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A review on Fibrodysplasia ossificans progressiva

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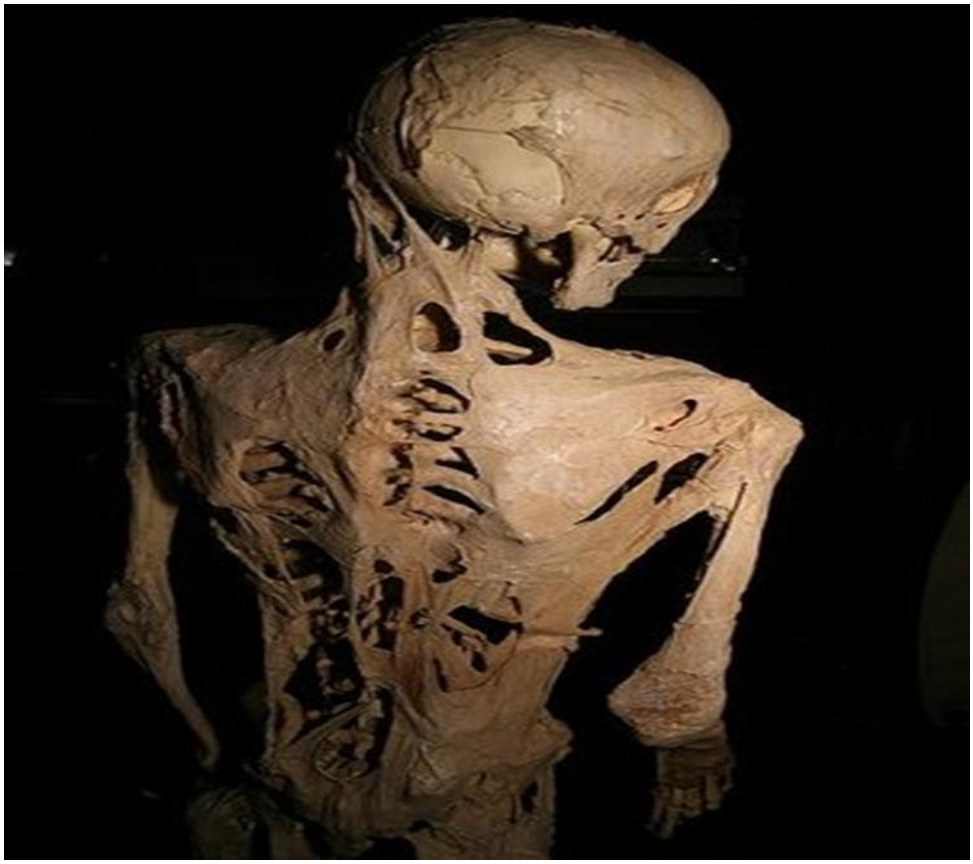
ABSTRACT

It is a very rare inherited connective tissue disease which involves the abnormal development of bone in the body in the areas where bone is not normally present (heterotopic ossification), such as the skeletal muscles, tendons and ligaments. The other names for this disease are munchmeyer disease, stone man disease. In this disease what happen are mainly the soft connective tissues and skeletal muscles changes into bone. The process is known as metamorphosis. The main problem with this disease is there is no proper cure or treatment; this is some kind of rare and severe disease. There is no other medical condition known till now in which one organ system changes into another organ system. This is more seen in the children's first it starts in the body parts like neck, shoulder regions, and then it moves down the body and then move into the limbs. The main clinical feature in the Fibrodysplasia ossificans progressiva is that they are born with malformed big toes. The main hallmark feature of this disease is hallux valgus (It is a progressive foot deformity in which the first metatarsophalangeal joint is affected) .one feature that helps to differentiate from other muscle and bone problems is the abnormality of the big toes. The patients with this disease can hardly live up to 40 years. The increased levels of alkaline phosphatase indicate this disease. This main problem is that there is no proper treatment or cure for this rare disease.

Keywords: Fibrodysplasia ossificans progressiva, Heterotopic ossification, Metamorphosis, Hallux valgus, Metatarsophalangeal joint.

INTRODUCTION

Fibrodysplasia ossificans progressiva is a rare inherited autosomal dominant disease, nothing but in each cell one copy of altered gene is enough for the occurrence of this disease. The main things that occur are that in this disease mainly the connective tissue and skeletal muscle, such as ligaments, and tendons are slowly replaced by the bone. This condition ultimately leads to formation of bone outside the skeleton (Extra-skeletal or heterotopic bone) which does not allow any movement. [1]



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

HISTORY

Fop (or) Fibrodysplasia ossificans progressiva (Fibro-dis-play-sha os-sih-fih-cans pro-gress-ev-a) means "soft connective tissue that slowly changes to the bone". In the early 17^{th} and 18^{th} centuries itself the research studies were started.

- 1692: French physician Guy patin met with Fop patient and he added in his writings.
- 1736: British physician John free explained an adolescent whose diagnosis included swellings total on his back.
- 1900: The disease called as myositis ossificans progressiva, which means muscle turns slowly into bone.
- 1970:Dr.victor Mckusick, who is considered as the father of medical Genetics officially, changed its name to Fop Fibrodysplasia ossificans progressiva.
- After years of research recently in 2018: Regeneron's LUMINA-1 trial written its First patient. [2]

Epidemiology

It is an extremely rare disease. Most cases emerging because of spontaneous new mutation. It occurs rarely that is only one person is effected among 2 million people.so we can imagine how rare is this disease. [3]

Etiology

Fop is caused by a mutation in the gene ACVR1 (Also known as activin-like kinase 2 ALK2), which is involved in Growth and development of bones.Because of this mutation it resulted in the growth which has not checked properly. In some cases, the gene can be inherited from one parent, but in most of the cases, it's a new mutation without any family history of the disease. Some evidence suggests that the disease can cause Joint degradation separate from its characteristic bone growth.

ACVR 1 gene encodes activin receptor type-1, a BMP (Bone morphogenetic protein) type -1 receptor. The substitution of codon 206 from arginine to histidine in the ACVR 1 protein is

mainly because of this mutation. And the substitution leads to the changing of connective tissue and muscle tissue into a secondary skeleton. This causes Endothelial cells Change to mesenchyme stem cells and then to bone. [4]

Signs and symptoms

Mainly identification of the disease is important. Abnormalities in the big toe are the hallmark symptom of Fibrodysplasia ossificans progressiva. When the body starts to produce new bone, the patient usually experience a painful flare-up tissue swelling, joint stiffness and serious discomfort can occur. These changes in the skeleton are present at birth (congenital) and are the First-clinical signs of this disorder. Slow bone formation in areas of the body where bone is not normally present (heterotopic ossification) Chronic swelling in various parts of the body is a common physical characteristic of the FOP patients. These patients cannot move properly and they fall easily more often and lead to injuries. In some special cases they may even show hair loss (or) mild cognitive delay. Nearly 50% of the population affected with this FOP disease will suffer from hearing problems. [5]

Symptoms of Fibrodysplasia ossificans progressiva

Pathophysiology

The pathophysiology of Fibrodisplasia ossificans progressiva is unknown. It is an inherited autosomal dominant disorder with complete penetration but variable gene expressivity. A recurrent mutation in the BMP type 1 receptor ACVR 1 causes inherited and sporadic FOP. FOP is caused by a mutation of the gene ACVR 1. The body's repair mechanism is affected by this mutation so ultimately it leads to ossification of some fibrous tissue which includes muscle, tendons and ligaments, either according to the situation or when damaging because of trauma. Two unique mutations in the ACVR 1 gene have also been seen in two FOP patients from the United Kingdom with some atypical digit abnormalities and other symptoms. A patient from Japan with an ACVR 1 gene mutation. He had normal development until age 17 years and later a mild clinical course.

The mutations were shown to result in local structural changes in the ACVR 1 protein as given by interrogating homology models of the native and mutated ACVR 1 kinase domains. Impaired binding to a FKBP 1 A and an altered subcellular distribution by R206H ACVR 1 mutation may activate osteogenic BMP signaling in extra skeletal sites, leading to delayed and slow ectopic bone formation . A novel ALK2 mutation L 196 P was identified in a mild form of Fibrodisplasia ossificans progressiva. [6]

Diagnosis

Simply by seeing the individual's toes we can diagnose FOP. By characteristic physical findings, clinical Evaluation and sequencing of the ACVR 1 gene the diagnosis may be confirmed. If we see any rapid swellings on the head, back and neck we can say that the patient may have chances of this particular disease. Because of the lack of knowledge of FOP, it is estimated that 80 percent rate of misdiagnosis has occurred. And because of the misdiagnosis it created many invasive procedures which are not required all, and because of the biopsies and they lead to some of the permanent complications like loss of movement. [7]

TREATMENT

Non-pharmacological therapy

As there is no proper non pharmacological therapy for this disease, general ways of preventive measures are advised as prevention is better than cure. Avoid biopsies and all non-emergent surgical procedures. Avoid sports as there might be a chance of harming any soft tissues present. Avoid passive range of motion. Warm water hydrotherapy may be helpful. Use school aids to protect. Anti-biotic medication must be used only in case of necessity else avoid it. Follow the occupational therapy. Some of the devices such as wheel chairs and walkers can be used by the patients. Psychological and social sport should be given to the patient and their family members.

Pharmacological therapy

There is currently no definitive treatment but some of the drugs have been used to decrease the pain and swelling associated with FOP during acute flare ups.Brief course of high-dose-corticosteroids, such as Prednisone, started within 24 hours of a flare up, may help reduce the intense inflammation and tissue swelling seen in early stages of FOP. Other medications, such as muscle relaxants, mast cell inhibitors, and amino bisphosphonates, should be checked properly by a physician. Surgery is not a proper option for the treatment of FOP because it is risky and can even cause painful new growth of bone which doesn't disappear easily by their efforts. Intramuscular injections (immunizations) must be avoided. Individuals should avoid some situations like falling which cause blunt trauma, in turn leads to abnormal bone development in most cases. Many researchers are putting their efforts in investigating FOP and new treatments and I hope very soon we will have a perfect treatment for this rare disease. [8]

Drug of choice

Bisphosphonates and corticosteroids are only showing their action properly during the flares.Iontophoresis with steroids (or) acetic acid may improve diminished range of motion.one report of 3 patients suggested that combined formulation of propranolol and ascorbic acid may be benefited in the prophylaxis of flare-ups. Occupational therapy: special shoes, braces that assist in walking and weight bearing should be used to help people with FOP disease.

Complications

Most of the Fibrodisplasia ossificans progressiva cases are misdiagnosed and because of this it leads to some of the complications like:

Patient's with FOP develop thoracic insufficiency syndrome (TIS).This life threatening complication of cardiopulmonary function can lead to right side heart failure and pneumonia. Swelling of the submandibular region can be life threatening complication. Hearing problems also can be seen. Sometimes alopecia and deafness also occurs as the complications of this disease. [9]

CONCLUSION

Fibrodisplasia ossificans progressiva is a rare inherited autosomal dominant disease. Although treatment to some extent is available researchers are trying to find out ways of better treatment than this. So our job is to at least prevent the disease by following necessary preventive measures. Avoid unnecessary surgeries. Physicians shall take utmost care during diagnosis as misdiagnosis may lead to disastrous consequences. Also we need to spread knowledge to the physicians and the patient's family members about the disease. "PREVENTION IS BETTER THAN CURE" hence follows the preventive measures to avoid further consequences of this rare disease.

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