Hardened Hope: Care Advances for Fibrodysplasia Ossificans Progressiva

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> *Yesterday there came a Boy of healthy Look, and about Fourteen Years old, to ask us at the Hospital, what should be done to cure him of many large Swellings on his Back, which began about Three Years since, and have continued to grow large on many Parts as a Peny-loaf, particularly on the Left Side: They arise from all the* Vertebrae *of the Neck, and reach down to the* Os Sacrum*; they likewise arise from every Rib of his Body, and joining together in all Parts of his Back, as the Ramifications of Coral do, they make, as it were, a fixed bony Pair of Bodice.*[1]
>
> —John Freke, 1736

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic connective-tissue disorder that is characterized by the progressive and incapacitating formation of bone in extraskeletal locations.[2,3] It is the most debilitating and life-shortening disorder of heterotopic ossification, a condition defined by the abnormal, ectopic growth of bone. Beginning in childhood, FOP affects tendons, ligaments, aponeuroses, fasciae, and muscles, which become infiltrated with fibrous cells that mature into bone.

The condition was first documented in detail by the English surgeon John Freke in a letter he penned to the Royal Society of London in 1736.[1] The disease phenotype was subsequently broadened in the 19th century to include monophalangism and brachydactyly of the great toes, and the term *myositis ossificans progressiva* was introduced in 1868.[4] In the early 20th century, the terms *fibrositis* and then *fibrodysplasia* were proposed to replace *myositis*, to acknowledge that the primary pathology of FOP begins in the connective tissue.

Perhaps the most notable case report of FOP is that of Harry Eastlack, who was born in 1933 in Philadelphia with the hallmark malformations of FOP in his great toes. A subsequent leg fracture secondary to trauma at the age of 5 years was followed by heterotopic bone formation in the affected limb and later throughout his body.[5] During his lifetime, Harry sustained multiple surgeries in misguided attempts to biopsy and remove excess bone; however, the traumatic procedures only exacerbated his condition. His jaw became permanently fused at the age of 15 years, and he could no longer eat solid food. In adulthood, Harry became bedridden and died of pneumonia at the age of 39 years. He donated his completely fused skeleton to Philadelphia's Mutter Museum, where it remains on display.

FOP affects approximately 1 in 2 million individuals worldwide, or 3500-4500 people; however, only about 900 cases have been identified.[2,6] There is no observed predisposition to FOP on the basis of sex, ethnicity, or geography. The overwhelming majority of individuals with FOP harbor a specific point mutation in the activin A receptor type 1/activin receptor-like kinase 2 (*ACVR1*/*ALK2*) gene, which otherwise regulates the growth and development of bone.[7]

Because FOP is rare, its possibility is frequently overlooked, thereby leading to misdiagnoses, mismanagement, and unnecessary iatrogenic trauma, which can exacerbate abnormal bone formation. At present, the treatment of FOP remains symptomatic and is focused on the prevention of flare-ups (inflammatory soft-tissue swellings) and associated pain and rehabilitation to preserve and restore function. However, several novel targeted therapies are in development that are designed to address the genetic mutation of FOP, interrupt heterotopic ossification, and thereby potentially transform the course of illness. The accompanying articles will further discuss in detail the timely recognition and diagnosis of FOP and its current recommended and anticipated future management. ■

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FOP	Fibrodysplasia ossificans progressiva

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