Mild clinical phenotype and subtle radiographic findings in an infant with cartilage-hair hypoplasia

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SUMMARY: Türkkanı-Asal G, Alanay Y, Turul-Özgür T, Zenker M, Thiel C, Rauch A, Ünal Ş, Gürgey A, Tezcan İ. Mild clinical phenotype and subtle radiographic findings in an infant with cartilage-hair hypoplasia. Turk J Pediatr 2009; 51: 493-496.

Cartilage-hair hypoplasia (CHH) is one of the well-known immuno-osseous dysplasias (IOD), which are a combination of skeletal dysplasia and immunodeficiency. It is characterized by disproportionate short stature, fine sparse hair, ligamentous laxity, hematological abnormalities with anemia, a predisposition to malignant tumors, and recurrent infections usually due to cellular and/or humoral immunodeficiency. However, there is a significant overlap of clinical findings among the other IODs such as Schimke's IOD. Here, we present a case of CHH with mild skeletal changes and immunological findings associated with recurrent otitis media, neutropenia, and lymphopenia. With this report, we once more emphasize the difficulty in assessing young individuals with CHH presenting with mild ectodermal findings and subtle radiographic changes.

Key words: cartilage-hair hypoplasia, immunodeficiency, RMRP gene.

The combination of skeletal dysplasias and immunodeficiencies defines a clinically diverse group of conditions known as immuno-osseous dysplasias (IOD)[1]. The common immunological defect can be of cellular, humoral or combined immunodeficiencies of different types. One of the best known of this group of disorders is cartilage-hair hypoplasia (CHH, OMIM 250250) characterized by disproportionate short stature, fine sparse hair, ligamentous laxity, anemia, and predisposition to malignant tumors and recurrent infections secondary to immunodeficiency. It is caused by mutations in the RNA component of RNase MRP (RMRP, ribonuclease mitochondrial RNA processing). The remaining IODs - Schimke IOD (SIOD), spondylo-mesomelic-acrodysplasia and skeletal dysplasia with combined immunodeficiency (OMIM 200900) also present with overlapping clinical findings[1,2].

Herein, we present a case of CHH with subtle skeletal changes and recurrent otitis media, and with neutropenia, anemia and lymphopenia. The difficulties in differential diagnosis when the skeletal findings are subtle are discussed.

Case Report

A 15-month-old boy of nonconsanguineous healthy parents was admitted to Hacettepe University İhsan Doğramacı Children's Hospital with short stature, recurrent otitis media, and oral moniliasis since seven months of age. He was born at term with a birth length of 43.5 cm. On physical examination, he had a height of 68 cm (<3rd centile for age) and weight of 8000 g (<3rd centile for age), with a head circumference of 43.5 cm (-2SD for age). All measurements were compatible with a male infant six months of age. His hair was fair-colored with mildly thin texture, but otherwise normal. A triangular face and disproportionately short-limbed dwarfism with pudgy hands with normal nails were noted. Laboratory evaluation revealed neutropenia, anemia, lymphopenia and low CD3, CD4, CD8 and CD19 counts[3]. In vitro lymphocyte proliferation was strikingly low (Table I). Serum immunoglobulin levels and antibody responses to polio virus were normal[4]. Peripheral blood smear showed anisocytosis, spherocytosis, elliptocytosis, and

Table I. Laboratory Investigations and Immunological Features of the Patient

	Patient	Normal values
White blood cell count (/mm³)	3200	6000-17500
Absolute neutrophil count (/mm³)	1088	1500-8500
Absolute lymphocyte count (/mm³)	1472	4000-10500
Hb (g/dl)	10.3	10.5-14
Htc (%)	28.8	33-42
MCV (fl)	65	70-74
Ig G (mg/dl)	1650	(605-1430)[1]
Ig A (mg/dl)	192	(30-167)[1]
Ig M (mg/dl)	180	(66-228)[1]
Ig E (IU/ml)	5.6	(0-50)[1]
Lymphocyte subsets (/mm³)		
CD3	463	(1600-6700)[2]
CD4	194	(1000-4600)[2]
CD8	284	(400-2100)[2]
CD19	463	(600-2700)[2]
CD16-56	314	(200-1200)[2]
Antibody titer to poliovirus		
Type 1	1/1024	
Type 2	1/1024	
Type 3	1/1024	
Anti HBs:	negative	
In vitro lymphocyte proliferation (Cpm x 10³)		
PHA	6.9-5	68.8-93*
Con A	5-3	29-64*
PMA+I	6-8	33-2*
Anti-CD3	1.6-1.9	5.4-42*
RMRP gene mutation analysis	Compound heterozygosity; (g.-4_-23dupTACTCTGTGAAGCTGAGGAC and g.146G>A)	

1. Ref 4 Aksu G, Genel F, Koturoğlu G, et al. Serum immunoglobulin (IgG, IgM, IgA) and IgG subclass concentrations in healthy children: a study using nephelometric technique. Turk J Pediatr 2006; 48: 19-24.
2. Ref 3 Ikincioğullari A, Kendirli T, Doğu F, et al. Peripheral blood lymphocyte subsets in healthy Turkish children. Turk J Pediatr 2004; 46: 125-130.
*Values for normal controls are the results obtained in the same day from healthy controls.

hypochromic microcytic anemia. Bone marrow examination revealed erythroid hyperplasia and dyserythropoietic changes including increased binucleated normoblasts (17%) indicative of dyserythropoiesis.

Radiological findings included very mild ovoid vertebral bodies, and small femoral epiphyses. Mild metaphyseal irregularities in distal femora were present without angulation in the shaft. Subtle metaphyseal changes suggesting a "bullet-shape" in the proximal phalanges were noted in the hand X-ray (Figs. 1, 2). CHH was considered; however, the thin but normal hair texture with normal nails in addition to subtle skeletal findings placed SIOD in the differential diagnosis.

Direct sequencing of the whole coding region of the RMRP gene and the promoter region revealed two heterozygous mutations: g.-4_-23du pTACTCTGTGAAGCTGAGGAC and g.146G>A. The parents of the patient were shown to be heterozygous carriers of the two mentioned mutations, confirming the diagnosis as CHH.

Fig. 1. The proband, a 15-month-old boy with triangular face and mildly disproportionate short-limbed dwarfism, with pudgy hands and normal nails. His red-colored hair was mildly thin in texture, but otherwise normal in pattern.

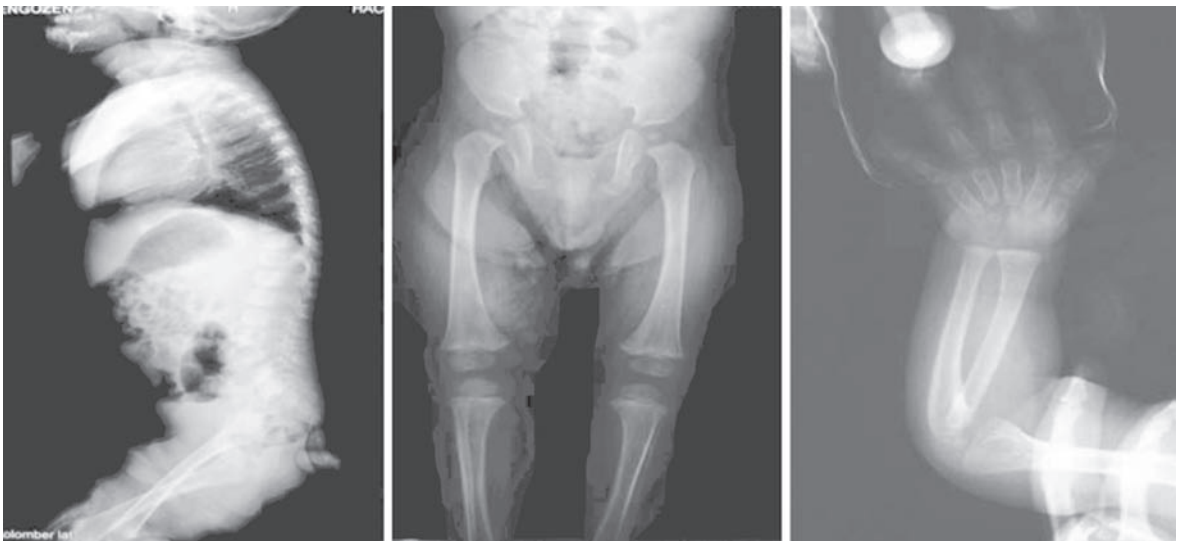

Fig. 2. 2a. Lateral spine radiography showing mild ovoid vertebral bodies.
2b. Lower extremity radiography showing small femoral epiphyses and mild metaphyseal irregularities in distal femora without angulation in the shaft.
2c. Hand forearm radiography showing subtle metaphyseal changes in the proximal phalanges.

During the last six months the patient has been doing well without infections under trimethoprim-sulfamethoxazole and antifungal prophylaxis. The presented patient is currently followed biannually, and immunological follow-up and possible occurrence of malignancy are monitored.

Discussion

Cartilage-hair hypoplasia is a highly pleiotropic entity. The main features are short-limbed dwarfism and hypoplastic hair in association with a clear-cut immunodeficiency (usually T-cell type and occasionally combined), hypoplastic anemia, gastrointestinal dysfunction, ligamentous laxity, and predisposition to malignant tumors like lymphoma[5]. Chronic neutropenia and abnormal cellular immunity is a well-known finding[6]. A relation between immune deficiency states with chondrodysplasia has been noted in the literature dating back to 1970[7]. Radiological findings develop during infancy and childhood and become characteristic in time. Shortened long tubular bones, curved femora with rounded distal epiphysis, short ribs, and anterior angulation of the sternum may be detected in infancy. It is usually beyond two years of age when metaphyseal changes specific for CHH, i.e. metaphyseal dysplasia of tubular bones, disproportionately long fibula and lumbar lordosis become evident[8]. Clinicians familiar with the clinical phenotype readily consider CHH as a possible diagnosis in infancy even when radiology is not distinctive. However, in suspicious cases lacking ectodermal findings, as in the case presented here, the diagnosis can only be made by demonstrating a mutation in the RMRP gene.

Schimke IOD is also a multisystem disorder presenting with short stature and immune deficiency. Dwarfism is short-trunked in SIOD, in contrast to short-limbed in CHH. However, infants with SIOD also present with mildly dysmorphic facies, fine hair texture and recurrent infections due to cellular immunodeficiency. The skeletal findings may be subtle or suggest an unclassifiable spondyloepiphyseal dysplasia. Lymphopenia, neutropenia, anemia, thrombocytopenia as well as T-cell proliferation defects are encountered in both entities. The present case also had T-cell proliferation defect besides lymphopenia, anemia and neutropenia. Profound immune deficiency, yet no life-threatening sepsis, has been reported in mild cases with SIOD[9].

The subtle findings in the skeletal survey of the presented case were not helpful in clearly distinguishing CHH from SIOD at this age, as both may have normal to mild changes in infancy. The absence of proteinuria, which would highly suggest SIOD, may become

evident at later ages[9]. It was mainly the radiological findings in the proximal phalanges of the hands suggesting a "bullet-shape" and very mild metaphyseal changes in the distal femora that led us to perform mutation analysis for RMRP first.

The RMRP mutation analysis of our patient revealed compound heterozygosity for two known mutations: g.-4_-23dupTACTCTGTGAAGCTGAGGAC and g.146G>A. Both mutations have been reported in the literature in patients with CHH. The mutation g.-4_-23dupTACTCTGTGAAGCTGAGGAC, which is located between the TATA box and the transcription starting site, has been reported in the homozygous state as well as in compound heterozygosity with the mutation g.180G>A on the second allele, but no detailed clinical data was available[10,11]. The mutation g.146G>A has been described in compound heterozygosity with the mutations g.195C>T and g.-22_-10dupACTCTGTGAAGCT[12]. The latter genotype was identified in a CHH patient with hair hypoplasia and severe immunodeficiency, anemia and leukopenia. CHH mutations lead to RMRP promoter inefficiency or RNA transcript instability[13].

Recently, Boerkoel[14] discussed the molecular and phenotypical distinctive features of CHH and SIOD. They pointed out that both entities involve multiple systems and share phenotypic features as well as affect cytokine signalling and cell proliferation.

With this report, we once more emphasize the difficulty in assessing young individuals with CHH presenting with mild ectodermal findings and subtle radiographic changes. Despite recent progress made in the molecular genetics of both CHH and SIOD, our present knowledge is still insufficient to explain the hematological and immunological overlap between these two entities as the genes involved have not yet been connected in the molecular network.

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