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Dr. Shyam Srinivasan
MD Pediatrics, Senior Resident,
Grant Government Medical
College, Mumbai, India

Dr. Devanand Gulab Chaudhari
MD Pediatrics, Lecturer, Grant
Government Medical College,
Mumbai, India

Dr. MD Sabri Ahsan
Junior Resident (Pediatrics),
Grant Government Medical
College, Mumbai, India

Dr. Prachi Atmapoojya
Junior Resident (Pediatrics),
Grant Government Medical
College, Mumbai, India

Dr. Yugesh Kumar Agarwal
Junior Resident (Pediatrics),
Grant Government Medical
College, Mumbai, India

Correspondence

Dr. Shyam Srinivasan
MD Pediatrics, Senior Resident,
Grant Government Medical
College, Mumbai, India

A rare case of Fibrodysplasia ossificans progressive

Dr. Shyam Srinivasan, Dr. Devanand Gulab Chaudhari, Dr. MD Sabri Ahsan, Dr. Prachi Atmapoojya and Dr. Yugesh Kumar Agarwal

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Abstract

Fibrodysplasia ossificans progressiva (FOP), a rare and disabling genetic condition characterized by congenital malformations of the great toes and progressive heterotopic endochondral ossification (HEO) which is the most catastrophic of HEO disorders in humans. We hereby report a case of FOP in a 3 year old female child with multiple HEO and genetically confirmed missense variation of exon 6 of the ACVR1 gene.

Keywords: Fibrodysplasia ossificans progressiva, heterotopic endochondral ossification, ACVR1 gene

1. Introduction

1.1 Case Report

Our patient was a 3 year old girl who presented with complaints of multiple swellings over the back, fore head and neck on and off since 2 months of age, which used to disappear by themselves without treatment. When the child came to us she had restricted neck movements, hard, well defined, non-tender swellings on forehead, neck and sacrum.

MRI cervical spine done on 2014 showed hyperintense ill-defined signal in the muscular plane on right side of the neck. A repeat MRI and CT spine at our centre showed extensive intramuscular and subcutaneous calcifications extending along the entire length of the spine, bilaterally. X ray foot showed valgus deformity of the great toes. Histopathology of biopsy specimen from the cervical region showed fibrocartilaginous tissue. A genetic analysis was done which showed heterozygous missense variation in exon 6 of the ACVR1 gene (chr2:158630626; C>C/T; Depth: 165x) that results in amino acid substitution of Histidine for Arginine at codon 206(p.R206H; ENST00000263640).

2. Discussion

Fibrodysplasia ossificans progressiva is a rare disease involving progressive ossification of skeletal muscle, fascia, tendons and ligaments. FOP has a prevalence of approximately 1 in 2 million, and shows no geographic, ethnic, racial, or gender preference. Most cases are sporadic and dominant inheritance is supported by observations of 2 or 3 successive generations affected and the finding of a paternal age effect in sporadic cases [1]. The average age at the onset of ossification was five years. Children appear normal at birth except for great toe abnormalities (short, deviated, and monophalangeal). Heterotopic ossification occurs progressively over the course of a lifetime in a direction that was axial to appendicular, cranial to caudal, and proximal to distal; this pattern appeared typical for fibrodysplasia ossificans progressive [2] with most patients being confined to a wheelchair by the third decade of life and requiring lifelong care [3]. Malformations of the great toes and progressive heterotopic endochondral ossification (HEO) are the characteristic anatomic patterns. During the first decade of life, most children with FOP develop episodic, painful inflammatory soft tissue swellings.

While some flare-ups regress spontaneously, most transform soft connective tissues including aponeuroses, fascia, ligaments, tendons, and skeletal muscles into mature heterotopic bone. Minor trauma such as intramuscular immunizations, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls, or influenza-like viral illnesses

can trigger painful new flare-ups of FOP leading to progressive heterotopic ossification [4]. Surgical removal of heterotopic bone provokes explosive and painful new bone growth. Smith *et al.* (1996) reviewed FOP on 28 patients and found that ossification in the large skeletal muscles began from birth to 16 years (mean age 4.6 years), involving the neck and upper spinal muscles, and later around the hips, major joints, and jaw. Delay in diagnosis was mainly due to failure to recognize the abnormal toes, which were recognizable at birth in all cases. Radiographic changes were observable in the cervical spine and the metaphyses of the long bones [5]. Clinical suspicion of FOP early in life on the basis of malformed great toes can lead to early clinical diagnosis, and the avoidance of additional harmful diagnostic and treatment procedures [6].

In April 2006, an international team of researchers found that FOP is caused by a mutation of a gene on chromosome 2 (2q23-24) for a receptor in the BMP signaling pathway called ACVR1. Classic FOP is caused by a recurrent activating mutation (617G>A; R206H) in the gene ACVR1/ALK2 encoding Activin A receptor type I/Activin-like kinase 2, a bone morphogenetic protein (BMP) type I receptor. BMP receptors help determine the fate of the stem cells in which they are expressed. Classic FOP occurs when a particular amino acid in the ACVR1 protein is substituted for another amino acid at a specific location. Atypical FOP patients also have heterozygous ACVR1 missense mutations in conserved amino acids [7]. Shore *et al.* (2006) conducted a linkage analysis using a subset of 5 families with the most stringent and unambiguous features of FOP, congenital malformation of the great toes and progressive heterotopic ossification were found to be the characteristic anatomic patterns in all affected patients. This approach identified linkage of FOP to chromosome 2q23-q24, a genetic interval including the ACVR1 gene [8].

3. Points to Remember

Deformity of the great toe and HEO are the clinical pointers in the early suspicion and diagnosis of FOP.

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