Fibrodysplasia Ossificans Progressiva: A Literature Review and Case Study

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Abstract

Fibrodysplasia ossificans progressive is a rare and serious genetic disease that could have harmful and deadly results. The disorder, which has been called *Stone Man Syndrome*, has marveled mankind for ages with its unique characteristics and sometimes idiopathic nature. Cases will be presented to help give a better understanding of the hardships patients confronted with the disease might face.
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. There are currently no known cures for FOP.

Literature Review

FOP is a rare genetic disorder of the exoskeleton anatomy. “This disorder is caused by heterozygous activation mutations of the gene encoding activin receptor A type 1/activin-like kinase 2 (ACVR1/ALK2), a bone morphogenetic (BMP) type-1 receptor, in all classically affected individuals worldwide” (Kaplan et al., 2010, p. 687). This disease isn’t related to or more prevalent in any one particular gender, ethnicity, or geographical area. Patients affected with FOP usually experience multiple disabilities and are confined to a wheelchair by the third decade of life.

FOP Origins

The origins of FOP are still unknown today. It is possible that the biblical story of Lot’s wife (Genesis 19: 1-26) may be referring to FOP when they speak of her being turned into a
pillar of salt. However, the first person who described the disease in detail was French doctor Guy Patin in 1692. The genetic mutation of a Bone Morphogenic Protein (BMP) is the cause for this harmful disorder. BMPs are regulatory proteins that play an important role in bone formation and the reconstruction of fractures. These proteins are tied to a receptor called activin receptor type IA (ACVR1) and it has been traced all the way down to chromosome 2q23-24. The knowledge of this mutation may allow pharmacology to create a drug useful for the stimulation or inhibition of the mechanisms for this protein, therefore giving us the ability to regulate FOP.

**Case Studies**

In a study conducted at the Imam Khomein Hospital, data was taken from 12 children diagnosed with FOP. All of these kids were diagnosed and referred to the Pediatric Rheumatology Department over a time span of 25 years: from 1983 until 2008. One doctor was responsible for conducting the diagnoses and completing follow up studies. The study included six girls and six boys ranging from the ages of two through 13.5 with a mean age of seven. “90 percent of FOP patients worldwide are initially misdiagnosed, and 67 percent undergo avoidable procedures that have led to permanent harm and life-long disability in more than 50 percent of patients” (Raees-Karami, Jafarieh, Ziyayi, Shekarriz Foumani, & Aghighi, 2012, p. 1134). The most common incorrect diagnoses include malignancy, aggressive juvenile fibromatosis and desmoids tumors. However the observing physicians at Iman Khomein Hospital used criteria such as congenital skeletal malfunctions of the great toe and calcification of other anatomy, such as neck, trunk, and extremities to identify and diagnose FOP.

**Other Indications**

Other indications of FOP include soft tissue tumor lesions and painful swelling of connective tissue followed by progressive fibrosis, calcification and ossification. 11 of the 12
children experienced reduced joint mobility; the only patient that did not experience the reduced range of motion was a three year old girl, who was diagnosed from an unusual mass on her forehead at 6 months. None of the patients had a family history of FOP, leading doctors to believe that these patients contracted this disorder sporadically. In most of the cases in this study, trauma was the event that triggered most symptoms.

**Early Recognition**

Early recognition and diagnosis of FOP is critical in the treatment of the disease. Even though there is no known cure, this information can be used to prevent false and unnecessary procedures that may be harmful to the patient’s health. This early knowledge can increase the quality of life by helping in avoiding activity that may put the patient at high risk of trauma; trauma avoidance may delay, decrease, or even prevent the joint immobility. With this advantage, there is a possibility of reducing a lifetime of physical and emotional distress.

Over a 33 year study, info was gathered from a controlled population within a certain period of time and from a multiethnic controlled population which represents the areas. There was a huge difference shown by the log-rank test. There were 60 deaths reported, half of them were males while the other half were female. The main cause of death for the patients diagnosed with FOP was cardiorespiratory failure from thoracic insufficiency syndrome which caused over 54 percent of the deaths in this study of FOP. A few of the other causes of death included pneumonia, falls, and sepsis. The average age of death from the patients suffering with FOP is about 56 years old, compared to the normal age of the U.S. population which is 78 years of age.

A study was done in 2004 of a 24 year old woman, with a two year history of back pain and stiffness. “Examination revealed a stooped posture, restricted cervical and lumbar spine movements and a two by two centimeter firm mass in the right submandibular fossa” (Dugar,
2010, p. 863) which arbitrarily disappeared 2 months after being discovered. Later radiographs showed fused thoraco-lumbar facet joints. A diagnosis of undifferentiated spondyloarthritis was given to the patient, so in order to counteract this disorder, anti-inflammatory agents and exercises were prescribed. Soon after, her shoulder, hip and back pain started going away. However, while her pain was minimizing, she started developing another mass in her axilla without trauma to induce it. Physicians prescribed C-reactive protein which caused the mass to decrease within a few days. A follow up study was done on her four years later which showed back pain and stiffness once more. After a Computed Tomography exam was completed, a high level of heterotopic ossification (HO) was discovered which lead to a new diagnosis of FOP, even though she had no previous history of common signs from the disease. FOP has been known to mimic Ankylosing Spondylitis only in two other cases, which makes it difficult to identify especially if there had been no previous childhood flare up.

One man questioned his eight year old son Vincent’s abnormal stride as he walked down the hall. It all originated from a slight limp that was first noticed over four years ago, but never quite addressed. After multiple tests were completed, pediatricians diagnosed him with FOP. One night after being delivered the displeasing news, Vincent’s mother and father were glued to the books, trying to research the newly diagnosed issue. “We learned that FOP is a nightmarish disease that gradually transforms healthy people into living statues, permanently and painfully fusing every joint” (Zapata-Whelan, 1999, p. 134).

A year after receiving the diagnosis and researching the disease, Vincent developed a small bump on the right side of his spine. It eventually swelled up, but went away over the next few weeks. Even after it vanished, the once minor bump limited Vincent’s mobility in that area. A year after that, his complete left side became swollen, limiting mobility as well. Despite his
parents’ attempt to control the disorder, it continued to take over. All Vincent’s parents could do was try and comfort him with pain killers. Coming from a family of athletes, Vincent questioned in rage why he was cursed with this problem. Even in his hour of distress, he still managed to show up and support all of his family from the bleachers, even though deep down he wished he also had the opportunity.

There is still hope in the future for patients like Vincent. Scientists are in the lab working and researching for treatments for the FOP. Incredible bone advancements have been made from a study of a family with a history of multigenerational FOP in it. It is believed that the DNA of these families may have some insight to the treatment of FOP or any other bone diseases such as arthritis.

One study was done which was conducted over a 30 month period directly from patients with FOP, that involved observing the proximal portion of their tibia during a routine physical. Because of the sporadic reports that were cited, the proximal tibia was just the designated area to focus on. When gathering information about patients’ background, they were asked questions about their lower limb systems, such as if they experienced any swelling, pain, numbness, or paresthesias. This study also included a physical examination and visualization from radiographs of the proximal tibia in order to find osteochondromas.

Out of 96 patients studied for this case, 86 of the patients had at least one palpable mass located on their proximal tibia. Only two out of the 86 osteochondromas were located posterior medially, while the other 84 were found on the anterior medial portion of the tibia. 67 of those patients had had previous scans read by radiologist, with 62 of them visualizing a mass on the proximal tibia, Deirmengian et al. (2008) states:
This study specifically establishes proximal tibial osteochondromas as a common phenotypic feature of fibrodysplasia ossificans progressiva and expands the clinical consequences of endochondral bone formation associated with the recurrent activating mutation in ACVR1 to include not only congenital malformations and heterotopic skeletogenesis but also benign osteochondral neoplasms or orthotopic lesions of skeletal modeling (p. 369).

In another study, a 16 year old boy demonstrated symptoms of FOP yet had not been diagnosed with the disorder. He developed a lesion over his left scapular region. The patient ordered a biopsy of the lesion as it started to increase in size, even though it really gave no indications of being malignant. Malignant tumors are one of the most common misdiagnoses for FOP. “In a study of 138 patients with FOP, 92 had a biopsy performed shortly after initial presentation (FOP a new spotlight of an old disease)” (Hamilton, Roxburgh, & Renshaw 2008, p. 449). Therefore, a biopsy is a bad idea because theoretically, trauma or any invasive procedure may trigger an onset of the disease. For instance, the damage to the soft tissue around the affected area has the potential to cause rapid ossification within the region.

In yet another study a three year old boy was diagnosed with FOP due to the findings of congenital malfunctions of the great toe and the heterotopic ossifications found all over his body. Within the first decade of his life there had been identification of FOP lesions located from his neck down to his back, causing a lack of mobility throughout those areas. Despite all of these obstacles, this child did not allow these problems to take away from any of his childhood joy. At the age of 10 there was a noticeable increase in nosebleeds and easy bruising caused by a drop in his peripheral blood cell count. Physicians tested the bone marrow and found no marrow toxicity, but did find symptoms consistent with aplastic anemia were discovered linked to FOP. At the
age of 10 the patient had a transplantation of allogeneic bone marrow from his sister, and then shortly after that he received a second transplant from her. “Flare-ups of fibrodysplasia ossificans progressiva were notably absent following the second bone-marrow transplantation and for the ensuing fourteen years while the patient received immunosuppressive medications” (Kaplan et al., 2007, p. 349).

In 2004 a 47 year old man found himself restricted in all the of the girdle area for just over a years’ time. He had no past history of serious illness, nor was there any evidence of it from his family. There were no previous childhood indications of the disorder present such as the common malformed great toe or hypo plastic thumbs. From a young age, he led a normal life, even growing up to play nonprofessional football and going on to become a bus conductor. “Suddenly, as a middle aged seemingly healthy male, he sporadically developed Heterotopic Ossifications, a pathological process of lamellar bone formation in non-osseous tissues” (Jayasundara , Punchihewa, & Alwis, 2012, p. 83).

He first started experiencing symptoms in his hips, which later on moved to his shoulder. The disease slowly started affecting his ability to play football, and as symptoms increased, they eventually took a toll on his day to day routine. Being that he showed no symptoms in his childhood or a family history towards being FOP positive, when the unidentifiable masses started to appear, in fear of them being malignant, and to restore mobility back to the affected sites, doctors recommend they be removed by surgery. Over almost a two year time span, the patient underwent four surgeries, spreading them apart by four to eight months each. The surgeries were a success, but only for the moment. Mobility and strength were regained in the areas for about eight to nine months, but shortly after, the areas begin to re-ossify.
He continued to fight the disorder throughout the years, but eventually he lost the battle and was classified as bedridden in 2010, becoming a stone man in the lower portion of his body. The surgery of his shoulder girdle was the only surgery that showed improvement. The patient was able to use all of his upper limbs to eat and talk at the time the study was done, but could no longer enjoy the satisfaction of lower body mobility. All of the other surgeries were actually successful in helping this disease progress.

**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.
Figures

Figure 1. This is an image of a 13 year old patient demonstrating FOP throughout his spine, fingers and toes.


![Image of a 13 year old patient demonstrating FOP throughout the spine, fingers, and toes.](image)

Figure 2. This image is a reconstruction of a 12 year old child with FOP.

References


