Oral anomalies associated with the oculocerebrorenal syndrome of Lowe: Case report with multiple unerupted teeth and pericoronal radiolucencies

John K. Brooks, DDS,a and Rizwan Ahmad, DDS,b Baltimore, Maryland
UNIVERSITY OF MARYLAND DENTAL SCHOOL AND JOHNS HOPKINS HOSPITAL

The oculocerebrorenal syndrome of Lowe (OCRL) is a rare X-linked recessive disorder, chiefly characterized by ocular involvement, mental retardation, and kidney disease. A literature review is provided, detailing the diversity of oral anomalies associated with the OCRL syndrome. Reported abnormalities include delayed tooth eruption, odontogenic cyst formation, and constricted dental arches. In addition, we present an unusual case of an 18-year-old male affected with the OCRL syndrome and fetal alcohol syndrome. The oral radiographic examination was significant for multiple impacted permanent teeth, many with pericoronal radiolucencies, and an underdeveloped mandible.


The oculocerebrorenal syndrome of Lowe (OCRL), also referred to as the Lowe syndrome, is a rare X-linked recessive disorder, distinguished by a triad of organ system abnormalities, namely, ocular disease, such as neonatal-onset cataracts, mental retardation, and renal dysfunction (Online Mendelian Inheritance in Man #309000).1 Frequently associated skeletal consequences are vitamin D–resistant rickets, hypotonia, short stature, scoliosis/kyphosis, joint laxity, and recurrent fractures. Other attendant features may include glaucoma, seizures, dermal cysts, and maladaptive behavior.2 Typical facies consists of frontal bossing; less commonly found characteristics are progressively elongating face, deep-set eyes, protruding ears, and thin sparse hair. Obligate female carriers have an increased risk for lenticular opacities.3 Historically, the lifespan of affected patients extended only to the second or third decade, with the cause of death related to renal failure or infection. Recently, increased adult survival has been attributed to the implementation of aggressive medical care.4 The prevalence of OCRL has been estimated to occur in 1 out of 500,000 individuals, with only 190 affected patients having been identified in the year 2000.5 OCRL results from a mutation in the oculocerebrorenal gene (OCRL1), localized to Xq24-q26.6 This locus normally encodes for the protein inositol polyphosphate 5-phosphatase, derived from the Golgi apparatus and early endosomes.7 A deficiency of this enzyme leads to selective perturbations in cell surface proteins needed for intracellular regulation and membrane trafficking.8,9 Limited information is available in the extant literature concerning the oral features associated with OCRL and primarily consists of isolated case reports. The present report provides a review of these anomalies and includes a case with unusual dental radiographic findings.

CASE REPORT
An 18-year-old male, in no apparent distress, was brought to the University of Maryland Dental School for comprehensive dental care. Accompanying documents obtained from the patient’s care giver revealed a history of Lowe syndrome, fetal alcohol syndrome, blindness, chronic otitis media, generalized lymphadenopathy, learning disorder, and attention-deficit hyperactivity disorder. Additional records were subsequently procured for elaboration and documentation of the relevant medical concerns.

Medical history
The patient was born after a 40-week gestation to a 22-year-old gravida 2 para 1 woman and weighed 2.3 kg. Of note, there was prenatal exposure to alcohol, marijuana, and cocaine, and his mother had smoked 1½ packs of cigarettes per day. Moreover, his sister had been diagnosed with congenital hepatitis, attributed to maternal hepatitis B infection. Dense bilateral nuclear cataracts were diagnosed at a 2-week examination and surgically removed 4 weeks later. At 3 years, the constellation of clinical findings of hypotonia, failure to thrive, aminoaciduria, and congenital cataracts served to establish the diagnosis of mild Lowe syndrome and possible fetal alcohol syndrome. The physical examination at 6 years disclosed microcephaly, short stature, slightly prominent forehead, brachydactyly with hyperextensible metacarpo-
phalangeal joints and short nails, and generalized lymphadenopathy of unknown etiology. Mental retardation, hyperactivity, and motor developmental delay also were evident. Methylphenidate was prescribed for behavior modification. G-banding analysis demonstrated a normal karyotype (46,XY). Laboratory studies were significant for persistent proteinuria and elevations in serum acid phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and creatine kinase. Brain magnetic resonance imaging was normal. Under general anesthesia, retinoscopy revealed bilateral refractive errors of $-12$. By the age of 8 years, the patient was diagnosed with glaucoma and nystagmus. Nephrocalcinosis on ultrasound and hypercalciuria were noted, and as a consequence, the patient was prescribed chlorothiazide. At 15 years of age, the patient developed mild renal insufficiency, with elevation of creatinine, and was placed on sodium citrate with citric acid. Current medications are clonidine, desmopressin acetate, depakote, and haloperidol. At presentation, the patient’s height was 147 cm (<third percentile) and his weight was 47 kg (<fourth percentile). The patient had worn corrective glasses with thickened lenses but has repeatedly broken them.

Clinical oral and maxillofacial examination

The periodontal evaluation was remarkable for moderate to severe gingivitis associated with multiple 4 to 5 mm pockets and bleeding upon probing, thick plaque, and generalized tooth mobility. There was mild gingival hyperplasia of the maxillary incisors. None of the teeth manifested dental caries. The maxillary central incisors displayed incisal fractures, hypoplastic enamel, and were separated by a large diastema (Fig. 1). Occlusal findings were an anterior openbite and unilateral crossbites, affecting the left second premolars and first molars. Extraoral examination showed low-set ears, brachycephaly, lip incompetence, mild frontal bossing, wide nasal bridge, lateral nystagmus, and several pustular facial lesions.

Radiographic oral and maxillofacial examination

A panograph was conspicuous for multiple unerupted permanent teeth, involving all of the second and third molars and the maxillary canines. Considering the patient’s age, all of the second molars and the maxillary canines were regarded as impacted. The majority of the unerupted teeth exhibited enlarged pericoronal radiolucencies, with the mandibular second molars noted with the largest of these cyst-like lesions and associated with distal displacement. In addition, several teeth demonstrated widened periodontal ligament spaces. Diminished growth of the mandible was observed, as evidenced by the reduced height of the ascending rami, shortened condyles, and obtuse gonial angles (Fig. 2).

DISCUSSION

The oculocerebrorenal syndrome is a rare multisystem disorder primarily affecting the eyes, brain, and kidneys. A search of the literature was subsequently undertaken to catalog concomitant oral abnormalities. Various disturbances of tooth eruption have been found with the OCRL syndrome, notably over-retention of primary teeth and delayed eruption of permanent teeth. Ruellas et al. described an 18-year-old syndromic male with impacted maxillary canines. Tsai and O’Donnell reported a 30-year-old male with 4 impacted third molars, although the failure of eruption of these teeth may not be viewed as an unusual finding in the population, at large, and likely represented an aleatory event. Roberts et al. documented a case of an 11-year-old affected male with 4 unerupted second molars coincident with pericoronal radiolucencies. All of these molars were subsequently extracted and the associated excised soft tissue underwent histologic assessment. Two specimens were diag-

Fig. 1. Facial photograph depicting anterior open bite, enamel hypoplasia, and diastema formation.

Fig. 2. Panograph demonstrating multiple impacted permanent teeth and pericoronal radiolucencies, diminished growth of the condyles and ascending rami, and steep gonial angles.
nosed as “enlarged dental follicles” and 1 with a “follicular cyst with mild chronic inflammation.” The panograph of the present patient demonstrated similar cyst-like development, concurrent with multiple unerupted teeth, and may represent only the second reported case with these findings in an OCRL-affected patient in the English-language literature. The cystic lesions, seen in both of these cases, could have impeded the eruption of the second molars. In contrast to the earlier case, the present patient’s second molars were considered to be impacted because they had likely lost their eruption potential by the age of 18 years. 

Although it would have been warranted to ascertain the histologic diagnosis of the cystic lesions, surgical intervention was deferred owing to the lack of symptomatology in conjunction with concerns for the patient’s prevailing medical status and surgical outcome. No apparent changes had been discerned on a 1-year panographic follow-up at age 19, and the patient was to continue to periodically undergo radiographic reassessment. The differential diagnosis for the radiolucent lesions includes dentigerous cyst and odontogenic keratocyst and less likely glandular odontogenic cyst, adenomatoid odontogenic tumor, granular cell odontogenic tumor, ameloblastic fibroma, intraosseous squamous cell carcinoma, and intraosseous mucoepidermoid carcinoma.

Other affected patients with OCRL were identified with “eruption cysts” or unspecified “dental cysts.” Furthermore, a questionnaire given to the family members of affected patients reported an 11.5% (10 out of 87) incidence of unspecified “dental cysts.”

Reported anomalies of teeth reported with OCRL are hypoplastic enamel, loss of the lamina dura, hypodontia, elongated pulp horns, alteration of eruption sequence, enlarged pulp chambers, and dysplastic dentin formation. Various periodontal findings documented with affected patients have included anterior fibrotic gingiva, (attributed to anterior open bite and mouth breathing), excessive calculus, fibrotic marginal gingiva affecting the primary teeth, chronic gingivitis, severe periodontitis, tooth mobility, and widened periodontal ligaments. Prolonged bleeding after tooth extractions has also been recorded. Jaw abnormalities found with OCRL are constricted arches, malocclusion, anterior open bite, short ramus, obtuse gonial angle, high arched palate, hypermobility of the temporomandibular joint, maxillary prognathism, mandibular retrognathia, and diminished mandibular “bundle bone.” Miscellaneous circumoral features described with OCRL patients were prominent lips, incompetent lips, thin upper lip, and prominent and elongated philtrum. A summary of the oral features of the present case is listed in Table I.

It may not be possible to determine the precise etiopathogenesis of the dysmorphologic features seen in the present patient because he was affected with both OCRL and fetal alcohol syndromes. Several of these shared characteristics include mental retardation, growth deficiency, microcephaly, underdeveloped mandible (with short rami and obtuse gonial angles), and an anterior open bite. Finally, the presence of pericoronal lesions associated with multiple unerupted teeth may represent a previously underestimated phenotypic expression of OCRL. The actual prevalence of cyst formation with unerupted teeth in this subpopulation may not be fully substantiated as it is probable that many of the reported patients have not received a dental panographic examination. Additional clinical and radiographic studies are needed to better define the oral abnormalities in affected individuals overall and specifically regarding the extent of cystic development in the jaws.

Table 1. Oral features in propositus with oculocerebrorenal syndrome of Lowe

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<thead>
<tr>
<th>Clinical</th>
<th>Radiographic</th>
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<tr>
<td>Enamel hypoplasia</td>
<td>Odontogenic cysts</td>
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<td>Chronic gingivitis</td>
<td>Multiple unerupted teeth</td>
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<td>Malocclusion</td>
<td>Widened periodontal ligament spaces</td>
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<td>Incompetent lips</td>
<td>Shortened rami</td>
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<td>Obtuse gonial angles</td>
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REFERENCES

M. Membrane targeting and activation of the Lowe syndrome protein OCRL1 by rab GTPases. EMBO J 2006;25:3750-61.

Reprint requests:
John K. Brook, DDS
Department of Oncology and Diagnostic Sciences
Baltimore College of Dental Surgery
Dental School
University of Maryland
650 West Baltimore Street
Baltimore,
Maryland 21201-1586
oralpath5@comcast.net