

Fibrodysplasia ossificans progressiva (FOP)

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[Abstract](#)
[Key words](#)
[Disease name and synonyms](#)
[Excluded diseases](#)
[Diagnosis criteria/definition](#)
[Differential diagnosis](#)
[Prevalence](#)
[Clinical description](#)
[Etiology](#)
[Diagnostic methods](#)
[Genetic counseling](#)
[Antenatal diagnosis](#)
[Unresolved questions](#)
[References](#)

Abstract

Fibrodysplasia ossificans progressiva (FOP) is an extremely rare autosomal dominant form of connective tissue disorder characterized by congenital malformation of the great toes and progressive, disabling heterotopic osteogenesis in predictable anatomical patterns. Heterotopic bone formations lead to a debilitating, progressive ankylosis of the trunk, limbs and jaw. The mechanism by which bone forms out of muscles, tendons and ligaments is still poorly understood, but bone morphogenetic proteins (BMP), and particularly BMP4, are likely to play a direct or indirect role. The unraveling of the genetic defect is still hampered by the paucity of multigenerational families. Linkage studies suggest the FOP locus maps to chromosome 4. A putative genetic heterogeneity, once hypothesized, has not been confirmed. Genetic counseling for FOP is difficult because of the absence of specific biological markers or reliable linkage studies. The risk of having a second affected child is nevertheless limited in a given family with a sporadic case. Therapeutic measures are essentially preventive and aimed at reducing the impact of trauma and falls and iatrogenic complications.

Key words

fibrodysplasia ossificans progressiva, 4qter, toe malformation, myositis ossificans, flare-ups, bone morphogenetic proteins, BMP4, noggin.

Disease name and synonyms

-Fibrodysplasia ossificans progressiva (FOP);
-Myositis ossificans;
-Munchmeyer's disease.

-Progressive osseous heteroplasia.

Excluded diseases

-McCune-Albright's disease;

Diagnosis criteria/definition

The diagnosis of FOP is firmly established based on the combination of clinical and radiological criteria described below.

Clinical criteria

Male or female patient; age of onset around 3 to 4 years; acute episodes of swelling (flare-ups) occurring spontaneously, after minor trauma or surgery, localized in the upper spine or the neck, followed by endochondral bone formation in the same area. Over time, these heterotopic formations progress more distally and caudally thereby putting the patient at risk of being ankylosed and confined to a wheelchair in his/her twenties or thirties. Ankylosis of the jaws and rib cage are of particularly poor prognosis. The disease progresses in well-defined temporal and spatial patterns.

Radiological criteria

The shortening of the great toes is the best clue to the diagnosis. Other malformations are also sometimes noted: short thumbs, short femoral necks or malformed cervical vertebrae. No specific biological nor genetic markers are available to date.

BMP4 (bone morphogenetic protein type 4) overexpression was found in some FOP patients but cannot be used routinely for diagnostic purposes.

The genetic nature of the disorder is often difficult to establish as most cases (95%) are sporadic, thereby suggesting a high rate of *de novo* mutations. Dominant inheritance is nevertheless supported by observations of 2 or 3 successive affected generations and the finding of a paternal age effect in sporadic cases.

NB: muscle biopsy, given its potential risk of inducing heterotopic osteogenesis, is not warranted in FOP.

Differential diagnosis

The diagnosis of FOP is rarely questioned, as it is based on the association of typical heterotopic bone formation and shortening of the great toes. Nevertheless, the following diagnoses may be discussed in atypical cases:

- aggressive juvenile fibromatosis
- osteosarcoma
- McCune-Albright's disease
- progressive osseous heteroplasia (POH)

The first two diagnoses have to be considered very carefully, as they can lead to unnecessary limb amputation and/or chemotherapy.

Prevalence

FOP is an extremely rare but ubiquitous genetic disease. Around 700 cases, from all ethnic backgrounds, have been reported so far in the literature. A cohort of 200 patients is known to the international FOP patient support

group (IFOPA). The prevalence is particularly low, ranging from 0.6 to 1×10^{-6} , at least in Caucasians. The incidence is estimated at one per two million live births in the UK, France, and the USA.

Clinical description

FOP occurs in both sexes. People with FOP can be described as forming two skeletons, a normotopic one during embryogenesis and a heterotopic one after birth. The normotopic skeleton, however, presents characteristic malformation of the great toes, a hallmark of the disorder. Most cases are sporadic and, given the rarity of the condition and the poor awareness of clinicians, many of them are diagnosed late. Shortening of the great toes is present at birth but often overlooked. Typically, the age of onset is around 3 to 4 years with episodes of acute soft-tissue swelling (flare-ups) in the neck or upper spine. Large painful tumors of highly vascularized proliferating tissue develop spontaneously or after minor trauma (including intramuscular injections for immunizations) and give rise to heterotopic bone formations. Disease progression is also highly suggestive of FOP; the sites of heterotopic bone formation follow a specific pattern and mimic what happens in normal embryonic skeleton formation *i.e.* following dorsoventral, axio-appendicular, craniocaudal and proximodistal gradients. Most flare-ups result in bone formation after several weeks but some do not. The recurrence of these episodes is unpredictable and the disease may remain quiescent, sometimes for years. Gradually, bony masses immobilize the joints and lead to ankylosis. Ambulation is classically lost in the twenties or thirties due to ankylosis of the hip. The heart, diaphragm, extraocular muscles and smooth muscles are usually spared. Major complications arise from rigidity of the rib cage and ankylosis of the jaw causing restrictive lung disease and nutritional impairment, respectively. In the very few genuine FOP families (with more than 2 affected members), the phenotypic variability is not marked and there is no evidence of any anticipation.

Management including treatment

Therapeutic interventions are so far purely supportive and preventive.

Preventive measures

The main objective is to decrease the frequency and intensity of flare-ups. All surgical procedures are high-risk situations and should be avoided whenever possible. Muscle biopsy and surgical removal of heterotopic bone formations are

contraindicated. Local anesthesia should be avoided especially in dental procedures. Hyperextension of the jaw is potentially deleterious under the same circumstances. The management of scoliosis is particularly disappointing as bracing and spinal surgery are not feasible or dangerous for those patients. The prevention of falls and trauma is more difficult to achieve, especially in youngsters but can significantly decrease the rate of complications in the long run. In this context, parents and physicians can consult the guidelines which have been disseminated to the lay public by the IFOPA support group.

Pharmacotherapy

A large variety of medications have been tried in FOP without much success: Adrenocorticotropic hormone (ACTH), oral etidronate, non-steroidal anti-inflammatory agents, steroids, Ethylene diamine tetraacetic acid (EDTA). Clinical trials are under way to assess the efficacy of other drugs such as IV etidronate, interferon, thalidomide and squalamine. Short term prednisone is proposed within the 48 hours following an acute flare-up to suppress or abort the early lymphocytic infiltration into skeletal muscle. Long-term use of steroids is however deleterious. Much hope is expected from genetically engineered anti-noggin agents.

Etiology

Even though the vast majority of cases are sporadic, an autosomal dominant transmission has been documented. The overexpression of a bone morphogenetic proteins (BMP4) suggests that genes involved in bone formation and skeletal development could play a direct or indirect role in FOP pathogenesis.

Diagnostic methods

The diagnosis of FOP is essentially clinical and radiological. The combination of short great toes and heterotopic bone formations is highly suggestive. All invasive diagnostic methods should be avoided. Later on, the disease progression and characteristic pattern of heterotopic bone formation contribute to confirmation of the diagnosis. An early diagnosis is critical to take preventive steps.

Genetic counseling

The risk of transmitting the FOP genetic defect to the next generation is 50% in theory, irrespective of the child's gender. The rate of *de novo* mutations is particularly high as illustrated by 95% sporadic cases.

However, the risk of a second affected child in a given family is retrospectively very low. The risk is much higher when one of the parents

also exhibits the classical malformation of the great toes.

Antenatal diagnosis

Prenatal testing is not yet available in FOP. The situation may change once the genetic defect is identified.

The disease cannot be definitively detected *in utero*. In addition, there are no specific biological markers available for any prenatal testing. The positive linkage to chromosome 4q is not yet instrumental for prenatal testing since the genetic interval remains extremely wide. Furthermore, genetic heterogeneity cannot be excluded at this point.

Unresolved questions

Pathogenesis

The genetic defect and pathophysiology of the disorder are not known, although the BMP genes and other genes involved in the BMP pathway have been implicated as plausible candidate genes.

Genetic heterogeneity

Given the paucity of available multi-generational FOP families, definitive linkage analysis is difficult to perform. The results of the two studies conducted so far appear contradictory even if there is growing evidence to rule out *noggin* as the candidate gene.

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