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Fibrodysplasia Ossificans Progressiva (FOP): Genetic Mechanisms, Clinical Features, And Emerging Therapeutic Approaches

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Abstract
Fibrodysplasia Ossificans Progressiva (FOP) is an ultra-rare genetic disorder characterized by progressive heterotopic ossification, wherein soft tissues are gradually replaced by bone. This paper examines the genetic and clinical features of FOP, focusing on the ACVR1 gene mutation and its disruption of the bone morphogenetic protein (BMP) signaling pathway. The study analyzes the progression of the condition, including hallmark symptoms such as congenital malformations of the great toes, flare-ups following trauma, and loss of mobility. Current management strategies, such as corticosteroids and NSAIDs, are discussed alongside promising but untested future therapeutic approaches like CRISPR gene editing. Real-life case studies illustrate the diagnostic challenges, frequent misidentification with other conditions, and the severe lifelong impact of FOP. The findings emphasize the urgent need for increased awareness, early diagnosis, and sustained investment in research and healthcare infrastructure to develop effective treatments for this debilitating disorder.

Keywords: *Fibrodysplasia Ossificans Progressiva, ACVR1 mutation, heterotopic ossification, CRISPR therapy, rare genetic disease*

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I. Introduction

Ever heard of FOP? Likely not - it is an extremely rare disease affecting just 1 in 2 million people worldwide (Cleveland Clinic, 2022).

Fibrodysplasia Ossificans Progressiva (FOP) is an ultra-rare congenital skeletal bone disorder characterised by soft tissues like muscles and ligaments gradually turning into bone (ossification). This new bone formation eventually causes joint fusion (ankylosis), thereby severely restricting movement (NORD, 2024). FOP was first discovered by Guy Patin, a French physician, in 1692. He described a woman who "turned into wood"; the wood he described here actually referred to the formation of new bone (National Center for Biotechnology Information (US), 1998). However, the real cause for FOP was discovered only in 2006 by a team of researchers headed by Eileen M. Shore and Frederick Kaplan at the University of Penn (NORD, 2024). Their research identified a mutation in the ACVR1 gene that causes irregular bone formation.

FOP is frequently confused with Fibrodysplasia (FD). Though both may sound similar, their processes are exactly the opposite. Fibrodysplasia is characterised by normal bone getting slowly replaced by fibrous and softer tissue, leading to weakened and deformed bones. It is caused by mutations of a different gene – the GNAS gene. Although FD is rare, it is more common than FOP and occurs in approximately 1 out of every 5,000 individuals worldwide (Kim et al., 2023). This research paper, however, will focus solely on FOP.

FOP is a condition with no definite cure or treatment. Due to its rarity, it is often misdiagnosed by medical professionals and may worsen as a result of any random biopsy or regular injections. The need for early diagnosis is therefore imperative. In good news, several promising treatment strategies and targets have recently been reported, including physiotherapy, pain-reducing treatments, and other approved medications. The U.S. Food and Drug Administration (FDA), for instance, has approved Sohonos (palovarotene) capsules for reducing the rate and volume of new heterotopic ossification (extra-skeletal bone formation) in certain age groups with FOP (FDA, 2023).

In accordance with the aforementioned, **this research paper aims to examine the genetic and clinical features of FOP, analyse its progression, evaluate current treatment efforts and research predictions, and highlight real-life cases to illustrate the impact of this condition on humans.**

II. Background on FOP

As mentioned in the introduction, FOP was first described as early as 1692, but it wasn't until 2006 that Shore et al. discovered the ACVR1 mutation. Since then, FOP has become a subject of genetic, orthopedic, and pharmaceutical research, especially for targeting the BMP pathway.

A mutation in the ACVR1 gene causes FOP. It encodes activin A receptor, type I, also known as the ALK2 (activin-like kinase 2), which triggers a Bone Morphogenetic Protein (BMP) type I receptor (Shore, 2011). The BMP pathway is a cell-signalling pathway that contains multifunctional proteins (belonging to the Transforming Growth Factor-β family). Activity in the BMP was first discovered in the mid-1960s. Since then, BMPs have demonstrated the ability to induce fibroblast stem cells to differentiate into bone, thereby highlighting their role in bone and cartilage formation. These proteins are required for stimulating bone growth as well as maintaining tissue homeostasis, such as repairing muscle wear and tear. BMPs also play a significant role in embryonic development by initiating cardiac growth, mesoderm (tissue giving rise to muscles and connective tissues) formation, as well as developing extra-embryonic tissues such as trophoblast. Specifically, BMP2 and BMP4 play an extensive role in mesoderm differentiation during gastrulation (embryo transformation into a layer of epithelial cells). They are associated with the formation of primordial germ cells (PGCs) (Wang et al., 2014).

A classic example of ACVR1's effect on BMP signalling is the ACVR1 R206H mutation: it induces enhanced signaling through the canonical transducer of BMP ligand binding and receptor activation (Wang et al., 2014). This leads to dysregulated BMP signalling, resulting in abnormal bone formation, as seen in FOP.

While some cases of FOP are genetic, most cases are sporadic due to mutations in the ACVR1 gene. One copy of the mutated gene from either parent is enough to carry on the disease, i.e., FOP is developed in an autosomal dominant pattern. The mutation arises newly in the affected individuals and is not inherited.

Many clinical features can help identify FOP. Children having FOP usually appear normal at birth except for congenital malformations of the great toes (short, bent, or turned inward - present at birth). Painful and highly inflammatory soft tissue swellings (or flare-ups) occur, transforming soft connective tissues such as aponeuroses, fascia, ligaments, and skeletal muscles into a rigid structure resembling bone (Morovvati et al., 2014). Most patients become confined to wheelchairs in their thirties and fall victim to serious pulmonary problems. FOP is also frequently characterised by flare-ups triggered by trauma, surgeries, or injections, triggering myositis (muscle inflammation). Over time, the formation of extra-skeletal bone leads to joint immobilization and eventual loss of mobility. All these consequences lead to lifelong trauma, psychological effects, and emotional instability.

Since FOP is ultra-rare, it is often misdiagnosed as fibromatosis or soft tissue sarcoma, which usually leads people to undergo harmful interventions such as biopsies, potentially worsening the condition. Therefore, genetic testing for ACVR1 should be improved, and more focus should be given to research for the cure of FOP.

III. Pathophysiology, Treatment, and Challenges of FOP

Most symptoms of FOP are observed before the age of 10, while some are observed during the second decade of a person's life. An early sign of FOP is congenital malformation of the great toes, present in more than 95% of cases. This typically appears as shortened or malformed big toes, often with hallux valgus angulation, which is present from birth and distinct from acquired bunions seen in the general population. Congenital bilateral hallux valgus (commonly referred to as bunions) is a foot deformity where the big toe (hallux) angles inward, towards the second toe, and a bony bump forms at the base of the toe. This misalignment involves the first metatarsal bone deviating inward and the big toe moving outward, causing the formation of a "bunion" or bump. This usually results in swelling of the toes and can limit mobility to a great extent. Approximately 23% of adults aged 18-65 have hallux valgus, increasing to 36% in adults over 65 years of age (Nix et al., 2010).

A case report by Towler et al. (2017) confirms that while big toes remain the earliest indicator of FOP, it is still overlooked by many people. At a very tender age, children are prone to mandatory vaccinations and treatments. However, these can alter/generate mutations in the body, which may trigger genes associated with FOP, and flare-ups can often be neglected or misdiagnosed. Thus, such conditions need to be examined well and identified at an early age.

Another diagnostic feature of FOP is heterotopic endochondral ossification (HEO), resulting in bone formation in muscles, tendons, ligaments, and connective tissues. This is often preceded by painful, recurring flare-ups or episodes that may be spontaneous or triggered by trauma. The first flare-ups during FOP typically manifest as soft tissue swellings, often in the neck and shoulders, especially during early childhood. These flare-ups are characterized by inflammation, swelling, pain, and stiffness, and are often mistaken for tumors. Flare-ups transform skeletal muscles, tendons, ligaments, and aponeuroses (connective tissue connecting muscles to

bones) into heterotopic bone, making movement impossible. HEO in FOP is intermittent, but affliction is cumulative (De Brasi et al., 2021). Most patients with FOP are confined to a wheelchair by the third decade of life and require lifelong assistance in performing day-to-day functions

A few musculoskeletal features of FOP are related to dysregulated chondrogenesis, including abnormal articular cartilage formation, abnormal diarthrodial joint specification, and growth plate dysplasia. In FOP, mutations of ACVR1, the bone BMP type I receptor, are responsible for the osteochondrodysplasia that impacts developmental phenotypes of this illustrative disorder. Some other complications include severe weight loss, ankylosis of the jaw, right-sided heart failure due to rigid fixation of the chest wall, as well as thoracic deficiency syndrome (Kaplan et al., 2008). These are some major reasons why the mean life expectancy of people with FOP is reduced to 50-60 years of age (Ortiz-Agapito & Colmenares-Bonilla, 2015).

Currently, there is no definite cure for FOP due to the lack of understanding of such a complex disease. However, there is some medication available to reduce the explosiveness of FOP, such as corticosteroids, palovarotene, and non-steroidal anti-inflammatory drugs (NSAIDs) (Pignolo et al., 2011). Corticosteroids are most effective when used early to treat flare-ups in the jaw/mandibular area or major joints. Palovarotene, commonly sold as Sohonos, is a medication used for the treatment of heterotopic ossification and FOP, which the FDA has recently approved. It is a highly selective receptor gamma (RARγ) agonist that inhibits BMP signalling to promote bone formation (FDA, 2023). NSAIDs are often suggested for the treatment of acute or chronic conditions where pain and inflammation are present. These drugs can help with symptoms during a flare-up.

Apart from these approved methods, research is being conducted using CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) technology. This is used to specifically modify DNA in living organisms. The CRISPR-Cas9 holds promise as a potential treatment to rectify genes associated with FOP. Researchers are working on editing the ACVR1 gene in cells, such as stem cells, with the aim of preventing abnormal bone formation. Researchers are also exploring the possibility of delivering CRISPR-Cas9 directly into the body to target and edit the gene in affected tissues, thereby preventing new bone formations via the process of in vivo editing. Currently, there are no official clinical trials that have taken place, but the new advancements in such CRISPR inventions show promise.

It is also important to acknowledge that the effects of FOP are not only physically tolling, but also mentally and emotionally overwhelming. It can be quite frustrating for people who know that their condition does not have a proper treatment. It is also financially exhausting for families due to the high costs of healthcare for such a rare disease. Young children often feel isolated due to their physical limitations and often feel unsupported by their families. Hence, families must consider genetic counseling, and more awareness should be created for such silent yet life-threatening conditions.

IV. Case Studies

Case Study 1

Case Summary

This case is adapted from Mwende et al. (2021). It describes the state of a two-year-five-month-old boy diagnosed with FOP, based in Kenya. It elaborates on the diagnostic symptoms observed, clinical analysis of the growing condition, challenges faced by the child, and the consequent treatment/support.

Family History Analysis

The patient was previously treated with antibiotics for lymphadenitis (inflammation of lymph nodes), which was diagnosed by biopsy of the neck mass. There was no history of fever or contact with a patient known to have tuberculosis. He was born of a non-consanguineous union and had no family history of similar illnesses. He had received all relevant vaccinations as a child. However, it was noted that he had delayed speech.

Diagnostic Symptoms

He was seen having congenital deformities such as rigid bony formations consistent throughout the axilla (connection between an arm and a shoulder), neck, occiput (posterior part of the head), and the forehead for seven months. Consequently, he developed progressive immobility, characterized by an inability to lift his arms, move his neck, and a stiff posture while walking. The masses had a waxing and waning nature lasting about 4-5 days. He also complained of having painful flare-ups/episodes.

Physical Analysis

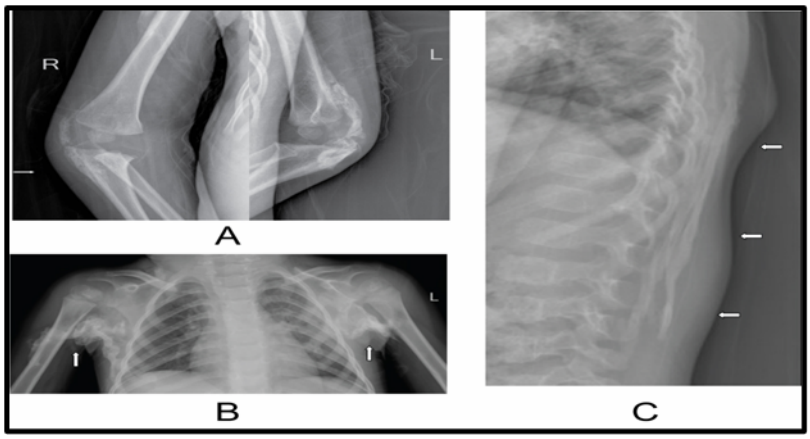
Upon physical examination, the child looked quite ill. He had bone-like formations on the posterior part of his neck, which were weak on palpation and attached to the underlying subcutaneous tissue (innermost layer of skin). He also had similar protrusions on his anterior and posterior chest wall, measuring 1 cm by 1 cm anteriorly and larger formations, measuring 5 cm by 5 cm posteriorly.

He started developing bilateral hallux valgus (big toe angles inward towards the other toes, often forming a bony bump called a bunion), and both elbows were held in a fixed bend. The lower limbs remained unaffected.

Diagnosis

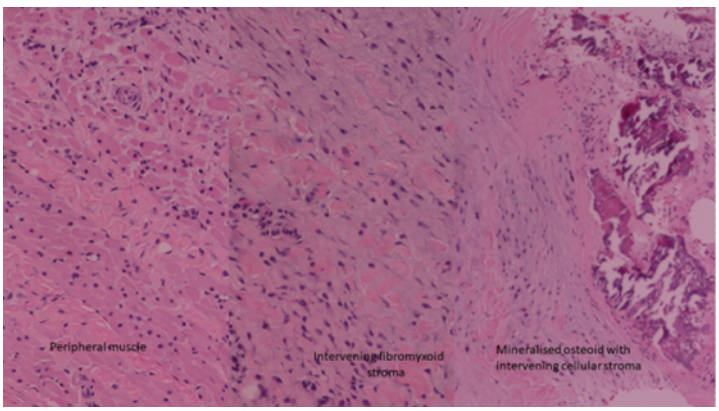
Laboratory evaluation included a complete blood count as well as a check-up for urea, electrolytes, creatinine (product of protein digestion), and liver health tests. Tests to check for rheumatoid arthritis were carried out, including anti-cyclic citrullinated peptide (anti-CCP), rheumatoid factor (a protein produced by the immune system), C-reactive protein, lactate dehydrogenase, and level of creatinine kinase, serum calcium, and phosphate, all of which were within normal ranges.

Bilateral forearm radiographs revealed extensive ossification of soft tissue around both elbows, outlining the joint capsules. A chest radiograph revealed similar appearing calcification in both axillae. Radiographs of the spine presented extensive "sheet-like" soft tissue ossification overlying the posterior part of the vertebral column, separate from the vertebrae (as shown below).



A) Radiograph showing ossification around the elbows
B) Radiograph showing ossification near the axillae
C) Radiograph showing calcification in the spine area

A core biopsy, following an ultrasound of the posterior chest wall mass, was performed under anesthesia. Results of the ultrasound showed muscle replacement by hyaline cartilage and bone, with intervening fibromyxoid stroma (connective tissue composed of collagen fibres) - as shown below.



Discussion

In FOP patients, minor trauma such as intramuscular immunizations, falls, or influenza-like viral illnesses can trigger painful new flare-ups. In this case, frequent falls while playing were likely the trigger for the patient's flare-ups. During FOP, following a rapid inflammatory stage, there is an intense fibroproliferative phase. Similarly, biopsies taken from this patient revealed mineralized osteoid with intervening cellular stroma. New features, such as a bilateral hallux vagus, were found. All the results align with the previous discussion of FOP.

Treatment and Recovery

The patient underwent physiotherapy, and parents were advised on the triggers for flare-ups. The family was enrolled in the international FOP support group and scheduled to have a follow-up hearing and speech assessment. His family was educated about the importance of avoiding injury and managing flare-ups to reduce the risk of excessive bone formation. They were also informed about the possible future need for adaptive devices such as wheelchairs if the patient's mobility declined.

Takeaway

Even though there are cases of FOP in Kenya, there is no treatment, cure, or perfect solution to this disorder, possibly because of a lack of awareness in a yet-to-be-developed country. This just goes to show how such a fatal disorder can go unnoticed and how focus should be given to finding a proper, accessible, and affordable treatment for FOP.

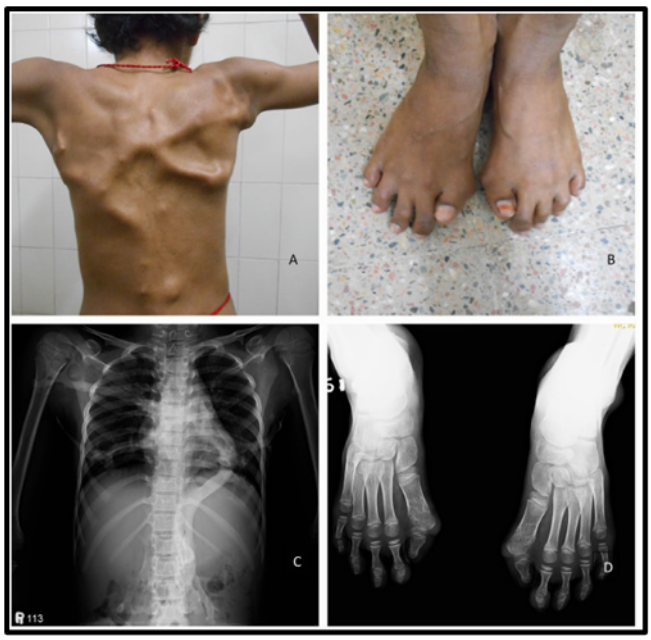
Case Study 2

Case Summary

This case is adapted from Sekaran et al. (2023). It describes an 11-year-old boy with a history of multiple swellings in the back since the age of three. This study also discusses occurrences of misdiagnosis and consequent challenges faced by the patient.

Physical Analysis

Upon evaluation, multiple bony hard swellings extending from the occiput to the sacrum were noted. Bilateral hallux valgus, clinodactyly of the digits (deformity around the fingers), and swellings over the shin bone (specifically the tibia) and proximal femur (connection between the hip joint and pelvis) were present.



A) Multiple bony hard swellings over the back extending from the neck to the sacrum.
B) Bilateral hallux valgus with short great toes.
C) X-ray showing ribbon-like ossified bands extending from the cervical region to the pelvis with branching on either side.
D) X-ray Bilateral foot showing hallux valgus with absence of proximal phalanx.

Misdiagnosis and Its Consequences

The child was initially examined in an outside hospital, suspected of having a tumor, and an excisional biopsy (a therapeutic procedure of removing a lump or mass for examination) of the mass from the back was performed. This resulted in an even worse condition - recurrence of the lesion and restricted mobility. A skeletal survey revealed a dense ribbon-like band extending from the neck to the sacral region, the absence of a proximal phalanx, and the presence of hallux valgus of the great toes.

New Diagnosis & Treatment

Since he presented with an increase in the number of painful swellings, a diagnosis of FOP with a flare-up was made. He showed improvement with oral corticosteroids. Furthermore, the parents were counseled on the disease condition and preventive measures, such as dealing with episodes/flare-ups.

Discussion

This case of FOP showcases a prolonged case of malformations in the body and an increasing number of swellings since a very young age. The presence of such swellings, bony formations, and flare-ups can help recognise FOP. However, this was misdiagnosed as a tumor earlier, and the biopsy, which took place, worsened the patient's condition.

Takeaway

This case study highlights how a rare disease like FOP can be easily misdiagnosed as a completely different condition, such as a tumor. It also underscores the widespread lack of awareness about this life-threatening disorder, as well as the critical consequences of delayed diagnosis and inadequate medical intervention.

V. Conclusion

FOP is a rare bone condition that is still underexplored. A perfect cure or treatment has not yet been found, which is why such a condition is either misdiagnosed or goes unnoticed. Although rare, FOP, if recognised in a person, can lead to lifelong repercussions. This research paper aimed to examine the genetic and clinical features of FOP, evaluate current treatment efforts and future CRISPR predictions, as well as highlight real-life cases to illustrate the impact of this condition on humans.

FOP is caused by a mutation in the ACVR1 gene (also called ALK2), which affects the bone morphogenetic protein (BMP) signaling pathway. This mutation causes the body to mistakenly form bone in soft tissues, particularly after minor trauma or inflammation. Although FOP is inherited in an autosomal dominant pattern, most cases result from spontaneous mutations (not inherited from parents), as confirmed by the case studies. The onset of FOP is seen as early as ten years of age, and some striking symptoms include malformations of the great toes, loss of mobility, and recurring flare-ups. Some effective measures to reduce the intensity of symptoms are taking corticosteroids or NSAIDs. Apart from this, some future CRISPR possibilities are currently being advanced. Although these have not been clinically tested, their potential shows promise.

Both case studies revealed a new diagnostic feature: bilateral hallux valgus, characterized by the big toe angling inward towards the other toes, often resulting in a bony bump (bunion) at the base of the big toe joint. The physical analysis and diagnostic symptoms align with those mentioned in the pathophysiology section. It is also interesting to note that none of the cases had any genetic association, i.e., FOP or signs of FOP were not seen in the family history of either patient. Hence, this reveals that FOP is not entirely a genetic disorder but is caused by a random mutation in an individual's body.

To reiterate, significant effort should be devoted to developing treatments or proper medication for curing FOP, and more awareness should be raised among the masses for regular check-ups, especially during childhood, which can be achieved by investing more in healthcare infrastructure.

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