Fibrodysplasia Ossificans Progressiva [FOP]

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Abstract-
Fibrodysplasia ossificans progressiva is a rare human genetic disease that is characterised by congenital skeletal malformations and progressive ossification of soft tissues that usually begins at around early childhood. This disease is episodic In nature and causes initiation of spontaneous bone forming lesions (flare ups) that closely mimic the bone forming process seen in early embryonic stage. Over time these lesions begin to form a secondary skeleton apart from the normal one. This article gives you a better understanding of the disease and how it can be managed and treated.
Keywords: FOP , Fibrodysplasia ossificans progressive, genetic disorder, human anatomy

Introduction

Fibrodysplasia ossificans progressiva (FOP) also known as stone man disease or myositis ossificans progressive is a congenital and genetic disorder in which skeletal muscle and connective tissue, such as tendons and ligaments and soft tissues of the body, are gradually over time replaced by bone. This condition leads to bone formation outside the normal skeleton (extra-skeletal or heterotopic bone) that restricts movement thereby affecting everyday activities such as eating, talking, etc. This generally becomes noticeable in early childhood, starting with the neck and shoulders and slowly works its way down the body to the limbs. Individuals with FOP are born with abnormally big toes (hallux valgus) which aidsin making an early diagnosis. Any trauma, such as a fall or minor/major invasive medical procedure, or a viral infection triggers episodes of muscle swelling and inflammation (myositis). These flareups can last for several days to months and often result in permanent bone growth in the injured area.

FOP is caused by a mutation in the ACVR1 gene and is inherited inan autosomal dominant manner. This condition occurs in about 1 in 1,600,000 new-borns and about 800 people worldwide are known to have FOP.[1]

Causes

This condition occurs due to a glitch or a mutation in the ACVR1 gene (which is the principle gene responsible for the occurrence of FOP).[2] The ACVR1 gene codes for the growth and development of bones and muscles, in this disease due to the mutation occurring in this gene it ultimately leading to skeletal maturation (ossification of cartilage). The ACVR1 gene provides instructions for producing a member of a protein family called bone morphogenetic protein (BMP)*type I receptors.

Bone morphogenetic proteins (BMPs) have multiple roles in skeletal development, homeostasis and regeneration. BMPs signal via type I and type II serine/threonine kinase receptors (BMPRI and BMPRII). They belong to the transforming growth factor-β super family. Bone morphogenetic proteins (BMPs) were discovered and named in 1965 by Marshall Urist, who initially identified their ability to induce ectopic bones in muscles. BMPs signal through cell-surface receptor complexes that consist of two distinct transmembrane serine/threonine kinase receptors, type I (BMPRI) and type II (BMPRII). Initially, BMP ligands bind with high affinity to BMPRI, followed by heterodimerization with BMPRII, which allows the BMPRII to phosphorylate a short stretch of amino acids in the BMPRI and activate kinase activity. Classically, after the

activation of BMPRI, intracellular signaling is initiated through the phosphorylation of the C-terminal SSXS motif of specific receptor-regulated Smads, including Smad1, 5, and 8. After being released from the receptor, the phosphorylated Smads form heteromeric complexes with common partner Smad, that is, Smad4. This complex is then translocated into the nucleus to regulate the transcription of genes, broadly influencing growth and differentiation. [3,7] (Fig.1)

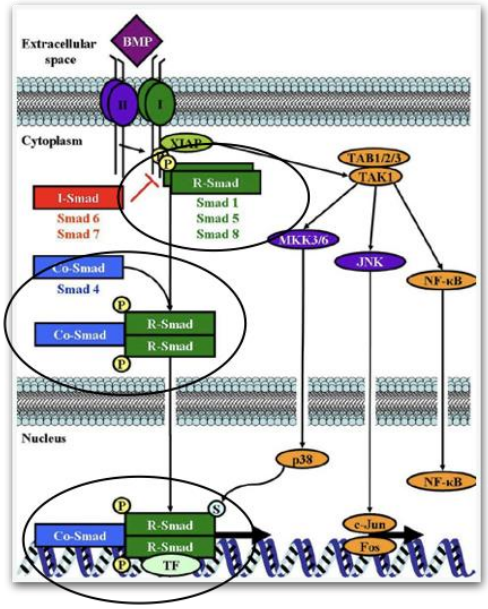

Figure 1 Signaling pathway

Mutations in the ACVR1 gene causes change in the shape of the receptor which in turn disrupts the mechanism that controls the receptors activity hence keeping it constantly turned on resulting in the overgrowth of bone and cartilage.[3,4]

Inheritance Pattern

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.[8](Fig 2)

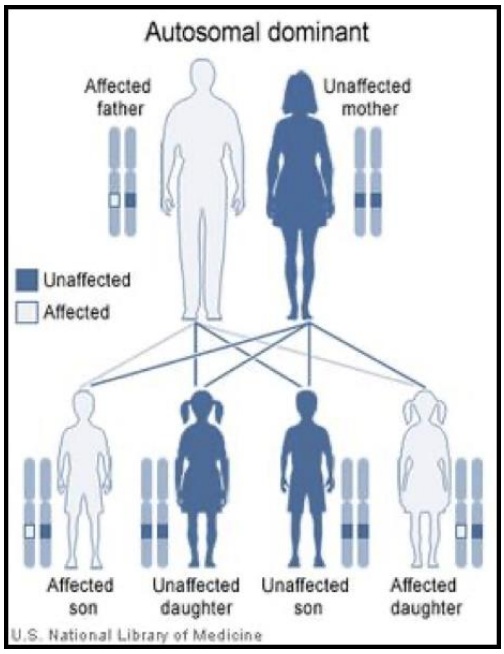

Figure .2 Autosomal dominant pattern

CLINICAL MANIFESTATIONS

The two clinical features that define classic FOP are: malformation of the big toes and progressive heterotrophic ossification in specific spatial patterns. At birth, individuals with FOP appear normal except for one characteristic feature – malformation of the big toes. This feature is seen only in those people affected by this disease. During the first 10 years of life, those individuals affected with FOP develop painful and highly inflammatory soft tissue swellings (also known as flareups). These swellings transform soft connective tissue (fascia, ligaments, tendons, aponeurosis, skeletal muscles, etc) into heterotrophic bone. Ribbons, sheets and plates of heterotopic bone replace skeletal muscles and connective tissues through a process of endochondral ossification that leads to permanent immobility. Minor trauma such as intramuscular immunizations, mandibular blocks for dental work, muscle fatigue and blunt muscle trauma from bumps, bruises, falls or influenza-like illnesses can trigger painful new flare-ups of FOP leading to progressive heterotrophic ossification.Surgical attempts to remove heterotopic bone lead to episodes of explosive and painful new bone growth at the site of incision. Heterotrophic bone formation in FOP progresses in characteristic patterns that mimic the patterns of normal embryonic skeletal formation. These flareups are usually seen first in the dorsal, axial, cranial, proximal regions of the body. The axial lesions appear as swellings and are often mistaken for tumours (these appear in the neck and back regions), in limbs the swelling is often diffuse and sometimes is commonly mistaken for acute thrombophlebitis (a common complication in patients suffering from FOP).The only muscles spared from this disease are- cardiac , diaphragm, tongue, extra ocular muscles and smooth muscles.Bone formation in FOP is episodic, but the disability caused is cumulative. Most patients with FOP are bound to a wheelchair by the third decade of life, and require lifelong assistance in performing activities of daily living. Severe weight loss may result following ankylosis of the jaw, and pneumonia or right-sided heart failure may complicate rigid fixation of the chest wall. The median age of survival is approximately 45 years, and death often results from complications of thoracic insufficiency syndrome (TIS). [5]Other milder symptoms also include- swelling and stiffness of the joint accompanied by low grade fever.[2] This disease is commonly misdiagnosed by physicians as aggressive juvenile fibromatosis (extra-abdominal desmoid tumours), lymphoedema or soft tissue sarcomas. [5]

RADIOGRAPHIC FEATURES

The primary tool for diagnosis of fibrous dysplasia is an X-ray. Normal bone appears solid in an X-ray, a fibrous dysplasia lesion has a relative characteristic appearance often described as "ground glass." An X-ray can also help your doctor determine how much of the bone is affected and whether there is any deformity in the bone.[6]

Joint malformations and soft tissue ossification are the characteristic radiographic features of FOP. Certain features that can make diagnosis more certain are - Malformation of the great toes (Fig.3), thumbs, cervical spine and proximal femurs, along with the presence of proximal medial tibial osteochondromas.Computerized tomography and magnetic resonance imaging of early lesions have been described, but are superfluous.Clinical diagnosis of FOP can be confirmed by DNA diagnostic testing of the ACVR1 gene.[5]

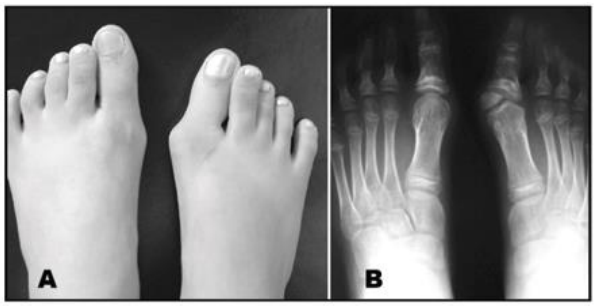

Figure 3 Big toes (hallux)

LAB FINDINGS

Routine biochemical evaluations of bone mineral metabolism are usually normal, although serum alkaline phosphatase activity may be increased, especially during disease flare-ups.

Urinary basic fibroblast growth factor levels may be elevated during disease flare-ups coinciding with the pre-osseous angiogenic phase of fibroproliferative lesions.

Nephrolithiasis is more common in older patients with FOP, and may be due to increased immobilization and dehydration in the setting of generalized increased bone remodelling and mineral turnover.[5]

COMPLICATIONS

Over time as bone starts to replace the affected individuals soft tissues and muscles, it leads to multiple complications. The complications caused are as follows:

- Breathing becomes difficult (your lungs can’t fully expand)
- Eating can also become difficult due to TMJ ankylosing (making it harder to get the nutrients you need thereby causing severe weight loss)
- Keep your balance
- Speak
- Walk or sit

For some people, it also leads to curves in the spine, either from side to side or top to bottom.[2,5]

TREATMENT/CURE

There is no particular treatment for this disease. There are couple of medications that can be administered to ease pain or to reduce inflammation. A brief course of high-dose corticosteroids,such as Prednisone, can be started within the first 24 hours of a flare-up, can help reduce the intense inflammationand tissue swelling seen in the early stages of fibrodysplasia ossificans progressiva.

Other medications, such as muscle relaxants, mast cell inhibitors, and aminobisphosphonates, if appropriate, should be closely monitored by your doctor.[1,5]

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