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Fibrodysplasia Ossificans Progressiva or Stone Man Syndrome is A Rare and Serious Disease (Mysterious Disease) - A Review

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ABSTRACT

Fibrodysplasia ossificans progressiva is a rare and serious genetic disease that could have harmful and deadly results. A mutation of the body's repair mechanism causes fibrous tissue (including muscle, tendon, and ligament) to be ossified spontaneously or when damaged. A rare idiopathic or autosomal dominant MIM 135100 condition of irregular penetration and pre-pubertal onset, in which connective/interstitial tissues undergo extensive fibrosis and heterotopic ossification of ligaments, tendons, muscle, fascia, aponeuroses and skin, first seen in late childhood as firm masses. The abnormal development of bone may lead to stiffness in affected areas and may also limit movement in affected joints, e.g., knees, wrists, shoulders, spine, and/or neck. Fibrodysplasia ossificans progressiva (FOP) is a 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. This process generally becomes noticeable in early childhood, starting with the neck and shoulders and proceeding down the body and into the limbs.

Keywords: Fibrodysplasia ossificans progressiva, Fibrous tissue, Autosomal dominant, Mutation.

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INTRODUCTION

Fibrodysplasia Ossificans Progressive (FOP) is an extremely rare genetic inflammatory disease that affects the connective tissue of the body. This disease may also be referred to as Stone Man Syndrome because it can cause joints to become permanently frozen in place. FOP is a mutation of the body's repair system that causes it to ossify the muscles, ligaments, and tendons of the. This disease usually starts from the top and progresses to the bottom of the body. However, FOP can be triggered by a trauma to an injury site. During the process in which the cells should be repairing the location of the injury, a mutation of the cells takes place, and the body starts to paralyze and decrease mobility at the site. FOP may also be triggered by flare ups such as influenza. Some patients suffer from malnutrition because of loss of movement in the mouth, disabling the early stages of digestion. Indications for this disorder include malformed big toes or short thumbs.[1]

Other names used for *fibrodysplasia ossificans progressive- Myositis ossificans, Myositis ossificans progressive, Progressive myositis ossificans, progressive ossifying myositis.*

Causes

FOP is caused by an autosomal dominant allele on chromosome 2q23-24. The allele has variable expressivity, but complete penetrance. Most cases are caused by spontaneous mutation in the gametes; most people with FOP cannot have children. A study has determined that it affects approximately 1 in every 2 million people. A similar but less catastrophic disease is fibrous dysplasia, which is caused by a post-zygotic mutation.[2]

A mutation in the gene ACVR1 (also known as activin-like kinase 2 [ALK-2]) is responsible for the disease. ACVR1 encodes activin receptor type-1, a BMP type-1 receptor. The mutation changes codon 206 from arginine to histidine in the ACVR1 protein. This causes endothelial cells to transform to mesenchymal stem cells and then to bone.

Mutations in the *ACVR1* gene cause fibrodysplasia ossificans progressiva. The *ACVR1* gene provides instructions for producing a member of a protein family called bone morphogenetic protein (BMP) type I receptors. The ACVR1 protein is found in many tissues of the body including skeletal muscle and cartilage. It helps to control the growth and development of the bones and muscles, including the gradual replacement of cartilage by bone (ossification) that occurs in normal skeletal maturation from birth to young adulthood.

Researchers believe that a mutation in the *ACVR1* gene may change the shape of the receptor under certain conditions and disrupt mechanisms that control the receptor's activity. As a result,

the receptor may be constantly turned on (constitutive activation). Constitutive activation of the receptor causes overgrowth of bone and cartilage and fusion of joints, resulting in the signs and symptoms of fibrodysplasia ossificans progressiva.[3,4]

Symptoms

Extra-skeletal bone formation causes progressive loss of mobility as the joints become affected. Inability to fully open the mouth may cause difficulty in speaking and eating. Over time, people with this disorder may experience malnutrition due to their eating problems. They may also have breathing difficulties as a result of extra bone formation around the rib cage that restricts expansion of the lungs.

Children born with FOP have deformed big toes, possibly missing a joint or simply presenting with a notable lump at the minor joint. The first "flare-up" that leads to the formation of FOP bones usually occurs before the age of 10. FOP is a genetic disease. The bone growth progresses from the top downward, just as bones grow in fetuses. Specifically, FOP involvement is typically seen first in the dorsal, axial, cranial and proximal regions of the body. Later the disease progresses in the ventral, appendicular, caudal and distal regions of the body. However it does not necessarily occur in this order due to injury-caused flare-ups. Often, the tumor-like lumps that characterize the disease appear suddenly.[5]

The gene that causes ossification is normally deactivated after a fetus' bones are formed in the womb, but in patients with FOP, the gene keeps working. Aberrant bone formation in patients with FOP occurs when injured connective tissue or muscle cells at the sites of injury or growth incorrectly express an enzyme for bone repair during apoptosis (self-regulated cell death), resulting in lymphocytes containing excess bone morphogenetic protein 4 (BMP4) provided during the immune system response. The bone that results occurs independently of the normal skeleton, forming its own discrete skeletal elements. These elements, however, can fuse with normal skeletal bone. Interestingly, the diaphragm, tongue, and extra-ocular muscles are spared in this process, as well as cardiac and smooth muscle. Since the incorrect enzyme remains unresolved within the immune response, the body continues providing the incorrect BMP4-containing lymphocytes. BMP4 is a product that contributes to the development of the skeleton in the normal embryo. Because the disease is so rare, the symptoms are often misdiagnosed as cancer or fibrosis. This leads doctors to order biopsies, which can actually exacerbate the growth of these lumps.[6]

Treatment

Attempts to surgically remove the bone result in more robust bone growth. While under anesthesia, patients with FOP may face problems, which include difficulties with intubation, restrictive pulmonary disease, and changes in the electrical conduction system of the heart. Activities that increase the risk of falling should be avoided, as injuries from falling can provoke the growth of bone.

As of November 2010, there are no registered clinical trials for FOP. Researchers believe that specific kinase inhibitors can be developed that will block the aberrant ACVR1 activity, and are actively investigating dorsomorphin and K02288 as lead compounds with the intention of developing effective therapies. For example, the more potent dorsomorphin derivative LDN-193189 reduced ossification in a transgenic mouse model, in which the engineering of adult ACVR1 activity created an inflammation-dependent ossification sensitive to corticosteroid treatment.[7]

Figure 1 skeleton of FOP

These resources address the diagnosis or management of fibrodysplasia ossificans progressiva and may include treatment providers. Genetic Testing Registry: Progressive myositis ossificans. You might also find information on the diagnosis or management of fibrodysplasia ossificans progressiva in Educational resources and Patient support.[8]

Some of the medicines that have been reported to be helpful are:

1-Corticosteroids like prednisone during the early part of a flare-up in major joint. Corticosteroids help decrease inflammation and swelling.

2-NSAIDs also reduce inflammation. If you've ever taken Advil or aspirin, you've taken an NSAID. **COX-2 inhibitors** (like Vioxx, which is no longer on the market, and Celebrex) are a particular kind of NSAID that seems to be very helpful in FOP treatment.

3-Aminobiphosphonates are **anti-angiogenic**, which means that they prevent the formation of blood vessels, which bone tissue needs to grow. They also keep too much bone resorption from happening by shortening the life span of osteoclasts. You would think that decreased bone

resorption would be a bad thing in FOP, but it turns out that it seems to help people. Doctors aren't sure why.

4-Thalidomide is also an anti-angiogenic. It appears to modify immune system responses and functions in a way that might help with flare-ups. To some people, thalidomide brings to mind news stories of birth defects in the 1960s, after doctors gave it to pregnant women to help with morning sickness. However, thalidomide is supposed to be safe in people who aren't pregnant.

For an adult with FOP, trying to stay as independent as possible can be a challenge. People with financial means or good insurance coverage could modify their homes to be wheelchair-friendly, making everything easier. For some people, it might be necessary to hire a caregiver.

DISCUSSION

FOP is a very serious and rare disease that usually affects victims during childhood, but sometimes does occur later on in life. Since then, incredible discoveries and large strides to understanding the mysterious disease have been made, but no complete cure or treatment for the condition has been identified. Deformities of the greater toe are the most common indication for the disease and can be identified early in childhood which helps increase patients quality of life.

This early knowledge informs the patient to avoid high contact activities that have a high chance of causing trauma to the body, which runs a high risk of causing flare-ups for the FOP. The beauty of modern day technology is that we are able to examine these cases using radiographic imaging to pinpoint exactly where the problem lies, yet sometimes it gets misdiagnosed and improper steps are taken that only worsen the problem.[9,10]

The International Fibrodysplasia Ossificans Progressiva (FOP) Association was founded by patient Jeannie Peeper in June of 1988 to educate patients, doctors, and the public about FOP; to raise funds and provide a patient base to support medical research into FOP; and to support patients with FOP and their families by providing a network of communication to help end the isolation that accompanies this rare and severely disabling condition.[11]

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