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CASE REPORT

Fibrodysplasia ossificans progressiva. An unusual cause of restricted mandibular movement

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A 9-year-old girl is presented who was initially misdiagnosed and finally diagnosed with fibrodysplasia ossificans progressiva only after presentation with progressive limitation of her mouth opening. The clinical, histopathological, and molecular biological aspects of this uncommon disorder will be discussed. Furthermore, dental and surgical guidelines will be described.
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Introduction

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder of connective tissue with progressive ectopic ossification of tendons, ligaments, facial and skeletal muscles, and characteristic skeletal malformations. Characteristically, the temporomandibular joints are among the last joints to be affected by FOP. However, approximately 70% of the FOP patients have jaw restriction by the age of 18 (Kabala *et al*, 1989; Aslan *et al*, 1999; Chichareon *et al*, 1999; Herford and Boyne, 2003).

The presented case is unusual by its diagnostic process. A 9-year-old girl was initially misdiagnosed and diagnosed with FOP only after presentation with progressive limitation of her mouth opening. This report is being made to emphasize the uncommon occurrence of this disease and to describe dental and surgical guidelines for patients with FOP.

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Case report

A 9-year-old girl was referred to the Department of Oral and Maxillofacial Surgery by her family physician because of progressive limitation of her mouth opening, noticed by her mother since 2 weeks. The recent history revealed a fall from the stairs 4 weeks previously; she experienced some mild pain of her mandible on the left side. Her relevant medical history mentioned the presence of several bony exostoses of the skeleton, an exostosis of the left clavicle developed after a fracture during birth, an exostosis on the medial side of the left proximal tibia developed 3 years after a fracture at the same location, and bony exostoses on the distal sides of both humuri. The combination of symptoms has led to the diagnosis hereditary multiple exostoses (HME), a benign disorder characterized by the formation of exostoses, which are cartilage-capped bony protuberances mainly located on long bones. The patient did not use any medication at presentation.

Physical examination revealed a mandibular trismus with a mouth opening of approximately 2 cm, and a deviation of the mandible to the left side on opening. The patient experienced no pain on palpation of the temporomandibular joints on both sides. No other abnormalities were found on physical examination.

A panoramic as well as an additional Towne radiograph did not show any abnormalities on the left side of the mandible. However, a computed tomogram showed bony appositions on the medial side of the left zygomatic arch in the area of the left temporal muscle, which most likely were responsible for the limited mouth opening (Figure 1). A possible relationship with HME was suggested and the patient was referred to the Paediatric Department. As HME only affects bones that are formed by endochondral ossification and thus never has any manifestations in the facial skull, further investigations, including total body radiographs and a whole-body scintigram, were performed. Apart from the known exostoses of the left clavicle, the medial side of the left proximal tibia, and bony exostoses on the distal sides of the left as well as the right humurus, several

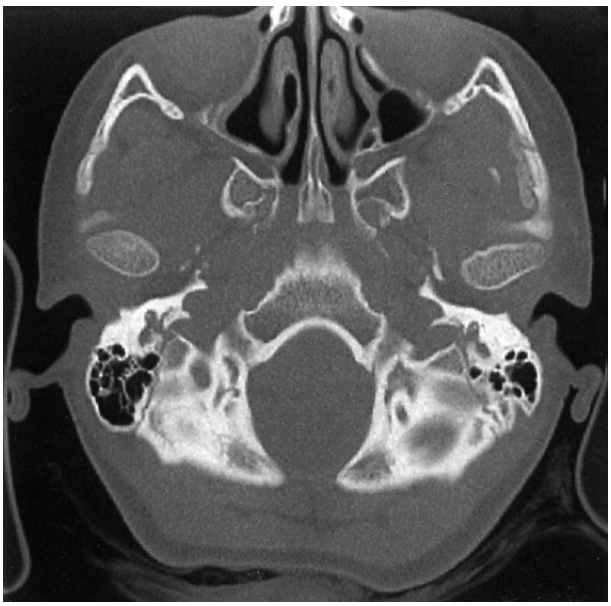

Figure 1 Computed tomography scan showing bony appositions on the medial side of the left zygomatic arch in the area of the left temporal muscle

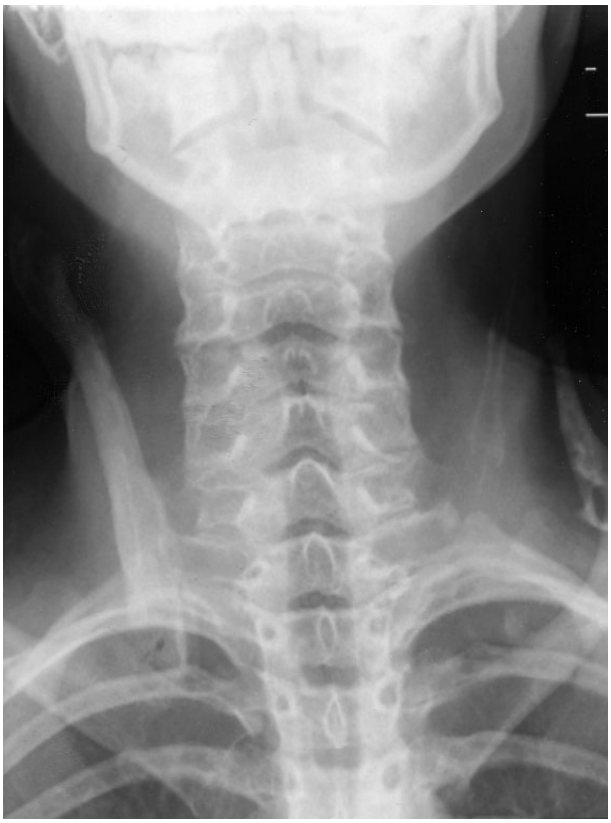

Figure 2 Conventional radiograph of the neck reveals a deformity of the left clavicle as well as bony appositions on both sides of the neck along the sternocleidomastoid muscles

other abnormalities of the skeleton were observed. On a radiograph of the neck a deformity of the left clavicle as well as bony appositions on both sides of the neck

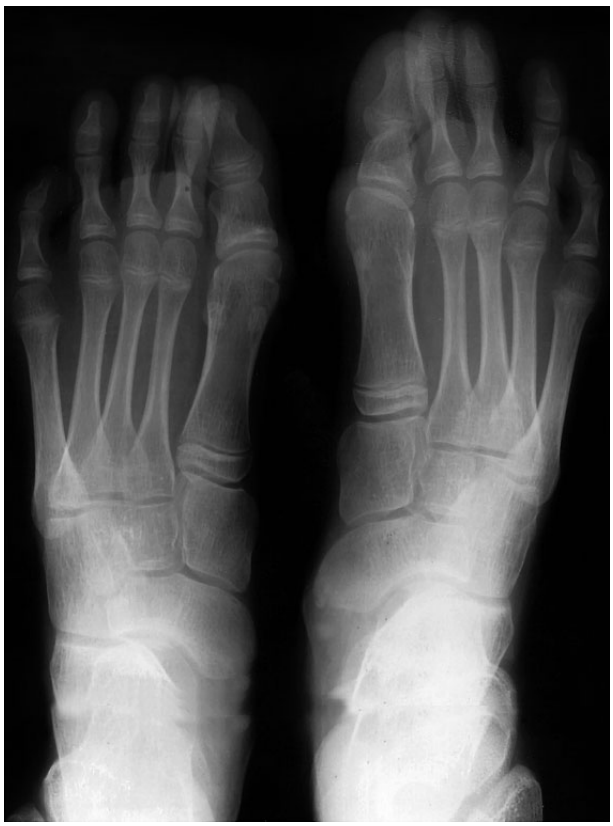

Figure 3 Conventional radiographs of the feet show a deformity of the hallux and shortened middle and endphalanges of the second, third, fourth and fifth toe on both sides

along the sternocleidomastoid muscles were noticed (Figure 2). Radiographic examination of the feet revealed a deformity of the hallux and shortened middle and endphalanges of the second, third, fourth and fifth toe (Figure 3). A whole body scintigram showed increased uptake in the region of the left zygomatic arch and on the right side of the neck along the sternocleidomastoid muscle (Figure 4). Based on these findings the previous assessed diagnosis of HME was rejected and a diagnosis of FOP was made.

Discussion

Fibrodysplasia ossificans progressiva was first described by Patin in 1648 as 'the woman who turned to wood' (Patin, 1692; Buyse *et al*, 1995). The term FOP was introduced by Bauer and Bode in 1800 (Taylor, 1984). Since then, over 700 cases have been reported. The estimated prevalence is approximately 1 per 2 million population (Mahboubi *et al*, 2001). Based on these figures, there are probably seven patients with FOP in The Netherlands.

Clinically, FOP is characterized by congenital malformation of the great toes and by progressive, disabling heterotopic osteogenesis of tendons, ligaments, facial and skeletal muscles in predictable anatomic patterns. Congenital malformation of the great toes, with shortening of the first metatarsal and proximal

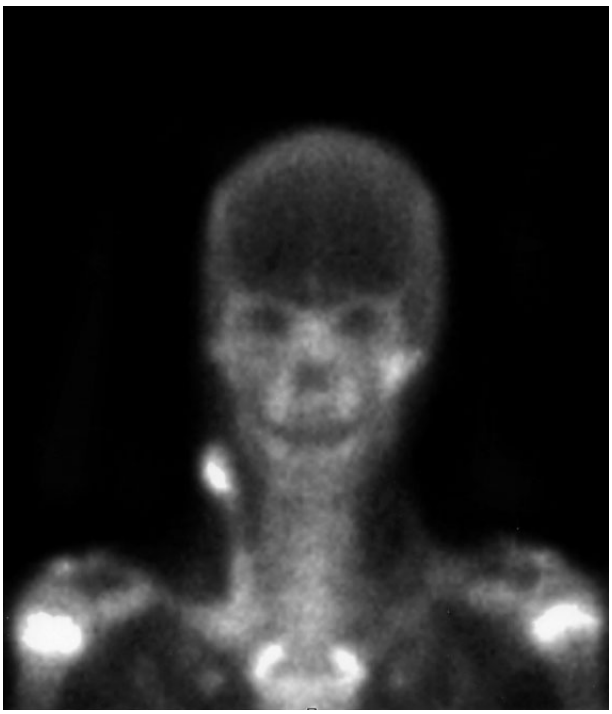

Figure 4 Bone scan demonstrating increased uptake in the area of the left zygomatic arch and along the right sternocleidomastoid muscle

phalanx, is the earliest phenotypic feature of FOP and is present in nearly all affected individuals at birth. Heterotopic bone formation usually begins in the first decade of life and progresses in characteristic anatomic patterns. Involvement is typically seen earliest in dorsal, axial, cranial and proximal regions of the body and later in ventral, appendicular, caudal and distal regions. These patterns of heterotopic ossification are similar to the patterns and progression of embryonic skeletal formation, although the significance of this similarity is unknown (Mahboubi *et al*, 2001).

The disease progresses by successive bilateral sporadic episodes, affecting one or several muscles, leading to restricted mobility of the major joints of the axial and appendicular skeleton. Although the rate of disease progression is variable, most patients are confined to a wheelchair by their early twenties. Death may result from complications by restrictive disease of the chest wall due to ankylosis of the spine and rib cage (Kussmail *et al*, 1998; Shore *et al*, 2000). Maxillofacial involvement leading to permanent restriction of mandibular opening is seen in approximately 80% of the cases and occurs on an average age of 18 years (Kabala *et al*, 1989; Debeney-Bruyerre *et al*, 1998; Aslan *et al*, 1999; Chichareon *et al*, 1999; Herford and Boyne, 2003). Disease flare-ups can occur spontaneously or can be induced by minor trauma, iatrogenic or not, as seen in the present case.

The initial misdiagnosis and eventually delayed diagnosis in the presented case is illustrative for patients with FOP in which delayed diagnosis often occurs even though they have characteristic skeletal malformations. Additional imaging is necessary in order to achieve a proper diagnosis of FOP and to differentiate from entities such as post-traumatic myositis ossificans circumscripta, progressive osseous heteroplasia, Albright hereditary osteodystrophy, and extraskeletal osteosarcoma (Shore *et al*, 2000). Although MR imaging, CT scanning and bone scans are abnormal before ossification can be seen by plain radiography, conventional total body radiographs are most often sufficient to assess an adequate diagnosis of FOP.

Although a lesional biopsy uniformly exacerbates the condition and is thus contra-indicated, failure to recognize the features of FOP often leads to biopsy of the acute lesion. Histopathologic examination of early FOP lesions reveals an intense perivascular lymphocytic infiltrate, followed by lymphocytic invasion into muscles and development of fibroproliferative tissue with extensive neovascularity (Gannon *et al*, 1998). The histopathologic picture of such an early lesion can be misdiagnosed as aggressive juvenile fibromatosis or sarcoma (Kaplan *et al*, 1993; Blaszczyk *et al*, 2003). The lesions mature over a period of several months showing characteristic features of endochondral ossification including chondrocyte hypertrophy, calcification of cartilage, and formation of woven bone with marrow elements. The excessive endochondral osteogenesis might be the result of a dysregulation of production of bone morphogenetic protein 4 (BMP 4). Overexpression of this potent bone-inducing morphogen and its messenger ribonucleic acid has been observed in cells derived from early fibroproliferative lesions in patients with FOP (Shafritz *et al*, 1996). The gene for BMP 4 has been mapped to chromosome 14q22–q23 (van den Wijngaard *et al*, 1995). However, no mutations have yet been found in the BMP 4 genes of patients with FOP, suggesting that BMP 4 signalling pathway components that stimulate expression of the BMP 4 gene or that impair the action of an inhibitor, such as products of the noggin gene, are primarily responsible for the heterotopic ossification.

As the exact pathogenesis of FOP is not understood no standard treatment protocol capable of stopping progression of the disease exists. Several treatment modalities have been described (Moore *et al*, 1986; Bruni *et al*, 1990; Crofford *et al*, 1990) including calcitonin, non-steroidal anti-inflammatory drugs, isotretinoin, warfarin, and diphosphonates showing diverse results.

Surgical treatment exposes the patient to the risk of exacerbation and recurrence within 2 months and can trigger an accelerated progression of the disease (Crofford *et al*, 1990; Chichareon *et al*, 1999; Herford and Boyne, 2003). Although bone can be removed surgically so that a fused joint may temporarily be more mobile, the bone is virtually guaranteed to reform, and often more abundantly than the original condition. Therefore, elective surgery on the muskuloskeletal system should be avoided. In case of acute surgical procedures unrelated to the muskuloskeletal system immobility of the neck may complicate anaesthetic management. Therefore, patients with FOP have been advised to be evaluated by an anaesthesiologist, so that a plan could be developed

for anaesthetic management of potential surgical emergencies.

As the majority of patients with FOP will have restriction of their mouth opening by the age of 18 (Kabala *et al*, 1989; Aslan *et al*, 1999; Chichareon *et al*, 1999; Herford and Boyne, 2003), making dental treatment more complicated, preventive dentistry is an important issue. All affected individuals should have early, regular, and periodic dental visits combined with oral hygiene instruction and nutritional counselling. The additional use of dental sealants, fluoride supplements, and plaque rinses should be considered as well (Nussbaum *et al*, 1996). Intramuscular injections of anaesthetics should be avoided, as reports have demonstrated a clear relationship between the use of local anaesthetics during dental procedures and subsequent trismus. At present, it is not possible to determine if the trauma of injection, the local anaesthetic agent itself, or a combination of both triggers the local ossification (Luchetti *et al*, 1996). Although mandibular block anaesthesia is contra-indicated, local anaesthesia can be applied as infiltration and/or intraligamentary anaesthesia. No patients have been reported with any problems related to FOP as a result of orthodontic procedures. There seems to be no contra-indication for orthodontic care in FOP patients, but dentists and orthodontists should avoid stretching of the jaw during application or removal of orthodontic appliances or during any other dental procedure (Nussbaum *et al*, 1996).

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