A rare presentation of Dysplasia Epiphysealis Hemimelica combined with Familial Hypocalciuric Hypercalcemia – Is this association possible?

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BACKGROUND

Familial Hypocalciuric Hypercalcemia (FHH; OMIM #145980) type 1 is a benign condition of hypercalcemia with autosomal dominant inheritance caused by pathogenic variants in the calcium-sensing receptor gene (CaSR). CaSR plays a crucial role in the regulation of calcium balance. Inactivating mutations in this gene results in altered calcium-sensing and inappropriate parathyroid hormone (PTH) release concerning the calcium concentration. Dysplasia Epiphysealis Hemimelica (DEH; OMIM 127800) is another rare developmental bone disorder characterized by localized, asymmetric osteochondral overgrowth affecting single or multiple epiphyses, mainly the distal femur, proximal tibia, and talus. It is more often in boys with no evidence of a simple mendelian basis.

CASE REPORT

We report a 9-year-old boy with dysplasia in his right ankle, associated with a leg length discrepancy observed since 1.9 years old. He had no history of consanguinity, previous surgeries or medication use. Skeletal X-ray depicted asymmetric epiphyseal enlargement of the proximal right femur, thinner in the medial portion with dysplasia of the acetabular roof characterized by verticalization and sclerosis with irregular margins. Right knee radiography showed distinctive bone densities that involve lateral femoral condyle. Ankle and foot radiography revealed asymmetrical mass-like osseous hypertrophy in the distal epiphysis of the fibula and talus, associated with irregularities and sclerosis of talus margins. These skeletal findings resembled DEH.

Patient was referred to a Geneticist who suggested a targeted sequencing panel, which revealed a heterozygous variant of uncertain significance (VUS, Chr3:122.282.171A>AG) in the CaSR gene. Considering the NGS result associated with clinical findings, we diagnosed this variant of uncertain significance (VUS; Chr3:122.282.171A>AG) in the CaSR.

The CaSR is expressed in chondrocytes, osteoblasts, osteoclast precursors and some osteoclasts. It may also play a role in the embryonic development of the skeleton, postnatal bone formation and osteoblast differentiation. To the best of our knowledge, patients with FHH type 1 did not present skeletal dysplasia. Based on blood and urine tests, it is possible to observe the hereditary pattern of FHH type 1. Our findings open up the possibility for further investigation relating DEH and FHH type 1 and/or the CaSR.

REFERENCES