Fibrodysplasia ossificans progressiva

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Introduction and history

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder of connective tissue characterized by congenital malformations and progressive ectopic ossification of striated muscle and connective tissue.\textsuperscript{1}

It was first described in 1692 by Patin, a French physician, and in more detail in 1740 by Freke, an English Surgeon. More recently Dr. Frederick Kaplan et al. at the University of Pennsylvania School of Medicine, Philadelphia, having identified many of the proteins involved in the development of the disease, in 2006, identified the causative gene mutation.

Epidemiology and genetics

The point prevalence of FOP is approximately 1 per 2 million of the population worldwide\textsuperscript{2} with no racial, ethnic, sexual or geographic predilection. The characteristic painful swelling of muscles progressing to ossification begins in childhood,\textsuperscript{3} and can be induced by surgical trauma, soft-tissue injury, intramuscular immunizations, injections for dental procedures, or influenza-like viral illnesses.\textsuperscript{4}

In 2006 Shore et al. mapped FOP to chromosome 2q23–24 by linkage analysis and identified an identical heterozygous mutation (617G-A; R206H) in the glycine-serine (GS) activation domain of activin receptor type IA (ACVR1), a bone morphogenetic protein (BMP) type I receptor, in all affected individuals examined.\textsuperscript{5} ACVR1 is 509 amino acids long, and in FOP histidine is substituted for arginine at position 206 in all affected individuals. ACVR1 is an important BMP signalling switch in cartilage cells of the growth plates of growing bones, especially in the hands and feet, as well as in the cells of skeletal muscle. In previous studies in chickens and zebrafish, other researchers have found an artificially made “trigger happy” copy of the ACVR1 gene (similar, but not identical to the FOP gene mutation) which makes muscle cells behave like bone cells; up regulating BMP4 expression, down regulating BMP antagonist expression (such as noggin) and expanding cartilage elements in growing bone, eventually inducing extra bone growth and stimulating joint fusion with clinical and molecular features similar to those seen in individuals with FOP.\textsuperscript{6}

Clinical features and diagnosis

There are characteristic clinical features; tumour-like swellings on the head, neck, back, or shoulders and characteristic congenital bilateral great toe abnormalities, reported in 79–100% of patients in one series.\textsuperscript{7}

Four subtypes of great toe abnormalities have been identified:

- The most common has the appearances of congenital hallux valgus but the toe actually has only one phalanx, which is often deviated laterally at the metatarsophalangeal joint. The single phalanx is clinically evident by the lack of a skin crease and can be seen on plain radiographs. Findings of a congenital hallux valgus should raise the possibility of FOP so that diagnosis is not delayed and inappropriate treatment and unnecessary invasive procedures such as biopsy are avoided.\textsuperscript{8,9}
- Great toes of normal length, but which become stiff from early childhood and show progressive bony fusion with increasing age.
Great toes clinically and radiologically normal in early childhood, become rigid in the second decade due to osteophytic lipping.

Feet where all toes show variable reduction defects with similar reduction defects present in the hands of these patients.\(^9\)

Hand malformations, including short first metacarpal and brachymesophalangy of the fifth finger with clinodactyly are seen in over 40% of patients (Fig. 1).\(^7,9,10\) Other radiological abnormalities reported include short broad femoral necks seen in over 50% of patients. In patients where radiographs of the cervical spine had been taken in early childhood, abnormal cervical vertebrae with small bodies, large pedicles and large spinous processes were often noted.\(^9\)

**Diagnosis**

The disease is commonly misdiagnosed on first presentation. Kitterman et al. initially reported incorrect diagnoses in 87% of individuals with FOP. The mean period from the onset of symptoms to correct diagnosis was 4.1 years, and the median number of physicians consulted before the correct diagnosis of FOP was 6\(^4\) The differential diagnosis includes: lymphadenopathy, Klippel–Feil syndrome, tuberculosis, post-traumatic myositis ossificans, wry-neck, haemophilia, scleroderma, post-meningitic stiffness and diaphyseal aclasis (Figs. 2 and 3).\(^11\)

The results of biopsy of early lesions can be misinterpreted as fibromatosis or sarcoma before the X-ray appearance of ossification.\(^11\) Radiological studies of the preosseous soft-tissue lesion in the early stage of FOP showed contrast enhancement on CT and MRI, mimicking a soft-tissue tumour. Hagiwara et al. found that the MRI appearance of spread along the fascial planes was a unique feature, and diagnosis of FOP should be considered even when ectopic ossification does not exist (Figs. 4–10).\(^12\)

It is important to remember that misdiagnosis and inappropriate treatment can result in permanent loss of mobility resulting from invasive medical interventions that then lead to post-traumatic ossification.\(^8\)

**Treatment**

There is currently no cure for FOP and management is based on the principle of “primum non nocere”, i.e. to prevent further abnormal ossification. Primary treatment therefore should aim to prevent soft-tissue injury and muscle damage. This can be as simple as preventing falls,\(^13\) avoiding intramuscular injection including diphtheria–tetanus–pertussis immunizations,\(^14\) and careful precautions in administering dental care.\(^15\)

Treatment for FOP is limited partly due to difficulties in studying such a rare disease, but also due to its fluctuating clinical course, which makes evaluation of new therapies difficult.

Current guidelines have classified drugs into three groups, but the authors of these guidelines have stressed that no medication to date has been proven to alter the natural history of FOP.\(^6\)

**Class I**

Corticosteroids and non-steroidal anti-inflammatory drugs have been widely used in the past as agents to control symptoms of acute symptomatic episodes of FOP with

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**Figure 1** Clinical evidence of heterotopic ossification in FOP.

**Figures 2 and 3** Clinodactyly of the fifth finger seen clinically and radiographically.
anecdotal reports of favourable clinical results, and to
generally minimize side effects.

Class II

Leukotriene inhibitors, mast cell stabilizers and aminobi-
sphosphonates have theoretical application to FOP, and may
be useful in selected cases. They are approved for the
treatment of other disorders, and have limited and well-
described effects.

Class III

Thalidomide, VEGF trap, Noggin (preclinical) are experi-
mental agents and should only be used in approved clinical
trials.

Surgery

Surgery to the musculoskeletal system of patients with FOP
must be avoided if possible. This is not because of technical
difficulties but because, while surgery to remove hetero-
topic bone and to free ankylosed joints may temporarily
improve the situation, the bone is virtually guaranteed to
reform, and often more abundantly than originally.

Patients with FOP may however require surgery for
abdominal pathology. Such surgery has been carried out
uneventfully and without formation of bone at the operation
site. Most problems relate to the anaesthetic management,
as FOP patients frequently have an immobile cervical spine,
making intubation difficult, and often necessitating awake fibre optic intubation. Patients may also have restrictive lung disease due to heterotopic bone, and therefore may benefit from respiratory assessment prior to anaesthesia.\textsuperscript{16}

**Conclusion**

FOP is a rare musculoskeletal condition that is unlikely to be encountered by most orthopaedic surgeons. However, two key points should be remembered by all those involved in the assessment of musculoskeletal disorders. First congenital abnormalities of the great toe should always raise the suspicion of FOP and secondly there is currently no known treatment for FOP. It follows that the first line of management involves not causing harm to patients by avoiding surgery to the musculoskeletal system, as this almost always leads to further abnormal heterotopic ossification.

**References**

5. Shore EM. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressive. *Nat Genet*. Published online 23 April 2006