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The Reported Underlying Systemic Causes of Molar Incisor Hypomineralization (MIH): A Review Article

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Introduction

Weerheijm was the first who introduced the term Molar-Incisor Hypomineralization in 2001 **(**1**)**. It was previously given the name of cheese molars, non-flouride, non-endemic mottling of enamel and idiopathic enamel opacities. Then it was refined and defined as "Hypomineralization of systemic origin, presenting as demarcated, qualitative defects of enamel of one to four first permanent molars **(**FPMs**)** frequently associated with affected incisors." This affected quality of enamel, during the developmental stage of enamel; caused by reduced mineralization and protein retention, resulting in interference with crystal growth and enamel maturation. This would be translated into this demarcated opacity and discoloration of enamel, with or without surface destruction of the affected teeth **(**2**)**.

Initially the condition was described to be affecting FPMs and incisors; however meanwhile, it is noticed that that tips of permanent cuspids might present similar defects, as they have the same histologic period of mineralization as the FPMs and Incisors. Steffen R. **(**2011**)** noted that these defects could be even seen in any primary or permanent tooth **(**3**)** .

Diagnostic Features

The European Academy of Pediatric Dentistry **(**EAPD**)** was the first international scientific organization that extensively studied molar-incisor hypomineralization **(**MIH**)** and developed a policy document **(**4**)**. EAPD reinforces the use of the specific signs and symptoms for the diagnosis of MIH. The main diagnostic features are listed as:

1. Teeth involved
2. Demarcated Opacities
3. Post-eruptive enamel breakdown
4. Sensitivity
5. Atypical restorations
6. Extraction of molars due to MIH

Table 1 EAPD Diagnostic criteria of MIH (adopted from Weerheijm et al. 2003; Lygidakis et al. 2010)

Diagnostic feature	Description of the defect
Teeth involved	One to all four permanent first molars (FPM) with enamel hypomineralisation Simultaneously, the permanent incisors can be affected At least one FPM has to be affected for a diagnosis of MIH The more affected the molars, the more incisors involved and the more severe the defects The defects may also be seen at the second primary molars, premolars, second permanent molars and the tip of the canines
Demarcated opacities	Clearly demarcated opacities presenting with an alteration in the translucency of the enamel Variability in colour, size and shape White, creamy or yellow to brownish colour Only defects greater than 1 mm should be considered
Post-eruptive enamel breakdown	Severely affected enamel breaks down following tooth eruption, due to masticatory forces Loss of the initially formed surface and variable degree of porosity of the remaining hypomineralised areas The loss is often associated with a pre-existing demarcated opacity Areas of exposed dentine and subsequent caries development
Sensitivity	Affected teeth frequently reveal sensitivity, ranging from mild response to external stimuli to spontaneous hypersensitivity MIH molars may be difficult to anesthetize
Atypical restorations	The size and shape of restorations are not conforming to the typical caries picture In molars the restorations are extended to the buccal or palatal/lingual smooth surface An opacity can be frequently noticed at the margins of the restorations First permanent molars and incisors with restorations having similar extensions as MIH opacities are recommended to be judged as that
Extraction of molars due to MIH	Extracted teeth can be defined as having MIH when there are: - Relevant notes in the records - Demarcated opacities or atypical restorations on the other first molars - Typical demarcated opacities in the incisors

These criteria are shown in details in **Table 1**.

Clinical Significance

MIH defects can be soft, porous, and vary in clinical presentation from white to yellow or brownish opacities, but always with a distinct demarcation between affected and sound enamel. Those porosities and opacities can result in functional and esthetic complications in MIH affected children. This porosity and weakness in enamel can cause loss of the tooth structure even under regular masticatory forces **(**5**)**.

Portella et al. **(**2019**)** have shown that MIH affected children have an adverse impact on the Oral Health-Related Quality of Life **(**OHRQoL**)** along with considerable increased negative perception of oral symptoms. **(**6**)**

Children with MIH are usually presenting with a higher caries rate, due to the increased teeth sensitivity causing the child to neglect their oral hygiene. This hypersensitivity is the result of the chronic pulpal inflammatory state, in addition to the presence of the micro-abscess, leading to difficulties in achieving a good anesthesia. The hypo-mineralized enamel is poor insulator and therefore, the pulp is not well protected from external thermal stimuli. As a result, the tooth becomes hypersensitive to hot and cold stimuli. This chronic stress on the pulp leads to an inflammatory

response within the pulp and pH changes at the periapical tissue level leading to hypersensitive pulp tissue which excite with less stimulation than normally necessary. **(**7**)**

This would be reflected on the patient behavior and cooperation under treatment if adequate anesthesia was not achieved, and so many cases might need to be treated under inhalation sedation. Difficulties in treating children with no known previous dental visits, need for long and/or multiple appointments, need for missing school for some days, diminished oral health related quality of life along with higher treatment costs as treatment done under general anesthesia. **(**8, 9, 10**)**

The retention of dental restorations and the esthetic concerns are also common problems to be faced in dental treatment of MIH affected teeth. Tooth loss can result from aggressive progression of caries, or recurrent loss of restorations.

Prevalence

Most recent studies are now routinely using the standardized EAPD diagnostic and epidemiological criteria for MIH, controlling the wide range of prevalence found out in older studies. **(**11, 12**)**

Lopes et al. **(**2021**)** systematic review and meta-analysis revealed a prevalence of 13.5% of MIH, of which 36.3% were moderate to severe. Affected incisors were seen in 36.6% of the cases. Prevalence of HSPM was observed in 3.6% of MIH cases. **(**13**)**

Reported Etiology

Lygidakis et al. **(**2010**)** Policy Document stated that "MIH is not caused by one specific factor". Numerous harmful conditions might act collaboratively increasing the risk of MIH occurrence additively or even synergistically. **(**14**)**

Tens of systemic etiological hypothesis have been discussed over the last years. Those different hypotheses can be linked as pre-, peri-, and post-natal periods, as alterations in the function of the ameloblasts during the maturation phase may occur between the end of pregnancy and the age of 4 years **(**15**)**. Indeed, the simultaneous or additive effect between the environmental and /or genetic factors would develop MIH.

A new proposed patho-mechanism, termed mineralization poisoning, has emerged by Hubbard et al. **(**2021**)**; which showed that localized failures in enamel hardening are associated with developmental exposures to serum albumin, rather than ameloblast injury. **(**16**)**

Genetic/Epigenetics

Evidence of genetic association predisposing to MIH was demonstrated in some studies, based on evidence related to MIH Family aggregation, however, there is limited knowledge regarding the genetic heritage of MIH.

Lygidakis et al **(**2021**)** reported a high quality of evidence related to genetics **(**SVP association**)** and epigenetics **(**monozygotic twins**)** as etiology of MIH. **(**4**)**

Epigenetics describe the way in which gene-environment and gene-gene interactions shape a phenotype during development. It describes alterations in genomic function, mainly mitotically heritable changes in gene expression, that occur through reversible chemical modifications to the structure of chromatin without altering the DNA sequence. **(**17**)**

Hocever et al. **(**2020**)** study was based on the analysis of HLA DQ2 , HLA DQ8 haplotypes and Single Nucleotide Pleomorphism Analysis of the ENAM gene. They found that neither alleles could be confirmed as a potential etiological factor for MIH. However, SNP rs2245803 in the MMP20 gene in a homozygous form in a recessive model was significantly associated with MIH development. **(**18**)**

Table 2 shows the published genetic factors that may contribute to MIH development.

Table 2
Published genetic factors that may contribute to molar–incisor hypomineralisation development.

Authors	No. of subjects and country	Possible association with MIH
Bussaneli et al. (2019)	391 subjects from Brazil	*TGFBR1*: rs10733708 (OR = 3.5, 95 % CI = 1.1–10.6)
Jeremias et al. (2013)	160 subjects from Brazil, 245 subjects from Turkey	*ENAM*: rs3796704 (OR = 17.36, 95 % CI = 5.98–56.78) *TUFT1*: rs4970957 (OR = 0.12, 95 % CI = 0.08–019) *TUFT1*: rs3790506 (OR = 0.19, 95 % CI = 0.11–0.33) *THP11*: rs5997096 (OR = 0.49, 95 % CI = 0.49–0.74)
Jeremias et al. (2016)	391 subjects from Brazil	*FAM83H*: rs7821494 (OR = 3.7, 95 % CI = 1.75–7.78) *AMBN*: rs34367704 (OR = 2.7, 95 % CI = 1.16–6.58) *BMP2*: rs3789334 (OR = 2.9, 95 % CI = 1.34–6.35) *BMP7*: rs6099486 (OR = 2.2, 95 % CI = 1.14–4.38) *BMP4*: rs762642 (OR = 2.3, 95 % CI = 1.38–3–65) *ENAM*: rs7664896 (OR = 2.1, 95 % CI = 1.19–3.51) *MMP20*: rs1711399 (OR = 0.4, 95 % CI = 0.20–−0.72) *MMP20*: rs1711423 (OR = 2.1, 95 % CI = 1.18–3.61) *DLX3*: rs2278163 (OR = 2.8, 95 % CI = 1.26–6.41) *FGFR1*: rs6996321 (OR = 2.7, 95 % CI = 1.20–5.88) *AMELX*: rs5979395 (OR = 11.7, 95 % CI = 1.63–84.74)
Kühnisch et al. (2014)	668 subjects from Germany	*TTLL12*: rs13058467 (OR = 4.38, 95 % CI = 2.48–7.8)

MIH, molar–incisor hypomineralisation; OR, odds ratio; CI, confidence interval.

Jeremaise et al. **(**2021**)** had investigated the segregation patterns of MIH in families, based on the genetics influence **(**19**)**. Their study suggests that the codominant model could be the most likely for inheriting MIH, signaling a genetically complex disease. In their previous study done on 2016; they established a link between rs5979395 SNP of AMELX gene and MIH; as 97% of MIH affected participants were carrying the rs5979395*G allele; being the first to identify the association of genetic

variation in BMP4 and MIH (20). Factors such as BMP4 (Bone Morphogenic Protein), DLX3 (distal-less), and FGFR1 (fibroblast growth protein) are also associated with MIH susceptibility. BM4 gene encodes a protein with a vital regulatory function throughout development in mesoderm induction, including limb formation, tooth development, bone induction, and fracture repair (21). Regarding FGFR1, the only association was found with FGFR1 gene SNP rs6996321, in agreement of other studies as amelogenesis is a dynamic process for dental tissue development, including cellular, biochemical, genetic and epigenetic changes. (22, 23, 24)

Systemic Factors

MIH is defined as a qualitative enamel defect of systemic origin. It is a multifactorial condition of medical, systemic and environmental factors that might act synergistically to the genetic factors.

The EAPD diagnostic criteria of MIH defined teeth involved as one of the diagnostic features. At least one PFM must be affected for a diagnosis of MIH. Simultaneously, the permanent incisors might be affected, and the defect may also be seen at the tip of the canines, and second primary molars (4).

Based on the knowledge that MIH is a dental defect involves Hypomineralization, it direct the attention toward the maturation stage of enamel development and allied disruption (injury) of the principal Ameloblast (25). So any systemic exposures in the developmental timing of these teeth affecting this fragile ameloblast, between the end of pregnancy and the age of 4 years, would be translated and shown as Hypomineralization.

Prenatal Exposures

Recent review of Garot et al (2021), concluded that no specific maternal illness during the last trimester of pregnancy is related to MIH. There was no evidence of the association also between maternal smoking or alcohol intake with MIH (26). Same was concluded in Silva et al (2016) systematic review (27). On the other side; Lygidakis et al. (2021) reported a moderate evidence of medication during pregnancy and MIH. Same was concluded in Fatturi et al. (2019) systematic review, in which maternal illness and psychological stress was associated with 40% higher odds of having MIH (28). A striking factor reported by Alaluusua S. (2010) is the urinary tract infection during the last trimester of pregnancy, but still no current evidence is found in the literature to support causality association with MIH (29).

Maternal Vitamen D Status during pregnancy was also studied in association with MIH and HSPM. Borsting et al. (2022) conducted a longitudinal study to find out any association. They found a significant association between insufficient (> 50nmol/l), in the mid pregnancy (18-22 weeks of gestation) and the number of affected teeth with MIH of the offspring at 7-9 years of age (30) . This was supported by Norrisgaard et al. (2019) study finding, that high dose vitamin D supplementation during the third trimester showed a 50% reduced odds of enamel defects in the offspring (31).

Perinatal Exposures

Different parameters could be related to MH, including hypoxia, premature birth, low birth weight, birth complications and caesarean section.

Hypoxia at birth showed a substantially increased possibility of having MIH (26). Studies on children with history of the need of incubator reported a moderate evidence of association with MIH (4). Birth medical problems could be associated with the hypoxia, or it might be because of the prolonged delivery.

One systematic review concluded that only limited studies showed any significant association between prematurity and birth complications with MIH (27). Bensi et al. (2020) showed a strong association between Developmental Defects of Enamel and preterm birth (32). Wu et al. (2018) had reported that premature birth and low birth wight do increase the occurrence of MIH (33). Ghanim et al. (2013) found higher odds of MIH with low birth weight (34). Increases of the amount of 100g in birth weight were found to reduce the odds of MIH by 0.955 fold (35).

Mode of delivery was also studied for association with MIH, giving conflicting results as per different studies. While some studies showed positive effect of caesarean section (26, 36), other showed no association between them (28).

Postnatal Exposures/ Early childhood illness

Several retrospective studies were conducted for association between early childhood illness up to 4 years of age and MIH, as been these first 4 years of life are the critical period for MIH development (37).

Both recent systematic reviews concluded that no link between breastfeeding and MIH (26, 28), in contrast to the Finnish study that suggested this association, by assessing the adverse effects of dioxins (38).

Childhood illnesses were found to be associated with MIH, including: bronchitis, gastric disorders, urinary tract infections, measles, otitis asthma, fever and pneumonia (26). On the other hand, some diseases didn't show any association with the MIH, such as: rubella, sinusitis, jaundice, rhinitis, malnutrition, throat infections, allergies and diarrhea. Medications related to MIH are mainly the antibiotics (28). The type of antibiotic was not shown to be related to MIH (34).

Amoxicillin might modify the inflammatory and immunological response when taken for certain illness, interfering with some growth factors expressed by the ameloblasts. This alteration in response lasts longer than the actual taken antibiotic course (14).

Tourino et al. (2016) found out a higher prevalence of MIH in children with a history of asthma/bronchitis during the first few years of life. This could be explained by the oxygen deprivation at the time of asthmatic attacks, which will adversely affect the amelogenesis process (39). Oliveira et al. (2013) reported 2 cases of MIH with a history of asthma. First case was for a 7 years old girl, with a history of 3 days fever due to asthma at 6 months of age. Two months later she had a chickenpox. The other case was for a same age girl, required nebulization due to asthmatic attack at 3 months of age (40). Fatturi et al. (2019) analysis concluded that; only the respiratory diseases and fever in the postnatal period are significantly positively associated with MIH (28).

As vitamin D is essential for bone and teeth mineralization, van der Tas et al (2017) ran a population-based, prospective cohort study, to find out the association between prenatal, early postnatal and late postnatal vitamin D levels with MIH. They found no association, encouraging further future observational studies (41). However Kuhnisch et al (2015) found out that a 10 nmol/l increase in serum 25(OH)D concentrations was significantly associated with a lower odds ratio of having MIH (42) . Lygidakish et al (2021) also reported a strong evidence of association between MIH and vitamin D deficiency. (4)

Zameer et al (2020) published a case report of a 12 years old boy presented with MIH, diagnosed with Congenital Intestinal Pseudo-obstruction (CIPO). His medical history revealed a preterm birth caesarean section delivery due to polyhydramnios at the gestational age of 30 weeks. (43)

Discussion

MIH is a dental developmental anomaly of systemic origin, considered as an important public health issue, as it is affecting 1 in 5 of children worldwide, requiring the need of early diagnosis and early prevention and treatment, to limit the suffer of pain.

Hypomineralization is thought to be related to disruption in the Ameloblast cells function, mainly its resorptive potentiality, resulting in protein retention in enamel. **(**1**)**

Studies had revealed the multifactorial model of causality, with a synergistic of effect of genetics/epigenetics and environmental exposures. Conflicting results were shown through different studies as many of those studies was of retrospective mode, as randomization wouldn't be possible in such studies.

Many perinatal factors as hypoxia, low birthweight and prematurity were studies for association with MIH, but recent systematic reviews showed conflicting results, that might be related to the different number of studies included in each review **(**26, 28**)**.

Postnatal causes; including childhood illnesses were linked to MIH. However, different results of association were revealed, taking into consideration that medications given for those childhood diseases could play a confounding factor for the association.

The mineralization poisoning theory opened a new direction of research that might eventually lead to medical prevention of MIH, which would help in major reduction in childhood tooth breakdown or decay **(**16**)**.

Conclusion

MIH is considered an important health issue, affecting around 13% of children worldwide. MIH dental treatment carries multiple challenges, due to behavioral, psychological, functional, and esthetic problems. The different etiological causes are linked to the pre-, peri-, and post-natal periods, as alterations in the function of the Ameloblast cells during the maturation phase may occur between the end of pregnancy and the age of 4 years. Early detection of Hypomineralization in second primary molars, or even the known previous medical history would provide a clue for early preventive measures to avoid any further extensive dental treatment.

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