Predisposing factors involved in the aetiology of Molar Incisor Hypomineralization: a case-control study

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Abstract

Aim The aetiology of Molar Incisor Hypomineralisation (MIH) is currently unclear. Over time, several aetiological hypotheses have come forward, including pre- and perinatal medical problems and postnatal illness. The aim of this case-control study is the identification of possible predisposing factors involved in MIH aetiology.

Methods Study Design: By hypothesising the probability of at least one predisposing factor present 2.5 times more in MIH cases than in controls, with an estimated prevalence of MIH patients requiring therapy equal to 30%, at a unilateral alpha level of 5% and a power of 80%, 63 couples of subjects are needed with an allocation ratio of 1:1; individual matching for age and gender was carried out. After clinical examination, 78 children with MIH (EAPD criteria) were recruited (mean age 9.36 years). An anamnestic form filled-in by a parent was used to collect data on possible predisposing factors including demographic characteristics, pregnancy, birth, childhood medical illness and medications' intake. Statistics: One-tail McNemar chi square test was used to evaluate the significance of the association between predisposing factor and MIH; odds ratio and 95% confidence intervals were computed.

Results Defects were detected in 249 permanent teeth. Demarcated white-creamy opacities were more frequent in incisors, while yellow-brown opacities were found in first permanent molars ($p<0.001$). The frequency of enamel breakdown was higher in molars with yellow-brown opacities than white-creamy ($p<0.001$). Among prenatal factors, smoking during pregnancy ($p=0.0005$) and among perinatal and postnatal factors, newborn jaundice ($p=0.020$), genetic syndromes ($p=0.009$) and antibiotic intake during the second year of life ($p=0.033$) were associated to MIH. As for genetic syndromes odds ratio was equal to 1.30 (95% CI:1.14–1.48) being that a syndromic child risk 30% more to develop MIH.

Conclusions A multifactorial aetiology may be advocated for MIH development; in particular, further investigations are required to confirm and clarify the role of genetic factors.

KEYWORDS Aetiology; Molar Incisor Hypomineralisation (MIH); Predisposing factors

Introduction

Molar Incisor Hypomineralisation (MIH) was defined in 2001 as a "hypomineralisation of systemic origin, presenting as demarcated, qualitative defects of the enamel of one to four first permanent molars (FPMs) frequently associated with affected incisors" [Weerheijm et al., 2001]. The hypomineralization defects can affect the tooth ranging from demarcated white/creamy opacities to yellow/brown defects with/without hypersensitivity [Giuca et al., 2020; Beretta et al., 2020]. FPMs with extensive defects often manifest hypersensitivity to cold, heat and brushing with consequent difficulty in maintaining good oral hygiene, thus exposing the patient to a high caries risk. As recently reported, molars with yellow/brown opacities are more susceptible to early post-eruptive enamel breakdown (PEB) [Neves et al., 2019].

Since it is not possible to prevent MIH development, the efforts of clinicians are focused on reducing the functional, psychological, and social discomforts resulting from this condition.

Regarding pathogenesis, it was hypothesised that hypomineralisation defects are linked to disturbances of systemic or environmental origin during the maturation stage of amelogenesis of FPMs and incisors. Over time, several aetiological hypotheses have come forward, including pre- or peri-natal medical problems, postnatal childhood illness, environmental factors, medication use (e.g., antibiotics, or those used for the management of asthma) and genetic influences [Silva et al., 2016]. However, two recent systematic reviews and meta-analyses [Garot et al., 2021; Fatturi et al., 2019] emphasized that the actual aetiology of MIH has not yet been defined, concluding for a likely multifactorial aetiology.

The aim of this pilot case-control study is the identification of possible predisposing factors involved in MIH aetiology.

Materials and methods

The research protocol of this study was approved by the local Ethics Committee of the Bologna University Hospital Authority St. Orsola-Malpighi Polyclinic (PG. N 0019293). In full accordance with the ethical principles of the Helsinki Declaration, the written informed consent for participation and publication was obtained from the adults responsible for each individual.

Sample size calculation

The global MIH prevalence is widely variable and highly

influenced by the diagnostic criteria adopted and the geographic location. Therefore, the prevalence of MIH cases requiring therapy was used for sample size calculation in this paper because of its higher homogeneity among the different studies. Moreover, no difference in the aetiological factors may be suspected between MIH patients needing or not needing therapy. By hypothesising the probability of at least one predisposing factor present 2.5 times more in MIH cases than in controls, with an estimated prevalence of MIH patients requiring therapy equal to 30% [Schwendicke et al., 2018], at a unilateral alpha level of 5% and a power of 80%, 63 couples of subjects are needed with an allocation ratio of 1:1.

Subjects

Al the children attending the Unit of Special Needs Dentistry and Pediatric Dentistry, Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy, were recruited from January 2018 to March 2021. Among these, the cases (MIH+) were selected according to the following inclusion criteria: MIH diagnosis according to the EAPD criteria [Weerheijm et al., 2003]; age ≥ 5 years; no previous or present orthodontic treatment with fixed appliances cemented to FPMs and permanent incisors (PIs); absence of non-MIH enamel defects (enamel hypoplasia, enamel hypomineralization following dental trauma, Turner tooth, fluorosis, amelogenesis imperfecta).

Individual matching for age and gender was carried out between cases (MIH+) and controls (MIH-).

Data collection

Step 1: clinical examination

The clinical dental examination was performed on the same dental chair by the same paediatric dentist, who received an extensive training on the application of the EAPD diagnostic criteria for MIH [Weerheijm et al. 2003]. Clinical examination was performed on wet teeth after cleaning. To be included in MIH+ cases, an individual had to present at least one FMP showing demarcated opacity, post-eruptive breakdown, atypical restoration or an extraction due to MIH. MIH+ teeth were further described according to the classification proposed by Ghanim et al. [2011]. The air blast reaction was measured using the Schiff Cold Air Sensitivity Scale (SCASS): sensibility was dichotomised as absent (SCASS score 0-1) or present (SCASS score 2-3) [Schiff et al.,1994]. For each MIH+ tooth, the presence/absence of dental caries was assessed.

Step 2: anamnesis

An anamnestic form, part of the dental record adopted in our Service, filled-in by a parent was used to collect the following data: age, gender and ethnicity of the child; maternal illness during pregnancy (hypotension, hypertension, anaemia, gestational diabetes, toxoplasmosis, pre-eclampsia); smoking during pregnancy; mother's age at childbirth; pre-term birth; type of birth and weight at childbirth; medical illness during the first month of life (newborn jaundice, neonatal hypoxia, respiratory distress, hypocalcaemia); breastfeeding duration; infant formula; fluoride supplements and topical fluoride; illness during the first 30 months (syndromes, congenital heart diseases, respiratory infectious diseases, otitis, tonsillitis, urinary tract infections, high fevers, viral exanthems, neoplastic diseases); medication during the first 30 months; age of the first antibiotic intake.

Statistical analysis

The analysis unit is the couple (70 couples made of an MIH+ matched to an MIH- individual of the same age and gender). Bivariate tables described the data.

One-tail McNemar chi square test was used aiming to evaluate the significance of the association between predisposing factor and MIH. Odds ratio and 95% confidence intervals were computed. Alpha level was set *a priori* at 0.05. SPSS for Windows (vers. 27.0, SPSS Inc., Chicago, IL, USA) was used.

Results

Sample description

The total sample included 140 individuals: 78 (56%) were males and 62 (44%) were females (mean age 9.36 years; range: 5–17 years).

The 70 MIH+ individuals, 94% of Italian origin, included 39 males (56%) (mean age 9.13 years; range: 5–16 years) and 31 females (44%) (mean age 9.65 years; range: 6–17 years).

MIH+ subjects were matched for age and gender to 70 MIH- subjects, 93% of Italian origin.

Defect description

In MIH+ subjects, the hypomineralisation defect was detected in 249 permanent teeth: 91 (37%) upper FPMs, 90 (36%) lower FPMs, 34 (13%) upper PIs, 34 (14%) lower PIs. The characteristics of the affected teeth according to the classification proposed by Ghanim et al. are described in detail in Table 1. Score 4 was not assigned because no extraction was carried out in MIH+ children. Scores from 6 to 10 were not reported due to the exclusion criteria (non-MIH enamel defects).

Demarcated white-creamy opacities were significantly more frequent in PIs, whereas yellow-brown opacities were significantly more frequent in FPMs ($p<0.001$; chi-square test).

Excluding teeth with atypical restorations, PEB was reported in 51 (30%) FPMs, while 116 (70%) presented only opacities without PEB. The frequency of PEB was significantly higher in FPMs affected by yellow-brown opacities when compared to white-creamy opacities ($p<0.001$; chi-square test).

A marked sensitivity was reported in 2 (3%) PIs (Ghanim score 1 and score 2) and in 56 (31%) FPMs ($p< 0.001$; chi-square test). Twenty-eight (50%) FPMs suffering from marked sensitivity were classified as Ghanim score 2, 23 (41%) FPMs as score 2a, and 5 (9%) FPMs as score 1. The difference among the groups was statistically significant ($p=0.001$; chi-square test).

	1 Demarcated white-creamy opacity without PEB	1a Demarcated white-creamy opacity with PEB	2 Demarcated yellow-brown opacity without PEB	2a Demarcated yellow-brown opacity with PEB	3 Atipycal restoration	5 Partially erupted with MIH
PIs	41 (60%)	0	27 (40%)	0	0	0
FPMs	41 (23%)	4 (2%)	75 (42%)	47 (26%)	13 (7%)	1

TABLE 1
Characteristics of MIH+ teeth according to Ghanim et al. [2011].

Factors	n. of couples	p-value
Pre-natal factors		
Maternal illness during pregnancy		
Hypotension		
MIH+ yes and MIH- no	2	
MIH+ no and MIH- yes	2	0.50
Hypertension		
MIH+ yes and MIH- no	3	
MIH+ no and MIH- yes	2	0.50
Anaemia		
MIH+ yes and MIH- no	8	
MIH+ no and MIH- yes	3	0.113
Gestational diabetes		
MIH+ yes and MIH- no	2	
MIH+ no and MIH- yes	1	0.50
Toxoplasmosis		
MIH+ yes and MIH- no	0	
MIH+ no and MIH- yes	0	NA
Pre-eclampsia		
MIH+ yes and MIH- no	0	
MIH+ no and MIH- no	0	NA
Smoke during pregnancy		
MIH+ yes and MIH- no	6 (60%)	
MIH+ no and MIH- yes	25 (41.7%)	0.0005*
Mother's age at childbirth (years)		
MIH+ < 20 ed MIH- > 20	0	0.50
MIH+ 20 – 35 ed MIH- <20 o>35	10	0.212
MIH+> 35 ed MIH-<35	16	0.163
Perinatal factors		
Pre-term birth		
MIH+ yes and MIH- no	8	
MIH+ no and MIH- yes	16	0.076
Type of birth		
Natural		
MIH+ yes and MIH- no	9	
MIH+ no and MIH- yes	15	0.154
Epidural		
MIH+ yes and MIH- no	6	
MIH+ no and MIH- yes	3	0.252
Cesarean		
MIH+ yes and MIH- no	13	
MIH+ no and MIH- yes	11	0.419
Weight at childbirth		
MIH+ under and MIH- above	0	
MIH+ above and MIH- under	0	NA
Medical illness during 1st month		
Newborn jaundice		
MIH+ yes and MIH- no	15 (83.3%)	
MIH+ no and MIH- yes	5 (9.6%)	0.020*
Hypossia		
MIH+ yes and MIH- no	5	
MIH+ no and MIH- yes	4	0.50
Respiratory distress		
MIH+ yes and MIH- no	6	
MIH+ no and MIH- yes	6	0.50

Factors	n. of couples	p-value
Postnatal factors		
Breastfeeding		
No		
MIH+ yes and MIH- no	7	
MIH+ no and MIH- yes	10	0.314
<12 months		
MIH+ yes and MIH- no	12	
MIH+ no and MIH- yes	8	0.251
>12 months		
MIH+ yes and MIH- no	8	
MIH+ no and MIH- yes	12	0.251
Infant formula		
MIH+ yes and MIH- no	20	
MIH+ no and MIH- yes	13	0.148
Fluoride supplements		
MIH+ yes and MIH- no	13	
MIH+ no and MIH- yes	18	0.238
Topical fluoride		
MIH+ yes and MIH- no	19	
MIH+ no and MIH- yes	18	0.500
Diseases during first 30 months		
Syndromes		
MIH+ yes and MIH- no	3 (75%)	
MIH+ no and MIH- yes	15 (23.1%)	
Congenital heart diseases		0.009*
MIH+ yes and MIH- no	4	
MIH+ no and MIH- yes	6	
Respiratory infectious diseases		0.377
MIH+ yes and MIH- no	10	
MIH+ no and MIH- yes	6	
Otitis		0.227
MIH+ yes and MIH- no	13	
MIH+ no and MIH- yes	13	
Tonsillitis		0.50
MIH+ yes and MIH- no	10	
MIH+ no and MIH- yes	9	
Urinary tract infections		0.50
MIH+ yes and MIH- no	5	
MIH+ no and MIH- yes	4	
High fevers		0.50
MIH+ yes and MIH- no	17	
MIH+ no and MIH-yes	14	
Viral exanthems		0.360
MIH+ yes and MIH- no	14	
MIH+ no and MIH- yes	7	
Neoplastic diseases		0.094
MIH+ yes and MIH- no	0	
MIH+ no and MIH- yes	2	NA
Medications during the first 30 months		
MIH+ yes and MIH- no	21	
MIH+ no and MIH- yes	13	0.229
Age at first antibiotic intake		
Never		
MIH+ yes and MIH- no	4	
MIH+ no and MIH- yes	3	0.50
1-year old		
MIH+ yes and MIH- no	6	
MIH+ no and MIH- yes	12	0.119
2-year old		
MIH+ yes and MIH- no	14 (93%)	
MIH+ no and MIH- yes	5 (20%)	0.033*
3-year old		
MIH+ yes and MIH- no	3	
MIH+ no and MIH- yes	6	0.252

TABLE 2 Pre-, peri- and post-natal factors predisposing to MIH (*: a statistically significant association; McNemar chi square test).

Caries was diagnosed in 1 (1%) PI (Ghanim score 1) and in 36 (20%) FPMs (p<0.001; chi-square test).

Nineteen (53%) carious FPMs were classified as Ghanim score 2, 14 (39%) carious FPMs as score 2a, and 3 (8%) carious FPMs as score 1. The difference among the groups was statistically significant (p=0.026; chi-square test).

Predisposing factors description

Table 2 reports the examined predisposing factors.

Among the prenatal factors, smoking during pregnancy was significatively associated with MIH (p=0.0005). Smoking habit during pregnancy was present in 60% of couples including MIH+ with a smoking mother, and MIH- with a non- smoking mother vs. 42% of couples including MIH- with a smoking mother and MIH+ with a non-smoking mother (OR: 0.93; 95% CI: 0.24-3.66).

Among perinatal and postnatal factors, newborn jaundice (p=0.020), syndromes (p=0.009) and antibiotic intake during the second year (p=0.033) were significantly associated to MIH+.

Jaundice was present in 83% of couples including MIH+ with jaundice and MIH- without jaundice vs. 10% of couples

including MIH+ without jaundice and MIH- with jaundice (OR: 1.88; 95% CI: 0.40–8.81).

Genetic syndromes were present in 75% of couples including MIH+ syndromic children and MIH- non syndromic children vs 23% of couples including MIH+ non syndromic children and MIH- syndromic children; Odds ratio was equal to 1.30 (95% CI:1.14–1.48) meaning a syndromic child has a 30% higher risk of developing MIH. Among the 4 MIH+ syndromic children, 2 were affected by neurofibromatosis type 1, 1 by Noonan syndrome, and 1 by DiGeorge syndrome.

Antibiotic intake during the second year were present in 93% of couples including MIH+ antibiotic + children and MIH- antibiotic - children vs 5% of couples including MIH- antibiotic + children and MIH+ antibiotic - children (OR:0.29; 95% CI: 0.03-2.72).

Discussion and conclusion

The majority of teeth affected by MIH presented opacities without PEB, in accordance to previous studies [Borrego-Martí et al., 2021; Arslanagic-Muratbegovic et al., 2020; Glodkowska and Emerich, 2019; Mulic et al., 2017]. The frequency of PEB was significantly higher in molars affected by yellow-brown opacities, as recently reported by Neves et al. [2019] in a longitudinal study with a 12-month follow-up. The results showed that the worsening from opacities to breakdown occurred in 16.3% of the white-creamy ones and 41.8% of the yellow-brown ones. PEB is a consequence of the structural frailty of MIH affected teeth, compared to teeth without such defects. The hypomineralized enamel, in fact, has a high carbon content, low phosphorus and calcium content, less distinct prism edges and crystals and evident interprismatic spaces that make it more porous and frailer [Weerheijm et al., 2001].If the molar is not adequately protected, the occurrence of PEB has been seen to increase with the age of the patient when the vigorous masticatory forces undermine the integrity and the stability of the weak enamel [Bagattoni et al., 2021].

A marked sensitivity was reported in 31% of FPMs, in accordance with Raposo et al. [2019]. Hypersensitivity is associated with difficulty in maintaining good oral hygiene thus exposing the patient to a high caries-risk.

In the present study, 20% of the MIH+ FPMs were affected by caries, particularly those with yellow-brown opacities with/without PEB. In a recent paper, da Costa Silva et al. [2011] found a relationship between dental caries activity and MIH severity and suggested that it is possible that PEB is increased by the action of cariogenic bacteria that initially invade intact hypomineralised enamel and subjacent dentin and rapidly destroy the originally hypomineralised tissue.

In the present study, considering the possible prenatal predisposing factors to MIH, a positive association was observed between MIH and smoking during pregnancy. Regarding this potential risk factor, two systematic reviews [Silva et al., 2016; Fatturi et al., 2019] did not find an association with MIH. Fatturi et al. [2019] highlighted the absence of a standardized method to measure and report smoking exposure in the included studies. Interestingly, a prospective study in twins documented an association between hypomineralized second primary molars and smoking during pregnancy [Silva et al., 2019]. The mother's age at childbirth did not have a significant association with MIH and no previous data are available on this topic.

Two recent literature reviews [Fatturi et al., 2019; Butera et al., 2021] showed that maternal illness during pregnancy may be associated to children with MIH with a 40% higher risk.

In the present study, considering the possible perinatal predisposing factors to MIH, a positive association was found between newborn jaundice and MIH. This data is in accordance with a very recent cross-sectional study conducted in Saudi Arabia showing a statistically significant association [Alhowaish et al., 2021]. A recent review showed that a greenish pigmentation of the primary teeth is seen in children in remission from severe jaundice. Bilirubin is exatensively deposited throughout the body during hyperbilirubinemia and after remission may remain incorporated in hard tissues. [Giuca et al., 2021; Sciveres et al., 2019]. Further studies are needed to clarify if neonatal jaundice may have an aetiopathological link to MIH.

No association was found between MIH and preterm birth, type of delivery and weight at childbirth. In contrast, two recent reviews [Fatturi et al., 2019; Butera et al., 2021] show that cesarean delivery and delivery complications (hypoxia and respiratory distress) are significantly associated with MIH.

Regarding premature birth and low birth weight, the results from different studies are conflicting. Wu X et al. [2018] in a recent systematic review and meta-analysis described an association with MIH, while Fatturi et al. [2019] did not find a positive association. The authors emphasized that the absence of standardised criteria to assess preterm birth makes the results difficult to compare.

In the present study, considering the possible postnatal predisposing factors to MIH, a positive association was found between MIH and genetic syndromes and antibiotic intake during the second year of life.

As for smoking, jaundice and antibiotic intake, the strength of the association was not confirmed by the odds ratio and the amplitude of the confidence intervals denote a low precision of the estimate.

In a case-control study involving 50 children with neurofibromatosis type 1 and 50 healthy children, tooth malformations including enamel defects were reported in the study group without a significant difference with the control group [Bardellini et al., 2011].

Enamel hypomineralisation defects were previously described in children affected by DiGeorge syndrome [Nordgarden et al., 2012] and were considered secondary to some manifestation of the syndrome, such as premature birth, hypocalcaemia, hypoparathyroidism.

Previous studies reported an association between the use of antibiotics, particularly amoxicillin, and MIH: a case-control study conducted in Lebanon showed that children exposed to antibiotics during early childhood had a 2.15 times higher odds of MIH [Elzein et al., 2020]. The review by Fatturi et al. [2019] did not support this association. The main issue in data interpretation is that the effect of the disease cannot be easily distinguished from the effect of the medication, as the studies are either retrospective or cross-sectional.

No association was found between MIH and infant feeding, fluoride intake, systemic diseases, and medication during the first 30 months. Fatturi et al. [2019] highlighted the absence of a standardised method to measure and report infant feeding in the included studies. The influence of childhood illness has been broadly investigated but the variability in the definition of "illness" limits the data interpretation. Despite this limitation, the review by Silva et al. [2016] showed that a considerable evidence for an association between early childhood illness and MIH exists. The ameloblast function is sensitive to changes in the surrounding environment, including changes produced by

systemic illness [Bagattoni et al., 2014]. The mechanism for how such factors lead to MIH is still unclear.

The major limitation of the present study is that data were obtained directly from parents, not from medical records, which makes it subject to memory bias. There is strong evidence that mothers accurately recall perinatal factors such as gestational age, birthweight and mode of delivery, even many years after the events. However, some aspects of maternal health during pregnancy, recall of breastfeeding duration, child illness and medication use are less likely to be reliable Silva et al. [2016].

In this study, only environmental factors were evaluated. This represents a limitation, since it has been hypothesised that MIH might have a complex aetiology in which environmental factors and genetic factors influence each other.

From a statistical point of view, these preliminary data suggest that an increase of the power of the study could help the evidence of significant risk in developing MIH among the pre and post birth factors investigated.

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