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Case Report

When clubbing isn't just clubbing: genetically proven primary hypertrophic osteoarthropathy in a child

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ABSTRACT

Hypertrophic osteoarthropathy (HOA) is a rare syndrome characterized by digital clubbing, periostosis and arthropathy. It manifests as abnormal proliferation of the skin, soft and osseous tissues in the distal parts of extremities. The disease can be classified into two forms: primary and secondary. Primary hypertrophic osteoarthropathy is most often autosomal recessive, though autosomal dominant and sporadic cases are described. Pathogenic variants in HPGD and SLCO2A1—key regulators of prostaglandin metabolism—lead to elevated prostaglandin E_2 levels, causing abnormal bone and soft tissue proliferation. Secondary hypertrophic osteoarthropathy is linked to a variety of pulmonary, cardiac, and other systemic conditions. Herein this report presents a case of an 18-year-old male who presented with progressive grade 4 clubbing, varicosities of the right lower limb, bilateral lower limb pain and exertional breathlessness since early childhood. Examination revealed craniofacial dysmorphism, bulbous fingertips and toes, clinodactyly and chest deformity. Radiographs demonstrated acro-osteolysis with prominent bones. Laboratory parameters were largely normal except for mildly elevated parathyroid hormone and erythrocyte sedimentation rate (ESR). Echocardiography was normal. Genetic analysis identified a homozygous missense variant in exon 4 of the HPGD gene, confirming the diagnosis of primary hypertrophic osteoarthropathy. This case highlights the importance of considering genetic causes in pediatric patients presenting with unexplained clubbing and skeletal deformities. Early recognition of primary HOA can prevent unnecessary evaluation for secondary causes and guide genetic counseling.

Keywords: Hypertrophic osteoarthropathy, HPGD gene, Clubbing, Pediatrics, Rare case

INTRODUCTION

Hypertrophic osteoarthropathy (HOA) also known as pachydermoperiostosis is a clinical syndrome characterized by digital clubbing, periostosis of tubular bones and arthritis. It manifests as abnormal proliferation of the skin, soft and osseous tissues in the distal parts of extremities.[1] The disease can be classified into two forms: primary and secondary. Mutations in 15-hydroxyprostaglandin dehydrogenase - HPGD and solute carrier organic anion transporter family member 2A1 - SLCO2A1 genes have been implicated in primary HOA while secondary hypertrophic osteoarthropathy is linked to a variety of pulmonary, cardiac, and other systemic conditions. Reports of genetically confirmed pediatric cases are scarce. The precise incidence and prevalence of PHO are unknown.[2]

We report a child with clinical, radiological and genetic features of HOA due to HPGD mutation.

CASE REPORT

An 18-year male, 2nd issue of a non-consanguineous marriage, was brought with complaints of exertional breathlessness, bulbous and enlarged fingertips (grade 4 digital clubbing, varicosities of the right lower limb and bilateral lower limb pain (Figures 1 and 2). These abnormalities had been noticed since the age of 3–4 years and were progressive. Scholastic performance of the child was average, with no developmental delay. A family

member reportedly had similar complaints with dysmorphism and clubbing.

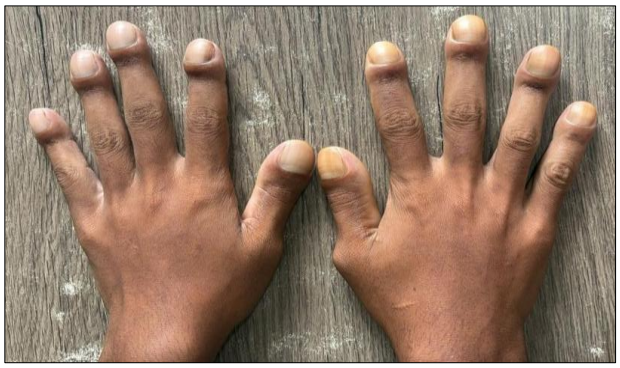

Figure 1: Grade 4 bulbous clubbing of fingers.

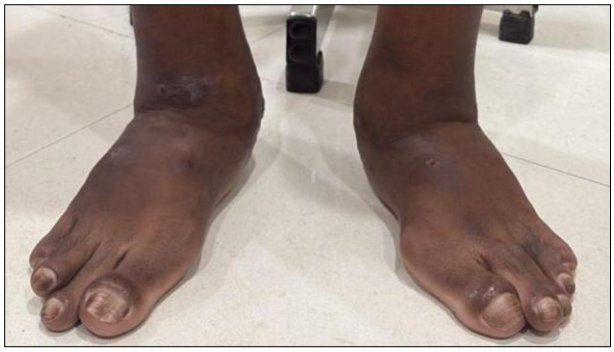

Figure 2: Pedal edema with clinodactyly.

On examination, the patient had brachycephaly, frontal bossing, midface retrusion, mild hypotelorism, broad nasal bridge, short columella, cupped small ears with notched helix, deep philtrum, and thick lips.

Peripheral findings included wet, clammy palms, grade 4 bulbous clubbing of fingers and toes, bilateral pedal edema, clinodactyly of toes, varicose veins in the right lower limb and eversion of the feet. Chest examination revealed a flat chest with low-placed nipples, high-placed clavicles, and pectus carinatum.

Radiographs of the hands showed acro-osteolysis and prominence of bones, more marked on the right side. Laboratory tests revealed elevated parathyroid hormone (79.5 pg/ml) and ESR (27 mm/hour), with other parameters within normal limits. Echocardiography was normal, excluding cardiopulmonary causes. Genetic analysis confirmed a homozygous missense variant in exon 4 of the HPGD gene, consistent with primary hypertrophic osteoarthropathy.

DISCUSSION

Primary HOA is a rare genetic disorder, accounting for 3–5% of all cases.[3] The inheritance pattern is most commonly autosomal recessive, though autosomal dominant and sporadic cases have been reported.[4] It typically presents in childhood or adolescence with pachydermia, periostosis, and clubbing. Secondary HOA, in contrast, is commonly associated with pulmonary malignancy, cyanotic heart disease or chronic infections.

Our patient had typical craniofacial features, severe digital clubbing, and skeletal deformities, with genetic confirmation of an HPGD mutation. The HPGD gene encodes 15-hydroxyprostaglandin dehydrogenase, the key enzyme in prostaglandin degradation. Mutations result in elevated prostaglandin E2 levels, leading to vascular proliferation, periostosis and digital clubbing.

Few cases of genetically confirmed HOA have been described in Indian children.[5] The presence of similar findings in another family member suggests an autosomal recessive inheritance.

The diverse clinical features observed in primary hypertrophic osteoarthropathy (PHO) are largely attributable to the multifaceted physiological roles of prostaglandin E2 (PGE2). PGE2 exerts its effects through the E-prostanoid receptor family and participates in multiple biological processes. It increases vascular permeability, promotes inflammatory cell recruitment and enhances the release of pro-inflammatory mediators. In the skeletal system, PGE2 stimulates bone resorption, inhibits bone formation, and can contribute to osteolysis. Elevated PGE2 levels also play a central role in pain perception, intensifying nociceptive signaling, while its influence on cell proliferation and differentiation may further facilitate the regeneration of bone and other tissues. Collectively, these mechanisms help explain the complex constellation of symptoms characteristic of PHO.

The major clinical significance lies in differentiating primary from secondary HOA. Primary hypertrophic osteoarthropathy (PHOA) should be distinguished from secondary hypertrophic osteoarthropathy (SHOA), thyroid acropachy, acromegaly and other conditions causing clubbing or periostosis. SHOA is associated with underlying pulmonary, cardiac, or gastrointestinal diseases and usually presents in adulthood without prominent skin changes. Thyroid acropachy occurs in Graves' disease and is accompanied by pretibial myxedema and hyperthyroid features. Acromegaly presents with coarse facial features and enlarged extremities, with elevated growth hormone and IGF-1 levels. Other rare genetic or familial disorders may cause isolated clubbing without periostosis or pachydermia. Key distinguishing features include age of onset, presence of skin changes, distribution of periostosis, and associated systemic disease. Secondary HOA mandates extensive evaluation for underlying cardiopulmonary disease, primary HOA requires genetic confirmation and counseling. Early recognition and appropriate management are crucial in improving the quality of life for patients with PHO. Genetic counseling is recommended for affected families, given the hereditary nature of the disorder. If the family mutation is known, disease can be detected prenatally.

The disease is generally benign, slowly progressive, non-life threatening with normal life expectancy. It tends to progress slowly over years, usually stabilizing after adolescence.[6,7] Once skeletal maturity is reached, progression often halts. Quality of life may be affected by pain, cosmetic disfigurement and joint stiffness. With supportive care, patients usually have normal life expectancy.

CONCLUSION

PHOA is a rare but important genetic disorder that can easily be mistaken for secondary causes of clubbing and periostitis. Though the condition may appear disfiguring, its course is largely benign and stabilizes over time. Awareness among pediatricians and general physicians about this entity can lead to timely diagnosis, reassurance of families, improvement in overall quality of life for affected individuals and informed family planning for future pregnancies.

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