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FIBRODYSPLASIA OSSIFICANS PROGRESSIVA [FOP]: A REVIEW

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ABSTRACT

Fibrodysplasia ossificans progressiva (FOP) is also known as Munchmeyer disease, Stoneman disease. It is a rare inherited connective tissue disease characterized by **heterotopic ossification** (atypical development of bone in the regions of the body where bone is not generally presen). A mutation in the gene **ACVR1** is responsible for the disease. Specifically, ossification is typically first seen in the dorsal, axial, cranial and proximal regions of body. Diagnosis can be done by measuring clinically elevated levels of **alkaline phosphatase.** There is no approved treatment for **FOP**.

KEYWORDS: Heterotopic ossification, ACVR1 gene, Alkaline phosphatase.

INTRODUCTION

*Fibrodysplasia ossificans progressiva (FOP) is very rare inherited autosomal dominant connective tissue disorder. It is the only identified condition in which where **one organ system changes into another**.

*The mutations in the gene ACVR1 gene affects the body repair mechanism leading to fibrous tissues including muscle, tendons, ligaments to be ossified spontaneously or when damaged as result of trauma.

*Majorly minor injuries lead to joints to become permanently fused as like that of the newly formed bone formations (heterotopic ossifications) and replaced the damaged muscle tissue.

*These heterotopic ossifications eventually form a secondary skeleton and eventually restrict the patient ability to move. The bone formed as a result of this process is identical to normal bone.

*Some evidence suggest that the disease can cause joint degradation irrespective of their bone growth.[1]

*Other skeletal malformations of the cervical spine and ribs and the abnormal development of bone may lead to stiffness in affected areas and ankylosis of affected joints (neck, shoulder, elbows, hips, knees, wrists, ankles, jaw).

*Pre-osseous soft tissue swelling of FOP usually begin during early childhood and progress throughout lifetime.

*FOP occurs as the result of a sporadic mutation. The mutation of a gene in the **Bone morphogenetic protein (BMP)** pathway, which is important in the formation of skeleton in the embryo.

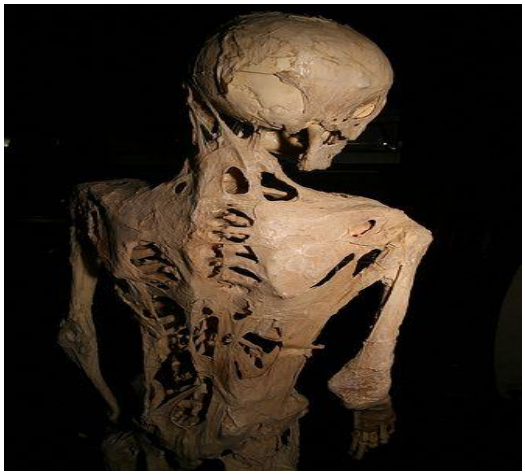

Figure 1: Showing patient affected with FOP.

HISTORY

*FOP dates to seventeenth century and it originally called **Myositis ossificans progressiva** and was imagined to be caused by muscular inflammation (myositis) which causes bone formation.[2]

*The disease was renamed by **Victor A. McKusick** 1970 following the discovery that soft tissues other than muscles (e.g. ligaments) were also affected by the disease.[2]

*some of the FOP affected patients donated their bodies to science.

Harry Eastlack (1933-1973) and **Carol Orzel** (April 20, 1959- February 2018) their skeletons are now at the **Mutter Museum** in Philadelphia.[3] [4]

EPIDEMIOLOGY

-The first case of FOP was described by Patin in 1692 and by Freke in 1739.[5]
-An Extensive review of the medical literature was conducted by Rosentirn, describing 115 cases of FOP.[5] [6]
-The International Association for Fibroplasia ossificans Progressiva reported that less than 200 people affected by the disease in 2001.[7]
-Kaplan et al. reported about 700 known cases around globe in 2008.[8]
-FOP is a rarest disease with an incidence of about 0.61 case per million inhabitants.[9]
-Most of the reports concern to Caucasian population, it also effects all ethnic groups with a predilection for males at a proportion of 4:1.[10]
-The Brazilian association for FOP has registered 49 cases of the disease.[11]

CAUSES

*FOP is caused by an Autosomal dominant allele. Each chromosome designated as short arm "P" and long arm "q". FOP caused by dominant allele on chromosome 2q23-24[12], this allele has various **Expressivity** (Degree to which a phenotype is expressed by individuals having a genotype) but complete **Penetrance** (the proportion of individuals carrying a variant of a gene that also express an associated trait).
*Majority of the cases are by spontaneous mutations in the gametes.

GENETICS

*A mutation in the gene ACVR1-Activin A receptor, type 1 (also known as activin like kinase 2-ALK2) is responsible for the disease.[13]
*ACVR1 encodes **activin receptor type--1** (Activin and Inhibin are two closely related proteins complexes that have directly opposite biological effects), a **BMP type-1 receptor. (BMPs** are Bone Morphogenetic Proteins are a group of growth factors also known as cytokines and as metabologens, they induce the formation of bone and cartilage).[14]

*The mutations lead to substitution of codon 206 from **arginine** to **histidine** in the ACVR1 protein**.** These substitution leads to activation of ACVR1, leading to the transformation of connective tissue and muscle tissue into a secondary skeleton.[14]

*This led **endothelial cells** to transform to **mesenchymal stem cells** and then to **bones.**[15]

***FOP is an **autosomal dominant** disorder**;** a child of a heterozygous parent and an unaffected parent has a 50% probability of being affected. Two affected individuals can produce an unaffected child. As a result of mutation two unaffected individual can produce affected offspring. The homozygous dominant form is more severe than the heterozygous form.[16]

*The Deactivation of Proteins that causes ossification is normally done by an inhibitory protein after a foetus bones are formed in the womb, but in patients with FOP, the proteins keep functioning.

*Aberrant bone formation in patients with FOP occurs when injured connective tissue or muscle cells at the site of injury. The growth incorrectly expresses an enzyme to bone repair during apoptosis, this results in lymphocytes containing excess Bone Morphogenetic protein 4 (BMP4) provided during the immune response.[17]

*The bone that independently of the normal skeleton, forms its own discreet skeletal elements. These elements, however, can fuse with the normal skeletal bones. The diaphragm, tongue, extra-ocular, cardiac, smooth muscles.[18]

*Since the incorrect enzyme remains unresolved within the immune response, the body continues providing the incorrect BMP4 containing lymphocytes.

*The Typical mutation, **R202H**, makes the inhibitor **FKBP1A** (peptidyl-prolyl cis-trans isomerase enzyme) binds less tightly to the activation GS-loop.[19]

*The result is that ACVR1 is not effectively turned off, and an over growth of cartilage and bone and fusion of joints takes place.[20]

*Most of the cases of FOP is that result in new gene mutation, these people had no history of disorder in their family.

CLINICAL FEATURES

Two clinical features define classic FOP
-Malformation of the great toes
-Progressive HO (heterotopic ossification)
*Individuals with FOP appears normal at birth except for the malformation of the great toes which are present in all classically affected individuals.[21]

*During the first decade of life children develop painful and highly inflammatory soft tissue swellings that transforms the soft connective tissues, including aponeuroses, fascia, ligaments, tendons, skeletal muscles into an encasement of bone.

*The first "flare up" that leads to the formation of bone usually occurs before the age 10. The bone generally grows from the top of the body to downwards, just as bones grow in foetus.

*FOP involvement is typically first seen in dorsal, axial, cranial, proximal regions of the body and lateral in the ventral regions of the body.

*In most of the patients, very peculiar characteristics are high risk of congenital anomalies associated with the thumb and hallux for about 75% to 90% of cases.[22]

*Other alternations include macrodactyly, interphalangeal ankylosis and clinodactyly, narrow lumbar canal, psuedoexostosis, decreased humerus epicondylar angle.[23]

*Addition to malformations in great toes and thumbs, early developmental anomalies are frequently observed.

ANOMALIES IN FOP

1. Cervical Spine

-Stiffness of neck is an early finding.
-Large posterior elements.
-Tall narrow vertebral bodies.
-Fusion of facet between C2 and C7.[24]

2. The Temporomandibular joint (TMJ)

-Post traumatic extra-articular ankylosis of the TMJs.
-Severe disability with resultant difficulties in eating.[25] [26]

3. Submandibular swelling

-Association with massive anterior neck swelling and difficulty in swallowing, submandibular swelling can be a life-threatening complication.
-A course of Glucocorticoids and respiratory support may be warranted to measure to reduce swelling.[27]

4. Hearing impairment

-It may be due to middle ear ossification and it is conductive in nature.
-It is a common and occurs approximately about 50% of patients.
-Usually onsets in childhood or adolescence.
-In some patients it may be neurological in nature.[28]

5. Cardiopulmonary function

-Patients with FOP may develop **TIS** (Time of inversion scout- It is an imaging to choose nulling time of myocardium before blood pools) that can lead to life threatening condition.
-It includes Costovertebral malformations including orthotopic ankylosis of the costovertebral joints.
-Ossification of intercostal muscles, Paravertebral muscles and aponeuroses.
-Pneumonia and Right sided heart failure are the major life-threatening condition with TIS patient.[29] [30]

DIAGNOSIS

I. Physical examination

-By physically examining the body parts and their growth and abnormalities.

II. Elevated levels of alkaline phosphatase

-Isoenzyme studies using electrophoresis can confirm the source of the ALP.[31]

III. Radiographic features

-Malformations of great toes, proximal femur, thumbs, cervical spine, proximal medial tibial osteochondromas make the diagnosis more certain.
-Conventional radiographs can detect HO.
-Early lesions have been described by using the **computerized tomography** (CT) and **Magnetic resonance imaging** (MRI).[25] [26]

IV. Laboratory findings

-Elevation in urinary basic fibroblast growth factor levels during disease flare-ups coinciding with the pre-osseous angiogenic phase of fibroproliferative lesions.
-Due to increasing in the immobilization and dehydration in setting of generalized increased bone remodelling and mineral turnover **Nephrolithiasis** is more common in older patients.[26] [32]

V. Histopathology of Lesions

-Early lesions contain perivascular **B-cell** and **T-cell** lymphocytic infiltrate.[33]
-Migration of inflammatory mononuclear cells into affected muscles precedes widespread myonecrosis.
-This followed by an inflammatory stage, an intensive fibroproliferative reaction it associates with robust angiogenesis and neovascularity. During the intensive fibroproliferative stage, mast cells are found at a higher density than in any other inflammatory myopathy. These intermediate stage lesions are indistinguishable microscopically from juvenile fibromatosis.[33] [34]

As the lesion matures, fibroproliferative tissue undergoes an avascular condensation in to cartilage which follows a revascularization stage and osteogenesis in a process of endochondral ossification. The resultant HO is normal histologically mature lamellar bone with elements of marrow.[35] [36]

All stages of histological development are present in an active FOP lesion indicating that the lesions along with its different regions mature at a different rate.

MISDIAGNOSING FOP

-FOP can be misdiagnosed, often failed to associate the rapidly developing soft tissue swelling which appears on the neck, head and upper back with malformed great toes.

-Even before radiographic evidence of HO, the correct diagnosis of FOP can be done by rapid **waxing** and **waning** of **soft tissue lesions** which are associated with the symmetrical malformations of the great toes. When these associations are not made, FOP is commonly misdiagnosed as Aggressive juvenile fibromatosis, soft tissue sarcomas or lymphoedema.[37]

-Children who often undergo unnecessary and harmful diagnostic biopsies that worsen the progression of condition. This can be dangerous at any anatomical site, especially the neck or back asymmetric HO may lead to rapidly progressive spinal deformity and exacerbation of TIS.[37]

MANAGEMENT

- Currently there is no cure or approved treatment for FOP.

-Surgical removal of the joint contractures is generally unsuccessful and risk new trauma induced HO.

-**Osteotomy** of heterotopic bone to mobilize joints is generally counter productive because additional development of HO occurs at the operative site.[29]

-TO improve the overall functional status of the patient rarely, joint may be repositioned surgically.

-Surgical interventions is associated with numerous complications and spinal bracing is ineffective.[29]

-The utility of the Glucocorticoids in management of new flare-ups affecting the function of major joints in the appendicular skeleton.[38]

-The following category of drugs are useful in according to managing chronic discomfort and flare-ups

- **Mast cell stabilizers**

Includes

β2- adrenergic agonists.
Cromoglicic acid.
Ketotifen.
Methylxanthines.
Omalizumab.
Olopatadine.
Rupatadine.

- **Non-steroidal anti-inflammatory medications**

Includes

Aspirin.
celecoxib.
Ibuprofen.
Indomethacin.
Ketoprofen.
Naproxen.
Oxoprozin.

- **Leukotriene inhibitors**

Includes

Montelukast.
Zafirlukast.
Lipoxygenase inhibitors like Zileuton, Hypericum perforatum.

- **Cyclooxygenase-2 inhibitors**[38]

Includes

Celecoxib.
Meloxicam.

But till to date there is no proven efficacy in altering the natural property of the disease.

Bone marrow transplantation

- A study documented the failure of the bone marrow transplantation to cure the condition.

*Although if not recommended **Chronic immunosuppression** may have some utility.[26]

PROPHYLAXIS

- **Dental therapy**

-It must involve assiduous attention and must avoid Intramuscular injection of local anaesthetics, especially mandibular blocks and stretching of the jaw.[39]

-All IM injections must be avoided.[40]

- Prophylaxis against prevention of the diseases, as follows

*Respiratory infections
-Pneumonia.
-Influenza.
*Cardiopulmonary complications.[41]

REHABILITATION

*Due to Heterotopic ossification of bone, range of motion is progressively lost ultimately leading to complete immobility.

*Rehabilitation approaches should be focused on enhancing the daily activities of life.

*Vocational educational consultations and occupational therapy may be useful.[42]

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