

# Spondyloepimetaphyseal dysplasia with multiple dislocations (Hall type): three further cases and evidence of autosomal dominant inheritance

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Three additional patients, including a father and daughter, with spondyloepimetaphyseal dysplasia and multiple dislocations are presented. This is the first report of dominant inheritance, with variable intrafamilial expressivity of this disorder. All patients showed facial dysmorphism with a short, broad, upturned nose. There were striking epiphyseal and metaphyseal changes of the long bones and joint laxity with multiple dislocations of the large joints, which were particularly incapacitating at the knees. This skeletal dysplasia showed some overlapping features with SPONASTRIME dysplasia, but with the addition of epiphyseal changes with abnormal articular bone modelling and premature osteoarthritis.

The spondyloepimetaphyseal dysplasias (SEMD) are a large group of disorders of variable severity, classified by their clinical and radiological manifestations. They are a genetically heterogeneous group of disorders.<sup>1,2</sup> A recently delineated form is SEMD with multiple dislocations (MIM 603546).<sup>3</sup> This is characterised by a generalised epiphyseal dysplasia, gracile metacarpals, a small carpus, and mild platyspondyly with vertebral end plate irregularity.

SPONASTRIME dysplasia, first described by Fanconi *et al*<sup>4</sup> in 1983, was further delineated by Langer *et al* in 1997<sup>5</sup> and falls into the SMD group of disorders. The word “SPONASTRIME” is a mnemonic from *spondylar* and *nasal* changes with *striations* of the *metaphyses*. Patients with SPONASTRIME dysplasia show striking midface and nasal hypoplasia. Characteristic changes in the shape of the vertebral bodies with time are the most consistent diagnostic criteria. Inheritance is autosomal recessive.

Patients with SEMD with multiple dislocations and patients with SPONASTRIME dysplasia both have metaphyseal irregularity and develop sclerotic, short, longitudinal striations in the metaphyses.

## CASE REPORTS

### Case 1

Case 1 was the first child of healthy, unrelated parents of normal stature. Birth weight was 3100 g at 41 weeks' gestation following induction of labour and a normal delivery. There was stridor soon after birth and at about 6 months short stature was noted. He underwent a laryngotracheal reconstruction. At 13 months of age his height was 65.4 cm (<3rd centile) and weight 7.6 kg and he was disproportionate with rhizomelic short stature, the limbs being –4 SD below the mean, whereas his crown rump length was only –2 SD below the mean. He always appeared slightly weak with hypermobile hips and knees. He had some dysmorphic features with a short neck, a large head, a flat midface, a depressed nasal bridge, anteverted nares, small, rotated ears, and an unusual skin crease over the mid-forearms (fig 1A). He also had nail dysplasia.

He started sitting at 7 months, walking at 18 months, and complained of some pain in the knees on walking. He

developed subluxation of the knees after starting to walk and had marked joint laxity. His global development corresponded to his chronological age but speech was slightly delayed. This has significantly improved with speech therapy and attending nursery. Cranial MRI scan, EEG, VEP, ERG, and eye examination were normal at this time. He underwent bilateral grommet insertion after recurrent middle ear effusion and mild conductive hearing loss of about 20 dB bilaterally.

From 2 years of age he received daily growth hormone treatment of 30 U/m<sup>2</sup> weekly based dosage for his growth retardation. By the age of 5 years he was 95.2 cm tall (still below the 3rd centile) and had developed a lower thoracic kyphosis. His mobility was restricted because of a progressive “wind swept” deformity of his lower limbs with 30° valgus of the left knee and 16° varus of the right for which he underwent bilateral corrective osteotomies.

Radiologically, at 1 year of age there was a severe epiphyseal dysplasia with absent ossification of the carpal centres (fig 1B) and capital femoral epiphyses (fig 1C) and small, flattened epiphyses at the knees (fig 1D). At this age the femoral necks were long, slender, and tapered proximally. By the age of 5 years, there was a mild thoracic kyphosis and thoracolumbar scoliosis. The thoracic vertebral bodies were pear shaped, being slightly constricted posteriorly, and in the lumbar region there is posterior scalloping and mild vertebral end plate irregularity. L4 and L5 were low set between the iliac wings and the interpedicular distances failed to widen in the normal manner (fig 1E). The femoral necks remained long and slender (fig 1F). The epiphyses were small and flattened but at the knees the metaphyses were flared and irregular with sclerotic longitudinal short striations (fig 1G). The MRI scan showed that the metaphyseal irregularity was related to longitudinal cartilage rests extending into the metadiaphyses (fig 1H). By the age of 7 years, the characteristic hand changes were apparent with short, gracile metacarpals, small, flattened, delayed phalangeal epiphyses with some ivory epiphyses and cupped metaphyses. The tufts of the distal phalanges were prominent. There was ossification of only the capitate and hamate. These were small and the overall size of the carpus was reduced. The distal radial epiphysis was flattened and the adjacent metaphysis irregular with short sclerotic striations (fig 1I).

### Case 2

Case 2 was born to unrelated parents following assisted conception and is the daughter of case 3. This twin pregnancy and delivery was uncomplicated and no intrauterine femoral length discrepancies were noted. Her non-identical twin sister is normal. Her psychomotor milestones were within the normal range. At 3 years, she was noted to be proportionately short. Her height was 77.5 cm (3rd centile) with upper segment 47.5 cm (–3 SD) and lower segment 31 cm (–3 SD). Her head circumference was 50.2 cm (90th centile). She had a waddling gait and could not run. She had a protruding sternum with prominent costochondral junctions. Elbows and



**Figure 1** (A-I) Case 1. (A) Facial appearance, aged 5 years. (B-I) Radiographs. (B) Hand, aged 1 year. (C) Pelvis, aged 1 year. (D) Knee, aged 1 year. (E) Spine, aged 5 years. (F) Pelvis, aged 5 years. (G) Knees, aged 5 years. (H) MRI of knee, aged 5 years. (I) Hand, aged 7 years.

hips were in fixed flexion of 5-10° and wrist, knee, and ankle joints were prominent and hyperextensible with marked joint laxity. She had pronounced facial dysmorphism with midface hypoplasia, a broad face, a flat nasal bridge, a short upturned

nose, and a broad nasal tip (fig 2A). By 4 years 9 months her lower segment measurement was -4 SD although the upper segment remained at -3 SD. She could walk only very slowly with a high stepping gait and had developed (in contrast to



**Figure 2** (A-H) Case 2. (A) Facial appearance, aged 3 years. (B-H) Radiographs. (B, C) AP/lateral spine, aged 3 years. (D) Pelvis, aged 3 years. (E) Knees, aged 3 years. (F) Knees, aged 6 years. (G) MRI of knee, aged 6 years. (H) Hand, aged 3 years.

her father) a pronounced lumbar lordosis. The hip joints were held in 5-10° flexion and external rotation. There was subluxation of both knees with laterally displaced patellae and the legs were bowed. There was mild brachydactyly. Plasma

calcium, phosphate, alkaline phosphatase, growth hormone levels, thyroxine stimulating hormone, and thyroxine were within the normal ranges. Chromosome analysis showed a normal female karyotype.



**Figure 3** (A-E) Case 3, aged 41 years. (A) Facial features. (B-E) Radiographs. (B) Lateral spine. (C) Pelvis. (D) Knee. (E) Hand.

Radiologically, at the age of 4 years, there was mild generalised platyspondyly with some irregularity of the vertebral end plates. In the thoracic region, the vertebral bodies had a distinctly pear shaped configuration on the lateral view with some posterior constriction and on the AP view appeared rather narrow with mild scoliosis. The interpedicular distance failed to widen in the normal manner in the lumbar spine and L5 was low set between the iliac wings. There was also some mild lumbar posterior scalloping of the vertebral bodies and

anterior wedging of L2 (fig 2B, C). The femoral necks were unusually slender and tapered and the capital femoral epiphyses were small and flattened (fig 2D). The long bones showed quite striking metaphyseal irregularity especially around the knees where there was some flaring and sclerosis. There was a mild genu varum deformity. All the epiphyses were small and flattened and the epiphyseal plates were narrowed (fig 2E). These changes were more striking by the age of 6 years and the metaphyses now showed short longitudinal

sclerotic striations (fig 2F). MRI at this age showed that the metaphyseal irregularities were the result of cartilage rests (fig 2G). At 4 years of age, in the hand there was absent ossification of the carpal centres with delayed ossification of the epiphyses. The metacarpals were rather short and slender. There was mild metaphyseal irregularity of the distal radius (fig 2H).

### Case 3

Case 3 is the father of case 2, aged 41 years. He presented with short stature (156 cm) with a normal trunk and upper limbs, short lower limbs, and marked upper segment/lower segment disproportion. His parents were of normal stature and had no dysmorphic features. His head was relatively large and he had facial dysmorphism similar to his daughter. His face appeared coarse with prominent supraorbital ridges, midface hypoplasia, and a large, square chin. He had a depressed nasal bridge, a short upturned nose, a broad nasal tip, anteverted nares, and a long philtrum (fig 3A). He had stiff hips, clicking knees and elbows, and generalised muscle aches. His gait was slightly deliberate and broad based. There was no increase in the normal lumbar lordosis, in contrast to his daughter, and his knees were straight with only mild laxity. Elbows and hips were held in 5-10° fixed flexion and the hips were externally rotated. His hands were broad with some brachydactyly owing to short distal phalanges. He was of normal intelligence and was able to perform heavy manual work on a building site but complained of some hip pain.

Radiologically there was mild generalised platyspondyly with biconcave vertebral bodies. The lumbar pedicles were short (fig 3B). L5 was low set between the iliac wings. The femoral necks were short bilaterally and were also extremely slender. The greater trochanters were high riding (fig 3C). There were severe changes of osteoarthritis affecting the knees, elbows, and wrists with abnormal modelling secondary to abnormal epiphyseal development. In particular at the knees the femoral condyles were flat and the tibial plateaux were flat because of absence of the tibial spines (fig 3D). In the hands, the metacarpals were unusually slender. The carpus overall was small and the carpal bones of the proximal row were particularly small and irregular. The distal phalanges were short but with rather prominent tufts (fig 3E).

### DISCUSSION

The clinical and radiological features of three cases with SEMD with multiple dislocations are presented. There have only been five previously published cases.<sup>3-5,6</sup> The dysmorphic features of these three cases are similar to those also seen in SPONASTRIME dysplasia. The radiological findings of cases 1 and 2 are identical to those of previously published cases, which have all been children without long term follow up.<sup>3</sup>

The radiological findings in case 3 are those of SEMD with multiple dislocations in an adult. These have not previously been described. They show some similarities to those of SPONASTRIME dysplasia, with markedly biconcave vertebral bodies and mild metaphyseal striations. However, there is also evidence of significant epiphyseal involvement with abnormal modelling of articular surfaces and premature osteoarthritis of the knees, wrists, and elbows. These epiphyseal changes are

not features of SPONASTRIME dysplasia.<sup>5</sup> He also has asymmetrical, short, slender femoral necks, a reduced overall size of the carpus, and slender metacarpals, all features of SEMD with multiple dislocations.<sup>3</sup>

The skeletal dysplasia in cases 2 and 3 appears to be inherited in an autosomal dominant manner although X linked dominance cannot be excluded. Other published cases of SEMD with multiple dislocations have all been sporadic. This is in contrast to SPONASTRIME dysplasia, which is inherited in an autosomal recessive manner. The dysmorphic features of the two conditions are virtually the same. The radiological findings show some similarities, with sclerotic irregular striated metaphyses and changes in the spine, but differ in the severe epiphyseal involvement and diagnostic appearances in the hands in SEMD with multiple dislocations. Both conditions show changes over time. In SPONASTRIME dysplasia there is severe platyspondyly in infancy and early childhood. This gradually improves leaving only mild platyspondyly with striking biconcave vertebral bodies in later childhood.<sup>7</sup> These changes are in contrast to the very mild platyspondyly and irregular vertebral end plates in SEMD with multiple dislocations in early childhood. We do not know at what age the biconcave appearance of the vertebral bodies, seen in case 3, develops.

Cases 2 and 3 show the range of severity of skeletal manifestations within a family, the daughter being more severely affected and more physically handicapped than the father. It is likely that the adult skeletal changes seen in case 3, the father, are at the mild end of a spectrum of abnormalities. This phenotypic intrafamilial variability is a common feature of autosomal dominantly inherited disorders.

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### REFERENCES

- 1 **International Nomenclature Group**. International nosology and classification of constitutional disorders of bone. *Am J Med Genet* (in press).
- 2 *Online Mendelian Inheritance in Man* (OMIM, database online) MIM 603546: John Hopkins University, Baltimore, MD.
- 3 **Hall CM, Elcioglu NH, Shaw DG**. A distinct form of spondyloepimetaphyseal dysplasia with multiple dislocations. *J Med Genet* 1998;**35**:566-72.
- 4 **Fanconi S, Issler C, Giedion A, Prader A**. The SPONASTRIME dysplasia: familial short-limb dwarfism with saddle nose, spinal alterations, and metaphyseal striation. *Helv Paediatr Acta* 1983;**38**:267-80.
- 5 **Langer LO Jr, Beals RK, Scott CI Jr**. Sponastrime dysplasia: diagnostic criteria based on five new and six previously published cases. *Pediatr Radiol* 1997;**27**:409-14.
- 6 **Camera G, Camera A, Pozzolo S, Costa P**. Sponastrime dysplasia: report on a male patient. *Pediatr Radiol* 1994;**24**:322-4.
- 7 **Offiah AC, Lees M, Winter RM, Hall CM**. Sponastrime dysplasia: presentation in infancy. *J Med Genet* 2001;**38**:889-93.