

Transformation of Man into Stone- Rare and Dreadful Disease: Fibrodysplasia Ossificans Progressiva

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Received: May 01, 2018; **Published:** June 28, 2018

Abstract

Dangerous diseases with high prevalence and unknown pathophysiology always gained significant attention. Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder which is characterized by *de novo* osteogenesis - a developmental process occurring during embryonic skeletal formation induced aberrantly and progressively in the soft connective tissues during the early childhood. Patient suffering from FOP is characterized by painful swelling in the muscles and connective tissue at the early stages of life, which leads to the development of ossification at a mean age of 4 - 5 years. Globally the FOP has high prevalence rate approximately 1/2,000,000. However, there is no ethnic, gender, racial and geographic prediction reported for FOP. An infant, who has been attacked by FOP appear to be normal at birth except for congenital malformations in the great toes. In early decades of life, the episodic movement of painful soft tissue swellings results in the precipitation of soft tissue injury, viral infection, muscular stretching, falls, fatigue and aponeuroses into heterotopic bone rendering movement impossible. This review is focused on FOP with special attention to its diagnosis and treatment.

Keywords: Fibrodysplasia Ossificans Progressiva (FOP); Autosomal Dominant; Bone; *de novo* Osteogenesis

Introduction

Pathological formation of bone in extraskeletal tissues is commonly termed as heterotopic ossification (HO). HO is an extremely rare clinical finding in children although it is common in adults. HO is commonly associated with a number of common conditions that involve a severe trauma such as spinal cord, head injury and hip replacement surgery [1]. HO is further categorized into three subtypes as traumatic, neurogenic and genetic-based on the organ which is either injured or fractured. Normally, the traumatic HO occurs in response to the injuries of acetabular fractures, fracture-dislocations of the elbow, knee and shoulder, burns and blast-injuries. The occurrence of neurogenic HO is due to the injury to the central nervous system (CNS) including spinal cord injury (SCI) and traumatic brain injury (TBI). Genetic HO occurs in patients with the rare inherited or mutated conditions i.e. Fibrodysplasia Ossificans Progressiva (FOP) and Progressive Osseous Heteroplasia (POH), which led to the understanding of the mechanisms of HO formation [2]. The present review is focused on the literature on the FOP, underlying mechanism, epidemiology, prophylaxis and approaches for the treatment of FOP.

Fibrodysplasia ossificans progressive

Fibrodysplasia ossificans progressive (also known as Myositis ossificans; Myositis ossificans progressiva; Myositis ossificans; Myositis ossificans progressiva; Progressive myositis ossificans; Progressive ossifying myositis), is an extremely rare inherited connective tissue disorder and is the most severe and disabling disorder of extraskeletal ossification in humans [3]. FOP is caused by mutation of the body's repair mechanism and characterized by the abnormal development of bone in areas, where a bone is not normally present such as the ligaments, tendons, and skeletal muscles. In FOP, the body's skeletal muscles and soft connective tissues usually undergo metamorphosis, essentially a transformation into bone and progressively locking joints in place and making movement difficult. These disease conditions

are generally noticeable in early childhood, initiated with the neck and shoulders and further affected the body and into the limbs. The bone formations are episodic and progressive leading to an extra-articular ankylosis of all major joints of the axial and appendicular skeleton, rendering joint movement [4]. The patients affected with FOP disease are born with abnormal big toes (hallux valgus) which can be helpful in making the diagnosis and episodes of muscle swelling and inflammation (myositis) is triggered by trauma, these flare lasts for several days to months and often result in permanent bone growth in the injured area.

FOP is almost always caused by a mono-allelic gain of function mutation at the activin receptor type IA in the ACVR1 gene and is inherited in an autosomal dominant manner [1,5]. In United Kingdom, the prevalence rate of FOP was estimated at 1 case per 1.64 million persons [6]. Whereas, in France a prevalence rate of 1.36 per million inhabitants has been reported. Approximately, more or less 200 FOP cases have been described worldwide [7]. Usually, the FOP encountered in vast majority of cases are due to the same alteration, R206H, and results from a spontaneous *de novo* mutation [1]. FOP has no ethnic, gender or geographic predisposition, nevertheless, the FOP is mainly occurring in whites, but it is also reported in blacks and more common in females than in males. Observed male-to-male transmission of the FOP excludes X-linked inheritance [7].

In 17th century, medical reports described the individuals affected by FOP. Initially, the FOP conditions were called myositis ossificans progressiva (MOP), which was thought to be caused by muscular inflammation (myositis) that caused bone formation. Further, the name of FOP was renamed by Victor A. McKusick in 1970. McKusick discovered that the soft tissues other than muscles (e.g., ligaments) may also be affected by the disease process [8]. The best-known FOP case of Harry Eastlack was reported early 19th century (1933 -1973). At the age of 10 years, his body began to develop at the age of ten, and by the time of his death from pneumonia in November 1973, six days before his 40th birthday, his body had completely ossified, leaving him able to move only his lips. Harry Eastlack only survived to meet one other person suffering from same condition. Before the death of Harry Eastlack, he declared that his body will be donated to science community so that it would be able to help and find a cure for understanding of this cruel disease. Pursuant to his wishes, his skeleton was preserved in Mutter Museum in Philadelphia, and it has been proven to be an invaluable source of information to understand the deadly FOP disease conditions.

Prevalence of FOP

The first cases of FOP were described by Patin in 1692 and by Freke in 1739 [9]. In 1918, Rosenstirn conducted an extensive review of the medical literature, describing 115 cases of FOP. The disease was first named myositis ossificans progressiva (MOP) [10], 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 FOP by Victor McKusick in 1970 [11].

As an extremely rare and autosomal dominant disease, FOP is always characterised with a very high prevalence rate. Among them, approximately 95% patients manifest HO before the age of 15, whereas, it is 56 years for oldest patient [12,13]. Around the world, the prevalence rate of patient suffering from FOP or HO is different such as statistical data for Europe indicate that 30 cases have been confirmed in the UK among about 49 million residents, with a prevalence of 0.61 per million. Whereas, Spain is estimated with a prevalence rate of 0.36 per million and France indicates a prevalence of 1.36 per million [13]. At present, most patients reported are in the United States, accounting for about 25.6% of all registered patients. This is followed by China, which accounts for about 10.8% of registered patients. Patients with FOP in Brazil account for about 8.4%. Compared to European and American patients, Asian patients are younger [14]. Despite the extremely low incidence of FOP, there are still a large number of patients with FOP in China due to its huge population. Although definite figures for China are still unclear, the prevalence of FOP can be used to estimate the number of patients. Based on the incidence of FOP, there are at least 650 patients with FOP in China [15]. For various reasons such as the level of medical research into the condition, however, only about 70 cases are reported, accounting for no more than 12% of all such patients in China. Understanding of the symptoms and mutations of FOP needs to be increased and the condition needs to be better diagnosed.

Sign and symptoms

FOP is usually characterized by the progressive replacement of muscle tissue and connective tissue (such as tendons and ligaments) by bone, which restricts the movement. The progressive condition becomes noticeable in early childhood, affecting neck and shoulders and proceeding down the body and into the limbs [16]. Development of an extra-skeletal bone causes the progressive loss of mobility as

the joints become affected. Speaking and eating might also become difficult as the mouth becomes affected. Over the time, people affected with FOP may become malnourished because of their inability to eat and develop respiratory difficulties due to the formation of extra bone formation around the rib cage, which restricts expansion of the lungs [17]. At age 10, the first flare-up that leads to the formation of FOP bones top downward, just like bones grow in fetuses. Individuals affected from classical FOP have malformations of the great toes and thumbs. Traumatically attack to the muscles of a FOP individual may trigger episodes of muscle swelling and inflammation followed by rapid ossification in the injured area. However, the flare-ups formation might also be caused by viral illnesses like flu [18]. People with FOP are generally born with malformed big toes. The abnormality in the big toes is helping to distinguish FOP between other bone and muscle problems. Affected individuals may also have short thumbs and other skeletal abnormalities [19,20].

Eventually, the FOP might result in the complete immobilization. The individuals affected with FOP may experience progressive pain, stiffness in injured areas, complete fusion of the spine and abnormal bony growths, which compress the nerves in these areas (entrapment neuropathies). On the next level, an affected individual has increased susceptibility to second level infection affecting other organ system such as respiratory infection or right sided congestive heart failure. Similarly, the FOP variants may exhibit hair loss, mild cognitive delay and hearing impairment. Due to the rare autosomal character, the FOP symptoms are sometimes misdiagnosed as cancer or fibrosis. This misconception leads to the physicians to order biopsies, which exacerbate the growth of these lumps and increase consequences [21].

S. No.	Signs and Symptoms	Approximate number of patients (when available)
1.	Abnormality of the first metatarsal bone	Very frequent (present in 80% - 99% of cases)
2.	Abnormality of the vertebrae	Very frequent (present in 80% - 99% of cases)
3.	Ectopic ossification in ligament tissue	Very frequent (present in 80% - 99% of cases)
4.	Ectopic ossification in muscle tissue	Very frequent (present in 80% - 99% of cases)
5.	Limitation of joint mobility	Very frequent (present in 80% - 99% of cases)
6.	Short hallux	Very frequent (present in 80% - 99% of cases)
7.	Spinal rigidity	Very frequent (present in 80% - 99% of cases)
8.	Subcutaneous nodule	Very frequent (present in 80% - 99% of cases)
9.	Alopecia	Frequent (present in 30% - 79% of cases)
10.	Aplasia/ Hypoplasia of the phalanges of the hallux	Frequent (present in 30% - 79% of cases)

Table 1: Appearance of abnormalities of FOP patients with number of patient affected.

Diagnosis

Accurately, the diagnosis and estimation of FOP are made based on a patient's big toe malformation and additionally the rapid changing in swellings on the head, neck or back. The outbreaks are measured clinically by an elevated level of alkaline phosphatase (ALP) and bone-specific alkaline phosphatase [22]. The rate of misdiagnosis of the disease is estimated at 80 percent or higher due to a lack of knowledge of FOP among doctors, which cause pain and suffering for FOP patients and their families worldwide. The misdiagnosis leads to an unnecessary invasive procedure such as biopsies which shows the permanent complications and implication of medical interventions and loss of mobility. Usually, the aggressive juvenile fibromatosis, also called desmoid tumors and progressive osseous heteroplasia (abnormal growth of bone) are reported as misdiagnosis of a FOP. The early misdiagnosis of Fibrodysplasia ossificans progressiva disorder (FOPD) can be avoided by examination of an individual's toes for the characteristic feature of short great toes. To confirm FOP existence, the diagnosis is confirmed by a characteristic physical findings, thorough clinical evaluation and sequencing of the ACVR1 gene.

In FOP there are no specific changes in laboratory tests. Acute phase tests, as well as the metabolism of calcium, phosphorus and parathormone (PTH) are normal. Biochemical analyses of bone mineral metabolism can be normal, however; the serum alkaline phosphatase (ALP) activity might increase. Blood composition and renal and parathyroid hormone levels are all within normal limits [23]. In urine, the level of basic fibroblast growth factor may be increased during FOP outbreaks coinciding with the pre-osseous angiogenic phase [8].

Pathophysiology

At a cellular level, FOP penetrates completely, however, the gene expressivity is variable. Basically, the FOP maps to band 4q27 - 31, which contains a region with at least 1 gene involving the bone morphogenic protein (BMP) signaling pathway [24]. BMPs are members of the transforming growth factor-beta superfamily, which plays a significant role in the development of bone and other tissues [25]. This is a multifocal condition, usually, develop after traumatization. Genetically, the FOP cause lies within the ACVR1 gene, which encodes a type I BMP transmembrane receptor. The occurrence of a recurrent mutation in the BMP type I receptor ACVR1 is responsible for the inherited and sporadic FOP [26]. Recently, in one report the FOP was mapped to 2q23 - 24 by linkage analysis [3].

In the last years, several mutations have been documented. A mutation of the noggin (NOG) gene in a FOP family was described [27]. A FOP encoding gene in the 17q21 - 22 region has been observed with several mutations described in the region of NOG gene (located in 17q22) in 4 FOP patients. This includes G91C mutation, which was transmitted dominantly in a Spanish family affected with FOP. These mutations are responsible for a change in the guanine to adenine nucleobases at the nucleotide 283 (283G → A) present at NOG gene, however, this could be transmitted by a FOP affected mother to her children. To understand the physiology of FOP, the continuous attempts are being made by researchers. Mutation in the activin A type 1 receptor gene has been reported in one patient. His analysis showed that the patient was heterozygous for a mutation i.e. G356D [28,29]. The FOP affected patients have been mainly categorized into 2 categories: first is FOP-plus (classic defining features of FOP plus one or more atypical features). Secondly, the FOP variants (major variations in one or both of the 2 classics defining features of FOP). Moreover, the typical mutations were found in all the cases of a classic FOP and most cases of FOP- plus.

On the other side, novel ACVR1 mutations were identified in the FOP variants and some of them with FOP-plus [30]. Mainly, the ACVR1 gene mutations (two unique mutations) have also been identified in 2 FOP patients belonging to the United Kingdom with some atypical digit abnormalities and other clinical feature [31]. The ACVR1 gene mutations were interpreted as resulting in local structural changes in the ACVR1 protein. This was revealed by interrogating homology models of the native and mutated ACVR1 kinase domains. Impaired FKBP1A binding and an altered sub-cellular distribution by R206H ACVR1 mutation may activate the estrogenic BMP-signaling in extracellular sites. This cause a delay and progressive ectopic bone formation [32]. The other mutation such as a novel ALK2 mutation, L196P has also been identified and reported in a mild form of FOP [33].

Treatment

Unfortunately, at the current stage, there is no cure or approved treatment for FOP [8]. Usually, in FOP treatment the biopsies should be avoided because the tests may result in rapid bone formation in the injured area or where the tissue is removed [13].

- The occurrence of various virus illnesses mainly influenza and influenza-like illnesses may provoke the formation of flare-ups.
- In FOP affected individuals, those are prone to increased susceptibility for respiratory and other organ infections due to progressive mobility impairment, preventive measures may be taken to stop an infection, such as preventative (prophylactic) antibiotic therapy.
- During anesthesia, FOP people may encounter difficulties with restrictive pulmonary disease, intubation and changes in the electrical conduction of the heart [34].
- The phenomenon that may increase the risk of falling or soft tissue injury must be avoided. Because even a minor trauma may provoke the formation of heterotopic bone.
- Reduction in the intense inflammation and tissue swelling is seen in the early stages of FOP by a brief course of high-dose corticosteroids, such as Prednisone, started within the first 24 hours of a flare-up.
- Other medications, such as muscle relaxants, mast cell inhibitors, and amino bisphosphonates can be given with close monitoring by a physician.
- Surgery to remove heterotopic and extra-skeletal bone is risky and can potentially cause painful new bone growth [35].
- FOP affected individuals may be benefitted from the occupational therapy i.e. special shoes, braces and other devices. This will assist the patient in walking and weight-bearing.
- Counseling or genetic counseling of family may benefit the families.

- Combined efforts for infants with special social, educational, and medical services with this disorder will also be of benefit. The other treatments are symptomatic and supportive.
- An individual born with FOP, extra bone formation may not appear at a birth time. The patient may go months or years without experiencing a flare-up, which signals the development of new bone.

Conclusion

Fibrodysplasia ossificans progressiva (FOP), a rare genetically disabled disorder characterized by congenital skeletal malformations and progressive heterotopic ossification (HO). FOP is found to be one of the most catastrophic disorders of HO in humans. The episodic disease flare-ups are precipitated by soft tissue injury. To the best of our knowledge, the existing literature strongly suggests that an occurrence of recurrent mutation in activin receptor IA/activin-like kinase 2 (ACVR1/ALK2) and a bone morphogenetic protein (BMP) type I receptor presents in all sporadic and familial cases of classic FOP and other forms of FOP. This makes the FOP one of the most highly specific disease-causing mutations in the human genome. The discovery of the FOP causing gene has established a critical milestone in understanding of FOP revealing a highly conserved target for development of drug molecules for transforming growth factor (TGF)- β /BMP signaling pathway and compels therapeutic approaches for the development of small molecule signal transduction inhibitors for ACVR1/ALK2 (enzyme characterized as target in FOP). Currently, the FOP management involves an early diagnosis, assiduous avoidance of harmful effects and symptomatic amelioration of painful flare-ups and swelling. To treat FOP, the effective therapies may potentially be based on future interventions that block ACVR1/ALK2 signaling mechanism.

Acknowledgements

Authors would like to acknowledge SPS-MVN University for providing facility and support.

Conflict of Interests

The authors declare no conflict of interest.

Authors' Contribution

Atul Sharma (A.S.) and Reshu Virmani (R.V.) performed the survey of literature and wrote the manuscript. Gaurav Upadhyay (G.U.) also contributed in the literature survey and manuscript writing. Jyoti Gupta (J.G.) contributed in manuscript writing and formatting. Tarun Virmani (T.V.) and A.S. were the investigator was the investigator of this review and designed the manuscript.

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Volume 6 Issue 7 July 2018

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