Craniofacial findings in fibrodysplasia ossificans progressiva: computerized tomography evaluation

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Objective. The aim of this study was the evaluation by using computerized tomography (CT) of craniofacial abnormalities in fibrodysplasia ossificans progressiva (FOP) patients regarding jaw restriction and retrognathia.

Study design. Seven FOP patients were evaluated retrospectively in this observational study. Inclusion criteria were detection of ACVR1 gene mutation and complete craniofacial CT examination. The age of jaw restriction and presence of retrognathia were clinically determined. The features analyzed were skull base structures and heterotopic ossification (HO).

Results. Of this group (age range 4-23 years), the 3 oldest patients presented with jaw restriction and retrognathia as well as displayed elongation of the lateral pterygoid plate with HO of the pterygoid muscles that reached the medial surface of the right mandibular ramus. They had significant history of trauma or surgery. The other 4 patients did not have retrognathia or HO involving the facial or masticatory muscles, and the mouth opening was normal.

Conclusions. CT evaluation can reveal HO of the pterygoid muscles that probably may cause jaw restriction and retrognathia in older FOP patients. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:499-502)

Myositis ossificans (MO) is a term used to describe the formation of heterotopic bone involving muscle or any other soft tissue. When it is localized and self-limited, trauma is usually recognized as a trigger event. It is also named nonhereditary heterotopic ossification (HO), MO traumatica, or MO circumscripta. When progressive and cumulative, it is actually known as a specific genetic disease: fibrodysplasia ossificans progressiva (FOP).1

FOP is a rare autosomal dominant genetic disorder (OMIM 135100) of the connective tissue that is characterized by progressive HO and developmental skeletal defects. The classic FOP phenotype is characterized by congenital malformation of the great toes and childhood onset of soft tissue swellings that progress through an endochondral pathway to form mature heterotopic bone. The swellings transform soft connective tissues, including aponeuroses, fascia, ligaments, tendons, and skeletal muscles, into an encasement of bone. Progressive episodes of HO lead to ankylosis of major joints. The swellings could be spontaneous or triggered by influenza-like illnesses, blunt muscle trauma, minor trauma, such as intramuscular immunizations, mandibular blocks for dental treatment, and muscle fatigue.2-4

The estimated FOP prevalence is ~1 in 2 million. A heterozygous mutation in the ACVR1 gene, a bone morphogenetic protein receptor, is the cause of FOP in all cases that exhibit the classic or atypical phenotype.3

Mandibular hypoplasia leading to retrognathia and maxillary overbite is an abnormality frequently described in FOP patients. It is usually associated with limited jaw movement causing eating restriction after infancy.4-6 However, few studies of the craniofacial features peculiar to FOP have been reported, particularly those including computerized tomography (CT) in the work-up of these patients. Specifically, the causes of retromicrognathism in FOP are also incompletely understood.6-8

In earlier reports that studied CT imaging, the diagnosis of FOP was based on clinical features and was not confirmed by detection of the ACVR1 mutation.8-14 In some of these reports, the study was not focused on the craniofacial region or there was not sufficient data to exclude MO circumscripta.15-17

The aim of the present study was to describe craniofacial abnormalities observed by CT evaluation in FOP patients, especially those that correlated to clinical manifestation of jaw restriction and mandibular hypoplasia.

MATERIAL AND METHODS

Seven patients were evaluated retrospectively from the outpatient clinic. The study was approved by the
Institutional Review Board. All patients or legal guardians signed informed consents. They underwent radiologic evaluation as part of their follow-up at the Medical Genetics Unit.

Inclusion criteria were FOP diagnosis with \textit{ACVR1} gene mutation, as detailed elsewhere, and a full CT examination of the craniofacial region. Clinical data were obtained by reviewing the medical records. The age of mouth aperture limitation (jaw restriction) and presence of retrognathia were clinically determined. Radiologic features from 2 patients (nos. 5 and 6) in this group were previously reported. Patients underwent head and neck CT in a Somatom Sensation 64 multislice scanner (Siemens, Erlangen, Germany). Following the as-low-as-reasonably-achievable principle, the CTDIvol average in our examinations was 13.5 mGy (range 10.9-15.5 mGy). All images were obtained in a volumetric acquisition with bone and soft tissue algorithms. Scans were performed between January 2007 and December 2009. The images were analyzed by 2 board-certified radiologists (B.J.A.F.M. and L.F.), and any divergence in opinion was resolved by consensus.

The primary goal was to evaluate each patient’s skull base structures, including jaw, temporomandibular joints (TMJs) and paranasal sinuses. Evaluation regarded pterygoid plate shape, assessment of pterygoid muscle ossification, extra-articular ankylosis of the TMJ, and mandibular condyle shape in patients with retromicrognathia. Any other additional finding was also listed.

Two patients underwent magnetic resonance imaging (MRI) evaluation because brain abnormalities were seen on head CT. These scans were performed in a Signa HDxt 1.5-T scanner (General Electric, Milwaukee, WI) with an 8-channel head coil. They included at least sagittal spoiled-gradient recalled (SPGR) T1- and axial T2-weighted images.

### RESULTS

The main clinical features and radiologic findings for these 7 FOP patients are summarized in Table I. All except for patient 6 had the classic \textit{ACVR1} gene mutation (c.617G>A; p.R206H) and normal cognitive function. Patient 6 was also affected by FOP but she had another less frequent mutation in the \textit{ACVR1} gene (c.983G>A; p.G328E) and mild cognitive impairment.

Three patients presented restricted jaw movement and retrognathia. Patient 5 had severe trauma to the right cheek at 7 years old. Patient 6 had mandibular blocks after intramuscular local anesthesia, and her soft tissues over the jaw were stretched for dental treatment at 10 years of age. Patient 7 had surgical resection of a soft-tissue swelling in the submandibular and posterior neck regions at 8 years old. These 3 patients displayed HO of the pterygoid muscles with elongation of the lateral pterygoid plate reaching to the medial surface of the right ramus of the mandible. This was defined as an extra-articular ankylosis of TMJ by HO between the right ramus of the mandible and lateral pterygoid plate (Fig. 1, B). Additional findings in these patients included ossification of the posterior longitudinal ligament of spine (Fig. 1, C) and of the stylohyoid ligaments.

The 4 patients without mouth aperture restriction or retrognathia had no history of facial trauma, surgical procedures, or prolonged dental treatment. They did not have HO involving the facial or masticatory muscles. They also displayed ossification of at least 1 stylohyoid ligament.

Two patients with corpus callosum abnormalities underwent MRI evaluation. Patient 1 had complete agenesis, and patient 6 had only part of the genu of corpus callosum. No other major brain abnormalities were noted.

### Table I. Relevant clinical data, age at examination and radiological craniofacial findings for the 7 fibrodysplasia ossificans progressiva patients

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<td>Age at examination (y)</td>
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<td>13</td>
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<td>Age of HO onset (y)</td>
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<td>Age of jaw restriction (y)</td>
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<tr>
<td>Pterygoid muscle ossification</td>
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<td>R extending to mandible</td>
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<td>Extra-articular ankylosis of TMJ</td>
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<tr>
<td>Abnormal lateral pterygoid process</td>
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<td>R</td>
<td>B, large in R</td>
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<td>Irregular mandibular condyle</td>
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<td>Flat shape mainly at R</td>
<td>Flat shape mainly at R</td>
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<td>Ossification of stylohyoid ligament</td>
<td>L</td>
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HO, Heterotopic ossification; TMJ, temporomandibular joint; R, right; B, bilateral; L, left.
DISCUSSION

CT evaluation of this group of FOP patients revealed HO involving the pterygoid muscles with elongation of the lateral pterygoid plate that extended to the mandibular ramus in 3 patients. These patients were the oldest of the group and they also had mouth aperture restriction and retrognathia which were clinically noticeable. Although HO could appear even spontaneously in FOP, they were the only patients who had significant history of trauma or surgery in midface. Each one had some striking clinical risk factor that may have triggered HO in the craniofacial region before jaw restriction had occurred.

Extra-articular ankylosis of the TMJ is common in FOP, but it is not obligatory. Our findings reinforce earlier observations that jaw involvement in FOP is correlated with age. In previously published series of FOP cases, jaw restriction was less frequent in younger patients. Extra-articular ankylosis of the TMJ is a major complication in FOP patients. It can cause mouth aperture limitation with alimentary problems and severe weight loss.

Although only 7 patients were evaluated in our study, we obtained important data about mandibular hypoplasia in this rare disease. The preceding CT craniofacial study of FOP had 3 cases.

In the present case series, there was a time interval between mouth aperture restriction and retrognathia. Three patients suffered from mouth aperture restriction before adolescence and later developed retrognathia. We suggest that the HO of the pterygoid muscles extending from the lateral pterygoid plate over the mandibular ramus constitutes a mechanical restraint that reduces the normal anteroposterior mandibular growth during the period of facial development. It is important to remark that the flat aspect of the mandibular condyle was more pronounced on the same side where HO reached the mandible.

Other authors have suggested that retrormicrognathia may be intrinsic abnormal mandibular growth unrelated to TMJ ankylosis or HO of the facial muscles. We propose that mandibular hypoplasia in FOP may be secondary to disturbed mandibular growth due to HO of the masticatory muscles, which is not usually detected by conventional radiographic studies. In our study, the HO of the pterygoid muscles possibly restrained the mandibular development and contributed to mandibular hypoplasia in FOP.

In 2 patients reported by other authors, extra-articular ankylosis of the TMJ was caused by HO, also revealed by CT study, that involved the coronoid process of the mandible and extended to the zygoma. None of our patients had similar findings, but we think...
that this could represent an additional cause of jaw restriction.

All of the patients in our case series had ossification of the stylohyoid ligament. They did not have the pain that is characteristic of Eagle syndrome related to this specific sign.23 Even the youngest child of our group had this radiologic finding. Additional CT studies of FOP children are necessary to determine whether ossification of the stylohyoid ligament could be part of the disease spectrum or only a concurrent finding.

Evaluation of the brain with MRI in FOP patients is seldom performed, because neurologic impairment is rarely observed in this disorder. It is not clear whether corpus callosum abnormalities are simply an incidental finding or are instead part of the spectrum of brain lesions that are present at a higher frequency in FOP patients compared with the general population. Additional brain CT or MRI studies of FOP patients may provide more information.

In conclusion, craniofacial CT evaluation in FOP patients can reveal HO of the pterygoid muscles. In our case series, it occurred only in patients with history of trauma or surgery in craniofacial region. We suggest that HO of the pterygoid muscles is possibly a factor that may cause jaw restriction and retrognathia in older patients.

REFERENCES


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