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Fibrodysplasia (myositis) ossificans progressiva: clinicopathological features and natural history

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Summary

Patients with fibrodysplasia (myositis) ossificans progressiva (FOP) ($n=28$) were studied for up to 24 years. All had characteristic short big toes potentially recognizable at birth; there were radiographic changes in the toes, thumbs, cervical spine and metaphyses of the long bones, including exostoses. Ossification in the large skeletal muscles began from birth to 16 years (mean age 4.6 years) initially in 25 patients in the neck and upper spinal muscles, and later around the hips, major joints and jaw. The rate and extent of disability was unrelated to the time of onset. There was no evidence that any form of treatment produced consistent benefit. Despite the unique combination of skeletal abnormalities and ectopic ossification, the first diagnosis in patients with FOP was often wrong and usually delayed after ectopic ossification began (mean 2.7 years, range 0–14). Except where presentation was unusual, such as progressive stiffness, this delay was mainly due to failure to recognize the significance of the abnormal toes. The most frequent erroneous histological diagnoses were soft tissue sarcoma or fibromatosis. This series emphasizes the usually incorrect initial diagnosis, the misinterpretation of the histology, the unpredictable prognosis and the failure of current treatment. Despite its extreme rarity, there is a need for wider knowledge of this condition both to avoid clinical errors and to stimulate research.

Introduction

Fibrodysplasia (myositis) ossificans progressiva (FOP) is a very rare (less than one per million persons) and cruel experiment of nature in which characteristic skeletal abnormalities, especially short big toes, are associated with progressive ossification of the large striated muscles leading to gross and progressive disability.[1–3] This combination currently suggests that the presumed causal mutation may be found within the bone morphogenetic protein gene family which contributes both to limb patterning and to ossification.[4–7] Recent reviews demonstrate the spatial and temporal progression of ectopic ossification in FOP, which almost universally begins in the upper paraspinal muscles and spreads later from axial to appendicular, cranial to caudal and proximal to distal sites.[3,8] In addition, they highlight the failure of early diagnosis and the erroneous interpretation of histology.[9] Together with genetic studies which confirm the autosomal dominant nature and variable expression of the presumed defective gene,[10,11] there is now an increasingly firm clinical background for the diagnosis and prognosis of FOP and for research into its cause.

Apart from the work of Connor and Evans,[2] reviews describing the nature of FOP rely largely on postal surveys; these provide information from which very useful general conclusions can be drawn, but which is perhaps less useful for the individual patients. The parents of affected children (and eventually the children themselves) need to know the certainty of the diagnosis, the likely progression and outcome, the possibility of treatment and the genetic risks. It is abundantly clear that despite its unique clinical picture, the diagnosis of FOP is often arrived

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at with difficulty and delay, and the disease remains a mystery to its medical attendants.

The aim of this review is to provide information on twenty-eight FOP patients followed personally for periods of up to 24 years, and to draw some clinical lessons from this experience. Aspects of some of these patients have been described previously[12,13] and in abstract form.[14]

Methods

All patients were referred from elsewhere at variable times after the diagnosis had been established. In Figure 1, they are arranged according to the length of follow-up, from the age of onset of the first recognizable episode of myositis or related symptoms until they were last seen. Some subsequent postal information is also available. All patients were seen and followed personally. Patients 16, 21, and 23–27 were included in a previous paper.[13] Abnormalities of the feet are classified according to Connor and Evans.[2] Conventional methods were used for histology and biochemistry.

Results

For brevity, individual clinical details are incorporated in Figure 1; in all patients the diagnosis of FOP was made from the combination of skeletal abnormalities and ectopic ossification. Many had other abnormal features; four examples are given.

Patient 2

In this twelve-year-old boy with pain and swelling in the upper paraspinal muscles, unexplained bony lumps had previously been removed from his forehead (after a fall) and over the sacrum. His toes and thumbs were abnormal and short from birth. Two consultant pathologists diagnosed embryonal rhabdomyosarcoma from a biopsy of affected paraspinal muscle; he was given a full course of chemotherapy (ifosfamide, actinomycin D and vincristine) and the muscle swellings subsided. The skeletal features of FOP were identified in subsequent radiographs.

Patient 3

This baby with abnormal big toes and thumbs at birth had an unaffected twin. She developed a lump in her left arm with ossification after immunization.[15] Because of motor delay, an MRI scan was done. This showed a neuronal migration defect, with abnormal formation of the superior parietal gyri, enlarged ventricles and delayed myelination. The pons and medulla were also malformed. She subsequently developed 'myositis' in the right axilla and deltoid region, and radiographs also showed ossification of the left thigh muscles; she died of a respiratory infection in infancy.

Patient 6

In this boy, the advice given was unduly optimistic. When first seen by a geneticist at the age of eleven because of short big toes and thumbs present from birth, no diagnosis was made (Figure 2). Ossification around his left hip at 16 years was considered to be post-traumatic. At 18, his geneticist advised that he had an unusually mild form of FOP. A year later, he was unable to open his mouth and by 20 had extensive ossification of his upper paraspinal muscles.

Patient 13

This boy, born in 1973, is the only patient with any evidence of sustained improvement after surgery; removal of ectopic bone from the right hamstring area significantly reduced a flexion deformity and this improvement has been maintained for 2 years. Despite the bizarre abnormalities in his hands and feet (Figure 3), the ectopic ossification in the tendinous insertions led his consultant to a 'certain' diagnosis of diaphyseal aclasis.

Additional clinical points (which may or may not be relevant to FOP) are; patient 5, dysplastic kidney removed at fourteen months; patient 17, hair very sparse; patient 18, progressive stiffness from infancy with long delay in diagnosis; patient 22, drove a car and managed stairs unaided until the age of 44; patient 25, bilateral above knee amputation at the age of 41 because of pain in the legs; patient 27, extensive reduction defects of the hands and feet, mild mental retardation, webbing of the neck and partial alopecia (Case 4, reference 13); patient 28, known to be alive but completely disabled at age 74 (last seen age 62, Figure 1). Patients 5, 8, 18 and 21 had variable deafness.

Family history

In this series there was no family history of skeletal abnormalities or ectopic ossification, and none of the patients had children.

Skeletal abnormalities

All 28 patients had abnormal big toes. In seventeen, this abnormality was noted at birth or soon after,

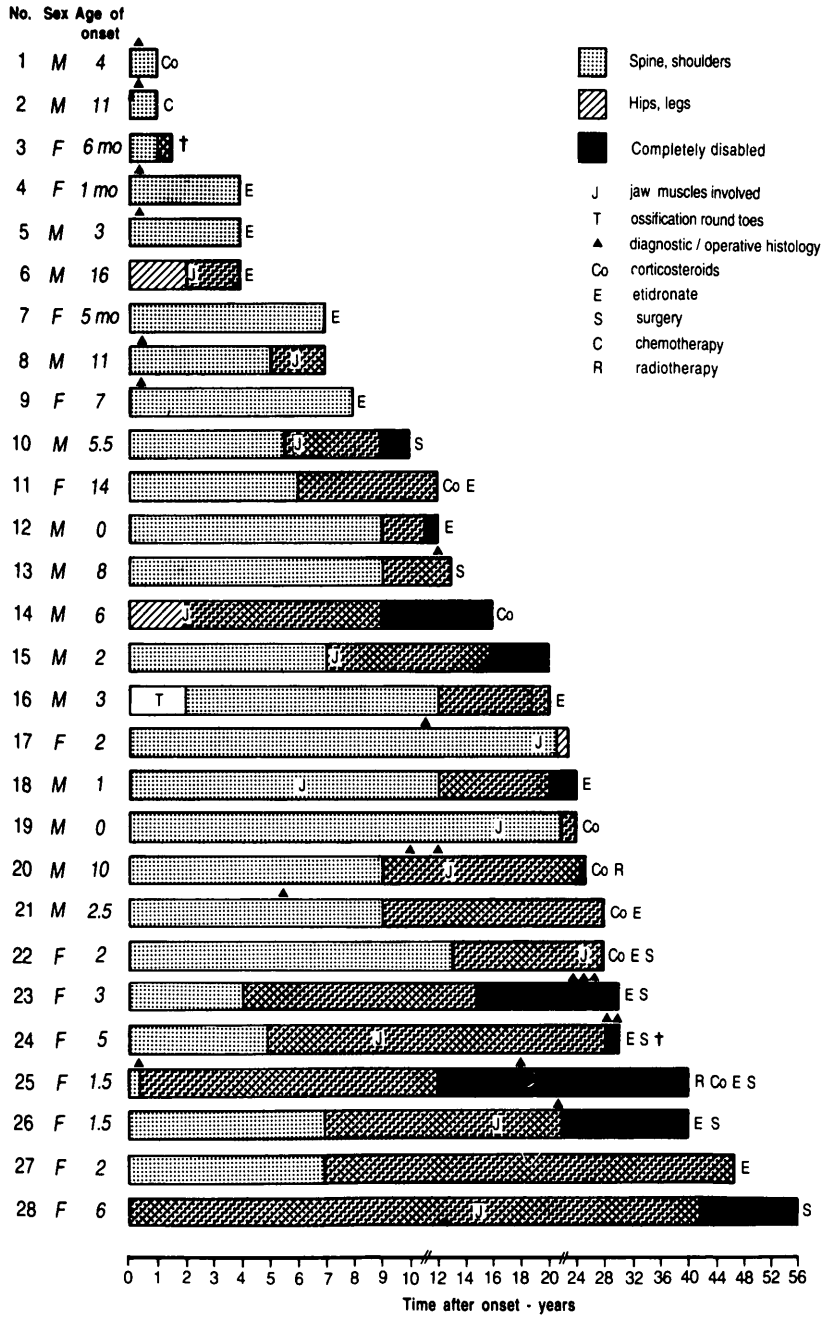

Figure 1. Clinical details of 28 patients with FOP. They are arranged according to the time of follow-up after onset of 'myositis' or related feature. The affected muscle groups are indicated together with the main forms of treatment and times of biopsy. Complete disability means that the subject is confined to a chair or bed and entirely dependent on others. (In patient 28, ectopic ossification occurred early but the order of muscle involvement is not certain).

but the possible significance was not recognized; in seven, no comment was made about the toes at birth; and in four, the toes were only checked when myositis occurred. The diagnosis of FOP was never made from the abnormal toes alone.

The toes were short and deviated, and subsequently became monophalangic when the abnormal epiphyses had fused. Twenty-six had the features of Type I described by Connor and Evans.[2] Examples are given in Figures 2–4. In patient 11, only one big toe was monophalangic. In patient 27 (already referred to) there were multiple reduction defects (Type 4).

Hands

Fewer patients had clinically abnormal short thumbs. Moderate shortness of the thumbs is less easy to recognize than that of the big toes. Where radiographs of the hands were available (thirteen cases) the thumbs were always abnormal. The most frequent change was a short first metacarpal (Figure 5).

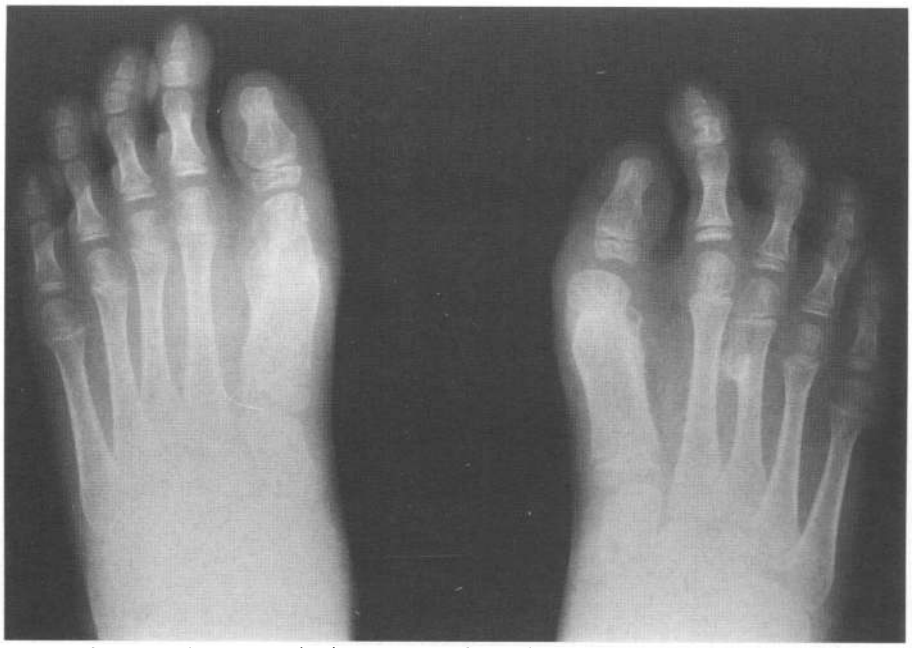

Figure 2. Patient 6. Typical Type I changes in the big toes in a boy of ten years. The big toes are short and monophalangic. In addition, there is an exostosis on the right third metatarsal.

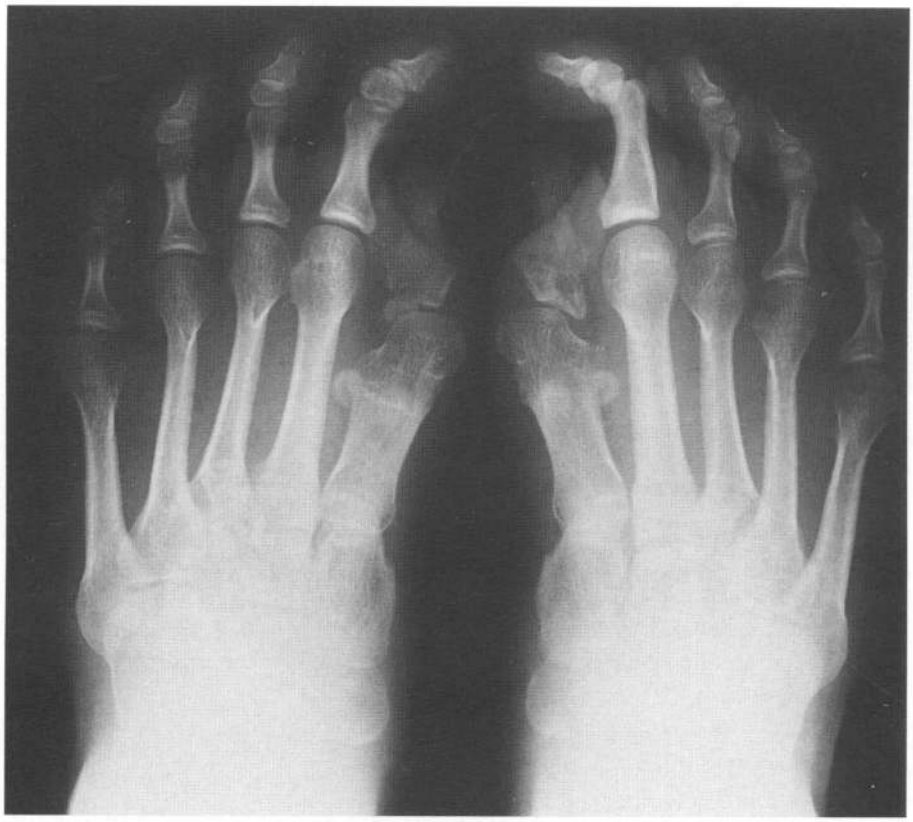

Figure 3. Patient 13. Bizarre short monophalangic (Type I) big toes.

Spine

Radiographs were available on 17 patients. The cervical spine showed variable abnormality. The most frequent was fusion of the large lateral masses, and small vertebral bodies (in 14 cases) (Figure 6). In three patients the appearances were near-normal. Fusion of the cervical spine appeared to be independent of ossification in the overlying muscles.

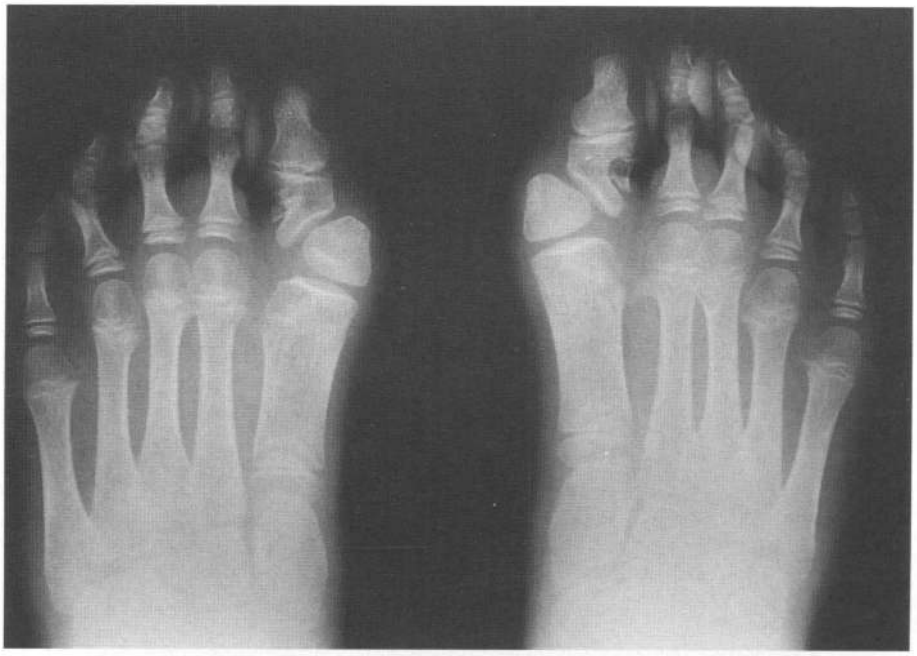

Figure 4. Patient 8. Abnormal big toes with unusual centres of ossification in a boy of eleven years.

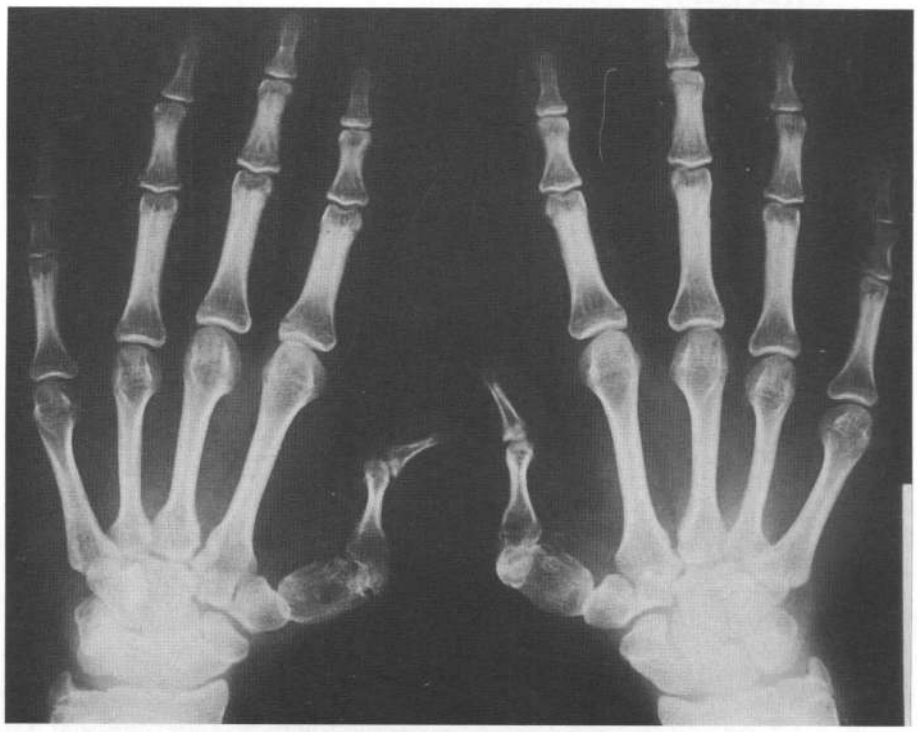

Figure 5. Patient 13. Shows the abnormal short thumbs. The first metacarpal is abnormally short; the middle phalanx of the fifth finger is also short.

Long bones

Other recognised features were the broad femoral necks, widened metaphyses, and ossification of the tendinous insertions into the long bones. Ectopic ossification may give the appearance of exostoses (Figure 7). The severity of the skeletal changes may vary from one site to another in the same individual (for example Case 13 with very abnormal big toes and thumbs had an apparently normal cervical spine).

Ectopic ossification

The onset of 'myositis' presumed to lead to ossification varied from birth until 16 years of age (mean 4.6 years). It was not always easy to time these events. For instance, patients 12 and 19 were noted

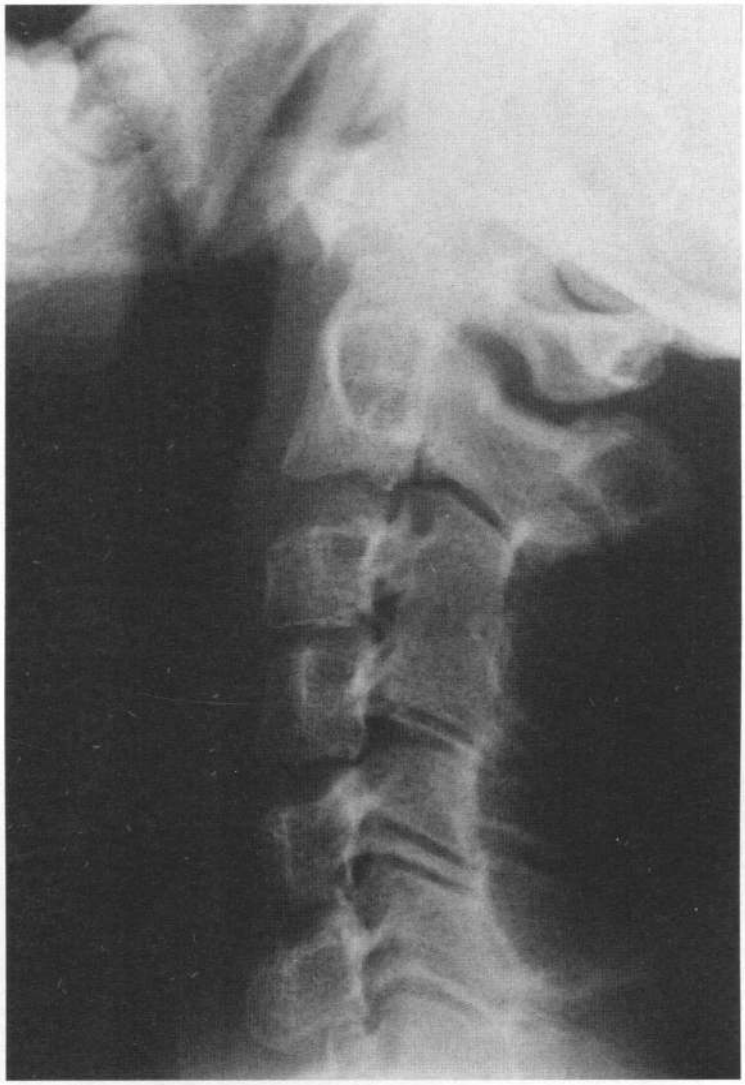

Figure 6. Patient 8. Typical changes in the cervical spine, unassociated with ectopic ossification in cervical muscles. The lateral masses of the third and fourth cervical vertebrae are partly fused and the vertebral bodies are small.

to have extreme stiffness of the neck from birth; and in patient 18, rigidity of the neck from infancy was followed by increasing stiffness into adolescence without recognizable 'myositis'. The formation of bony lumps over the skull, as in patients 2 and 27, may precede recognisable myositis; also in patient 2 ectopic bone formed over the sacrum without myositis.

Despite these difficulties, it is clear that the preferred site of ossification was in muscles of the neck or upper paraspinal region (25 patients, including patient 3, whose ossification in the left arm at 6 months old was attributed to immunization). In the remaining three, ossification began first in relation to an operation (patient 14 in the leg muscles after the use of a tourniquet; patient 16, ossification around the site of attempted correction of 'hallux valgus') or apparently spontaneously in the muscles of the left leg (patient 6).

'Myositis' often occurs without a recognizable predisposing cause; there are occasions when large masses of muscle are involved, associated with pain and considerable oedema, for instance around the neck, the shoulders and the arms; this can be most striking after an injury such as a wheelchair accident (patient 21).

In most patients, ossification eventually fixed all the larger joints around the shoulder, the upper and lower spine, and the hips and knees. Ossification around the hips, often in adolescence, rapidly increased the disability. The jaw muscles were not always involved; the time of involvement was unpredictable, and not always recognized. It could be precipitated by dental extraction (patient 15).

The mean delay in diagnosis of FOP after the first episode of myositis was 2.7 years (range 0–14).

Histology

Where biopsies of the affected muscles were done, the initial histological diagnosis was usually incorrect

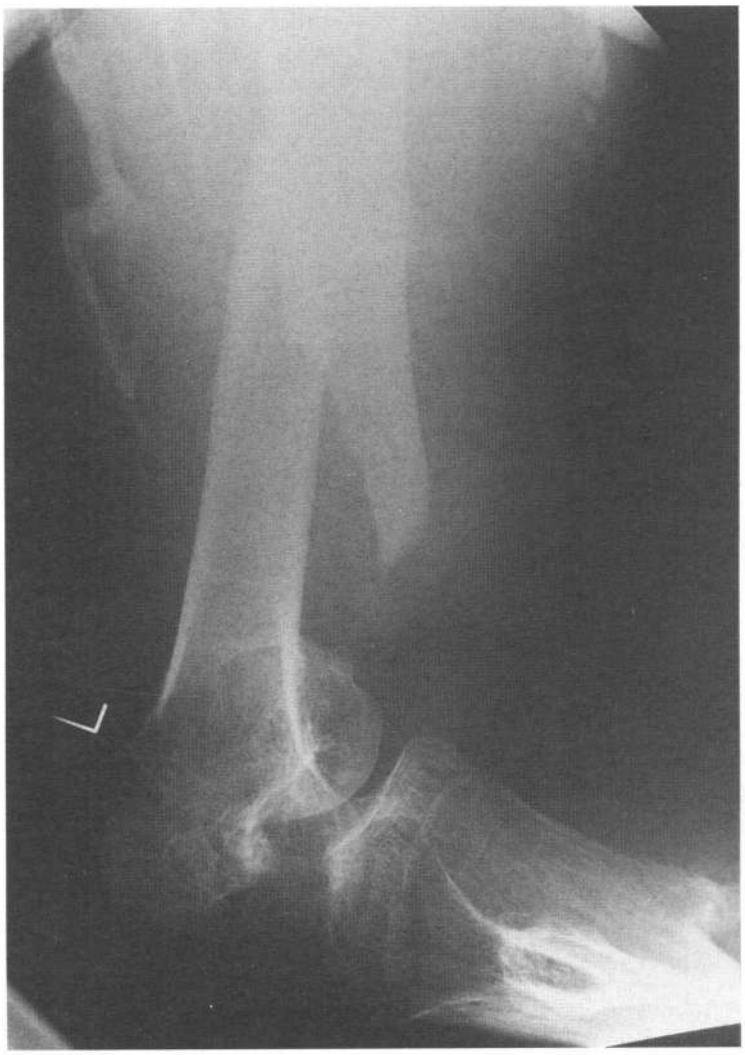

Figure 7. Patient 21. There has been a fracture of the femoral shaft following a fall. The film also shows ectopic ossification in the thigh muscles and the abnormally wide proximal tibia with an exostosis.

(patient 1, juvenile fibromatosis; 2, embryonal rhabdomyosarcoma; 4, osseous metaplasia; 5, rhabdomyosarcoma; 8, fibromatosis; 9, juvenile fibromatosis; 25, sarcoma). Except for patient 25, the histology of all these cases has been reviewed.

Muscle was also examined from biopsies taken when the diagnosis had already been made, or at the time of operation (patients 23–26). These showed varying stages of ectopic bone formation (together with the effects of bisphosphonate treatment (see reference 13). Histology of early lesions showed appearances resembling those of granulation tissue or reparative fibrous tissue, with oedema, congestion, increased vascularity and an increase in collagen formation and fibroblasts between striated muscle fibres; a variable chronic inflammatory infiltrate, predominantly of macrophages and lymphocytes, was occasionally noted. Fibroblasts were plump and hyperchromatic with occasional brisk mitotic activity; all mitotic figures were morphologically typical. Alkaline phosphatase activity could be demonstrated histochemically in the fibroblastic cells.

Evidence of bone and cartilage formation was always found in biopsies from more mature lesions. The bone formed was initially woven in type; it contained irregular cement lines, and on the bone surface prominent osteoblasts and osteoclasts; irregular areas of bone formation appeared to coalesce to form a trabecular network of woven bone. This was later remodelled to mature lamellar bone. Muscle fibres in the vicinity of the lesion showed degenerative changes. A zone of fibrous tissue of variable cellularity and collagen formation was often found adjacent to the zone of bone or cartilage formation within soft tissue.

Using an indirect immunoperoxidase technique and a panel of monoclonal antibodies, immunohistochemistry was carried out on three lesions to examine whether a number of antigens found on cells in other known fibroproliferative lesions, such as fibro-

matosis, myofibromatosis and nodular fasciitis, are also expressed in FOP. We also examined whether this pattern of immunophenotypic expression could be used to distinguish FOP from these and other conditions commonly considered in the histological differential diagnosis. All fibroblastic spindle-shaped cells and bone and cartilage cells within both early and mature FOP lesions were strongly positive for vimentin intermediate filaments. Although cartilage cells in mature lesions were strongly positive for S100 protein, only a few fibroblast-like cells in the vicinity of the cartilage were found to be positive for this antigen. In early lesions containing only fibroblastic cells, evidence of cartilaginous differentiation, as shown by S100 positivity was not noted. Both early and late lesions also contained spindle-shaped fibroblastic cells which were positive for proliferating cell nuclear antigen (PCNA). A few infiltrating leucocytes present within the lesions stained positively for leucocyte common antigen, and most of these cells were also positive for macrophage markers (CD68 and HLA-DR). Endothelial cells within the lesions were also positive for HLA-DR and Factor 8. There was no staining for muscle and myofibroblast markers (desmin intermediate filament and smooth muscle actin); or epithelial markers (cytokeratin intermediate filament and epithelial membrane antigen).

Disability

Progression to severe disability occurred in most patients, but it was unpredictable and not clearly related to the age of onset (Figure 1).

Treatment

Patients had various forms of treatment (Figure 1). These included intermittent courses of corticosteroids; and etidronate (in doses of 20 mg/kg body weight) combined with surgery in an attempt to mobilize the joints. Two patients (patients 20 and 25) had radiotherapy and one (patient 2) chemotherapy. In addition, patients 23 and 27 had a prolonged low vitamin D diet and avoided sunshine; and patient 21 had a low calcium diet and avoided phosphate. There was no convincing evidence that any form of treatment altered the progress of the disease. The deleterious reversible effect of a large daily dose of etidronate on the juvenile metaphyses and growth plate of patient 21 has been described (Case 6, reference 13).

Discussion

Fibrodysplasia (myositis) ossificans progressiva is one of the most disabling and mysterious inherited disorders of connective tissue. Because of its extreme rarity (approximately 1 per 2 000 000), and despite its unique clinical picture which combines characteristic skeletal abnormalities and progressive ectopic endochondral ossification of the major striated muscles the diagnosis is often delayed and erroneous. The progress of ossification from proximal axial upper spinal to distal appendicular muscles has been analysed in detail and used as a basis both for prognosis[8] and a clue about possible cause.[4] These investigators have also emphasized the problems of correct histological diagnosis,[9] and contributed to family studies which confirm the dominant nature of the postulated mutation and the variable phenotypic expression.[10,11]

Our personal series adds further information about this disease; it confirms that FOP often remains unrecognized and misdiagnosed, and that despite generalizations about its progress, the course of ossification remains unpredictable. It also demonstrates that current treatment is ineffective.

Genetics

The absence of any family history of skeletal abnormalities or myositis in this series confirms the impression that FOP is usually due to a new mutation and that affected families are very rare,[10,11] with the caveat that individuals carrying the mutant gene may have mild skeletal abnormalities only and hence go unrecognized.

Case reports

These were chosen for specific reasons. Patient 2 shows how misdiagnosis can lead to inappropriate treatment; patient 3 demonstrates ectopic ossification after immunization; patient 6 illustrates how the diagnosis may be delayed and the prognosis misleading; and patient 13 raises the possibility (which must be rare) of maintained improvement after surgery.

Skeletal abnormalities

The main diagnostic abnormality is the short laterally deviated big toes noted at birth. These are described as Type I by Connor and Evans[2] and details are given by Schroeder and Zasloff[16] and elsewhere.[12] The paediatrician or orthopaedic surgeon will probably not have seen toes like this before (an ignorance expressed often in the patients' record). The diagnosis, if any is made, is of congenital hallux valgus or delta toes. Surgical correction may be attempted in early childhood after which ossification may first occur, either around the site or in leg muscles after the use of a tourniquet (patients 14 and 16). Even at this stage, the diagnosis of FOP may be missed.

Likewise, in patient 2, whose first recognizable episode of myositis occurred in the spinal muscles at the age of eleven, bony lumps had previously been removed from the forehead and sacrum. These events, together with Type I toes might have suggested FOP and dispensed with the need for a misdiagnosed biopsy.

It is not clear how specific these abnormal toes are for FOP, but they are certainly rare and should suggest the diagnosis. For instance Guidera[17] gives the other rare causes of perinatal hallux valgus as Down's syndrome, popliteal pterygium and ectrodactyly; and of short big toes as trisomy 18, Greig syndrome, hand-foot genital syndrome, Jackson-Weiss syndrome and Taybi syndrome, all recognizable by their own specific features. They may also be seen in Apert's syndrome.

Clinically abnormal thumbs are less common than abnormal big toes, and our series agrees with this. This may be partly because short thumbs are less easy to recognize than short big toes, but previous reports also show that the thumbs may be radiographically normal. In our patients radiographs of the hands were always abnormal. There was no example of an FOP patient with clinically abnormal thumbs and normal big toes.

In other parts of the skeleton, the abnormalities are radiographic. The early fusion of elements of the cervical spine and the small vertebral bodies appears to be progressive but not related to the degree or position of ectopic ossification. Our series extends those previously described.[18] In 14/17 patients in whom suitable radiographs were available, the cervical spine was abnormal with large lateral masses and small vertebral bodies. Fusion of lateral masses could be present at birth, and preceded fusion of the small vertebral bodies.

The changes in the long bones may be misinterpreted as diaphyseal aclasis, although it is well recognized that in FOP there may be widening of the metaphyses, ossification of the ligamentous attachments to the bones and the formation of exostoses.[1,2,19] Unusual changes, likely to be coincidental, include enchondromata[20] and synovial chondromatosis.[21] In a growing child with FOP, the changes in the metaphyses with widening and distortion of the growth plate may also be due to excessive treatment with the bisphosphonate EHDP.[9,22]

Ectopic ossification

The episodes of myositis which precede ectopic ossification by more than 2 to 3 months cause the muscles to be swollen, hard, oedematous and painful and may suggest neoplasm, infection or injury. Myositis may not always present in this way. Thus in patient 18, the main feature of the disease for many years was progressive stiffness and it was not until late adolescence that ectopic ossification was detected. Previous diagnoses (by paediatricians and rheumatologists) had included Stills disease (at 18 months) and an unusual form of Klippel-Feil syndrome. When the myositis occurs in the muscles around the jaw it may suggest mumps or dental abscess.

The ossification in the muscles may be demonstrated by scintigraphy (the isotope uptake is considerably increased) or by CT scanning (where calcification is detected earlier than on plain films). Other methods which have been used include ultrasound, angiography and magnetic resonance imaging.[23] None of these should be necessary, and their use emphasizes failure to make the clinical diagnosis, almost invariably because the feet are not examined.

Kaplan and his associates[3] emphasize the usual progression of ectopic ossification which almost invariably begins in the upper cervical and paraspinal muscles and only later affects the appendicular muscles and those of the lower limbs. The major events of ectopic ossification which lead to progressive disability involve the spine, the shoulders, the hip joints and the jaw. Perhaps the most catastrophic is ossification around the hip muscles, often in late adolescence, which limits walking and accelerates a wheelchair existence. The time of ossification of the jaw muscles is the least predictable: it is not always associated with dental work; it may lead to variable fixation of the jaw and submandibular oedema can cause difficulty in breathing and swallowing. However, this described sequence of myositis (leading to ossification) in a group of FOP subjects may not be adhered to in individuals. Perhaps the most common cause for this is injury, operation (patients 14 and 16), or other invasive procedure (immunization—patient 3). It is because of such individual variation in position and timing of ossification that it is very difficult to give an individual prognosis. This disagrees with Rocke *et al.*[8] who reanalysed a postal survey of 44 patients and suggested, using life data methods, that new joint involvement could be usefully predicted in individuals.

Pathology

Failure to make the clinical diagnosis usually leads to biopsy of the affected muscle. Kaplan and his colleagues[9] reviewed the histology of twelve such biopsies taken from eleven FOP patients. All had been taken from children in order to exclude a malignant lesion. Despite the fact that there was always some evidence of endochondral ossification varying from cartilaginous foci (or evidence of chondroblasts suggested by S100 protein) to endochondral

bone the main erroneous diagnoses were fibromatosis or sarcoma. Kaplan *et al.*[9] regard these diagnoses as understandable where no evidence of bone or cartilage is detected, since the early lesion is locally aggressive and may blend imperceptibly into the surrounding connective tissue without significant inflammatory infiltrate. Our experience of diagnostic biopsies is the same; in patients 1, 8, and 9 the original histological diagnosis was fibromatosis; more importantly, because of its therapeutic implications, was a misdiagnosis of rhabdomyosarcoma which led in patient 2 to a full course of chemotherapy. On review of the histology of the biopsy from this case, and biopsies from other early FOP lesions, it was evident that, although these lesions are actively proliferating, being highly cellular and containing frequent typical mitoses, they do not show cytological features of malignancy. PCNA expression on numerous spindle cells in early lesions noted by immunohistochemistry confirmed that FOP is a highly proliferative lesion. Immunohistochemistry may also prove useful in distinguishing FOP from several of the sarcomatous and fibroproliferative lesions with which it is more commonly confused. Fibroblastic spindle-shaped cells in early FOP lesions were only strongly positive for vimentin, and negative for smooth muscle actin and desmin. In contrast, rhabdomyosarcoma tumour cells are usually positive for desmin, and myofibroblasts in fibromatosis are often smooth-muscle-actin-positive and occasionally show desmin positivity.[24] A strongly positive reaction for S100 protein was only really found on spindle shaped cells in the vicinity of cartilage nodules of mature FOP lesions; S100 is therefore unlikely to prove discriminatory in those early lesions which are often confused for other fibroproliferative lesions, these all being generally S100 negative.

Treatment

No treatment has a clearly beneficial effect on this disease. In fact the extreme variability of ectopic ossification, both in time and position, makes it difficult to assess any therapeutic measure. Our series illustrates the various approaches which have been used, which include corticosteroids, etidronate, radiotherapy and surgery. In early myositis, especially where large amounts of muscle are involved with extensive swelling it is reasonable to use anti-inflammatory drugs, including corticosteroids, as well as analgesics and an increased amount of etidronate until the acute phase subsides. Very rarely the submandibular and neck swelling may be sufficient to obstruct the airway, when tracheotomy needs to be considered. We have described the use of etidronate to prevent recurrence of ectopic ossification after the removal of bone,[13] and our subsequent experience does not suggest that this is useful. However, if etidronate is given for this reason, or to ameliorate ossification after naturally occurring myositis, it is important that the dose should not be excessive, since it will have a deleterious but reversible effect on the metaphyses. Recently rachitic-like changes have been described in the metaphyses on an Italian child given etidronate in a prolonged daily dose of 30–40 mg/kg for 8 years.[22]

Outcome

One conclusion of this personal series is that it is impossible to give an accurate individual prognosis, although in general terms the progression of the sites affected by ectopic ossifications is well established. Thus in patient 6 the first manifestation of the disease (apart from the abnormal Type I toes) at the age of 16 was inability to straighten the left leg, with subsequent ectopic ossification attributed to injury. At this stage, the geneticist gave a good prognosis. However, by the age of 20 he was unable to open his mouth and had extensive ossification of the neck and spinal muscle. In contrast the first symptom in patient 22 began at two years of age, and 28 years later she has relatively little disability despite episodes of ossification at the hip and jaw 13 and 25 years after onset, respectively.

Cause

The cause of FOP remains obscure. Any advance must explain the constant association between the characteristic skeletal changes and the ectopic endochondral ossification. For the present, the most likely candidate for a dominant mutant gene (or genes) responsible for this disorder will be found within the large transforming growth factor (TGF) beta gene family which includes molecules capable of inducing bone formation and of controlling the patterning of the skeleton.[6]

Kaplan and his colleagues[4] pointed out the resemblance between the developmental gradients characteristic of FOP and the developmental anomalies produced by mutations in the *dpp* locus of *Drosophila*. Since the protein encoded by the *dpp* locus is a member of the TGF beta family of molecules, and shares sequence homology with some human bone morphogenetic proteins (BMP), it is clear that these are molecules which can both control skeletal patterning and induce endochondral ossification. The close relationship between genes which control cell–cell interactions and polarity in Drosophila and the mouse[5] suggest that they are strikingly conserved in evolution. Of the mouse short-ear mutations,[6] one is a chromosomal deletion which eliminates the entire *BMP-5* gene and pro-

duces alterations in the morphology of particular skeletal elements. Kingsley[6] suggests that study of further mutation in the *BMP* genes should help to clarify their importance in the development of higher animals. It may be that FOP will eventually turn out to be a human equivalent of such mouse mutations and abnormal regulation of *BMP-4* expression has recently been described in FOP.[7] Experimentally inactivation of the *BMP-4* gene in the mouse shows that it is essential for mesoderm formation and patterning;[25] and recent work demonstrates the likely importance of *BMP-4* in normal fracture healing.[26]

Mutations in one or more of the *BMP* genes seem the most likely cause of FOP, but mutations in the genes responsible for other important developmental proteins such as cFos and fibroblast growth factors cannot be excluded. It is clear that the mechanisms of limb patterning are complex.[27] Recently, a mutation in the gene for growth differentiation factor 5 has been identified as a cause of the animal disorder brachypodism.[28]

Whilst this problem is being elucidated, it is clear that physicians need to be fully aware of the clinical aspects of this disabling disease. Many of these were dealt with at a recent conference.[29]

Clinical lessons

The lessons from this prolonged follow-up study of 28 patients confirm those of previous reviews, and provide useful individual examples. It is clear that the diagnosis of this disease is clinical and that recognition of the skeletal abnormalities cannot be over emphasized. Examination of the toes (if necessary with confirmatory radiographs) should make biopsy of affected muscle and investigations such as isotope bone scans, CT and MRI scans unnecessary. Although the general pattern of ectopic ossification is established, individual follow-up suggests that it is unwise to give a detailed prognosis. As yet no useful form of treatment is available but the clinical features now provide useful clues about its possible cause.

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