Fibrodysplasia Ossificans Progressiva

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Abstract

Fibrodysplasia ossificans progressiva (FOP) is a highly rare and debilitating disease that causes areas of fascia, ligaments, tendons, and skeletal muscle to ossify. Characteristics of FOP may vary but three prominent ones are malformed toes, swelling nodules, and heterotopic ossification. The process through which this ossification takes place is initially started by a mutation on the ACVR1 receptor. Scientists are currently studying this mutation in hopes of better understanding the manner in which the mutation functions so as to procure methods of treatment for this disorder.
Fibrodysplasia Ossificans Progressiva

Out of the 10 individual systems in the human body, there are two distinct systems, which main purposes are to support and protect the body as well as allow for movement. The first system that gives the body structure is the skeletal. The second, which produces voluntary and involuntary movements, is the muscular system. In Fibrodysplasia ossificans progressiva (FOP) the line between these two systems becomes somewhat blurred. Also known as myositis ossificans progressiva, FOP is a severely debilitating, autosomal dominant disorder that results in loss of mobility due to progressive heterotopic ossification of tendons, ligaments, fascia and skeletal muscle (Mahboubi, Glaser, Shore, & Kaplan, 2001). Unlike striated muscle and soft tissues, smooth muscle structures such as the heart, diaphragm, larynx, tongue, and sphincter are not affected by this disorder (Baysal, Elmali, Kutlu, & Baysal, 1998). FOP is exceedingly rare with the occurrence rate being roughly 1 in every 2 million people and is not specific to race, ethnicity, gender, or geographic location (Kaplan & Xu et al., 2008). The first case of FOP was reported in 1692 by Guy Patin (Connor, Evans, & Evans, 1981). Since then the most notable case was that of Harry Eastlack (See Fig. 1), who donated his skeleton to the Mutter Museum of the College of Physicians in Philadelphia to aide in research (IFOPA, 2009). As of 2008, the number of known living patients with FOP has been estimated to be 300 people (Frew & Kelly, 2008).
Characteristics of FOP

Manifestations of FOP can vary from patient to patient, but there are certain characteristics that the majority of those with FOP demonstrate. The biggest indicator that alludes to this disorder is congenital malformation of the great toes (hallux valgus) (See Fig. 2). This appears in approximately 95% of diagnosed patients (Kitterman, Kantanie, Rocke, & Kaplan, 2005). While the malformation of the great toes is present at birth, postnatal progressive heterotopic ossification does not profess itself until later on in the affected person’s life. Heterotopic ossification describes bone formation that is found in any abnormal anatomical site such as soft tissue. Heterotopic ossification takes place quite early on in an FOP patient’s life; usually within the first decade. The start of this process can be seen by multiple nodules rapidly appearing on regions of the head, neck, or back (See Fig. 3). Other
features of FOP that are commonly seen include, but are not limited to, cervical spine malformation, proximal medial tibial osteochondromas (See Fig. 4), a short/broad femoral neck, conductive hearing impairment, thinning of hair, and thumb malformation (Piram et al., 2010).

**Pattern of malformations**

In studying patients with FOP, a pattern for anatomical progression of heterotopic bone formation has been observed. This characteristic pattern is usually exhibited first in dorsal, axial, cranial and proximal regions of the body. As the disorder progresses, ventral, appendicular, caudal, and distal regions are then affected (Mahboubi et al., 2001). Interestingly enough, this pattern of heterotopic ossification closely resembles that of embryonic skeletal formation. If there is any significance in this resemblance of pattern, it has yet to be discovered. Due to this progression pattern of bone formation, the majority of patients are severely limited in the mobility of their upper limbs by the age of 15. As ossification moves caudally, movement is restricted even more causing many patients to be confined to wheelchairs by the age of 30 (Frew & Kelly, 2008).

**Process of Ossification**

A common misconception of how the ossification process takes place is that of transdifferentiation of mature cells into other cell types. Rather, it is a pathological process in which the normal function and structure of one tissue or organ are replaced by those of a different functioning tissue. The bone morphogenetic protein (BMP) signaling pathway is a very complex and diverse pathway that regulates countless developmental and post-developmental processes. In every FOP case worldwide, an identical heterozygous missense activating mutation has been discovered on the ACVR1 receptor for BMP which is believed to be the instigator of the FOP disorder. This single nucleotide missense mutation transforms a morphogen receptor
gene into a metamorphic gene. The resultant transformation alters the basal set point in turn altering the ligand-dependent sensitivity for BMP signaling in connective tissue progenitor cells (CTPs). Unfortunately, the role that ACVR1 plays in cell differentiating is not completely understood and leaves some room for interpretation (Kaplan & Shen et al., 2008).

**Inflammation as a trigger**

Although heterotopic ossification can occur on its own, inflammation and injury can aggravate and quicken the process of bone formation. One such study performed by Kaplan and Shen et al. (2008) suggested that the new FOP mutation creates a pH-sensitive switch within the cytoplasmic domain of the mutant ACVR1 receptor. This not only leads to ligand independent activation, but also to ligand-dependent hyper-responsiveness of mutant ACVR1. Therefore, when a soft tissue injury occurs it creates an inflammatory and acidic microenvironment. Along with prostaglandins, free radicals, and hypoxia, inflammatory cells of hematopoietic origin stimulate resting CTPs. These CTPs express the mutant ACVR1 receptor which is supposedly hyperactive in mildly acidic, intracellular environments. This then results in misregulated BMP signaling through increased basal leakiness. Once fibroproliferative cells in the FOP lesion have been formed, they produce copious amounts of a certain BMP known as BMP4. By then, overactivity of the BMP signaling is sufficient to complete the process of endochondral ossification in the absence of inflammatory stimulus.

**Misdiagnosis**

Because of its rare nature, diagnosis of FOP is frequently delayed. This delay in diagnosis is due in part to lack of knowledge of medical professionals (See Fig. 5) Many physicians are unfamiliar with indications of FOP, resulting in 90% of FOP patients being misdiagnosed before finally receiving the correct diagnosis (Kaplan & Xu et al., 2008). One such misdiagnosis is
myositis ossificans traumatica (MOT). Similar to FOP, MOT results in ossifications due to trauma, but at the peak of their maturity, masses will begin to shrink (Baysal et al., 1998). Another common misdiagnosis is that of ankylosing spondylitis, which is an inflammatory disease that can cause fusion of the spinal vertebrae restricting movement. Although it is somewhat comparable to FOP, ankylosing spondylitis doesn’t embrace the full extent of the disorder as it is only limited to the spine while FOP ankylosis takes place in every joint of the body. Undoubtedly, the most dangerous and commonly made misdiagnosis would be that of lymphedema, soft tissue sarcomas, or any kind of tumors suspected of cancer in the nodules that are presented on the head, neck, and back of young children (Kaplan & Shen et al., 2008). This misdiagnosis is harmful as it usually involves invasive procedures that are needless and only worsen the condition of the patient since FOP responds to inflammation as a result of injury to muscles and tissue.

**Iatrogenic harm**

Since numerous clinicians are not familiar with the classic features of FOP or with the clinical implication of congenital malformation of the great toes, unnecessary procedures that are performed, which could be avoided, may exacerbate the soft tissue causing the heterotopic bone formation to progress even faster (Kaplan & Shen et al., 2008). Harm such as this, caused by a physician that aggravated the condition rather than helped, is known as iatrogenic harm.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. Given the Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>32</td>
</tr>
<tr>
<td>Fibromatosis*</td>
<td>19</td>
</tr>
<tr>
<td>Bunions (or hallux valgus)</td>
<td>9</td>
</tr>
<tr>
<td>Injuries attributable to trauma or overuse</td>
<td>7</td>
</tr>
<tr>
<td>Myositis (including myositis ossificans)</td>
<td>6</td>
</tr>
<tr>
<td>Calcified hematoma</td>
<td>6</td>
</tr>
<tr>
<td>Arthritis (including rheumatoid arthritis)</td>
<td>5</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>4</td>
</tr>
<tr>
<td>Exostoses</td>
<td>4</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>3</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>3</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>2</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>3</td>
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Kitterman et al. (2005) trusts this is partially due to the lack of available information given to those studying in the medical field. This belief lead to a search through numerous medical books to see just how many of them made reference to this rare disorder.

Although a search of the PubMed database (of the National Library of Medicine) for FOP yielded 584 references from the past 20 years, of which 204 referred directly to FOP, a cursory review of medical textbooks revealed that few mentioned FOP or described its clinical features (p. 655).

Kitterman et al. (2005) sent out a questionnaire to patient-members of International Fibrodysplasia Ossificans Progressiva Association (IFOPA), which reported that only 13% of the 138 individuals who completed the survey were given FOP as their initial diagnosis. Conversely, many patients were given more than one incorrect diagnosis. For 80 of the patients, delay in diagnosis was greater or equal to one year while the delay in diagnosis for 56 of the patients was greater or equal to two years. Meanwhile, interventions that were used for either therapeutic or diagnostic purposes continued to cause people damage. Side effects, some of which were extremely debilitating, were reported by 71 patients. Out of those 71, 70 of them stated that they had experienced a permanent loss of movement. The 1 patient who did not report this loss had received a complete forequarter amputation. One mother told of her son who had underwent 5 operations to remove heterotopic bone saying, “After each operation, there was more loss of movement and more lumps, but each specialist insisted on removing more” (p. 658). Even more perplexing is the fact that after being diagnosed with FOP, 34 patients stated that they received inappropriate procedures such a mandibular blocks or stretching of the temporomandibular joint, and surgical procedures that caused serious loss of motion. Also, after the diagnosis was given, multiple patients received erroneous information pertaining to the severity of the disorder. Some
parents were told that their child would die soon while other parents were told that FOP would “burn out” at a certain age. In both instances, these pieces of information were grossly misstated.

**Causes of Death**

Without a doubt, patients with FOP have a significant shortening in life span compared to that of an average human being. The explanations behind this shortening are debatable, however. Kaplan and Zasloff et al. (2010) found that cardiorespiratory failure due to thoracic insufficiency syndrome (TIS) was the main culprit causing 54% of FOP deaths. Pneumonia constituted 15% and complications from falls was 11%. Many factors can contribute to TIS such as early orthotopic ankylosis of the costovertebral joints, fusion of ribs (See Fig. 6), or ossification of inter costal muscles. Connor et al. (1981) argue, however, that the severity of TIS is not incapacitating enough to cause death. Only in severe thoracic kyphoscoliosis is cardiorespiratory failure likely. This, however, is quite rare in cases of FOP. Instead of focusing on cardiorespiratory failure, they believe that more attention should be devoted towards the prevention and therapy of chest infections. Such therapies may include chest physiotherapy, prompt antibiotic treatment of early chest infection, and pneumococcal and influenza vaccines (p.423). Therapeutic use of oxygen should not be implemented as it can lead to further loss of respiratory drive and heighten the manifestations of the disorder (Kaplan & Zasloff et al., 2010).

**Treatment**
As of now, there is no effective treatment for FOP. “This disorder’s rarity, variable severity, and fluctuating clinical course hamper the evaluation of experimental therapies” (Kartal-Kaess et al., 2010, p.1420). In a study done by Kaplan and Glaser et al. (2007), a patient was studied who had been diagnosed with severe aplastic anemia at the age of 10. Chronic graft-versus-host disease developed after the patient received a bone marrow transplant. The patient was then given steroids to fight the rejection for 14 years. During this 14 year period no notable occurrences involving FOP took place. Gradually after the medications had been discontinued, flare ups of FOP began to manifest themselves. After being officially diagnosed with FOP when he was 35, researchers pondered what could have caused the disorder to be dormant for so long in the young man. They were optimistic that if hematopoietic cells were replaced, they would take over and produce normal tissue. This, however, was not the case. Instead it appeared that the treatment with steroids suppressed the immune system which in turn suppressed inflammatory responses to any injuries that could have triggered heterotopic ossification. Therefore, future studies will most likely be done on the affect steroid treatments can have on FOP.

**Prevention**

Pre-symptomatic genetic testing of children has been debated much over the years as to whether or not it is ethical. Although it is possible for FOP to be inherited, reproductive fitness is low due to the early onset of symptoms, which leaves spontaneous mutation as the most common cause. Therefore, because of this rare spontaneity and brutal nature of FOP, such genetic testing would be justified. Once a diagnosis of FOP has been confirmed, avoidance of injuries to soft tissue such as trauma, preschool immunizations, dental injections, and possible future lesional biopsies may perhaps slow down the progression of the disorder allowing for a longer life (Kaplan & Xu et al., 2008). Also, while physical therapy may seem like a powerful prevention
tool, it is essentially the opposite. While stretching, a muscle may be strained and could cause painful flare ups once again causing unnecessary ossification (Kocyigit, Hizli, Memis, Sabah, & Memis, 2001).

**Conclusion**

Although fibrodysplasia ossificans progressiva is an extremely rare disorder, more studies should be done to explore the pathological processes that are occurring to be able to target the process and prevent FOP from fully developing. Research is also important in finding treatments that may help those who have already been diagnosed with FOP to possibly regain some mobility or extend their life expectancy. Optimistically, more opportunities for research will present themselves through those select few patients that have been diagnosed or through Harry Eastlack’s donated body and will assist in answering some unresolved questions.
References


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