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Review Article

# A BRIEF OVERVIEW OF THE VERY RARE FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (STONE MAN SYNDROME)

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**ABSTRACT**

Fibrodysplasia ossificans progressiva (FOP) is an extremely rare disorder with only about 800 million people affected worldwide. It occurs as a result of the mutation in Activin A receptor type 1 (ACVR1) gene leading to extraskeletal structure formation which further gradually progresses to skeletal deformities and premature death. This disorder is also known as stone man syndrome as it causes joints to become frozen resulting in mobility impairment. It is generally identified in early childhood and affects almost every organ. Though there is no approved treatment for this rare disorder, researchers are in progress. Supportive therapy and care can help the patients to some extent by providing temporary relief. In this review, we will briefly outline the information regarding FOP which is difficult to diagnose and whose misdiagnosis is dangerous.

**Keywords:** Fibrodysplasia Ossificans Progressiva, Stone Man Syndrome, Activin A Receptor Type, Misdiagnosis, Supportive Therapy


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## INTRODUCTION

Fibro dysplasia ossificans progressiva (FOP) is an extremely rare connective tissue disorder. It is caused by a mutation in the body's repair mechanism resulting in ossification of fibrous tissue, thus forming bone outside the skeleton. The disease was first named by Victor A. Mc Kusick in 1970. In severe conditions, it can cause joints to become permanently frozen in place and the body becomes immovable as like a stone. So, the condition can also be referred to as stone man syndrome [1]. It can gradually lead to progressive joint ankylosis, skeletal deformities, growth impairment, breathing difficulty, and premature death [2].

The condition affects many areas of the body including the neck, spine, chest, shoulders, elbows, wrists, hips, knees, ankles and jaw. It is a very rare disorder and only a few cases are reported. About only 800 million people worldwide are known to be affected approximately. Though most of the cases of FOP were due to a gene mutation, there are some cases in which people inherited the mutation from one of their parents who are affected [3].

### Symptoms

FOP is generally identified in early childhood, starting with the neck and shoulders and gradually proceeds down the body and into the limbs. The main symptom of FOP is a malformation of a newborn's big toe. This malformation, which is apparent at birth, consists of a short big toe with an abnormal turning of the toe called as the valgus deviation (fig. 1) [4].

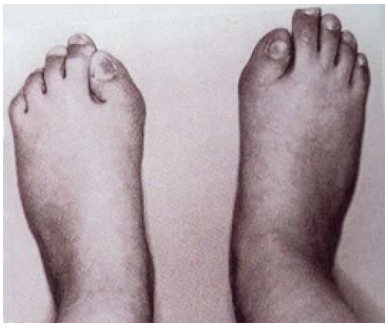

**Fig. 1[5]**

Most of the people with FOP exhibit painful tumor-like swellings over the neck, back and shoulders. These swellings develop after experiencing any trauma to the body such as a bump or fall. This is because such traumas to the muscles of an individual with FOP (even due to invasive medical procedures) can trigger episodes of muscle swelling and inflammation (myositis) followed by more rapid ossification in the injured area. Flare-ups may also be caused by viral illnesses such as influenza [6].

FOP causes loss of mobility to the affected joints including the inability to fully open the mouth, limiting speech and eating. Extra bone formation around the rib cage restricts the expansion of lungs and diaphragm causing breathing complications like asthma, chronic obstructive pulmonary disease. As the disease continues to progress, patients eventually become unable to perform simple tasks of daily life such as cooking or bathing or walking [7].

FOP also results in cervical spine abnormalities which appear as large posterior elements, tall narrow vertebral bodies, and fusion of the facet joints between C2 and C7 [8]. The cervical spine often becomes ankylosed early in life (fig. 2). Other skeletal features associated with FOP are short malformed thumbs, clinodactyly, short broad femoral necks and proximal medial tibial osteochondromas [9].

**Fig. 2[10]**

Hearing loss is rarely seen and may be mainly due to middle ear ossification. However, in some patients, the hearing impairment is sensorineural, involving the inner ear, cochlea, or the auditory nerve [11]. Other life-threatening complications include severe weight loss due to ankylosis of the jaw, as well as pneumonia and right-sided heart failure resulting from thoracic insufficiency syndrome [12].

The Human Phenotype Ontology (HPO) from Orphanet, an European rare disease database shows that in approximately 80-99% of cases, the most commonly observed symptoms of all others are abnormality of the first metatarsal bone, cervical abnormalities, ectopic ossification in ligament tissue, ectopic ossification in muscle tissue, limitation of joint mobility, short hallux, spinal rigidity, subcutaneous nodules, alopecia [13].

**Development**

FOP is an autosomal dominant disorder. It is mainly caused by a spontaneous mutation in the gametes. Mutation of a gene on chromosome 2 (2q23-24) coding for a receptor in the BMP signalling pathway called ACVR1 [Activin A receptor, type1] is responsible for the disease.

[ACVR1 helps to control the growth and development of the bones and muscles. including the gradual replacement of cartilage by bone (ossification)] [14].

Normally, this ACVR1 gene that causes ossification is deactivated after fetus's bones are formed in the womb. But in patients with FOP, the gene keeps on working. This mutation in the ACVR1 leads to the transformation of connective tissue and muscle tissue into a secondary skeleton. This process of ossification occurs through the transformation of endothelial cells to mesenchymal stem cells and then to bone [15].

The abnormal bone formation also occurs when connective tissue or muscle cells at the injury site repeatedly express an enzyme for bone repair during apoptosis (self-regulated cell death), resulting in accumulation of lymphocytes containing an excess of bone morphogenetic protein 4 (BMP4). The bone formation occurs aberrantly forming discrete skeletal elements. Since the incorrect expression of enzyme remains unresolved, the body continues providing the BMP4-containing lymphocytes resulting in secondary skeletal formation.

[BMP4 is mainly involved in bone and cartilage development, tooth and limb development and fracture repair. It is also responsible for the formation of optic vesicle during early development of eyes] [16].

**Diagnosis**

FOP is so rare that the diagnosis is very difficult. Misdiagnosis as cancer or fibrosis is more common and dangerous. This is because performing biopsies as a result of misdiagnosis can exacerbate the growth of the extra bones. However, the malformed toes or thumbs in FOP patients can help to distinguish this disorder from other skeletal problems. The disease can also be identified clinically by elevated levels of alkaline phosphatase and bone-specific alkaline phosphatase [17].

Plain X-rays can help to detect more subtle great toe abnormalities. Abnormal findings on the bone scan can be detected by conventional radiography. Confirmatory genetic testing is also helpful and is currently available at several laboratories [18].

**Treatment**

Currently, there is no cure or approved treatment for FOP (stone man syndrome). Though the research is going on, the rarity of the disease and patient's fragility are making it still difficult. Surgeries to remove the additional bone is not advantageous due to chances of explosive bone growth. Anesthesia is also avoided due to problems like restrictive pulmonary disease, and changes in the electrical conduction system of the heart [19].

However, supportive therapy can be given to providing relief by controlling symptoms to some extent. This includes usage of high-dose corticosteroids [for example prednisone at a dose of 2 mg/kg/day] to reduce inflammation and tissue swelling. Non-steroidal anti-inflammatory drugs (NSAIDs) or Cycloxygenase2 (COX2) inhibitors (in conjunction with a leukotriene inhibitor) can also be given to control inflammation. Others such as muscle relaxants and other anti-inflammatory drugs can also be used.

In individuals with more susceptibility to infections, preventive (prophylactic) antibiotic therapy can be followed. However, these symptomatic treatments do not stop the progression of the disease, but only help to manage the symptoms.

Special shoes, braces and other devices that assist in walking and weight-bearing can be helpful to the people with FOP [20].

**Ongoing research**

Currently, the research is being mainly directed towards preventing the excessive signalling of the BMP1 receptor. This is because many studies found that blocking the BMP1 receptor activity is the most effective way of decreasing the progression of a FOP.

Some of the other similar researches which are under progress are:

- Small-molecule kinase inhibitors are being designed to selectively block ACVR1 receptors and are still under design [21].

(One of such is LDN-212854 which can effectively increase BMP selectivity. The 5-quinoline substituted pyrazolo [1,5a-] pyrimidine compounds such as LDN-212854 could be advantageous for the treatment of FOP by minimizing toxicity) [22].

- Palovarotene, a retinoic acid receptor gamma agonist blocked abnormal bone formation in animal models through inhibition of secondary messenger systems in the BMP pathway. Still, it is under research for being used in humans. [This is because endogenous retinoid signaling is normally attenuated during chondrogenesis and this attenuation is required for chondrogenic differentiation] [23].

(Investigations on Palovarotene are in Phase 2 clinical trials for adults and children as young as six years old with FOP to evaluate the impact of different doses on new heterotopic bone formation during and after a flare-up) [24].

- Another potential therapeutic approach involves allele-specific RNA interference that targets mutated mRNA but preserves normal ACVR1 gene expression [25].

The ultimate goal of the research is to develop a treatment so that FOP affected individuals can enjoy a higher lifespan.

**CONCLUSION**

Most patients with FOP are bedridden by an early age of 20. However, by taking proper and careful measures, the lifespan can be extended to 40 y*. But still, improper diagnosis, carelessness and negligence of symptoms further decrease the survival period. As the prevention is better than cure, patients with FOP should try to avoid injury or traumas, infections and falls. As like other disorders, proper diagnosis and treatment in time can control the symptoms through the complete cure is not possible.

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**AUTHORS CONTRIBUTIONS**

All the author have contributed equally

**CONFLICT OF INTERESTS**

There is no conflict of interest regarding publication of this review article

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