FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

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ABSTRACT
The first cases of FOP were described by Patin in 1692 and by Freke in 1739. In 1918, Rosenstirn conducted an extensive review of the medical literature, describing 115 cases of FOP. The disease was first named myositis ossificans progressiva, meaning a muscular inflammation that gradually turned into bones. However, this process affects not only muscles, but also soft parts such as articular capsules and ligaments. Thus, the name was changed to fibrodysplasia ossificans progressiva by Victor McKusick in 1970. Fibrodysplasia ossificans progressiva affects only one in every 2 million people worldwide, according to the U.S. National Institutes of Health (NIH). The International FOP Association says there are 800 confirmed cases across the globe, 285 of them in the United States. The genetic defect in this disorder has not been characterized in Indian patients till date.

KEYWORDS: FOP- Fibrodysplasia ossificans progressive, ACVR1 - activin-like kinase 2 (ALK2), Glitch- a sudden malfunction or fault, Desmoid Tumor - an abnormal growth that arises from connective tissue.

GENERAL CONCEPT: Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disorder in which muscle tissue and connective tissue such as tendons and ligaments are gradually replaced by bone (ossified), forming bone outside the skeleton (extra-skeletal or heterotopic bone) that constrains movement.

Bone Morphogenetic Proteins (BMPs) bind to the ACVR1 receptor, a cascade of intracellular events results. This signaling helps form bones. The team at Regeneron determined that in addition to BMPs, another ligand, Activin A, can also engage ACVR1 but that when it does so it turns off the ACVR1-BMP signaling. What is surprising in the new study, the researchers observed that in a mouse model of FOP, the ligand Activin A, acting through the mutant ACVR1 receptor, turned on the ACVR1-BMP signaling rather than turning it off.[1]

The switch in the function of Activin A in these complex receptor-ligand interactions is believed to be the cause of FOP pathophysiology and equally important, this knowledge can be used to develop a treatment for these patients.

PATHOPHYSIOLOGY
Most cases are caused by spontaneous mutation in the gene.

A mutation in the gene ACVR1 (also known as activin-like kinase 2 (ALK2)) is responsible for the disease.

Fig 1: The effects of fibrodysplasia ossificans progressiva, a disease which causes damaged soft tissue to regrow as bone.

This process generally becomes noticeable in early childhood, starting with the neck and shoulders and proceeding down the body and into the limbs.

PATHOLOGY
Under normal conditions, ACVR1 receptor protein is involved with bone growth. More specifically, when
Mutation in gene ACVR1/ALK2

Costovertebral malformations → Ankylosis of costovertebral joints → Asymmetrical ossification of back and chest wall → Progressive ossification of paravertebral and intercostals muscles

- Chest wall deformity
- Thoracic insufficiency syndrome
- Decrease vital capacity
- Pulmonary hypertension
- Right ventricular stain
- Right ventricular hypertrophy
- Rt congestive heart failure

CLINICAL MANIFESTATIONS

(fig-2 big toe, fig-3 tumor like swelling, fig-4 painful fibrous nodules, fig-5 radiological image of big toe bone).

- The hallmark symptom of fibrodysplasia ossificans progressiva (FOP) is a malformation of a newborn's big toe.
- painful fibrous nodules, or tumor-like swellings, over the neck, back and shoulders
- joint stiffness and serious discomfort can occur.
- Loss of mobility
- Speaking and eating difficulties
- Over time, people with FOP may become malnourished develop breathing difficulties as a result of extra bone formation around the rib cage that restricts expansion of the lungs.
- Any trauma to the muscles of an individual with FOP (a fall or an invasive medical procedure) may trigger episodes of muscle swelling and inflammation. \(^\text{[3,4]}\)

DIAGNOSIS

- History – family history (any known case FOP in family)
- Physical examination- the short and inward-pointing toes and the tumor like growths on the shoulders, back, and neck.
- Laboratory findings - by elevated levels of alkaline phosphatase and bone specific alkaline phosphates’.

- Blood test that looks for the glitch in the gene that causes it.

The rate of misdiagnosis of the disease is estimated at 80 percent or higher. Three of the most common misdiagnoses for FOP are cancer, aggressive juvenile fibromatosis, also called desmoids tumors, and progressive osseous heteroplasia, another rare disease characterized by the abnormal growth of bone.

TREATMENT

There is no cure and the treatment is limited. Only symptomatic management is prescribed. Medicine, such as corticosteroids, can provide relief from pain and inflammation during flare-ups.
• Surgery is not an option for removing the excess bones because surgery often results in more bone formation.

The good news is that researchers are investigating FOP and new treatments. For example, a drug is being developed that may help to control bone growth.\[5\]

PROGNOSIS
The prognosis for fibrodysplasia ossificans progressiva is poor because of the involvement of thoracic muscles and restrictive lung disease. Most fibrodysplasia ossificans progressiva patients are bedridden by the time they are in their 30s, and they usually die before they reach age 40 years.\[2\]

REHABILITATION
Occupational therapist may be able to help with braces, shoes, and other tools to assist with day to day activities.

REFERENCES
5. .https://www.ucsfbenioffchildrens.org/conditions/fibrodysplasia_ossificans_progressiva