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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 epiphysis, 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 tibia, and talus, associated with irregularities and sclerosis of talus margins. These skeletal findings resembled DEH.

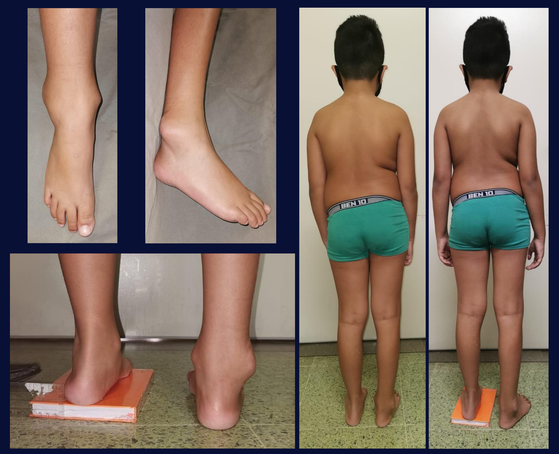

Image 1: Patient's deformities on his right leg.

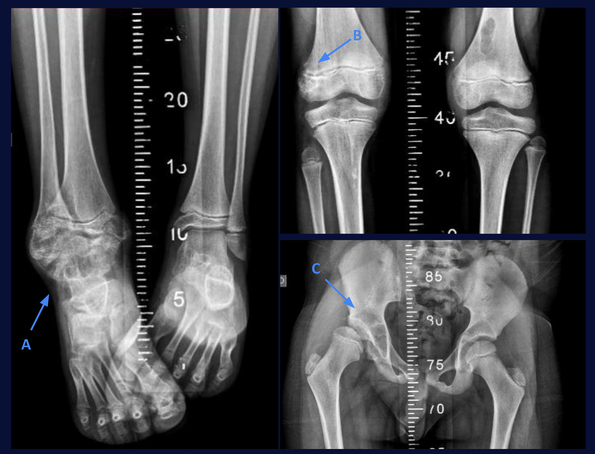

Image 2: Radiographic images with dysplasias on right ankle and foot (A), right knee (B) and right hip (C).

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. It promotes the replacement of the amino acid glutamate in position 558 by glycine and creates a premature stop codon for protein translation (p.Glu558Glyfs*7). Considering the NGS result associated with clinical findings, we diagnosed this patient with FHH type 1. Parents and brother have not yet performed mutational analysis.

Table 1: Patient's laboratory test results

Parameters	Results	Reference range	Alteration
Total calcium	11.0 mg/dL	9.1 – 10.2 mg/dL	↑
Ionized calcium	1.55 mmol/L	1.20 – 1.38 mmol/L	↑
Magnesium	2.4 mg/dL	1.3 – 2.7 mg/dL	–
Parathormone	30.1 pg/mL	18.5 – 88.0 pg/mL	–
Phosphorus	4.3 mg/dL	4.0 – 5.7 mg/dL	–
Vitamin D	26.98 ng/mL	> 20 ng/mL	–
Creatinine	0.57 mg/dL	0.41 – 0.68 mg/dL	–
Urinary calcium	41 mg/24h	100 – 250 mg/24h	↓
Urinary creatinine	526.23 mg/24h	800 – 2000 mg/24h	↓

Table 2: Patient's family's laboratory test results. High levels marked in blue, low levels marked in green.

Parameters	Mother's Results	Father's Results	Brother's Results	Reference range
Total calcium	9.8 mg/dL	11.1 mg/dL	10.7 mg/dL	9.1 – 10.2 mg/dL
Ionized calcium	1.28 mmol/L	1.53 mmol/L	1.54 mmol/L	1.20 – 1.38 mmol/L
Magnesium	2.1 mg/dL	2.1 mg/dL	2.0 mg/dL	1.3 – 2.7 mg/dL
Parathormone	60.9 pg/mL	45.1 pg/mL	49.0 pg/mL	18.5 – 88.0 pg/mL
Phosphorus	4.5 mg/dL	2.4 mg/dL	3.6 mg/dL	4.0 – 5.7 mg/dL
Vitamin D	18.5 ng/mL	11.78 ng/mL	19.64 ng/mL	> 20 ng/mL
Creatinine	0.77 mg/dL	1.14 mg/dL	1.04 mg/dL	0.5 – 1.2 mg/dL
Urinary calcium	365 mg/24h	75 mg/24h	58 mg/24h	100 – 250 mg/24h
Urinary creatinine	1764 mg/24h	1504 mg/24h	2000 mg/24h	800 – 2000 mg/24h

CONCLUSION

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.

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