CASE REPORT

Enlarged follicles and temporomandibular joint abnormalities in mucopolipidosis Type III

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Mucopolipidosis Type III, or pseudo-Hurler polydystrophy, is a rare genetic abnormality, the result of a mutation to one of two genes that encode the hexameric protein *N*-acetylglucosaminyl-1-phosphotransferase (Glc-NAc-PT). The abnormality results in the accumulation of unprocessed macromolecules in cell and tissue compartments throughout the body. In this case report, we describe the clinical and radiographic findings of a 15-year-old male with this disorder. He presented with bilateral ectopically developing mandibular molar teeth with enlarged follicles and multiple joint involvement, including the temporomandibular joints. The patient underwent surgical removal of the molar teeth and curettage of the associated follicles. The subsequent histopathological examination of the tissues revealed hyperplastic follicles suggestive of dentigerous cysts. This report presents the plain film and cone beam CT examinations of the patient.

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Introduction

Mucopolipidosis Type III (MLIII), otherwise known as pseudo-Hurler polydystrophy, is a rare autosomal recessive lysosomal disorder characterized by progressive accumulation of unprocessed macromolecules in cell and tissue compartments due to a deficiency of the enzyme *N*-acetylglucosaminyl-1-phosphotransferase (Glc-NAc-PT). Glc-NAc-PT is a hexameric protein consisting of two α , two β and two γ subunits, which are encoded by two genes, *GNPTAB* and *GNPTG*. Mutations to *GNPTAB* on chromosome 12q23.3 produce MLIII α/β while mutations of the *GNPTG* gene on chromosome 16p13.3 produce MLIII γ .¹ Biochemically, Glc-NAc-PT is crucial in the phosphorylation of mannose to mannose-6-phosphate, yielding a recognition marker that is necessary for targeting newly synthesized lysosomal enzymes into lysosomes. The inability to do so results in the increased plasma activity of the lysosomal enzymes, decreased

serum hydrolase activity and a build-up of unprocessed macromolecules in various cell and tissue compartments of the body.

Mucopolipidosis Type II (MLII) results in a near-total absence of Glc-NAc-PT activity, severe skeletal (including craniofacial) manifestations, growth retardation and decreased cognitive function. In the oral and maxillofacial region, Melo and Obeid⁵ reported macroglossia, hyperplasia of the alveolar processes and gingiva and multiple missing teeth in a case report of a 12-year-old male with MLII. This patient presented with multiple well-defined radiolucent entities in the jaws associated with impacted teeth. MLIII is a milder form of the disease, and those affected typically survive into adulthood.² In addition, these individuals retain some, albeit low, Glc-NAc-PT activity and display fewer skeletal manifestations. Patients with MLIII may also present with mild intellectual disability, short stature, hearing loss, valvular heart disease, visual impairment, craniosynostosis, carpal tunnel syndrome and multiple progressive skeletal abnormalities.^{3,4}

We report a case of a 15-year-old male with ectopically developing teeth, enlarged, fused follicular

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spaces and abnormalities involving the temporomandibular joints. This is the first report of a patient with MLIII where multiple intraosseous mandibular radiolucencies are accompanied by temporomandibular joint abnormalities.

Case report

The patient was a 15-year-old male previously diagnosed with MLIII. At the age of 2½ years, the patient was not showing progression of fine motor skills at a local children's daycare centre. He was referred to a physician with privileges at a local children's hospital, who ordered plain images of several joints. Bilateral hip dysplasia was noted on some of these images. On further examination, the physician referred the patient to a medical geneticist who suspected one of the mucopolysaccharidoses. Subsequent genetic testing later revealed MLIII.

The patient was originally seen by one of the authors (HSG) to orthodontically manage unerupted mandibular right and left permanent second molar teeth. At this time, the patient had already undergone surgery for spina bifida and carpal tunnel syndrome in the previous year. Neither the patient's parents or siblings nor distant family members had MLIII. A referral was subsequently made to the Special Procedures Clinic, Discipline of Oral and Maxillofacial Radiology, Faculty of Dentistry, at the University of Toronto, Toronto, Canada, to investigate any potential pathosis that might have caused the delay in eruption of the mandibular second molars.

Clinically, our patient presented with normal intelligence, but was short in stature with coarse facial features (Figure 1). Intraorally, the mandibular right and left second molars were partially erupted. A radiological examination that included a panoramic

radiograph, intraoral radiographs and a cone beam CT (CBCT) examination of the temporomandibular joints was performed. Panoramic and mandibular periapical radiographs (Figure 2), as well as axial and reconstructed oblique sagittal CBCT images showed bilateral, well-defined, unilocular, corticated, radiolucent entities associated with the crowns (specifically, the cemento-enamel junction areas) of the partially erupted second and ectopically developing third molar teeth. The follicles of the second and third molar teeth on both sides appeared continuous, and were sizeable enough to have produced thinning of the endosteal surfaces of the lingual cortices, but with minimal lingual expansion. Furthermore, the crowns of both second molar teeth had tipped distally, and the developing third molar crowns had become rotated and displaced distally into the mandibular rami.

Axially corrected sagittal and coronal CBCT images of the temporomandibular joints (Figure 3) revealed both mandibular condylar heads to be anteriorly and inferiorly positioned in their respective glenoid fossae. There was flattening of the superior articulating surfaces of both condylar heads, and these surfaces also appeared minimally concave. In addition, there was flattening of the roofs of the glenoid fossae, and surface erosions could be seen within these surfaces.

The patient was referred to an oral and maxillofacial surgeon who, after observing that the mandibular second and third molars on both sides shared the same follicle, removed both the second and the third molars. Surgical extraction of the mandibular molars was performed and the patient experienced an unremarkable course of recovery. The tissues associated with the impacted mandibular molar teeth were sent to an oral and maxillofacial pathologist for processing and interpretation. The patient is now undergoing orthodontic management of his malocclusion.

Figure 1 (a) Profile and (b) frontal facial photographs showing coarse facial features. (c) Partially erupted mandibular second molars.

Figure 2 (a) Panoramic and (b) mandibular periapical radiographs, and (c) axial and (d) reconstructed oblique sagittal cone beam CT reconstructions demonstrating bilateral, well-defined, unilocular, corticated, radiolucent entities associated with the crowns of the second and third molar teeth. The follicles of these molar teeth are not only continuous, but have also produced thinning of the endosteal surfaces of the lingual cortices. There is, however, only minimal lingual expansion at this time

Discussion

MLIII is a rare genetically heterogeneous group of lysosomal storage disorders characterized by a mutation to

one of two genes encoding one of the subunits of Glc-NAc-PT, a phosphorylation enzyme. Glc-NAc-PT plays a critical role in the phosphorylation of a mannose sugar on newly synthesized lysosomal enzymes. Phosphorylation

Figure 3 Axially corrected cone beam CT reconstructed sagittal and coronal images of the temporomandibular joints revealing both condylar heads to be anteriorly and inferiorly positioned in their respective glenoid fossae. There is flattening of the superior articulating surface of the condylar heads and there are surface erosions involving the temporal components of both joints

of the molecule is a necessary requirement for transport into lysosomes. Failure to do so not only increases plasma lysosomal enzyme activity, but also causes a build up of stored, unprocessed macromolecules in tissue compartments.

The patient presented initially to one of the authors (HSG), an orthodontist, for evaluation of partially erupted mandibular permanent second molar teeth. Radiographic examination of these areas revealed bilateral partially erupted second molars as well as bilateral ectopically developing mandibular third molars. The second and third molars on both sides also seemed to have similarly appearing enlarged follicular spaces that, radiographically, were interpreted as dentigerous cysts. Similarly appearing radiolucent entities were identified in each of the 4 quadrants in a 15-year-old patient with the more severe MLII by Melo and Obeid.⁵ The histopathology in that case was inconclusive; epithelial islands of odontogenic origin with a dense myxoid fibrous stroma were reported without evidence of a cystic space. Interestingly, Melo and Obeid did not consider dentigerous cysts in their differential diagnosis. Rather, theirs included primordial cyst, odontogenic myxoma, keratocystic odontogenic tumour and central giant cell lesion. For our patient, if the diagnosis had not already been made genetically, a reasonable differential interpretation of the images might have included (in addition to dentigerous cysts) keratocystic odontogenic tumours and (less likely) central giant cell lesions. Beyond these entities, it would be considered highly unusual for a patient to present with simultaneously occurring multiple primordial cysts or myxomas, so nothing further was considered. While patients may present with multiple keratocystic odontogenic tumours and central giant cell lesions, other stigmata would presumably be seen, raising the possibility of nevoid basal cell carcinoma syndrome or hyperparathyroidism. Because of the associations that we were able to visualize on our imaging series between the radiolucent entities and the cemento-enamel junction areas of the teeth, our interpretation of these entities was of dentigerous cysts. Our patient was subsequently referred on to an oral and maxillofacial surgeon who removed the second and third molar teeth on both sides. Histopathological examination of the excised tissue by an oral and maxillofacial pathologist revealed hyperplastic follicles suggestive of dentigerous cysts. Interestingly, the surgeon did not note the presence of any unusual contents within the follicles when they were entered surgically, and the patient had not experienced this situation with other teeth that had erupted normally into his mouth.

In addition to the dental anomalies that may include multiple enlarged and fused tooth follicles, a spectrum

of bone changes may also be seen.^{7–9} In perinates, decreased bone density has been reported, as have fractures of the long bones and ribs. These changes have been diagnosed as neonatal hyperparathyroidism. Beyond 4 months of age, deformation or bending of the bones may be observed; this has been characterized as the osteodystrophy of mucopolipidosis. In patients surviving beyond 12 months, the findings of dysostosis multiplex may be identified; these may include the appearance of a J-shaped sella turcica, oar-shaped ribs, anterior–inferior beaking of vertebral bodies, flared iliac wings and constricted iliac bodies, bullet-shaped phalanges and pointing of proximal metacarpals.

Bone metabolic abnormalities have also been identified in patients with MLIII. In the patients reported by David-Vizcarra *et al*,⁸ high bone turnover was noted with elevations in serum osteocalcin and urine creatinine; calcium, phosphorus, alkaline phosphatase, parathyroid hormone and parathyroid hormone receptor levels were normal in these patients. These authors hypothesized there to be an abnormality in tissue parathyroid hormone receptor transduction, making tissues hypersensitive to circulating parathyroid hormone. They further described these effects as being reminiscent of pseudohyperparathyroidism. In an attempt to reduce osteoclast activity, some patients have been treated with cyclical infusions of intravenous pamidronate, although there have been variable results.^{6,7}

Early onset bone pain and joint stiffness in patients with MLIII may be mistaken for a rheumatological disorder because of the appearance of progressive bone destruction.^{9,10} As such, without the benefit of the genetic diagnosis of the patient, juvenile idiopathic arthritis might be considered. Temporomandibular joint involvement has previously been reported once in the literature in association with MLIII.⁶ While our patient reported progressive involvement of multiple joints in his body, he also noted progressive restriction of jaw opening. Our radiological examination revealed flattening of the articulating surfaces within both temporomandibular joints, although we noted that the articulating cortices of both condylar heads remained intact. Additionally, we observed erosions within the surfaces of the glenoid fossae that could easily mimic a degenerative bony process.

In view of this case, mucopolipidosis may be considered in patients with early onset temporomandibular joint destruction and enlarged follicles with delayed teeth eruption. In patients already diagnosed with mucopolipidosis, an examination of the temporomandibular joints may be useful, particularly if there has been a history of other involved joints.

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