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A case of molar-incisor hypomineralization with genetic and environmental influences

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Abstract

Background: Molar-Incisor Hypomineralization (MIH) is a common childhood dental pathology. This paper describes a case with familial involvement and environmental risk factors. **Case Description**: A 35-year old female has yellowish-brown opacities present on central and lateral maxillary incisors, right and left maxillary canines, right and left maxillary first molars, and right and left maxillary second molars. A 33-year old male sibling has yellowish-brown opacities on the right and left central and lateral maxillary incisors. The male sibling's fraternal twin does not have evidence of MIH. A maternal grandmother also had evidence of MIH, though involved teeth are not known. **Practical Implications**: MIH is a condition with both genetic and environmental components. Practitioners should consider both etiologies when patients present with the condition.

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Introduction

Molar-Incisor Hypomineralization (MIH) is diagnosed by the presence of yellowish-brown or white/cream enamel opacities [1]. Prior to 2001, the nomenclature of MIH was not standardized [1]. Other terms for this condition included: hypomineralized first permanent molars (FPM), idiopathic enamel hypomineralisation in non-fluoride, hypomineralization in FPM, and cheese molars [1]. These names were eventually subsumed under Molar-Incisor Hypomineralization (MIH). Weerheijm et al. suggested the term "MIH" and the attendant definition: "hypomineralization of systemic origin of 1-4 FPM, frequently associated with affected incisors"[2]. Weerheijm et al. further defined MIH by noting enamel defects are occasionally present on the permanent canines and second molars in addition to the first molars and incisors.

The prevalence rate for MIH is estimated at 2.8% to 25% depending on the study and the geographical region. Some evidence for differing rates of MIH in the mandible and maxilla has been found, but studies do not agree on which location is more common [1]. There also does not appear to be a significant difference in MIH instances between the sexes [1].

Environmental Factors

Several environmental factors have been linked to MIH. Alaluusua et al. linked exposure to dioxin in breast milk to enamel hypomineralization in children [3,4]. The authors found a correlation between the "frequency and severity of lesion and total exposure." Jalevik et al. found a significant correlation between early life respiratory illnesses and MIH [5]. Beentjes et al. found children with MIH became ill more frequently in the first four years of life than those without MIH. The authors assert there "appears to be an association with pneumonia, otitis media and high fevers, specifically" [6]. Muratbegovic et al. also found an association between MIH and childhood illnesses with a high fever [7]. In another study, the development of MIH has also been associated with the use of antibiotics in early life [8].

Genetic associations

Genetic association studies in MIH are few. A 2013 genome-wide association study identified single nucleotide polymorphisms on chromosomes 4, 9, 16, 20, and 22 associated with MIH [9]. The low

Table 1. SNPs and genes involved in amelogenesis			
SNP	**Gene**	**SNP**	**Gene**
rs7821494	*FAM83H*	rs7664896	*ENAM gene*
rs34367704	*AMBN gene*	rs1711399	*MMP20*
rs3789334	*BMP2*	rs1711423	*MMP20*
rs6099486	*BMP7*	rs2278163	*DLX3*
rs762642	*BMP4 gene*	rs6996321	*FGFR1*

est p-value was found in the region that encodes the *SCUBE1* gene. 21.8 % of children who carried the minor allele of rs13058467 had MIH. Of children who were homozygous for the major allele, 10.6 % had MIH. *SCUBE1* is a BMP inhibitor involved in the development of the tooth germ. The *SCUBE* gene family is involved in epithelial to mesenchymal signaling during tooth development, although it's role is not yet well understood. The authors hypothesize that the *SCUBE1* polymorphism may "disturb regular tooth development and mineralization...or distinct systemic etiological factors may influence the protein functionality [9]."

More broadly, the development of enamel has been linked to certain genes. Some evidence can be found in the regulation of the genes linked to amelogenesis imperfecta (AI) [10]. Most AI follows an autosomal dominant expression pattern. Bailleul-Forestier et al. linked several genes including *TUFT1*, *AMBN* and *AMTN* to non-syndromic deficient enamel formation[10]. A 2016 family-based association study investigated 63 SNPs and 21candidate genes related to AI [11]. This study built on earlier work [12]. The study cohort was 65 individuals without MIH, 96 of unknown MIH status and 130 individuals with MIH. Significant results were obtained for 11 SNPs associated with genes involved in amelogenesis (Table 1). The authors conclude these variations confer underlying susceptibility to MIH.

Vieira and Kup argue MIH is a genetic disease because the disease affects teeth in different morphogenic fields [13]. The authors assert that additional gene variants may influence the presentation of MIH on teeth adjacent to the first molars and on incisors. The authors argue there is a genetic basis of MIH based on diverse geographic prevalence rates and lack of clearly associated environmental factors. Based on the large number of associated genes and possible environmental associations, MIH is likely a multifactorial condition.

Case Report

A 35-year old female with yellowish-brown opacities present on central and lateral maxillary incisors, right and left maxillary canines, right and left maxillary first molars, and right and left maxillary second molars. The patient had veneers on the right and left central and lateral incisors and right and left canines. The patient's first dental restoration was performed at 16 when resin composite veneers were installed. These were replaced with the same resin composite material at age 25. The current veneers were installed at age 35.

The patient's early medical history includes a high fever treated with amoxicillin at age 3. Also at age 4, the patient had facial reconstruction surgery following a fall from a bed.

An evaluation of familial history identified a 33-year old male sibling with yellowish-brown opacities on the right and left central and lateral maxillary incisors. The patient's fraternal twin was unaffected by MIH, but did have more than 13 carious lesions before age 30. Composite resin restorations were performed on this patient several times. The patient smoked for 11 years. Interviews with family members revealed that the maternal grandmother also had yellowish brown opacities on her incisors.

Discussion

The history of MIH is obfuscated by the lack of standardized naming before 2001 [1,6]. This had led some authors to question whether the disease is of modern origin [14]. The small portion of the archeological record that has been assessed for the presence of MIH offers differing conclusions. Additionally, the dif-

ferential preservation of carious teeth associated with MIH may skew any evaluation of an archeological population. Ogden et al. found an MIH prevalence rate of 93.2% in a London cemetery population dating to 1559 [15]. However, the study's sample size was small and focused on sub adults. Kühnisch et al. found a prevalence rate of 3.1% among a late medieval period German cemetery population, leading the authors to conclude MIH is linked to contemporary living conditions [14].

Another archeological population, dating to the 11th-16th centuries from Thuringia, Germany, had an MIH prevalence rate of 12.2% [16]. The authors postulate the prevalence of MIH may have been higher than this, but factors such as more prevalent antemortem tooth loss, heavy wear, and extended carious lesions may have masked the true prevalence. Hence, MIH is likely not a modern disease, but the prevalence rate may have changed in modern times with the introduction of new environmental stressors that affected underlying genetic variation.

The cases reported in this paper present an interesting problem. The 35-year old female patient was exposed to a high fever, amoxicillin and an additional stressful injury. A high fever and amoxicillin have both been linked to MIH [5-8]. The presence of MIH in the male sibling suggests a genetic component. This male was not yet born at the time the female was exposed to the fever, so had no exposure himself. The male's fraternal twin did not develop MIH, suggesting environmental or epigenetic factors may have been contributory. Additionally, the maternal grandmother likely had MIH, further arguing for a genetic component.

It is possible the family has an underlying genetic susceptibility to MIH that was acted upon by environmental factors. The female had more affected teeth than the male and was also exposed to more environmental stressors. This argues for underlying susceptibility exasperated by environmental stressors, or multifactorial inheritance. To determine the role of genetic variations in the development of MIH in this family, genotyping of both male twins and the female would be advised.

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