Spondylo-mesomelic-acrodyplasia with joint dislocations and severe combined immunodeficiency: a newly recognised immuno-osseous dysplasia

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Abstract

A newborn girl is described with an association of spondylo-acrodyplasia, mild short limbed dwarfism without significant metaphyseal changes, joint dislocations, and severe immune system dysfunction. This association is distinct from other known immuno-osseous dysplasias, including Schimke dysplasia, ADA deficiency with osseous changes, and Omenn phenotype with short limbed dwarfism.

(J Med Genet 1997;34:854–856)

Keywords: spondylo-acrodyplasia; short limbed dwarfism; SCID

Case report

The proband, a female, was the first child of healthy, unrelated parents. The family history was unremarkable. She was born at term after an uneventful pregnancy and normal delivery. Short fetal extremities were detected by prenatal ultrasonography in the 20th week of gestation and confirmed at birth. Birth weight was 2610 g (10th centile), birth length 44 cm (10th centile), and head circumference 34 cm (50th centile). Physical examination showed both mesomelic and rhizomelic limb shortening, with a trunk to lower limb ratio of 1.93 (normal value 1.7). There was also limitation of pronation and supination, single palmar creases with a trident shaped hand, lumbar kyphosis, a small chest, limitation of hip joint movement, bilateral Ortolani’s sign, a disproportionately large head compared to the body, and a peculiar facial appearance, with downward slanting palpebral fissures, long lashes, depressed nasal bridge, bulbous nasal tip, long philtrum, and thin lips (fig 1). Transient thrombocytopenia and renal failure developed soon after birth. Immunoglobulin levels were within the normal range.

X rays showed significant mesomelic and mild rhizomelic limb shortening. There was also mild metaphyseal widening of the long bones, normal metaphyseal end plates, epiphyseal ossification delay of the distal femur and proximal tibia, and proximal fibular overgrowth (fig 2A). The upper limbs showed bilateral radial head dislocation and generalised, severe brachydactyly with metaphyseal cupping of the metacarpals and phalanges (fig 2B). The lumbar vertebrae were progressively hypoplastic and ovoid in shape, while the sacral vertebrae were normal in height (fig 2C). There were 11 pairs of mildly shortened ribs, increased height and decreased width of the iliac wings, widened sciatric notches, hypoplastic acetabular roofs, normal ossification of the pubic bones, and bilateral hip dislocation (fig 2A). Bone age was delayed. Ultrasound showed markedly hyperechoic kidneys, probably as a result of an anoxic insult. No cerebral or cardiovascular abnormalities were detected.

By 1 month of age, the baby showed failure to thrive and disseminated moniliasis. Shortly thereafter, gastrointestinal symptoms with acute diarrhoea developed as well as an extensive dermatitis on the scalp. Investigations at that time showed severe combined immunodeficiency (SCID), with predominant involvement of the cell mediated immune function (table 1). When the baby was 3 months old, she...
Discussion

The association of inborn defects of skeletal development and dysfunction of the immune system has been recognised for a long time. Schimke et al. described a 6 year old girl with spondyloepiphysial dysplasia, nephropathy, pigmentary skin changes, lymphopenia, and signs of slowly progressive cellular immune defect. Similar findings, including the clinical and skeletal phenotypes, were found in five additional patients, in whom the disorder was reported as Schimke's immuno-osseous dysplasia. Other skeletal dysplasias characterised by short limbed dwarfism have been found in association with distinct immunodeficiencies. Based on the immune defects, three main categories have been recognised. Type 1 includes early lethal short limbed skeletal dysplasia (SLSD) with gross functional impairment of both cell mediated (T cell) and humoral (B cell) immune system, so-called severe combined immunodeficiency (SCID). About half of these patients also have deficiency of ADA. Type 2 includes SLSD with cell mediated immunodeficiency, an association similar to that occurring in cartilage-hair hypoplasia. Type 3 comprises SLSD with antibody mediated immunodeficiency. Skeletal changes are variable in type 1, with inconsistent rhizomelic limb shortening/bowing and metaphyseal changes of variable degree. In contrast, proportionate shortening of the extremities and signs of metaphysial chondrodysplasia are typical features in types 2 and 3. However, the skeletal phenotypes overlap considerably between categories and intermediate forms can occur. For example, the patient described by Shofer et al., who had features compatible with the Omenn syndrome, including severe panathytopoetoitypnoea with cellular immunodeficiency, hepatosplenomegaly, lymphadenopathy, and recurrent infections in association with short limbed dwarfism and metaphysial chondrodysplasia, meets the classification criteria of type 2. However, similar bone changes had been reported.
in two sibs with SCID similar to Swiss-type agammaglobulinaemia, a finding suggesting type 1 SLSD with SCID. In addition, the metaphyseal changes observed in the patients described by Shofer et al and Gatti et al cannot be distinguished from those occurring in cartilage-hair hypoplasia. They include metaphyseal flaring, cupping, and fragmentation, marked shortening of metacarpals, metatarsals, and phalanges, small vertebral, and prominent lumbar lordosis. Two additional patients with type 1 SLSD and SCID have been reported with similar radiographic findings, including rhizomelic shortening of the lower limbs, bowing of the long bones, absent upper tibial epiphyses, and mild to severe metaphyseal changes. In contrast, the clinical presentation was quite distinct, with an earlier onset and shorter survival in one patient, owing to a more severe immune defect.

Our patient showed a profoundly reduced number of T lymphocytes but an increased percentage and absolute number of B lymphocytes. In addition, she had circulating IgM but very low levels of IgG and IgA. These findings overlap those of the X linked variant of SCID, in which B lymphocytes develop normally but lack the required T helper cells to become functional and therefore are not triggered to produce immunoglobulins in response to antigens. However, since this patient was a female, we favor an autosomal recessive form of SCID rather than an X linked variant. Unfortunately the patient's early death precluded molecular characterisation of her defect. The diagnosis of SCID was based on laboratory and necropsy findings and was supported by the rapidly fatal course of the disease. Thus, this case resembles type 1 SLSD with SCID. However, skeletal changes, including severe platyspondyly, acrodysostosis, bilateral hip joint and radial head dislocations, and mild epiphyseal and metaphyseal changes, were quite different from previously reported cases of SCID with osseous abnormalities. Although it is known that skeletal changes are variable in type 1 SLSD with SCID, we suggest that our patient has a distinct disorder with primarily spondylo-acrodysplasia.

It is unclear at present if both the skeletal and immune system changes are the result of a unique mutation or whether different clinical types result from allelic mutations, or if they represent genetically heterogeneous disorders. It seems likely that the developing immune and skeletal systems share several enzymes, the normal function of which is required for optimal development. A model is provided by ADA deficiency, where the arrest in proliferation of both the immune cells and chondrocytes is likely to be the result of adenosine accumulation. However, it is difficult to explain why patients with combined SCID and ADA deficiency show different patterns of skeletal abnormalities and, conversely, similar skeletal findings can be seen in patients with SCID and normal ADA levels.

In conclusion, the radiographic features in our patient are complex and, to the best of our knowledge, do not correspond to previously reported associations between skeletal defects and immunodeficiencies. We believe that the girl described here has a distinct association of SCID with a spondylo-acrodysplasia, which probably should be added to the WHO classification of immunodeficiencies as immuno-osseous dysplasia.

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J Med Genet 1997 34: 854-856
doi: 10.1136/jmg.34.10.854

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