A new variant of spondylometaphyseal dysplasia with autosomal dominant mode of inheritance

J M GARCIA-CASTRO, C M ISALES-FORSYTHE, AND P DIAZ DE GARAU

From the Department of Pediatrics, Medical Genetics Section, School of Medicine, University of Puerto Rico, San Juan, Puerto Rico

SUMMARY Clinical and radiographic evaluation of an infant boy and his father revealed findings suggesting a new variant of spondylometaphyseal dysplasia with an apparently autosomal dominant mode of inheritance. The main clinical findings included short stature and marked ligamentous laxity in the infant. X-ray findings included severe and peculiar multiple metaphyseal involvement and striking vertebral under mineralisation in the infant, and platyspondyly in the father. However, all the epiphyses were normal. Laboratory studies were essentially normal except for an extremely raised serum alkaline phosphatase in the infant. The uniqueness of these findings suggests a new variant of the spondylometaphyseal dysplasias, distinct from the cases described initially by Kozlowski et al1 and subsequent investigators.

The nosology of skeletal dysplasias is badly in need of elucidation. Among these, spondylometaphyseal dysplasia is one of the most difficult to classify. In 1967, Kozlowski et al1 differentiated this entity from that of Morquio, noting the differences in clinical, radiographic, and metabolic findings. Various authors have since reported other cases of spondylometaphyseal dysplasia which were so varied in their manifestations that the possibility arises of multiple alleles in such a heterogeneous condition.2–7 We recently had the opportunity to study a family segregating for this gene. The proband was initially evaluated at one month of age, at which time the diagnosis of a chondrodystrophy was considered. Evaluation of his father confirmed the condition as a spondylometaphyseal dysplasia, with clinical and radiological findings quite distinct from the types reported up to the present, with an autosomal dominant mode of inheritance.

Case reports

CASE 1

The proband, a male, was born on 6.2.79 in San Juan, Puerto Rico after an uneventful term pregnancy and delivery. The parents were non-consanguineous, with maternal and paternal ages at the time of conception of 22 and 30 years, respectively. There was no history of maternal drug ingestion during pregnancy. Birthweight was 2466 g and length was 45.7 cm. He was diagnosed as a normal newborn at that time. At 3 days of age he developed diarrhoea, subsequently diagnosed as being caused by pathogenic E coli, and because of persistence of symptoms after therapy he was referred to our institution. During this admission we were called for consultation on the presence of some dysmorphic features.

On examination the following findings were observed: naevus flammeus over the left superior eyelid; prominent nasal bridge with a globular and beaked tip to the nose; small mandible with a high arched palate; asymmetrical bell-shaped thorax with the left side more prominent; asymmetrical placement of the nipples, the left being higher; no heart murmurs; liver palpable 1 cm below the right costal margin; normal male genitalia with a right inguinal hernia; cutis marmorata; hypotonia and normal deep tendon reflexes. Both upper and lower extremities were externally rotated with marked hyperextension of the elbows and wrists, the latter being also extremely wide. Radial deviation of the hands with the thumb adducted over the palm and the fifth finger overriding the others was present. The fingers were thin and tapered distally. A most surprising finding was the degree of ligamentous laxity; the upper extremity could be rotated through almost 360° and the lower through 180° with the utmost ease and without any discomfort to the patient.
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Dermatoglyphic findings were not outstanding except for a distal loop hypothenar pattern bilaterally and a 'r' right axial triradius.

Laboratory findings included normal blood counts, urine analysis, serum electrolytes, blood urea nitrogen, and fasting blood glucose. Screening for urinary amino-acids and mucopolysaccharides was also normal. Serum calcium and phosphorus levels were 2.4 mmol/l and 1.7 mmol/l, respectively, both within normal limits. Serum alkaline phosphatase levels, however, were increased to 468 U/l.

The most important findings were obtained from the x-ray studies. There was complete absence of mineralisation of all the vertebral bodies (fig 1), and abnormal metaphyses at the glenoid, proximal and distal humeri, radii, ulnae, femora, tibiae, and fibulae. The metaphyses, particularly the distal radii and femora, showed widening and severe lack of

**FIG 1** Case 1 at one month of age. Anteroposterior view demonstrating lack of mineralisation of the vertebral bodies.

**FIG 2** Case 1 at one month of age: (a) severe proximal and distal involvement of the metaphyses of the upper extremity. Note particularly the abnormality at the glenoid; (b) blown-out and irregular metaphyses of the lower extremities, accompanied by marked tibiae varum.
mineralisation, producing a blown-out appearance (fig 2a, b). All of the epiphyses examined were normal.

Re-evaluation at one year of age revealed delayed motor developmental milestones: he could hold his head without difficulty, prop himself up with his arm, remain seated when seated, and stand with support, but he could not sit or stand by himself or crawl. However, his intellectual development seemed adequate: he was alert, recognised his parents, and had a normal vocabulary for his age.

His recumbent length was 69.5 cm with a sitting height of 42.5 cm. His weight was 8 kg and the head circumference was 46.2 cm. Inner and outer canthal distances were 2.5 and 7.2 cm, respectively. Physical findings were similar to those already described. He still had marked ligamentous laxity. Radiographically there was an improvement from the previous films in that the vertebral bodies, as well as the metaphyses, showed some ossification. Recent films taken at 2 years of age (fig 3a, b, c) showed an even greater improvement, and his motor and intellectual development was normal for his age. He had not had any major medical problems.

**CASE 2**

The patient's father, born on 15.1.48, was found to be similarly affected. He was the penultimate of nine sibs, none of whom has the dysplasia. He presented with short stature, his height being

*FIG 3 Case 1 at 26 months of age. Some visualisation of the vertebral bodies is now possible in the anteroposterior (a) and lateral (b) projections. (c) Improved, but still abnormal, x-ray of the lower extremities; slight bowing of the femora is present.*
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144·0 cm, symphysis pubis to floor was 71·3 cm, and sitting height was 81·3 cm. He was also barrel-chested and had severe genu valgum and pelvic tilt owing to a very shortened left leg (68·2 cm vs 82·7 cm on the right) which had been operated upon when he was 13 years old. Details of this surgical procedure were not available. The patient described an osteotomy being performed to correct the curvature of the femur. In addition, there was almost complete accidental amputation of the left hand. Dermatoglyphs, as in his son, were not informative except for a distal loop hypothenar pattern and a t′ axial triradius on the right. Bilateral sensorineural hearing loss was documented, 68 db on the right and 73 db on the left, which he stated had been present since birth. X-ray studies demonstrated a spondylometaphyseal dysplasia. The

FIG 4 Case 2. Lateral view of vertebral column of affected adult showing slight thoracic platyspondyly with cephalad progression.

FIG 5 Case 2. (a) Abnormal modelling of the proximal end of the humerus; (b) widened distal end of the radius with unusual persistence of the epiphyseal line of fusion; (c) abnormal modelling of the distal femora and shortening of the left femur, probably the result of an osteotomy performed when the patient was 13 years old. Femoral necks are shortened also.
vertebral bodies showed slight platyspondyly of the mid-thoracic vertebrae with cephalad progression (fig 4). No scoliosis or kyphosis was present. Abnormal modelling was seen of the proximal humeri, distal radii and ulnae, proximal and distal femora (fig 5a, b, c), and distal tibiae and fibulae. Femoral necks were short and wide. It is interesting to note that the epiphyseal line of fusion at the lower end of the radius was still visible (fig 5b).

Laboratory findings included normal screening for urinary amino-acids and mucopolysaccharides and normal serum calcium (2.1 mmol/l), phosphorus (1.0 mmol/l), and alkaline phosphatase (53 U/l).

Discussion

The classification of the spondylometaphyseal dysplasias, among many clinically similar bone dysplasias, was begun by Kozlowski et al in 1967. An autosomal dominant mode of inheritance is clearly indicated in our cases, and a de novo mutation in our case 2 is highly likely because no other family members are affected, except for his son (case 1), which argues against limited penetrance of the gene, and because of his birth order, the penultimate, when his father and mother were 49 and 37 years old, respectively.

The x-ray findings observed clearly establish this condition to be a spondylometaphyseal dysplasia. In contrast to some of the other spondylometaphyseal dysplasias, this one can be diagnosed during the first month of life, probably at birth, by clinical and x-ray findings, and perhaps even prenatally. The ligamentous laxity as well as the extremely unusual x-ray findings of lack of ossification of the vertebral bodies and of the metaphyses, with normal serum Ca and P and raised serum alkaline phosphatase levels on repeated samplings, clearly excludes the possibility of hypophosphatasia and distinguishes it from the other cases of spondylometaphyseal dysplasia so far recorded.

Also of interest in our case 2 was the presence of congenital auditory deficit, a finding not described in other reported cases of spondylometaphyseal dysplasia, but observed in metaphyseal chondrodysplasia of the Jansen type. Whether or not this is a specific finding in this syndrome remains to be determined. So far we have not been able to document hearing loss in our case 1, but it might still be too early to detect. Intellectual impairment is not a feature of this condition, though motor developmental milestones might be somewhat delayed. This has been reported in other cases. We speculate that this motor delay might be in part the result of ossification delay and ligamentous laxity. The poor ossification would seem to make the bone more sensitive to stress and other forms of stimuli, as perceived by osseous nerve terminals, which could in turn retard muscular development as a defence mechanism. This is a temporary delay until adequate mineralisation takes place, as is observed in our adult case 2, where no gross impairment of function is present except what might be caused by the short stature and unequal length of the lower extremities. This might have been the result of early surgery, since unequal length of the legs, if present, is only minimal in our case 1. We expect that our continued surveillance of this patient will clarify some of these issues.

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Requests for reprints to Dr José M García-Castro, Instituto de Genetica Medica, GPO Apartado 1764, San Juan, Puerto Rico 00936.
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J M García-Castro, C M Isales-Forsythe and P Díaz de Garau

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