Molar root-incisor malformation: considerations of diverse developmental and etiologic factors

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Objective. The objective of this study was to evaluate the variation in the condition referred to as molar root-incisor malformation (MRIM) and elucidate the distribution of affected teeth. This study further aimed to identify associated environmental stressors.

Study Design. Individuals were identified through retrospective review of dental radiographs and through referral to the investigators. Histologic evaluation included examination of mineralized and decalcified sections of affected first permanent molar teeth.

Results. Thirty cases of MRIM were identified, with all having affected first permanent molars with dysplastic root formation. The primary second molars were affected in 57% of the cases, with permanent anterior teeth being involved in 40% of the cases. A variety of medical conditions were associated with MRIM, the most common being neurologic. Several affected individuals reported no significant past medical history or environmental stressors.

Conclusions. The etiology of MRIM remains unclear, and this unique developmental defect of the first permanent molar roots appears to occur in populations throughout the world. Clinicians identifying the MRIM phenotype should carefully evaluate the permanent incisors for associated developmental defects that could result in pulpal necrosis. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016;121:164-172)

A novel dental phenotype has recently been described in several reports. This rather unique and specific phenotype shows variation in its severity but is characterized by diminished and dysplastic root formation of the first permanent molars and a narrow abnormal pulp chamber. These are the cardinal or primary features of this phenotype. The second primary molars are affected in some cases and appear similar to the first permanent molar defect, whereas the permanent anterior teeth can be involved and have constrictions of the crown in the cervical area and changes in the pulp chamber morphology. The first report of this condition described it as a root malformation associated with a cervical mineralized diaphragm, and a subsequent report referred to is as "molar-incisor malformation."[1,2] In this report, we present 30 new cases and refer to this new dental phenotype as *molar root-incisor malformation* (MRIM) to add clarity to the condition's name and help reduce possible confusion with other molar-incisor defects, such as the highly prevalent condition called "molar-incisor hypomineralization."

Tooth development involves strict molecular control and regulation of developmental pathways that can be influenced by a variety of environmental factors. Through a series of epithelial—mesenchymal interactions, tooth formation begins with thickening of the oral epithelium and development of dental placodes. Tooth development can be divided into morphologically distinct steps, including the bud, cap, and bell stages. Specialized cells secrete unique extracellular matrices, which are processed to form the different mineralized tissues of dentin, enamel, and cementum.

Statement of Clinical Relevance

Molar root-incisor malformation appears to affect individuals with a past history of meningomyelocele, meningitis, or renal conditions more commonly but can occur in otherwise healthy individuals. Clinicians identifying affected individuals should carefully evaluate and monitor them for associated dental problems, including ectopic eruption, abscess, and tooth loss.

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Thousands of genes (the human dentome) are involved in the complex processes of tooth development, with many belonging to four major conserved pathways: TGF-β, Wnt, FGF, and Hedgehog.[3,4] Genetic defects and environmental influences can cause failure of tooth development or abnormal morphologic changes of the tooth.[5] There are hundreds of tooth abnormalities with a genetic etiology (nearly 100 affect enamel) and at least 100 known environmental causes of changes in tooth development.[6,7]

Compared with tooth enamel formation, the process of dentin development, or dentinogenesis, is thought to be relatively resistant to environmental insults or systemic conditions. It is the mesenchymally derived dentin that is the most abundant tissue in teeth and the tissue that determines much of the crown and root morphology. Hereditary dentin defects can be classified into dentinogenesis imperfecta (DGI) and dentin dysplasia (DD).[8] These hereditary conditions are associated with abnormal dentin mineralization and varying degrees of changes in tooth morphology. DGI type I (Online Mendelian Inheritance in Man [OMIM] #166200) is associated with osteogenesis imperfecta, whereas the clinically similar DGI type II (OMIM #125490) is not associated with a syndrome and is caused by mutations in the gene encoding dentin sialophosphoprotein (*DSPP*).[9] The DGI tooth phenotype can have a pronounced cervical constriction at the cementoenamel junction area that demarcates the junction of the clinical crown and the tooth root. Individuals with DGI often have dental root structures that are diminished in size and appear sharp and "tent peg−like." DD type II, or the coronal DD type (OMIM #125420) is an allelic disorder of DGI type II caused by *DSPP* mutations and is characterized by a similar phenotype in the primary dentition and slight or no discernable clinical phenotype in permanent dentition.[10] The phenotype in DD type I, or radicular DD type (OMIM #125400), is characterized by clinically normal-appearing tooth crowns and markedly altered dentin formation that has a pathognomonic cascading waterfall appearance histologically, pulp chamber obliteration, and abnormal to nearly missing root development. The etiology of this classic DD type I with normal crowns and unique histologic appearance is not known yet.[10] Two affected individuals in the same family who had a phenotype of short roots and microdontia are listed in OMIM as having radicular dentin dysplasia. These cases were associated with a mutation in the *SMOC2* gene found in the oral ectoderm and outer dental epithelium and in mesenchymal papillae facing the epithelial loops of molars and the only lingual loop of incisors.[11] Depletion of the SMOC2 protein in zebrafish altered the expression of three major genes involved in odontogenesis: *Dlx2*, *bmp2*, and *pitx2*.[11] These human and zebrafish studies confirmed the important role of the *SMOC2* gene in tooth formation. It seems likely that the classic phenotype of radicular DD described by Witkop et al. is caused by a different gene.[8,12]

Table I. Summary of molar root-incisor malformation cases

No.	*Gender*	*Past medical history*	*Affected teeth*
1	M	Chronic renal failure	3, 14, 19, 30
2	M	Chronic renal failure	3, 14, 19, 30
3	F	Meningomyelocele	3, 14, 19, 30
4	M	Sacral dimple, urinary tract infection	8, 9, 11, 3, 14, 19, 30
5	M	Meningitis	8, 9, 3, 14, 19, 30
6	F	Meningomyelocele	3, 14, 19, 30
7	M	Meningitis	8, 9, 3, 14, 19, 30
8	M	Meningitis	8, 9, 3, 14, 19, 30
9	F	Meningitis	6, 8, 9, 11, 22, 27, 3, 14, 19, 30
10	M	2 months preterm, hydrocephalus	8, 9, 3, 14, 19, 30
11	M	Stroke, hemiplegia	B, A, I, J, L, K, S, T, 3, 14, 19, 30
12	M	Meningomyelocele	K, T, 3, 14, 19, 30
13	F	Meningitis	A, J, K, T, 6, 8, 3, 14, 19, 30
14	F	Meningomyelocele	A, J, K, T, 6, 8, 9, 11, 3, 14, 19, 30
15	M	Speech disorder, meningitis	A, J, K, T, 3, 14, 19, 30
16	F	2 months preterm	A, J, K, T, 3, 14, 19, 30
17	M	Cerebral thrombosis	3, 14, 19, 30
18	F	Placenta previa, cerebral palsy	A, J, K, T, 3, 14, 19, 30
19	F	1 month preterm	3, 14, 19, 30
20	M	Meningomyelocele	A, J, K, T, 3, 14, 19, 30
21	F	Healthy	A, J, K, T, 3, 14, 19, 30
22	F	Sacral dimple	A, J, K, T, 3, 14, 19, 30
23	M	Healthy	8, 9, 3, 14, 19, 30
24	F	Meconium aspiration	8, 9, 3, 14, 19, 30
25	F	Healthy	3, 14, 19, 30
26	M	Severe *Escherichia coli* Infection, renal malfunction/ hemolytic anemia	A, J, K, T, 5, 6, 7, 8, 9, 10, 11, 22, 23, 24, 25, 26, 27, 28, 3, 14, 19, 30
27	M	Jaundiced birth, questionable cerebrovascular accident, short stature	A, J, K, T, 3, 14, 19, 30
28	M	Numerous childhood illnesses and treatments with antibiotics	A, J, K, T, 8, 9, 3, 14, 19, 30
29	M	Healthy	A, J, K, T, 3, 14, 19, 30
30	M	2 months preterm	A, J, K, T, 3, 14, 19, 30