Spondyloenchondrodysplasia with immune dysregulation and without neurological involvement: Report of two siblings with ACP5 gene mutation

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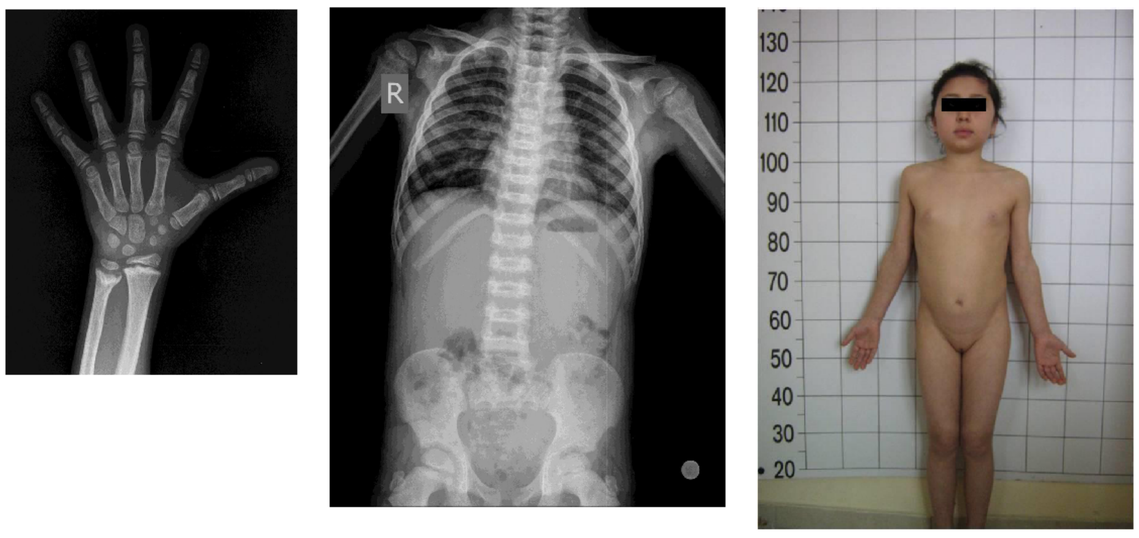
Background

Spondyloenchondrodysplasia (SPENCD) is a rare skeletal dysplasia characterized by metaphyseal enchondroma-like bone lesions and dysplasia of the vertebrae. SPENCD with immune dysregulation (SPENCDI) describes the syndrome of combined immunodeficiency, autoimmunity and spondyloenchondrodysplasia caused by the mutations in the *ACP5* gene on chromosome 19. Patients with SPENCDI and neurological manifestations including spasticity, developmental delay and cerebral calcifications have been reported. We present here two siblings born to consanguineous parents with genetically proven SPENCDI.

Picture 3&4 : Typical skeletal findings of SPENCD in Case 1



Picture 5 : General apperance of Case 2

Case 1

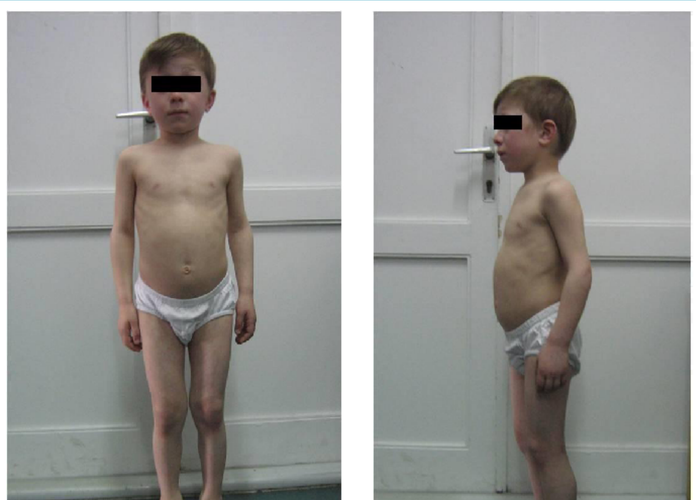
7 years and 2 months old male patient was referred from pediatric hematology department for evaluation of short stature. He was born in term, 2650 grams (-1.67 SDS) to healthy parents who were first cousins. When he was three months old, he was diagnosed with autoimmune hemolytic anemia. He received glucocorticoid treatment for two months and required no further treatment thereafter. His physical examination revealed markedly short stature; height: 100 cm (-4.43 SDS) with risomelia (arm span/height ratio: 0.97). His weight was 17 kg (-2.53 SDS), he had a round face, short neck, lumber lordosis and pes planus (Picture 1 and 2). His developmental milestones were normal and he was prepubertal. Other systemic evaluation was normal. His father's height was normal (175.4 cm), whereas the mother had short stature (146.5 cm, <3rd percentile). It was stated that the maternal uncle had also short stature. Blood count and biochemical analysis were within normal limits. Skeletal survey showed irregularities in distal metaphyses of ulna and radius (Picture 3). He also had platyspondyly and enchondroma like lesions in the vertebrae (Figure 4). The provocation tests for growth hormone (GH) revealed GH deficiency (peak GH in Klonidine test, 2.6 ng/ml; peak GH in insulin tolerance test 7.4 ng/ml) and a treatment recombinant-humanGH was started. The cranial MRI was normal with no intracranial calcification and 4mm of pituitary gland height. The growth velocity after one year rGH therapy was 8 cm. At the age of 8 years and four months he developed a malar rash and photosensitivity, livedo retikularis and Raynauld's phenomen. Laboratory investigations revealed positive anti-nuclear antibodies, but antibodies against DNA were negative and complement levels were normal. A therapy regimen including prednisolone and hydroxychloroquine sulfate began for SLE. After 3 yrs and 6 mo follow-up; the patient has a relief in SLE symptoms and his height SDS raised to -3.19.

Case 2

The older sister of the proband had also of short stature. She was diagnosed with AIHAby the age of 2.5 years and she was receiving methyl prednisolone ever since. On admission she was 9 yrs old, her height was 113 cm (-3.29 SDS), her height was 19.9 kg (-2.24 SDS). Physical examination was normal except short stature and Cushingoid appearance of the face (Picture 5). She had no signs of puberty and had a normal school performance. The biochemical and hormonal investigation was normal and the bone age was 8 years. She had no GH deficiency and Insulin like growth factor 1 (IGF-1) generation test showed no improvement in IGF-1 levels. At 13 yrs and 1 mo old, the patient underwent splenectomy. The radiographic findings were more subtle than her brother, but she had metaphyseal changes and platyspondyly. Her antibodies against DNA and nucleus were negative. At last visit her puberty was grade 3 and height was -5.19 SDS.Both patients were of normal intellect and neither had intracranial calcification.

Genetic Analysis

The mutation analysis for SPENCD was executed in the Genetic Medicine Department of the University of Manchester, UK. Three known mutations of the *ACP5* gene were found. Both siblings are homozygous for a c.155A→C (p.Lys52Thr) mutation. They are both also heterozygous for a c.790A→G (p.Met264Val) mutation. Their father is heterozygous for the Lys52Thr mutation. Their mother is heterozygous for both the Lys52Thr and the Met264Val variants.



Picture 1&2: General apperance of the proband

Conclusions

This rare skeletal dysplasia should be considered in patients with short stature and autoimmune disorders. SPENCDI should be included to the differential diagnosis of other skeletal dysplasias with immune involvement, such as Schimke type immuno-osseous dysplasia and cartilage hair hypoplasia.

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Bone

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