Fibrodysplasia ossificans progressiva (FOP) in South Africa: dental implications in 5 cases

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Fibrodysplasia ossificans progressiva (FOP) is a severe genetic disorder in which progressive ossification of subcutaneous tissues leads to immobility and profound physical handicap. Dental management of affected persons may be constrained by impaired mobility of the temporomandibular joints. Equally, the traumatic aspects of dental intervention can exacerbate the ossification process. In the later stages of the disorder, thoracic immobility impairs pulmonary ventilation and compromises dental anesthesia.

We have undertaken dental appraisal and treatment of 5 South Africans with FOP, with ages ranging from 2 to 52 years. The age relationship of the manifestations of FOP was apparent in these persons, as were the dental problems that emerged. These dental observations illustrate the importance of accurate diagnosis and the awareness of potential complications that may be encountered in dental management. Our observations are presented and discussed in this article. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:11-18)

Fibrodysplasia ossificans progressiva (FOP) is a rare, autosomal dominant (AD) heritable disorder that is characterized by ectopic ossification of skeletal muscle, tendons, ligaments, and fascia.1 This process occurs spontaneously in FOP, but it may also be initiated or aggravated by physical trauma and surgical intervention. Progressive soft tissue ossification results in loss of general movement, and physical handicap is eventually severe.2 The clinical manifestations of FOP are not apparent at birth apart from a variable malformation of the great toe, which can serve as an early diagnostic indicator.3

Dental management of persons with FOP can be very difficult because of restricted mouth opening associated with temporomandibular involvement and ossification of the orofacial soft tissues. The risk of exacerbating the ossification process during dental measures is a further problem. Dental anesthesia can also be compromised by restriction of chest wall movements and spinal rigidity. These constraints on dental care are exacerbated when available facilities for comprehensive and long-term care are suboptimal.

We have undertaken dental assessment and management in 5 South Africans with FOP and addressed the problems inherent in this process in a developing country. Our observations are documented, depicted, and discussed in this article.
The objectives of this study were to assess the dental manifestations in 5 persons with FOP, and to determine the significance of age and syndromic progression in the dental management of the disorder.

The 5 persons with FOP who we studied all had similar histories of inflammatory swellings during childhood that were spontaneous or precipitated by trauma and that were followed by ossification in the soft tissues. This ossification process commenced on the trunk and spread to the limbs. Ambulation and self-care became increasingly difficult and by adulthood, physical handicap was severe. There was no visceral involvement and apart from respiratory complications, general health was unimpaired. In the late stages of the condition, the affected persons were virtually immobile and entirely dependent on caregivers for assistance with all their bodily functions. The general medical status and management of patients 1 to 3 have been documented in detail. The diagnosis of FOP in these individuals was confirmed by the demonstration of the causal mutation in the AV1 gene at the chromosomal locus 4q 27 to 31. At the clinical level, all 5 patients had the characteristic abnormalities of their great toes.

Four of the affected persons were of indigenous Xhosa ancestry and were alive in 2010. The fifth, patient 4, had antecedents in Europe and had died at the age of 52 years. None had any similarly affected relatives.

For the sake of brevity, the case reports that follow have been largely confined to features that are relevant to dental practice. The clinical and dental manifestations in the affected persons have been summarized in Table I. The general medical and dental manifestations of FOP are summarized in Table II where key references are also provided. The dental management of FOP is outlined in Table III.

This project was undertaken with ethical approval from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC: REF 026/2010).

The authors have read the Helsinki Declaration and followed the guidelines in this investigation.

**Case 1**

A female, born in 1966, was diagnosed with FOP in 1975. When seen in 2009 she was experiencing toothache in the posterior regions of both jaws. She was bedridden and movements were virtually confined to her fingers and toes. Her handicap was severe and she was unable to eat efficiently or maintain proper oral hygiene. Temporomandibular joint (TMJ) mobility was limited and she had an interincisal distance of less than 1 mm. Extraoral radiographs showed multiple carious teeth and associated periapical radiolucencies. Dense opacities representing ectopic ossification were evident in the regions of her TMJs and masseter muscles. Ectopic ossification was widespread throughout her trunk, and her shoulders and hips were ankylosed (Fig. 1). The phalanges of her great toes were malformed, shortened, and fixed in ulnar deviation (Fig. 2).

The patient was referred to the Department of Maxillofacial and Oral Surgery at Groote Schuur Hospital, Cape Town, for dental management. Owing to the limited access to the carious teeth and the possibility of future caries, a decision was made to remove all her teeth. The type of anesthetic procedure to be under-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Year of birth</th>
<th>Year of diagnosis</th>
<th>Gender</th>
<th>Population</th>
<th>Medical status in 2010</th>
<th>Orodental abnormalities in 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1966</td>
<td>1975</td>
<td>Female</td>
<td>Xhosa</td>
<td>Immobile</td>
<td>Severe microstomia Caries Ectopic calcification in area of TMJ and masseter</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac and respiratory complications</td>
<td>Severe microstomia Widening of periodontal ligament space</td>
</tr>
<tr>
<td>2</td>
<td>1966</td>
<td>1978</td>
<td>Male</td>
<td>Xhosa</td>
<td>Limited movements of neck and shoulders</td>
<td>Hypoplastic mandible Extensive caries</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Died in 1986</td>
<td>TMJ ankylosis Gross limitation of mouth opening Inability to chew</td>
</tr>
<tr>
<td>3</td>
<td>2003</td>
<td>2010</td>
<td>Female</td>
<td>Xhosa</td>
<td>Limited arm movements</td>
<td>Indurated lesions on scalp</td>
</tr>
<tr>
<td>4</td>
<td>1934</td>
<td>1944</td>
<td>Female</td>
<td>European</td>
<td>Total immobility</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2008</td>
<td>2009</td>
<td>Female</td>
<td>Xhosa</td>
<td>Indurated lesions on scalp</td>
<td></td>
</tr>
</tbody>
</table>

Table I. Clinical and dental manifestations of fibrodysplasia ossificans progressiva in 5 affected persons
taken was extensively debated. Initially, general anesthesia was considered. However, concerns regarding her respiratory and cardiac function and the risk of possible complications persuaded the surgeons to remove her teeth under local anesthesia. The removal of her painful teeth and the prevention of sepsis was a priority at this point. The possibility that the trauma of surgery could initiate further ossification was a major factor in the discussion concerning dental intervention.

During the procedure, care was taken to keep the patient’s head in a neutral position without overextending her rigid neck and spine. The upper and lower anterior teeth were removed first to create access to the posterior region of the oral cavity. Minimal pressure was applied to the jaws to prevent iatrogenic injury and further ossification.

The patient was initially reluctant to undergo extraction of her teeth, and she was concerned about the esthetic and functional results of surgery. Nevertheless, removal of the teeth was necessary because of the risk of sepsis, which could have led to serious complications. The provision of dentures was considered but her immobility, together with...

## Table II. Conclusions of dental manifestations and medical complications in fibrodysplasia ossificans progressiva

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Mandible</th>
<th>Condyles</th>
<th>Temporomandibular joint</th>
<th>Spine</th>
<th>Perioral soft tissues</th>
<th>Soft tissues</th>
<th>Toes</th>
<th>Medical complications</th>
<th>Lungs</th>
<th>Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dental manifestations</strong></td>
<td>Hypoplasia</td>
<td>Broad, flat, misshapen occasional osteophytes</td>
<td>Ankylosis</td>
<td>Ossification of ligaments</td>
<td>C2-C7</td>
<td>Extensive progressive ossification leading to severe restriction of movements</td>
<td>Great toes shortened and malformed</td>
<td>Restricted function</td>
<td>Recurrent infections</td>
<td>Pneumonia</td>
</tr>
</tbody>
</table>

## Table III. Dental management of fibrodysplasia ossificans progressiva

<table>
<thead>
<tr>
<th>Dental management</th>
<th>Conservative</th>
<th>Restorative</th>
<th>Sepsis removal</th>
<th>Limited access to oral cavity/locked TMJs</th>
<th>Anesthetic management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate access to oral cavity</td>
<td>Atraumatic restorative techniques, avoid invasive application of local anesthetic</td>
<td>Try to prevent sepsis, alternatively extraction using local anesthetic</td>
<td>Antimicrobial mouth rinses</td>
<td>Specialized tooth brushes</td>
<td>IV conscious sedation</td>
</tr>
<tr>
<td>Patient compliance, financial and economic constraints, access to dental facilities</td>
<td>Late presentation making sepsis and periapical pathology unavoidable</td>
<td>May be limited to buccal surfaces of teeth</td>
<td>Possible damage to mental nerve</td>
<td>Lidocaine aerosol</td>
<td></td>
</tr>
<tr>
<td>Regular visits to dentist</td>
<td></td>
<td></td>
<td></td>
<td>Infiltrations, intrapulpal and intraligamental</td>
<td></td>
</tr>
</tbody>
</table>
her microstomia and limited jaw movements, would have posed difficulties in their removal and replacement. These potential difficulties weighed against the cosmetic benefits that she anticipated.

Case 2

A male, born in 1966 and initially diagnosed with FOP in 1978, was assessed for dental treatment at Groote Schuur Hospital, Cape Town, in 2009. At this time, he was barely ambulant and had limited mouth opening. The interincisal distance was approximately 3 mm, making oral examination difficult and limiting the radiographic examination to extraoral views. His oral hygiene was suboptimal under the circumstances. He had previously complained of toothache, but had refused dental treatment.

Lateral skull radiographs showed large carious lesions of his lower third molar teeth, generalized horizontal bone loss in the posterior areas of his mandible, and interproximal calculus spurs. Generalized widening of the periodontal ligament spaces was evident. During a further consultation, the patient once again refused dental treatment.

Case 3

A female born in 2003 was referred to the University of the Western Cape, Cape Town, Dental Faculty for routine dental screening in 2009 following recent diagnosis of FOP. She was ambulant but had the characteristic irregular bone swellings on her back with limitation of movements of the neck and shoulders. Previous invasive diagnostic procedures on her back had exacerbated her condition, and a hard bony mass was visible beneath a biopsy scar (Fig. 3).

On dental assessment, the girl did not have any evidence of TMJ ankylosis. She had 8 carious deciduous teeth, 2 of which were restored by an atraumatic restorative technique. The 6 carious anterior incisors remained untreated because the caries process had arrested. Topical fluoride was applied to these teeth and extensive guidance concerning oral hygiene was given to her mother, who was her primary caregiver.

Her mandible was hypoplastic but radiographic examination showed the presence of all developing permanent teeth (Fig. 4). It was apparent that the amount of space required for these teeth to erupt fully into the oral cavity exceeded the space available to accommodate them, and impaction and/or malocclusion was a future possibility. Arrangements were made for regular medical and dental follow-up.

Case 4

An affected female, born in 1934, resided in a special care facility and was referred to the Faculty of Dentistry, University of the Western Cape, Cape Town, when she was aged 44 years. She had been diagnosed as having FOP when she was about 10 years of age and she recalled in detail the progressive decline in her health. She reported that she had frequent respiratory problems and that occasionally she had to rely on a portable breathing system. Her initial referral was for dental pain that she had experienced over several months.

When assessed, she was unable to walk or sit in an upright position. Fusion of her cervical spine had resulted in her chin being approximated to her chest. Her physical handicap was severe and she was unable to move her head in any direction. Ankylosis of the TMJ resulted in limited opening of her mouth and her interincisal measurement was 12 mm. Although this space was sufficient to gain intraoral access for dental procedures, such as scaling, polishing, and dental restorations, it was difficult to perform extensive restorative procedures. As a consequence of her disability, consultations and procedures had to be limited and seldom exceeded 30 minutes. Consideration was given to her inability to masticate efficiently and advice was given in this regard. Regular visits for oral hygiene, scaling, and polishing were undertaken and this approach together with the use of a motorized toothbrush resulted in a satisfactory oral health status. In the terminal stages of her condition, it was necessary to remove 2 of her incisors to facilitate alimentation by means of a straw. She died in 1986, at the age of 52 years; by this time her
movements were limited to her fingertips, extrinsic ocular muscles, and her tongue. Nevertheless, her mouth remained in a functional healthy state.

**Case 5**

A girl, aged 2 years, was referred to the dental department at Red Cross Children’s Hospital, Cape Town. Her family lived in unsophisticated circumstances in a remote rural region and she had traveled for approximately 1000 km from her home with her mother for a routine dental consultation. Because of a language barrier, a medical history was elicited from her mother via an interpreter. The girl had developed limitation of arm movements at the age 15 months and the diagnosis of FOP had been confirmed radiographically. The characteristic hallux valgus and shortening of the great toes was evident (Fig. 5). Several firm swellings, which were present on her back and scalp, had started as

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**Fig. 2.** Patient 1, aged 44 years. Anteroposterior radiographs of the feet. The phalanges of the great toes are malformed, shortened, and deviated laterally.

**Fig. 3.** Patient 3, aged 6 years. Several irregular subcutaneous bony masses are evident on the posterior thorax. The scar of a biopsy, with consequent ossification, is present in the upper left lateral region.

**Fig. 4.** Patient 3, aged 6 years. Anteroposterior radiograph of the jaws. Space for the developing permanent teeth is constrained and impaction and malocclusion may occur in the future.
larger inflammatory lesions. She had fallen and damaged her upper lip during early infancy and ossification at this site posed a threat of future microstomia (Fig. 6). Apart from mild mandibular hypoplasia, her teeth and jaws were normal.

An extensive explanation regarding the importance of good dental hygiene was conveyed to the mother and arrangements were made for ongoing surveillance and regular follow-up. The paucity of local medical services and difficulties with transport in the region where the family was domiciled posed special problems in these respects.

DISCUSSION

The abnormal ossification in FOP affects the configuration and function of craniofacial structures and thereby influences dental management. In the dental context, it is relevant that although spontaneous ectopic osteogenesis is an inherent component of the disorder, it may be induced and exacerbated by traumatic events, such as dental injections and extractions and by anesthetic procedures.12

There is a disproportionate growth between the mandible and the maxilla, resulting in mandibular hypoplasia and an excessive maxillary overbite. The mandibular condyles may become broad, flat, and misshapen.5 It has been suggested that development of the mandible is hindered by ectopic bone formation.11 The paucity of available space for the developing permanent teeth, as seen in patient 3, may predispose to impaction and malocclusion.

As the condition progresses, the cervical spine may become fused from C2 to C7, and ossification of the nuchal ligaments in the cervical spinal area may limit neck movement.9 Involvement of structures in the neck region, notably the sternocleidomastoid muscles, may contribute to reduction of mobility in the neck. In some instances, a rigid “chin-on-chest” deformity develops owing to asymmetric fusion involving cervical vertebrae, the sternocleidomastoid muscles, anterior strap muscles, and the sternum. This deformity severely compromised dental management and anesthesia in patient 4.

Ankylosis of the TMJ is a major age-related problem in FOP and the adult patients who we treated were all affected in this way. Ectopic ossification of joint capsules and masticatory muscles can occur spontaneously and contribute to the stiffness of these joints.6-8 Oral trauma can also precipitate TMJ ankylosis and this factor was relevant in the management of the affected children. Some local anesthetic procedures used during routine dental treatment can induce FOP flare-ups resulting in marked swelling, stiffening, and permanent loss of jaw movement.12 For instance, intramuscular injections can result in heterotrophic ossification of the TMJ although anesthetic infiltrated locally or inserted into the periodontal ligament is usually innocuous. Flare-ups of FOP in the submandibular region may involve the mylohyoid and omohyoid muscles, and these acute submandibular swellings may lead to acute airway obstruction.

In addition to the problems posed for dental intervention in FOP by the inherent manifestations and complications, these also affect the approach to general anesthesia in dentistry. In particular, scoliosis and ankylosis of the costovertebral joints, together with ossification of the chest wall, result in restricted lung function and severely affected persons rely mainly on diaphragmatic breathing.2,10 These factors, together with an ineffective cough, predispose individuals with FOP to develop recurrent pulmonary infections and pneumonia. Persistent lung dysfunction may also lead...
to pulmonary hypertension and ultimately cause right-sided heart failure. Patient 1 had a marked restriction of respiratory excursion and this factor weighed heavily in the decision to undertake dental extraction with local rather than general anesthesia.

The understanding of the pathogenesis of FOP has advanced steadily over the past decade. Mutations in the bone morphogenic protein (BMP) type 1 receptor ACVR1 gene are causative. The 617 G > A missense mutation in this gene codes for a protein product that is a transmembrane receptor in the BMP signaling pathway, with resultant upregulation of basal activity of BMP, and an exaggerated response to ligand stimulation. An initial excessive immune response has been implicated and increased levels of BMP have also been described.

Most affected individuals represent new mutations of the FOP gene located on chromosome 4q 27 to 31. Approximately 1 person in every 2 million has FOP and there is no predilection for race, gender, or ethnicity. In this context, the condition has previously been documented in indigenous South Africans, and there have been other isolated reports of FOP on the African continent.

The individuals in this study represent a spectrum of the manifestations of FOP and the problems posed in dental management in the developing world. The young children presented the oral health professionals with obvious yet minor challenges, whereas the older persons portrayed an extreme, complicated situation. In the children, conservative, atraumatic management of the carious lesions was the treatment of choice. Great care was taken to avoid any tissue injury. The importance of oral hygiene was emphasized both to the children and their mothers, who were the primary caregivers. In these instances, the aim of future management was prevention.

The adults were difficult to treat. Functional challenges, such as limited limb movement, compromised their ability to practice good oral health care. Restricted or absent jaw movement affected the types of food they were able to eat. Their inability to chew limited their diets to soft, refined foods that promoted dental caries. Dietary insufficiency also led to malnourishment, as reflected by severe iron deficiency anemia, which was present in patient 1. Confined tongue movements prevented plaque-forming and cariogenic bacteria from being washed from the oral cavity. Impaired swallowing compounded the poor natural cleansing mechanism of the mouth and contributed to malnutrition. In addition, inadequate access to the oral cavity posed limitations to dental and general anesthetic procedures. In these circumstances, fiberoptic endotracheal intubation with or without prior sedation appears to be the anesthetic modality of choice.

Although the use of local anesthetic for dental procedures may be contraindicated, the affected individual’s circumstances necessitate consideration. The adult females who we treated benefited from the use of local anesthesia because the risk of systemic complications induced by general anesthesia outweighed the possibility of iatrogenic exacerbation of TMJ ankylosis.

The complications of untreated dental caries warrant special attention, and as with patient 1, decisions concerning dental treatment may be difficult. Cellulitis may spread via the fascial planes causing either Ludwig’s angina or cavernous sinus thrombosis, both of which can be fatal. The former occurs as a result of pus in the submandibular and sublingual areas and could compromise respiratory function. The surgical drainage of pus may induce iatrogenic trauma to the muscles, exacerbating swelling and resulting in additional airway obstruction.

Early diagnosis of FOP is essential and is made on clinical manifestations, radiographic features, and genetic testing. Avoidance of invasive diagnostic techniques is important. Prevention of oral disease and maintenance of good oral health is imperative in avoiding unnecessary complications in dentistry. The South African cases illustrate the importance of diagnostic accuracy and awareness of potential complications in comprehensive dental management of FOP.

The molecular diagnostic investigations in patients 1 to 3 were undertaken by Dr. C. Dandara, Division of Human Genetics, University of Cape Town.

REFERENCES

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