rise is also present in patients with osteoporosis resulting from osteogenesis imperfecta.¹⁶

Congenital heart disease has not been a known association of OPS. However, our three patients showed congenital closure defect (VSD) with cardiomegaly. This association may not be fortuitous and could indicate defective collagen synthesis during morphogenesis, continuing thereafter to involve the tissues of the eye, bone, muscle, and skin. In OPS, the pattern of bone disease and its progressive nature bears a resemblance to osteogenesis imperfecta.

Additional features in common between OPS and osteogenesis imperfecta in our family are the blue sclerae and raised alkaline phosphatase levels. Our cases were diagnosed initially as atypical osteogenesis imperfecta with ocular involvement, a situation similar to an Indian family recently reported from South Africa.¹² This family was in fact an example of OPS.^{14 17} Another earlier family with multiple fractures and blindness, but with incom-

plete ophthalmological reports, was also reported as atypical osteogenesis imperfecta.¹⁸

In OPS, the wide range of interfamilial variability and the different associations may point to multiple allelism or to genetic heterogeneity. In general, autosomal recessive inheritance seems proven^{13 15}; the present family, with parental consanguinity and affected sibs of both sexes, is consistent with this form of inheritance and may represent a new form of the disease.

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