Schimke immuno-osseous dysplasia: case report and review of 25 patients

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Abstract

Immuno-osseous dysplasia is characterised by spondyloepiphyseal dysplasia, lymphopenia with defective cellular immunity, and progressive renal disease. We describe a patient with a severe form of the disease, review the features of another 24 patients, and discuss the previous classification. The differences between the two groups are not striking, and although similarities are greater between affected sibs, the same diagnosis of Schimke immuno-osseous dysplasia should apply to them all. The aetiology and physiopathology of this rare osteochondrodysplasia of presumed autosomal recessive inheritance remain unknown.

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Immuno-osseous dysplasia is a rare autosomal recessive osteochondrodysplasia (MIM 242900).[1] It was first described in one patient by Schimke *et al*[2] and to our knowledge 23 other cases have been published with this possible diagnosis.[3-15] It is characterised by spondyloepiphyseal dysplasia, defective cellular immunity, and progressive renal disease.

We describe a Portuguese patient with immuno-osseous dysplasia, review the previous case reports and classification, and discuss the relevance of additional findings and variants.

Case report

The proband is the third child of nonconsanguineous, Portuguese parents (mother 38, father 40 years old). Both parents and the older brother, aged 9 years, have normal stature and are healthy. A male twin of his brother was stillborn of unknown cause. The proband was born at 32 weeks of gestation by caesarean section following ultrasound prenatal diagnosis of intrauterine growth retardation. Birth length (38 cm), weight (1020 g), and head circumference (27.5 cm) were all less than the 3rd centile.

He was referred at the age of 5 years because of short stature and proteinuria. Herpes zoster had been diagnosed at 2 years. He had short stature with a short neck and trunk (fig 1) and normal development. His length was 79 cm (<5th centile), his weight was 10.42 kg (<5th centile), and his OFC was 47 cm (5th centile). He had a triangular face, a broad nasal bridge, bulbous nasal tip, and multiple lentigines.

Figure 1   The proband at 5 years of age with disproportionate short stature, short trunk and neck, triangular face, broad nasal bridge, bulbous nasal tip, and multiple lentigines. (Photograph reproduced with permission.)

Blood pressure was normal (112/62 mm Hg). The voice was normally pitched and the hair, eyes, and teeth were normal. He had no ascites or oedema.

Skeletal *x* rays showed an increased anteroposterior skull diameter, a J shaped sella turcica, small iliac wings, small ossification centres of the capital femoral epiphyses (fig 2), platyspondyly (fig 3), slightly short metacarpals, and carpal bone age delay. A previous brain ultrasound scan had been described as normal and abdominal ultrasound scan and karyotype (46,XY) were normal.

He had increased urinary glycosaminoglycans (38 mg/mmol creatinine, mostly chondroitin sulphate) with normal chromatography of both glycosaminoglycans and oligosaccharides. Plasma and leucocyte enzymatic activities were normal.

Haematological studies showed haemoglobin 14.2 g/l, platelet count $387 \times 10^3/\mu l$, $8.7 \times 10^3/\mu l$ leucocytes with lymphopenia (absolute count $1.14 \times 10^3/\mu l$). Immunoglobulins IgG, IgM, IgA, IgE, IgG_1, IgG_3, and IgG_4 serum levels were normal, but the IgG_2 subclass level was decreased (<0.08g/dl). Circulating immuno-

Figure 2 Pelvic radiograph showing small iliac wings and small ossification centres of the capital femoral epiphyses, laterally placed, with mild hip subluxation.

Figure 3 Lateral spine radiograph showing platyspondyly with markedly short and rounded vertebral bodies.

complexes (<0.42 μg/ml, normal range <5.0 μg/ml) were normal.

Peripheral blood lymphocytes (flow cytometry) showed a decreased number of total CD3 T cells (52%) owing to a markedly decreased number of subpopulation helper CD4+ T cells (13%) with a decreased CD4/CD8 ratio (0.5%). The γδ T cell receptor CD3+ cells were increased (15%, normal range <7.5%). Activation molecules were slightly expressed in T lymphocytes: 25% of CD4+ lymphocytes were CD25+ and 18% were HLADR+. Also 50% of CD8+ T cells

were HLADR+. The subpopulation of memory T lymphocytes (CD45RO+CD4+) was increased (69%) and CD45+CD4+ naive lymphocytes were reduced (32%). Delayed hypersensitivity skin test to tetanus, diphtheria, tuberculin, streptococcus, candida, trichophyton, and proteus antigens was negative. Proliferative responses of T cells to the mitogens phytohaemagglutinin (PHA), pokeweed, and superantigen staphylococcus protein A were slightly reduced and the addition of recombinant interleukin 2 only enhanced the PHA induced proliferative response.

He had normal renal function and electrolytes, hypoalbuminaemia (30 g/l), and nephrotic proteinuria (80 mg/m^2/h). A renal biopsy was performed that showed focal segmental glomerulosclerosis and a steroid therapy trial was unsuccessful. The patient developed anasarca and hypertension in the third week of treatment that resolved with albumin perfusion, antihypertensive treatment, and prednisone decrease.

Discussion

Immuno-osseous dysplasia is characterised by spondyloepiphyseal dysplasia, cellular immune defect, and progressive renal failure with nephrotic proteinuria. The combination of all these features as previously described allows this diagnosis in the child reported here.

The combination of abnormalities of the immune and skeletal systems is also present in other osteochondrodysplasias, such as cartilage-hair hypoplasia, as well as progressive renal disease and skeletal dysplasia which are features of asphyxiating thoracic dysplasia, but it has been claimed that the presence of the immune, skeletal, and renal abnormalities is specific to immuno-osseous dysplasia.[6]

The association of focal segmental glomerulosclerosis with spondyloepiphyseal dysplasia has also been described in two patients without mention of the diagnosis of immuno-osseous dysplasia.[8] These two patients, the one described here, and the 22 case reports where this diagnosis was quoted can be classified into two different groups as was previously suggested,[11] a severe form and a more benign variant.

The features of the 17 patients with intrauterine growth retardation and severe growth failure since birth (group 1) and those of the other group of eight patients (group 2) are similar (table 1). They all are intellectually normal.

In group 1, patients develop nephrotic syndrome aged 3[4 8 11 13 14] to 14 years.[8] Immunosuppressive therapy has never been noted to be beneficial, with the one exception of cyclosporin that decreased the proteinuria in one patient.[5] If the patients do not die of severe infection (one death from sepsis at the age of 5 years (case 2[8]), another from bacterial pneumonia at the age of 5 years,[6] another from sepsis at the age of 6 years[2]) or because of absence of treatment of the renal failure (patients 1 and 2 died at the age of 8 years of renal failure, patient 4 at 5 years of pulmonary embolism[4]), they progress to end stage renal failure aged 5

Table 1 Phenotypic features of 25 patients with Schimke immuno-osseous dysplasia. The 17 with the severe form are in group 1 (this case report)[2 4-8 11 13-15] and the eight with the more benign variant in group 2[4 9-12]

Feature	Group 1 (17)	Group 2 (8)	All patients (25)
Prenatal onset short stature	17/17	0/8	17/25
Dysmorphology			
Triangular face	4/17	0/8	4/25
Broad nasal bridge	10/17	3/8	13/25
Bulbous tip of nose	10/17	2/8	12/25
Hair abnormalities	5/17	1/8	6/25
Multiple lentigines	14/17	3/8	17/25
High pitched voice	5/17	0/8	5/25
Normal intelligence	16/16	8/8	24/24
Spondyloepiphyseal dysplasia	17/17	8/8	25/25
Cellular immune deficiency	17/17	6/6	23/23
Renal			
Nephrotic syndrome	16/17	8/8	24/25
Global/focal segmental glomerulosclerosis	10/13	4/5	14/18
Other	Corneal opacities (3), microdontia (1), coarse, low voice (1), autoimmune haemolytic anaemia with thrombocytopenia (2), autoimmune enteropathy (1), mesangioproliferative glomerulonephritis (1), ventricular septal defect (1)		

(cases 1, 2, and 3[11]) to 15 years (case 1[8]) and kidney transplantation is required.

Positron emission tomography showed perfusion defects of both cerebral and cerebellar arteries in three transplanted patients with transient ischaemic attacks (cases 1, 2, and 3[11]) and moyamoya phenomenon was described in another three patients.[14 15] One patient died at 8 years old from cerebrovascular disease (case 2[11]). The others were alive at ages 3[13] to 15 years (case 1[8]).

In group 2, nephrotic syndrome starts late, in children aged 4 (case 5[4]) to 12 years (case 2[12]), who are only then noted to have spondyloepiphyseal dysplasia and cellular immune deficiency (not mentioned in case 5[11] or case 1[12]). The course of the renal disease is similar but partial remission of proteinuria has been reported (case 5[11]). Chronic renal failure required dialysis or renal transplantation at ages 6 (case 5[4]) to 22 years (case 2[12]). One patient died when he was 10 years old from cytomegalovirus pneumonia and encephalitis,[10] and another when he was 12 years old from acute lung oedema while he was on haemodialysis (case 1[12]). The others are alive aged 9 (case 5[11] and case 5[4]) to 23 years (case 2[12]).

Autosomal recessive inheritance is usually suggested for immuno-osseous dysplasia. Reviewing the family data in all the case reports there is a single sib pair in group 1 (cases 1 and 2[4]), two consanguineous couples,[15] and a single recurrence (case 2[4]) in four children born after the proband. Before the birth of the proband there are reports of 11 pregnancies with four stillbirths and seven healthy children. In group 2, there is one instance of a couple of first cousins who had three affected children.[12] The only child born after the proband was affected as well as one of the three older children.[12] The inheritance is therefore still not clear, but a recurrence risk of 25% should be given to the parents of children with immuno-osseous dysplasia.

The age of onset of the disease is similar within families, for example, the sib pair with prenatal onset[4] and the three sibs with late onset.[12] However, from the above description of the two variants, the differences are not striking

and the diagnosis of immuno-osseous dysplasia should apply to them all, although to establish the prognosis for a second affected child one should take into consideration the phenotype of the proband.

The only description of chondro-osseous pathology (case 2[4]) showed decreased cellularity of the resting cartilage, with irregular nests of chondrocytes below the growth zone and abnormal endochondral bone formation with complete lack of columnisation.

The immunological study of the patient with Schimke immuno-osseous dysplasia described in this case report, performed while without immunosuppressive therapy, showed recurrent lymphopenia with persistent reduction of T lymphocytes and defective function of cellular immunity. The number and function of B and NK cells were normal. In some cases hypogammaglobulinaemia was ascribed to persistent proteinuria.[9]

The cellular immune deficiency is usually described as recurrent lymphopenia and reduced stimulation to mitogens, often with failure to perform cytogenetic study of blood specimens. There is previous evidence of a decreased number of T cells[4 6 7 9 12] with reduction in CD4+ T cells.[4 7 10 12] The percentages of activated and memory T lymphocytes were increased and peripheral blood CD3+ T cells expressed an abnormally high proportion of $\gamma\delta$ TCR and reduced $\alpha\beta$ TCR (case 3[4]). The increase in peripheral blood immature $\gamma\delta$ TCR CD3+ T cells may reflect a defect in intrathymic T cell differentiation or selection pathways.[4] The histological study of one thymus (case 1[4]) had the appearance seen in other T cell immunodeficiencies.

The progressive renal disease is described as an immune complex nephritis with proteinuria which progresses to focal and segmental glomerulosclerosis and chronic renal failure. Histological and ultrastructural studies of the kidney have been described both from biopsy and at necropsy.

While there is only mild proteinuria, there is mention of minimal change nephrotic syndrome[13] or of basement membranes of the glomerular capillary loops covered by broadened foot processes of podocytes enclosing protein droplets with a slightly wide mesangial matrix that contains immune deposits more numerous and larger in the mesangial region (case 1[4]). This is similar to the description of a mild increase in the mesangium in some of the glomeruli and focal globular accumulation of hyaline material in Bowman's capsule.[10]

In the nephrotic syndrome, renal biopsies were described as showing extensive effacement and fusion of podocyte processes, tubuli with homogeneous material and moderate interstitial fibrosis,[6] increased mesangial matrix with inconsistent proliferation of the endocapillary cells (case 1[12]), or increased mesangial matrix and cellularity in most glomeruli, many with segmental or total hyalinisation, focal tubular atrophy, and increased fibrous interstitium.[9 10] There is often only reference to focal and segmental glomerulosclerosis.[5 8 11 14 15]

After end stage renal failure, biopsy specimens are described as focal segmental glomerulosclerosis with foci of tubular atrophy and fibrosis of the interstitium (case 1[8]) and necropsy studies mention diffuse and global sclerosis, atrophic or wide tubuli, fibrotic interstitium, and thickened and hyalinised arterioles (cases 1 and 2[4]).

The increased urinary excretion of chondroitin-6-sulphfate first reported by Schimke *et al*[2] was not present in any of the other patients with immuno-osseous dysplasia except for the one reported here and two cases described as having slightly increased urinary mucopolysaccharide levels, composed of chondroitin-6-sulphate and chondroitin-4-sulphate (case 1[4 7]). It also disappeared in the proband described by Schimke as he became older.[1]

The aetiology and physiopathology of Schimke immuno-osseous dysplasia remain unknown. Although it is likely that a primary immune disease may affect the kidney, it is more difficult to accept that it may interfere with bone growth starting before birth as happens in the severe spectrum of the disease.

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