New X linked spondyloepimetaphyseal dysplasia: report on eight affected males in the same family

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Abstract
We report on a probably new form of spondyloepimetaphyseal dysplasia (SEMD) with an X linked inheritance pattern. Eight males were affected in the same family. We were able to examine three adult patients and we studied the skeletal radiological aspect of one of these patients at 2 years 6 months and at 9 years of age. The main clinical features are severe short trunked dwarfism, brachydactyly, normal facies, and normal intelligence. Radiologically, the diaphyses of all the long bones are short and broad. The epiphyses of the distal portion of the femora and those of the proximal and distal portions of the tibia are embedded in their metaphyses and there is marked narrowing of the intercondylar groove. There is moderate platyspondyly. Several vertebrae show an anterior tongue in infancy and severe irregularities of the upper and lower surfaces are present in adulthood. The 11th or 12th thoracic vertebra is wedge shaped. The pelvis is narrow. The distal ulnae and fibulae are disproportionately long. The hands show radial deviation and brachydactyly is present in the hands and feet. This X linked SEMD was not detectable at birth.

Case reports
We were able to examine V.8 at 52 years, V.9 at 49 years, and VI.2 at 25 years of age. At 13½ years, VI.2 was diagnosed by a German orthopaedic surgeon as having pseudoachondroplasia and had grown 21 cm by 15 years of age. At the time of examination, V.8 measured 110 cm, V.9 109 cm, and VI.2 131 cm. The patients had a normal facial appearance, short stature, shortening of the trunk, pectus carinatum, moderate limitation of elbow extension, dorsal projection of the distal end of the ulna, short hands with radial deviation, and short feet (figs 2 and 3). Pregnancy, delivery, birth weight, and birth length was unremarkable in all the patients. They began walking at 15 to 16 months. Disproportionately short limbs were diagnosed at about 2 years of age. All the patients had normal intelligence. No associated extraskeletal anomalies were noted. Routine haematological, biochemical, hormonal, and cytogenetic studies gave normal or negative results. Mucopolysacchariduria and amino acids in plasma and urine were normal. No ocular abnormalities were present. The mothers of V.3 and VI.2 had moderate pectus carinatum and the dead mothers of the other patients had also had this defect.

Radiographical features
We describe the radiological skeleton changes in VI.2 at 2 years 6 months and at 9 years of age, and those present in V.8 and V.9 at 52 years and 49 years of age, respectively. Similar radiographic bone changes were observed in V.8 and V.9.

Skull
This was nearly normal. Mild maxillary hypoplasia was present in all the patients.

Figure 1  Family pedigree. Horizontal bar over symbol, personally examined.
Figure 2  V.9 at 49 years. (A,B,C) Patient's appearance.

Odontoid process
This was slightly hypoplastic in all the patients.

Spine, anterior view
Moderate platyspondyly was present; the interpedicular distance between the first and fifth lumbar vertebrae was normal at all ages. In adulthood, degenerative changes were observed (figs 4 and 5).

Spine, lateral view
At 2 years 6 months, VI.2 showed generalised mild platyspondyly, several vertebrae with an anterior tongue, and a hypoplastic 11th thoracic vertebra (fig 6). At 9 years, a severe kyphosis at the thoracolumbar junction with a wedge shaped 11th vertebral body was present (fig 7). V.8 and V.9 showed severe irregulari-
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hypoplasia of the femoral necks, and mild coxa valga (fig 9). In V.8 and V.9, the iliac bones were short in their craniocaudal dimension, the anterior iliac apophysis was hypertrophic bilaterally, and the femoral necks were very short (fig 10).

Upper limbs and hands
The humeri were short and broad with large metaphyses in all the patients. At 9 years, VI.2 showed short radii with cone shaped epiphyses in their distal portions, moderately long ulnae, and short and broad tubular bones of the hands. Cone shaped defects in ossification of the metaphyses accompanied by cone shaped epiphyses were seen in the metacarpals and proximal phalanges (fig 11). In V.8 and V.9, the distal ends of the radius were flared, the

Figure 6 V1.2 at 2½ years. Lateral view of the spine showing mild generalised platyspondyly, tongue-like anterior protrusion of the central portions of several vertebral bodies, and hypoplastic 11th thoracic vertebra.

ties of the upper and lower surfaces of the vertebrae and very hypoplastic wedge shaped 12th thoracic vertebra. The pedicles were short and there was increased angulation at the lumbosacral junction (fig 8).

Thorax and shoulders
The posterior ends of the ribs were moderately cupped. The scapulae were nearly normal and the clavicles were short. The upper humeral metaphyses were irregular.

Pelvis and hip joints
At 9 years, VI.2 showed hypoplastic iliac bones with horizontal acetabular roofs, severe

Figure 7 V1.2 at 9 years. Lateral view of the thoracolumbar junction showing kyphosis with wedge shaped 11th vertebral body.

Figure 8 V.8 at 52 years (A) and V.9 at 49 years (B). Lateral view of the thoracolumbar junction showing irregularity of the vertebral end plates and severely hypoplastic 12th thoracic vertebra (arrows).

Figure 6 V1.2 at 2½ years. Lateral view of the spine showing mild generalised platyspondyly, tongue-like anterior protrusion of the central portions of several vertebral bodies, and hypoplastic 11th thoracic vertebra.
ulna was dorsally subluxed and disproportionately long with a prominent ulnar styloid process bilaterally, there was radial deviation at the wrist, and the metacarpals and phalanges were short with metaphyseal widening and lack of trabeculation of their proximal and distal extremities (fig 12).

Knees
At 2 years 6 months, VI.2 had flared and irregular metaphyses and small, poorly ossified epiphyses with mildly fragmented margins. At 9 years, he had severe deformation of the condyle and central fusion of both femoral and tibial epiphyses within their metaphyses (fig 13). V.8 and V.9 had very large irregular metaphyses, markedly narrowed intercondylar groove, and mild osteoarthritic changes (fig 14).

Lower limbs
At all ages, the long bones had very short and broad shafts with severe metaphyseal irregularities, the fibulae were disproportionately long distally, and the distal tibial epiphyses
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were fused within their metaphyses bilaterally (figs 13 and 14).

_Foot_

In all the patients there was generalised shortening of the tubular bones with severe ossification changes in their extremities (fig 15).

**Discussion**

In recent years, a large number of distinct skeletal dysplasias have been delineated. Clinical, radiographical, genetic, and histopathological studies have allowed the identification of several types of SEMD. SEMD with joint laxity is characterised by severe dwarfism, oval facies, soft skin, articular hypermobility, and progressive spinal malalignment. This disorder has an autosomal recessive mode of inheritance.1

SEMD, Irapa type, is clinically detectable at birth; the affected children have severe, short trunked dwarfism, platyspondylly with tongue-like appearance of the vertebral bodies, pectus carinatum, increased lumbar lordosis, genu valgum, and shortness of the metacarpals and metatarsals. Autosomal recessive inheritance has been suggested.23

Spondylometepiphysial dysplasia (SMD), Strudwick type, is an autosomal dominant disorder characterised by short trunked dwarfism, normal facies, occasionally cleft palate, retarded ossification of the platyspondylly vertebral bodies, delayed epiphyseal maturation, “dapping” metaphyseal changes, and normally shaped hand and foot bones.4 Clinically and radiologically, this entity is indistinguishable from spondyloepiphyseal dysplasia (SED) congenita during infancy. There have been doubts about the distinction of the SEMD Strudwick type from SED congenita.5

SEMD with hypotrichosis is an autosomal dominant syndrome; the patients show congenital hypotrichosis associated with flared metaphyses, delayed epiphyseal ossification, and pear shaped vertebral bodies.6

Vichi et al7 have reported a female patient affected by severe dwarfism with symmetrical metaphyseal and epiphyseal changes, vertebral irregularities, disproportionately longfibulae, marked involvement of the iliac bones, and tarsal bone lesions.

Maloney8 has described two brothers and a third unrelated male with a distinctive type of SEMD. The patients showed short stature, hyperextensibility of the joints of the hands, bilateral club foot deformities, kyphoscoliosis, with wedged first lumbar vertebra, generalised mild platyspondyly, and minimal epiphyseal and metaphyseal irregularities.

Other bone dysplasias have major alterations in the epiphyses, metaphyses, and the spine, but have not been lumped under the term SEMD. Among them, a well known disorder is pseudoachondrodysplasia. This is usually detectable at 2 to 4 years of age through disproportionate dwarfism with relatively long trunk, short arms and legs, bowed knees, platyspondylly with tongue-like projections of the central portion of the vertebral bodies, delayed epiphyseal ossification, and metaphyseal irregularities.6,8,11 Almost all cases have an autosomal dominant inheritance pattern or represent new dominant mutations; cases previously reported as autosomal recessive inheritance represented parental mosaicism.12 However, some rare cases with autosomal recessive inheritance may exist.

Cone shaped epiphyses of the phalanges are common and have been reported in a large number of bone dysplasias,13 while the conical deformation of the epiphyses involving both the femora and the tibiae are very rare. Both in metaphyseal acroschydysplasia with severe brachydactyly and in metaphyseal trichoscyphodysplasia with alopecia, severe metaphyseal...
changes associated with cone shaped epiphyses of the long bones have been reported.14-16

The patients affected by these two uncommon bone dysplasias also had flat facies, nasal abnormalities, sometimes mental retardation, but a normal spine. Autosomal recessive inheritance has been suggested.

Our patients had short trunked dwarfism, normal facies, and normal intelligence. Their peculiar radiographic features were: normal interpedicular distance between the lumbar vertebrae; moderate platyspondyly with tongue-like protrusions of the central portion of several vertebral bodies in infancy; wedge shaped 11th or 12th thoracic vertebra; irregularities of the upper and lower vertebral surfaces in adulthood; narrow pelvis; short and broad shafts of the long bones with large metaphyses and small, cone shaped epiphyses fused within their metaphyses; disproportionately long distal ulnae and fibulae; radial hand deviation; cone shaped epiphyses in the proximal phalanges of the hand bilaterally; and brachydactyly in the hands and feet. Surprisingly, our patients showed no severe osteoarthritic changes.

The inheritance pattern of the SEMD reported here appears to be X linked and is not clinically detectable at birth. It should be noted that the two living female obligate carriers show moderate pectus carinatum. From the family history it appears that the same feature was present in the other patients' mothers.

Unfortunately, there were not enough family members available for study to allow linkage analysis. In our opinion, the clinical, radiological, and genetic findings in these patients do not conform to any of the bone dysplasias so far delineated.

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