Improving the Diagnosis of Fibrodysplasia Ossificans Progressiva

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Presentation and Disease Course

Fibrodysplasia ossificans progressiva (FOP) is a distinctive but often-overlooked disorder, owing to its extreme rarity and insidious presentation. However, the signs of classic FOP are evident at birth, and the disease clinically manifests typically within the first decade of life. The characteristic and invariably early sign of FOP is congenital malformation of the great toes (**Figure 1**).[1-3] In 50% of cases, the thumbs are similarly affected. Other findings at birth may include a broad femoral neck and bony malformation of the cervical spine.[4-6] Heterotopic ossification, the abnormal growth of bone in extraskeletal tissues, typically is not present at birth, although areas of soft-tissue swelling may be evident in neonates. Infants and children with FOP may present to pediatric orthopedic surgeons with progressive "bunions" or malformed great toes. However, it is rare that the disease is recognized at this stage. In most cases, unfortunately, the diagnosis of FOP is not made until affected persons have consulted several physicians and the associated deformity and disability are undeniable.[7] It is estimated that 3500-4000 people worldwide have FOP, although the disorder has been diagnosed in only about 900 people.[3] Although there are currently no approved treatments for FOP, early recognition and diagnosis is important to prevent unnecessary trauma, such as intramuscular vaccination or surgery, that may induce disease flares.

Progressive Heterotopic Ossification

The process of heterotopic ossification in FOP begins as inflammation of the fascia, aponeuroses, tendons, ligaments, and striated muscle and presents as 1 or more painful nodules.[1] These nodules are typically first observed over the neck, spine, and shoulder girdle (**Figure 2**).[8] The progression of heterotopic ossification in FOP generally follows a pattern in which the body is affected in an axial-to-appendicular, cranial-to-caudal, and proximal-to-distal sequence. Most people with FOP will experience a progressive loss of ambulation due to soft-tissue and joint ossification and the resulting loss of range of motion. Many will come to rely on wheeled mobility to access the home and community. Median age at the time of death is 42 years, and the median life expectancy is 56 years.[1]

Histopathologically, early FOP resembles aggressive juvenile fibromatosis, another rare connective-tissue disorder. Biopsy specimens of swellings in FOP show normal connective tissue being replaced by loose, proliferating fibroblasts along fascial planes. This microscopic finding is accompanied by increased vascularity and angiogenesis, perivascular infiltrates of B and T lymphocytes, and elevated numbers of mast cells.[9,10] The lymphocytes in FOP nodules, along with lymphoblastic cell lines in the blood of individuals with FOP, have been shown to overexpress bone morphogenetic protein (BMP)-4, a polypeptide known to induce cartilage and bone formation. The fibroblast-rich tissue in FOP nodules progressively ossifies to form cartilage matrices, which are eventually replaced by bone through the process of endochondral ossification. Ultimately mature bone, which sometimes includes marrow, replaces the soft tissue. It is not unusual for FOP lesions to appear at different stages of development within a single affected person. Notably the biopsy of nodular swellings in FOP is not advised because the trauma tends to precipitate painful flare-ups and exacerbate abnormal bone growth.

Flare-ups

FOP flare-ups, due to localized inflammatory soft-tissue swellings, most often are associated with pain, loss of joint range of motion (depending on the location and extent of the flare-up), stiffness, warmth, and redness.[6,10] In some cases, flare-ups have no identifiable trigger, but many occur as a result of physical trauma (including minor trauma), viral illnesses, or overuse and stretching. In one survey, intramuscular immunization was identified as the cause of an immediate flare-up in 25% of cases, which led to bone formation in the majority (84%) of those affected.[10] Other minor traumas, including anesthetic blocks for dental work and unskilled venipuncture, can precipitate

ACVR1	Activin A receptor type 1
ALK2	Activin receptor-like kinase 2
BMP	Bone morphogenic protein
CT	Computed tomography
FOP	Fibrodysplasia ossificans progressiva
MRI	Magnetic resonance imaging

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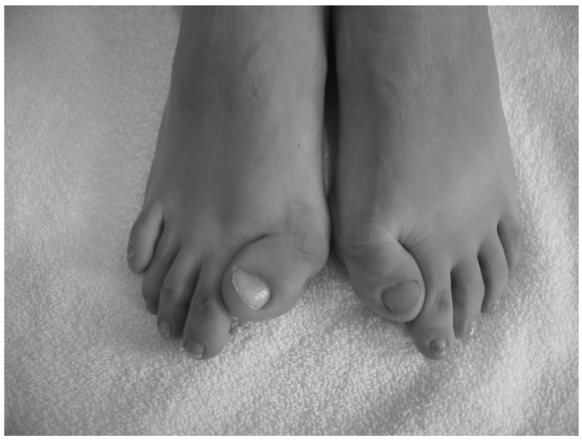

Figure 1. Characteristic malformed great toes and hallux valgus in a patient with FOP.[2] This image is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

flare-ups.[11] More invasive procedures, such as biopsies of soft-tissue swellings and especially surgical removal of heterotopic bone, are ill-advised because they can provoke explosive and painful new bone growth in persons with FOP. Most flare-ups have been reported to resolve within 8 weeks of onset, with the exception of back and hip flare-ups, which can last much longer.[10] Only a minority (12%) of people with FOP have reported the complete resolution of flare-ups without any loss of function, though only 50% of flare-ups result in heterotopic ossification.[12]

Natural History

The natural history of FOP is such that affected persons become increasingly debilitated by progressive heterotopic ossification as they age. Although heterotopic ossification in FOP is episodic, its related disability is cumulative.[5] Indeed, in a prospective study by Pignolo et al of 114 individuals with FOP, a cross-sectional analysis revealed that older age was significantly correlated with lower functioning, including measures of joint involvement, activities of daily living, and general physical functioning.[13] There was also an observed statistically significant correlation between older age and heterotopic ossification burden, as measured by low-dose whole-body computed tomography (CT). The progressive burden of heterotopic ossification is illustrated by 3 representative cases of a 4-year-old, a 10-year-old, and a 31-year-old patient with FOP from this study. By using reconstructed whole-body CT scans, Pignolo et al showed that heterotopic ossification burden increases significantly with the age of the affected individual (**Figure 3**).

In another study of 34 people with FOP, the progression of heterotopic ossification varied substantially from individual to individual, but certain disease milestones of heterotopic ossification progression were generally observed in sequence.[12] Severely restricted movement of the shoulder and spine was typical by the age of 10 years, and the hips were commonly affected by the age of 20 years. Most people in this study were wheelchair-reliant by the age of 30 years. An assessment of the mean age at which specific joints are severely affected by heterotopic ossification revealed early involvement of the spine and shoulders, followed by involvement of the hips and jaw. More distal joints were affected in the later stages of illness. The age-related observations of severe joint involvement in this FOP study illustrate the experientially observed progression of flare-ups and subsequent heterotopic ossification in an axial-to-appendicular, cranial-to-caudal, and proximal-to-distal pattern in FOP.[1,10] The culmination of heterotopic ossification in FOP is demonstrated by postmortem case reports.[14] Gross and microscopic examinations reveal profound ossification of the vertebral ligaments, particularly in the cervical region.

Morbidities

Cervical spine anomalies are characteristic in FOP. Neck stiffness is experienced early in the disease and precedes heterotopic ossification in that region.[15] Typical anomalies of the cervical spine in FOP include large posterior elements, tall and narrow vertebral bodies, and fusion of the facet joints between the C2 and C7 vertebral bodies. Other skeletal anomalies include short, malformed thumbs (microdactyly), clinodactyly (digit curvature), a short, broad neck of the femoral bone, and osteochondromas of the proximal medial tibia. Developmental anomalies of the temporomandibular joint also are observed in FOP. Extra-articular ankylosis of this joint, with stiffness and limited movement, is common. In cases of severe disability, eating and oral hygiene can be severely impaired and profoundly impact quality of life. Hearing loss, usually conductive, is experienced by up to 50% of people with FOP.[5,15,16] The onset of hearing loss typically occurs during childhood and progresses gradually. Commonly reported neurologic symptoms in FOP include neuropathic pain and recurrent headaches, particularly in postpubertal female patients.[5,17] People with FOP have an approximately 3-fold greater risk of renal stones than the general population, and this risk is increased significantly by immobilization, low dietary fiber, excess animal protein intake, and deficient hydration.[5,18] Gastrointestinal symptoms reported by people with FOP include swallowing difficulties, anorexia, abdominal pain, gastroesophageal reflux, nausea, intermittent vomiting, trouble digesting food, pressure ulcers, and constipation.[5,19]

Impairments in gait and an inability to compensate for physical limitations contribute to fall-related injuries in people with FOP.[20] One study reported that 81% of people with FOP experience injuries due to falls. In two-thirds of these cases, the fall initiated a painful flare-up that led to permanent loss of movement. More than one-half of all falls in this study led to permanent disability. Falls were most likely precipitated by imbalance or tripping (31%), a playground or sports mishap (16%), loss of traction on ice or another slick surface (13%), uneven flooring (11%), a bicycle or

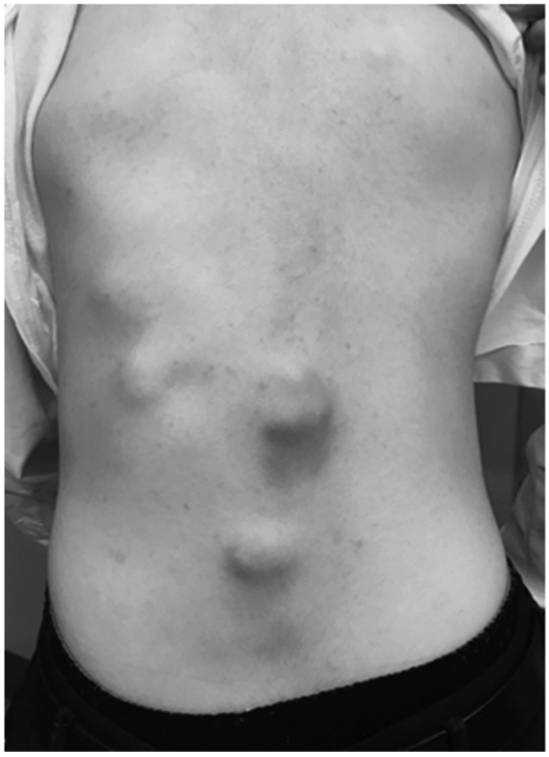

Figure 2. Soft-tissue indurations representing early heterotopic ossification on the back of a patient with FOP.[8] This image is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

motorcycle mishap (9%), a misstep on stairs (8%), imbalance during a transfer from a chair or bed (7%), and collision with others (4%). Fall-related trauma to the head is common in FOP and can produce traumatic brain injury, intracranial bleeding, and even death. Unfortunately, falls in people with FOP produce a perpetual cycle of instability and immobility, in which the fall-related trauma initiates a succession of flare-ups, heterotopic ossification, joint ankylosis, restricted mobility, imbalance, and instability, which further increase the risk of falls. People with advanced FOP develop thoracic insufficiency syndrome, the leading cause of death among these patients, and its concomitant life-threatening complications of pneumonia and cardiorespiratory failure.[15,21] Contributing factors include costovertebral malformations with orthotopic ankylosis of the costovertebral joints; ossification of intercostal muscles, paravertebral muscles, and aponeuroses; and progressive deformity of the spine, including kyphoscoliosis or thoracic lordosis.

Quality of Life

The quality of life for people with FOP can be severely compromised in the realm of physical function, most often as a result of extreme physical limitations and pain. A survey study of 8 adult patients with FOP reported very low quality-of-life scores with reference to physical function, especially among those people who relied on wheelchairs for mobility and were entirely dependent on others for self-care and transportation.[22] Greater quality-of-life physical scores among this group were associated with ambulatory independence. Pain also severely impaired quality of life in people with FOP whose disease was active or rendered them immobile. Yet, despite profound physical limitations and pain, most of the people surveyed reported surprisingly robust emotional health and, to a somewhat lesser extent, preserved mental health. Notably, no persons in this study were receiving psychological or psychiatric therapy in an effort to cope with their conditions and its consequent morbidities.

Diagnosis

Owing to its extreme rarity, FOP frequently is misdiagnosed in practice and often is disregarded in medical education. Academic medical textbooks, especially those concerning general internal medicine or pediatrics, rarely mention the disorder. In a seminal global questionnaire study of 138 people with FOP, nearly 90% reported receiving an initial incorrect diagnosis.[23] These diagnostic errors were reported across the globe and occurred regardless of a person's ethnicity and geographic location or their physician's specialty. The most common misdiagnosis was cancer (32% of respondents). Approximately two-thirds reported that they had undergone unnecessary diagnostic procedures, and roughly 50% of respondents said that they had suffered permanent immobility because of invasive medical procedures, which caused post-traumatic heterotopic ossification. The mean delay to a correct diagnosis of FOP exceeded 4 years, and a median of 6 physicians were consulted before an accurate diagnosis was rendered. In another report of 7 children with FOP, all had been evaluated by pediatric orthopedic surgeons for malformed great toes; yet none of these physicians had entertained the possibility of FOP.[7]

Differential Diagnosis

Malformed great toes are not solely limited to FOP, but FOP must be considered in the differential diagnosis.[7,24] Other diagnostic possibilities in cases of malformed great toes include isolated congenital malformations, isolated brachydactyly, and juvenile bunions. However, if soft-tissue swelling occurs in the context of malformed great toes, then the clinical diagnosis of FOP must be suspected.[7] Nevertheless, alternative diagnoses may be considered in children presenting with soft-tissue swellings or evidence of soft-tissue ossification. These conditions, like FOP, tend to be very rare disorders, and several are due to mutations in the *GNAS* gene—the products of which are involved in the signaling pathways that help regulate bone formation. Aggressive juvenile fibromatosis is a condition in which fibroblasts proliferate in tendons, ligaments, and other connective tissues, causing pain and disability.[3] The resulting lesions may resemble the soft-tissue swellings of FOP. However, individuals with aggressive juvenile fibromatosis do not

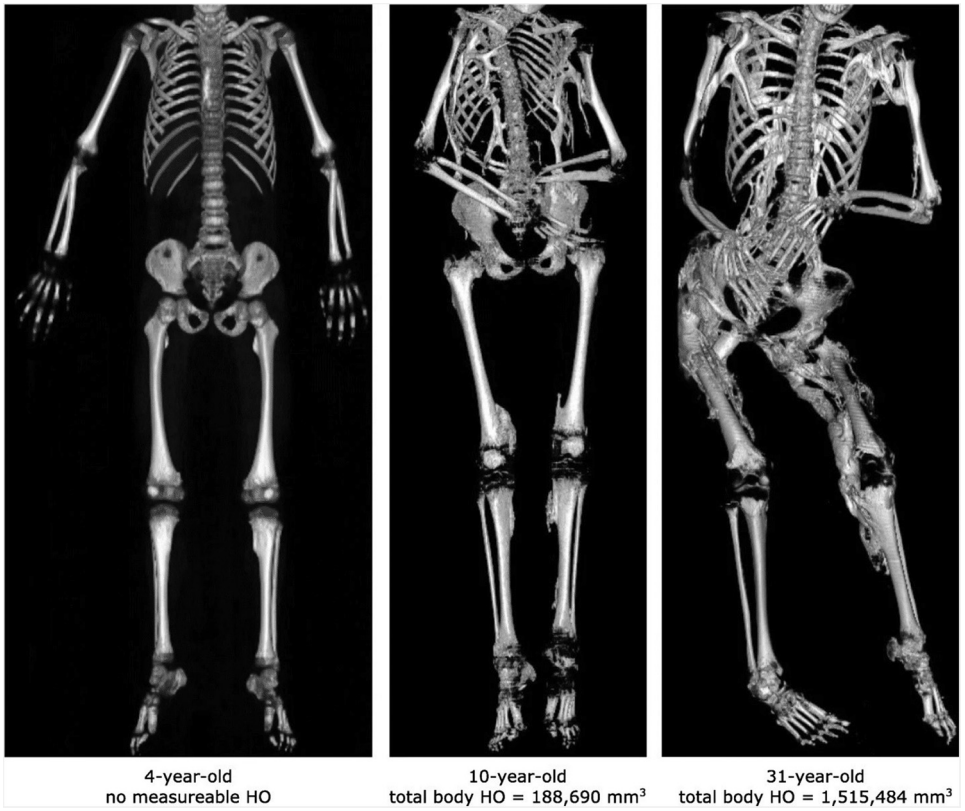

Figure 3. Reconstructed whole-body CT scans of 3 individuals with FOP at age 4 years (*left*), age 10 years (*center*), and age 31 years (*right*), showing the progression of heterotopic ossification with advancing age.[13] This image is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

have the toe malformations that are associated with FOP, nor do they develop heterotopic ossification. An autosomal-dominant condition due to a *GNAS* mutation, progressive osseous heteroplasia, presents in infancy with heterotopic ossification of the dermis and subcutaneous fat.[25,26] Later, ectopic bone formation involves other tissues such as skeletal muscle and tendons. Notably, people with progressive osseous heteroplasia also lack the characteristic malformed great toes of FOP, so their absence is a feature that differentiates the 2 conditions. Osteoma cutis is another rare cause of cutaneous ossification, which is likewise due to an inherited mutated variant of the *GNAS* gene. Similarly, Albright's hereditary osteodystrophy is an autosomal-dominant condition caused by a mutation in the *GNAS* gene, and it is characterized by subcutaneous ossification, along with the distinctive clinical features of short stature, moon face, obesity, and brachydactyly of the fingers and toes.[27]

Genetic Testing

When a child or adult presents with malformed great toes, soft-tissue swellings, and evidence of heterotopic ossification, the clinical diagnosis of FOP is presumed.[7] However, a definitive diagnosis of FOP is confirmed by means of genetic testing. The genetic cause of FOP was first reported when an international team of researchers discovered that people with the classic features of FOP—malformed great toes and progressive heterotopic ossification—showed the same identical point mutation in the activin A receptor type 1/activin receptor-like kinase 2 (*ACVR1*/*ALK2*) gene, which resides on the long arm of chromosome 2.[28] This gene encodes for the activin receptor type-1 (ACVR1) protein, which belongs to a family of transmembrane proteins called BMP type 1 receptors.[29] BMP proteins are regulatory proteins that play important roles in the formation of the embryonic skeleton and in postnatal bone repair.[3] The ACVR1 transmembrane protein receptor is located throughout the body, including in skeletal muscle and cartilage.[29] The ACVR1 receptor helps to control the growth and development of bone through its activating and inhibitory ligands, the binding of which regulates the activation and inhibition of the BMP signaling pathway.

The classic FOP-specific point mutation in the *ACVR1*/*ALK2* gene, labeled c.617 G > A, results in an amino-acid substitution (arginine to histidine, or R206H) in the ACVR1

receptor. This substitution causes a conformational change in the ACVR1 receptor that alters its sensitivity to its ligands and consequently its activity.[26,30] Animal data suggest that FOP is caused by an altered responsiveness of the ACVR1 receptor to its normally antagonistic ligand, activin A, thereby promoting overactivity of the BMP signaling pathway.[31] It is estimated that the c.617 G > A point mutation in the *ACVR1/ALK2* gene contributes to more than 95% of FOP cases.[32] However, at least 14 other different mutations have been identified that cause FOP, and all have been located on the *ACVR1/ALK2* gene.[33] These mutations can be associated with altered FOP phenotypes or clinical variants, including a later age of FOP onset.[32] It is notable that, although the gene mutation in FOP acts in an autosomal dominant fashion, most identified cases of FOP are sporadic.

Imaging

Radiographic imaging may be useful in FOP to confirm the diagnosis and document the extent of disease, especially the extent of heterotopic ossification.[4,34] Plain radiography can be used to further examine evident bony malformations, such as great-toe malformations and femoral neck abnormalities. In early FOP, evidence of heterotopic ossification on plain radiographs may be lacking, but later imaging may help identify ectopic calcifications within soft-tissues and skeletal muscle. Osseous bridging between the axial and appendicular skeleton may also be observed on plain radiographs in the later stages of the illness. CT imaging in FOP can provide more accurate information about the location of lesions, especially in the preosseous stages of disease, when swelling and edema of the muscular fascial planes and bundles are present. Magnetic resonance imaging (MRI) also may be useful in the early, preosseous stages of FOP. On MRI, preosseous lesions typically demonstrate a low signal intensity on T1-weighted images and a high signal intensity on T2-weighted images. Lesion-adjacent muscular bundles show high signal intensity on T2-weighted images, probably as a result of secondary changes.[35]

Conclusions

FOP is a rare genetic disorder, yet one with distinctive and recognizable pathognomonic clinical features of malformed great toes, multiple and recurrent soft-tissue swellings, and progressive and disabling heterotopic ossification. The condition is associated with morbidities, including fixed joints, progressive immobility, conductive hearing loss, and a predisposition to injurious falls. These morbidities significantly undermine a person's physical quality of life, although emotional and mental health remain remarkably preserved among individuals with FOP. Early recognition of FOP is important to avoid unnecessary traumas that may trigger flare-up and heterotopic ossification. Clinical diagnosis of FOP can be presumed if the hallmark signs of the disorder are recognized by alert and mindful physicians. The diagnosis is confirmed by means of genetic testing, which is used to identify the invariably mutated *ACVR1/ALK2* gene through polymerase chain reaction analysis of DNA. Use of radiographic imaging, including plain radiography, CT, and MRI, may support the diagnosis of FOP, as well as establish and monitor the extent and development of soft-tissue pathology and heterotopic ossification. Although there are currently no approved therapies for FOP, prevention and management of flare-ups, as well as rehabilitative care, are key for improving the patient's quality of life. These topics, as well as emerging treatments for FOP, are discussed elsewhere in this Supplement. ■

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Author Disclosures

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