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Cartilage Hair Hypoplasia: First report from Iran

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Abstract

Cartilage hair hypoplasia (CHH), is a rare cause of metaphyseal chondrodysplasia and short stature. Other features included hair abnormality, immunodeficiency, anemia, gastrointestinal disorders (Hirschsprung disease, celiac, …) and increased risk of cancer. The disease is an autosomal recessive disorder and previously has not been reported in Iran. We report a 9-year-old boy diagnosed as cartilage hair hypoplasia, with severe short stature, metaphyseal chondrodysplasia, hair hypoplasia, Hirschsprung disease, hypothyroidism, vesicouretral reflux and renal stone. Renal stone and hypothyroidism have been reported in cartilage hair hypoplasia with lower frequencies. This is the first report of cartilage hair hypoplasia in Iran.

Keywords: Cartilage hair hypoplasia, Short stature, Metaphyseal chondrodysplasia, Hirschsprung disease.

Introduction

Cartilage hair hypoplasia (CHH), also named McKusick type metaphyseal chondrodysplasia, is a rare hereditary disorder with autosomal recessive mode of inheritance (Online Mendelian Inheritance in Man: OMIM 250250) (1-3). Cartilage-hair hypoplasia was first described in the Amish population in 1964 (4,5). The hallmark of the disease is a combination of the metaphyseal chondrodysplasia and characteristic hair, which is also diagnostic for CHH. The mutation in the RMRP gene (9p12) is responsible for the disease (1,2,6, 7). Mutations in this gene have also been described in other types of short stature.(3, 8) The patients with cartilage hair-hypoplasia are symptomatic at birth including short puffy hands and multiple skin folds around the neck and extremities. Short-limb dwarfism at birth is observed in all cases. Although the size of head is normal, the scalp hairs, the eyebrows, and the eyelashes are blond, fine, and scattered. Other symptoms and signs may present later during life. Short stature with a final adult height of 107-157 cm (40-60 in) is a usual finding in CHH. Apart from short-limbed short stature and abnormal hair, immunodeficiency is another characteristic feature of this disease. The immune deficiency in CHH may be an isolated B-cell or T-cell immunodeficiency, or combined B-cell and T-cell immunodeficiency (9-11). Gastrointestinal disorders (such as Hirschsprung disease, primary malabsorption, anal stenosis and esophageal atresia) occur in approximately 18% of the patients while Hirschsprung disease is the most common one among them (9%) (7, 12). There is no definite treatment for this disorder.

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Case Presentation

An eight-year-old boy was visited in endocrinology clinic of the Kashan University of Medical Sciences. He was 15.5 kg in weight (3.5 standard deviation below mean) and his height was 92 cm (7 standard deviation below mean). Based on the available documents, he weighed 3.65 kg (50th centile) at birth, with a crown to heel length of 47 cm (10th centile). He had shown abdominal distention and vomiting in his neonatal period and eventually diagnosed as Hirschsprung disease that was confirmed using biopsy.

In physical examination he had severe short stature, disproportionate short-limbed dwarfism, short and puffy hands, and genu varum deformity. The sternum was abnormally prominent. Hyperextensibility of the joints was not detected.

His scalp hairs, eyebrows, and eyelashes were fair, very fine and sparse (Fig. 1). While no nail dysplasia or dental abnormality was found, intellectual development was normal for his age and no clinical evidence of immunodeficiency was observed. However he developed hypothyroidism in the age of 6 years. A 3-mm kidney stone was detected when he was 3 years old that enlarged to 8mm in size at the age of 8 and treated by lithotripsy.

Skeletal X-rays revealed typical metaphyseal dysostosis, including widening, cupping, and defective mineralization in the metaphysis of the tubular bones (Fig. 2). Vesicouretral reflux was detected in his voiding vesicocyctogram. Complete blood count, electrolytes, and renal function tests were normal. Sterile pyuria was found in several samples of urinalysis that may be as a result of the vesicouretral reflux or renal stone. Microscopic stool examination detected no fat globules. The patient had been assessed for celiac disease and cystic fibrosis during his infancy that was negative.

Fig.1. Severe short stature and genu varum deformity are evident in the patient. Hair of the scalp, eyebrows, and eyelashes is light, fine, and sparse.

Fig. 2. X-rays of his right and left lower limbs show metaphyseal changes (cupping, widening, fraying and sclerosis of the femur and tibia).

Discussion

Based on our literature review, this is the first report of cartilage hair hypoplasia in Iran. Cartilage hair hypoplasia originally described by McKusik et al in 1964 in Amish children, and later has been described in non-Amish persons throughout

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the United States, Europe, and Mexico. The genetic defect in cartilage hair hypoplasia is mutations in the RMRP gene, mapped to 9p12 (7). RMRP is a ribonucleoprotein present in the nucleus and mitochondria. RNase RMRP has 2 functions: cleavage of RNA in mitochondrial DNA synthesis and nucleolar cleaving of preribosomal RNA (pre-rRNA). RMRP is required for cell growth. In the Amish, the gene frequency was reported to be 1 per 1340 population with a carrier rate of 1 per 19 population (3). In Finland, the frequency of cartilage hair hypoplasia was reported to be 1 case per 23000 live births, with a carrier rate of 1 case per 76 live births. The frequency is equal in male and female. Cartilage hair hypoplasia has a diverse distribution of signs and symptoms including short stature (100%), skeletal dysplasia (100%), hair hypoplasia (93%), hypoplastic anemia of childhood (79%), immunodeficiency (56%), skin hypopigmentation, nails dysplasia, failure to thrive, gastrointestinal diseases (18%; including Hirschsprungs, malabsorption, celiac disease), defective spermatogenesis, and increased risk of malignancies (13). Our patient had normal birth weight with a birth height within 10th centile. He was also presented with Hirschsprung disease in neonatal period. Later he was referred to our clinic at the age of eight due to severe short stature. His weight was 15.5 kg and his height was 92 cm.

Radiographic features of cartilage hair hypoplasia are short and thick long bones with irregular metaphyseal borders of the growth plates, excessive distal length of the fibula, flaring and irregularity of the ribs at the costochondral junction (4). The metaphyseal ends are widened, scalloped and irregularly sclerotic, often with cystic areas; the epiphyses are less affected. The radiologic changes are most prominent in the knees and ankles; the hips are only mildly affected. Delayed ossification of the long bones are also characteristic findings on X-rays. (4,14) The costochondral junctions may show rachitic like changes (like Harrison grooves) and anterolateral chest deformity may be seen. These radiographic features develop by age 6-9 months and are diagnostic. During adulthood with the closure of the epiphyseal plates, the metaphyseal irregularities disappear but the ends remain somewhat flared and angulated. Hand and wrist x-rays may show rachitic changes and may be relatively normal. Makitie et al. analyzed 149 skeletal radiographic surveys of 82 Finnish CHH patients; skeletal age delay was observed in 14% of patients. One-fourth of patients had mild scoliosis. The spine shows few abnormalities. The vertebral bodies are usually normal and caudal widening of the interpediculate distances (though less obvious than normal) is present in most patients. Lumbar lordosis is increased (13). Glass et al. reported the radiologic changes in four CHH children under the age of 2 years. They reported angulation of the entire sternum, a sign not previously described in CHH (in a 2-week-old girl who also showed short ribs with anterior flaring). They also reported a 5-month-old girl with widening of the atlanto-axial space on lateral cervical spine radiograph (14). Bonafe et al suggested that a diagnostic sign of CHH is cone-shaped epiphyses in the phalanges. Patients with metaphyseal chondrodysplasia and cone-shaped epiphyses, should be evaluated for the presence of RMRP mutations even if they have not the other evidences of disease.(15) This finding was not seen in our patient. Our patient did not accept genetic study. Sequence analysis of RMRP identifies two causative mutations in the great majority of probands with a presumed diagnosis of a CHH-AD spectrum disorder, thus confirming the clinical diagnosis.

Our patient had disproportionate short-limbed dwarfism, short and puffy hands and genu varum deformity. Interestingly, his left hand x-ray was normal but he had typical metaphyseal changes of rickets in the lower extremities (cupping, widening, fraying and sclerotic changes in the metaphysis of both femur and tibia, Fig.2). The

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sternum was abnormally prominent. Our patient also had vesicouretral reflux detected in voiding vesicocyctogram. He had developed a 3mm kidney stone when he was 3 years old that reach to 8mm size at the age of 8 that treated by lithotripsy. He had also developed hypothyroidism when he was 6 years old. These findings have been less reported in cartilage hair hypoplasia.

Conclusion

Because of the high rate of consanguineous marriages in Iran and an increased rate of autosomal recessive disorders, we recommend physicians to consider CHH in the differential diagnosis of severe short stature associated with metaphyseal chondrodysplasia, hair hypoplasia and skin hypopigmentation. It should be noted that in cases without evidence of metaphyseal abnormality in hand x-rays, it might be found in lower extremities. Moreover, these patients may be at an increased risk for vesicouretral reflux, renal stone, or hypothyroidism.

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