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ORIGINAL ARTICLE

What are the Systemic Factors Associated with the Molar-Incisor Hypomineralization Etiology?

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ABSTRACT

Objective: To evaluate the systemic factors associated with Molar-Incisor Hypomineralization (MIH) etiology. **Material and Methods:** A total of 731 8-year-old schoolchildren enrolled in the public school system in Curitiba, Brazil, was randomly selected. The MIH diagnosis was performed by calibrated examiners (Kappa >0.80) according to the European Academy of Pediatric Dentistry criteria (2003). The systemic factors were collected through a semi-structured questionnaire and applied to the children's mothers, addressing the medical history from pregnancy to the first three years of children's life. Associations were analyzed by Poisson regression analysis with robust variance ($p<0.05$). **Results:** The systemic factors in the prenatal and perinatal periods were not associated with MIH ($p>0.05$). The children who used medications during the first years of life had a significantly higher prevalence of MIH (PRc = 2.18 CI = 95% 1.06–4.48; p=0.033). **Conclusion:** The use of medications during the first three years of children's life is associated with a higher prevalence of MIH.

Keywords: Epidemiology; Tooth Abnormalities; Dental Enamel Hypoplasia; Molar.

Introduction

Developmental defects of enamel (DDE) are defined as deviations from the normal appearance of tooth enamel resulting from enamel organ disfunction [1]. The amelogenesis is genetically controlled, but it could be sensitive to environmental disturbances; thus, any insult in their functions may result in defects in the mature enamel, as hypoplasia or hypomineralization [2]. The hypoplasia is a quantitative defect caused by disturbances in the secretory stage of amelogenesis [2] characterized by a reduction of enamel thickness [1], while the hypomineralization is a qualitative defect, occurring due to alterations during the transitional and/or maturation stages [2], resulting in enamel opacity [1].

The Molar-Incisor Hypomineralization (MIH) was defined as a specific DDE of systemic origin that affects one to four first permanent molars and frequently involves permanent incisors [3]. It is clinically characterized by demarcated white, yellow or brown opacities [4]. This defect represents a great significance in pediatric dental practice since the hypomineralized enamel presents higher porosity on account of its higher organic matter content and lower inorganic content [5]. It increases the risk of post-eruptive breakdown, facilitates biofilm retention and raises tooth sensitivity, making children avoid dental hygiene and consequently favoring development of tooth decay [6].

Literature supports the hypothesis that MIH has a multifactorial etiology with interactions between systemic factors and genetic predisposition [7]. Events during prenatal, perinatal and postnatal periods have been associated with MIH, such as maternal illness, cesarean delivery, delivery complications, premature birth, low birth weight, respiratory diseases, high fever and the use of medications in the first years of children's life [2,7-11]. However, the exact etiological factors of this condition remain unclear [2,7,8,11].

Regarding the negative clinical consequences of MIH for affected patients, it is important to know the etiological factors associated with this alteration, making it possible to identify children at risk [12] and prevent possible aggravations. Therefore, the purpose of this transversal study was to evaluate the association between systemic factors during prenatal, perinatal, and postnatal periods with the occurrence of MIH.

Material and Methods

Ethical Approval

This cross-sectional study was approved by the Committee of Ethics in Research in Human Beings of the Health Sciences of the Federal University of Paraná (Protocol number: 1.689.362) and from the Municipal Department of Education, Curitiba, Paraná, Brazil. The schoolchildren and their mothers were invited to participate in the study and they signed the informed consent.

Sample Size Calculation

The sample size was calculated using the parameters: the expected proportion of MIH in the population of 50%, a confidential interval of 95%, design effect factor of 1.8, and a boundary of 1.96. It was added 20% to compensate for occasional losses, resulting in a final sample of 690 to 865 children, as described by Reyes et al. [13].

The inclusion criteria were eight-year-old schoolchildren with the four permanent first molars erupted and those who had informed consent signed by their mothers. Exclusion criteria included children with syndromic conditions associated with other types of enamel defects and those wearing orthodontic fixed appliances that would impair visualization.

Calibration of the Examiners

Previously to the data collection, four examiners were trained and calibrated, aiming to achieve the intra- and inter-rater agreement. The diagnose of MIH was performed using the criteria proposed by the European Academy of Pediatric Dentistry (EAPD) [14], which includes the following scores: demarcated opacity (white, yellow or brown), post-eruptive breakdown (involving enamel or enamel and dentin), atypical restoration (satisfactory or unsatisfactory) and exodontia due to MIH. The training phase consisted of analyzing and discussing 20 intra-oral photographs representing different manifestations of MIH and clinical situations associated with differential diagnosis. For the calibration phase, other 30 photographs were analyzed by the examiners, independently. The results were compared with those obtained by an expert examiner and the inter-rater agreement was calculated using the kappa coefficient. After a 7-day interval, the examiners analyzed the same 30 photographs, independently, and the intra rater agreement was assessed by kappa coefficient as described in Reyes et al. [13]. For differential diagnoses between MIH and other types of DDE, the examiners were also trained and calibrated for modified-DDE Index [1].

Oral Exam

The children were examined at school environment by four calibrated examiners under artificial lighting conditions, using a dental mirror, dental probes blunt tip, and sterile gauze to dry the dental surfaces, improving the diagnostic conditions. MIH was evaluated according to EAPD criteria, considering only defects with a diameter greater than 1 mm [14].

Systemic Factors Data Collection

Before the oral examination, the systemic factors data were collected through a semi-structured questionnaire applied to the children`s mothers, addressing questions about the pregnancy to the first three years of children's life, as described in the literature [15-17]. The questionnaire was divided into three parts considering the prenatal, perinatal and postnatal periods.

The variables of the prenatal period analyzed were the presence of maternal malnutrition, use of drugs (alcoholic drink, tobacco, and illicit drugs), use of antibiotics and presence of maternal illnesses (diabetes, hypertension, fever, viruses and varicella). During the perinatal period, the variables were delivery complications, low birth weight (dichotomized at no greater than 2.500 g and greater than 2.500 g), need for an infant incubator, twins, breastfeeding, and the duration of breastfeeding. Variables of postnatal period were the presence of illnesses, presence of infections (high fever, throat infection, otitis media and urinary infection), use of medications, breathing problems (asthma, pneumonia, and bronchitis), food intolerance, and malnutrition during the first three years of children's life. Data collection was conducted between November 2016 and September 2017.

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences 25.0 software for Windows (IBM Corp. Released 2017. SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) and STATA 14.0 software (StataCorp, College Station, Texas, USA). Therefore, missing data were not included in the analyzes.

The independent variables were categorized and analyzed descriptively. Ethnicity was categorized according to maternal report. Family income was dichotomized into >2 Brazilian monthly minimum wage and

≤2 Brazilian monthly minimum wage, considering the median found in this sample. Parents' schooling was dichotomized into ≤ 8 years and > 8 years. The number of residents at home was dichotomized into <4 residents and >5 residents. For family structure, it was considered as nuclear when the child's parents or legal guardian were married or in a stable union, and as non-nuclear when the child's parents or legal guardian were single or widowed [13].

For the association analysis between MIH and systemic factors, the dependent variable was categorized as "with MIH" and "without MIH". The etiological factors were categorized as "present" and "absent". The prevalence ratios (PRc) and the confidence interval (CI) of 95% were calculated using the Poisson regression analysis with robust variance. The level of significance adopted was 5%.

Results

From the 784 schoolchildren who agreed to participate in the study (response rate of 90.6%), 51 were not present on the day of examination. Thus, 733 children were examined, but two of them were excluded due to wearing orthodontic fixed appliances. The final sample was composed of 374 (51.16%) boys and 357 girls (48.84%), totaling 731 schoolchildren. MIH prevalence was 12.10% (n=88) (Table 1).

Table 1. Sample socioeconomic characteristics.

Variables	N (%)
Gender	
Male	374 (51.16)
Female	357 (48.84)
MIH	
Yes	88 (12.10)
No	643 (87.90)
Ethnicity	
Caucasian	617 (84.4)
African	89 (12.18)
Asiatic	11 (1.50)
Indian	14 (1.92)
Family Income	
> 2 Wages	258 (35.30)
≤ 2 Wages	473 (64.70)
Parents' Schooling	
> 8 Years of Study	518 (71.65)
≤ 8 Years of Study	205 (28.35)
Number of Residents at Home	
< 4	487 (66.62)
≥ 5	244 (33.38)
Family Structure	
Nuclear Family	501 (69.58)
Non-Nuclear Family	219 (30.42)

No association was found between MIH and systemic factors in the prenatal period (p>0.05). Although MIH was more prevalent among children exposed to some complications during the prenatal period, the result was not statistically significant (Table 2).

Table 3 shows the possible perinatal systemic factors associated with MIH. There was no significant association between MIH and the evaluated factors, such as delivery complications, low birth weight, and breastfeeding.

Table 2. Systemic factors during prenatal period associated with MIH.

Systemic Factors		MIH[a] Yes N (%)	MIH[a] No N (%)	Total N	PR[b] (95% CI)[c]	p-value
Maternal Nutrition	Yes	32 (13.3)	208 (86.7)	240	1.02 (0.97–1.08)	0.373
	No	40 (10.9)	327 (89.1)	367		
Drugs	Yes	13 (13.0)	87 (87.0)	100	1.14 (0.65–2.00)	0.625
	No	67 (11.3)	525 (88.7)	592		
Antibiotics	Yes	2 (14.3)	12 (85.7)	14	1.02 (0.84–1.22)	0.832
	No	88 (12.3)	628 (87.7)	716		
Maternal Illness	Yes	19 (9.2)	188 (90.8)	207	0.65 (0.39–1.07)	0.095
	No	52 (14.0)	319 (86.0)	371		
Pregnancy Complication	Yes	43 (12.6)	297 (83.4)	340	1.01 (0.63–1.62)	0.944
	No	24 (12.4)	169 (87.6)	193		

[a]MIH= Molar Incisor Hypomineralization; [b]PRc= Crude Prevalence Ratio; [c]CI= Confidence Interval.

Table 3. Systemic factors during perinatal period associated with MIH (n=731; Curitiba, 2018).

Systemic Factors		MIH[a] Yes N (%)	MIH[a] No N (%)	Total N	PR[b] (95% CI)[c]	p-value*
All Perinatal Factors	Yes	29 (12.7)	199 (87.3)	228	1.18 (0.76-1.83)	0.456
	No	44 (10.8)	365 (89.2)	409		
Delivery Complication	Yes	16 (10.8)	132 (89.2)	148	0.92 (0.54–1.55)	0.759
	No	59 (11.7)	444 (88.3)	503		
Low Birth Weight	Yes	5 (9.4)	48 (90.6)	53	0.77 (0.32-1.81)	0.552
	No	83 (12.2)	595 (87.8)	678		
Infant Incubator	Yes	15 (12.0)	110 (88.0)	125	1.01 (0.59–1.70)	0.970
	No	67 (11.9)	497 (88.1)	564		
Twins	Yes	2 (14.3)	12 (85.7)	14	1.02 (0.85–1.23)	0.803
	No	82 (12.0)	605 (88.0)	687		
Breastfeeding	Yes	50 (10.9)	408 (89.1)	458	0.91 (0.81–1.03)	0.151
	No	9 (19.6)	37 (80.4)	46		
Breastfeeding less than or equal 6 months	Yes	18 (12.4)	127 (87.6)	145	1.01 (0.95-1.08)	0.656
	No	39 (11.0)	316 (89.0)	355		

[a]MIH= Molar Incisor Hypomineralization; [b]PRc= Crude Prevalence Ratio; [c] CI= Confidence Interval.

The use of medications by children during the postnatal period to the first three years of life was associated with MIH (p=0.033) (Table 4), while the other systemic factors showed no association (p>0.05).

Table 4. Systemic factors during postnatal period associated with MIH (n=731; Curitiba, 2018).

Systemic Factors		MIH[a] Yes N (%)	MIH[a] No N (%)	Total N	PR[b] (95% CI)[c]	p-value
Illness	Yes	59 (12.3)	422 (87.7)	481	1.62 (0.82–3.17)	0.159
	No	9 (7.6)	110 (92.4)	119		
Medication	Yes	52 (12.7)	356 (87.3)	408	2.18 (1.06–4.48)	0.033*
	No	8 (5.8)	129 (94.2)	137		
Infections	Yes	56 (11.7)	424 (88.3)	480	1.29 (0.72–2.29)	0.382
	No	13 (9.0)	131 (91.0)	144		
Breathing Problems	Yes	19 (11.4)	147 (88.6)	166	0.95 (0.58–1.55)	0.856
	No	62 (11.9)	456 (88.1)	518		
Food Intolerance	Yes	3 (12.5)	21 (87.5)	24	1.00 (0.87–1.15)	0.941
	No	80 (12.0)	587 (88.0)	667		
Malnutrition	Yes	6 (10.0)	54 (90.0)	60	0.83 (0.37–1.82)	0.644
	No	76 (12.0)	555 (88.0)	631		

[a]MIH= Molar Incisor Hypomineralization; [b]PRc= Crude Prevalence Ratio; [c] CI= Confidence Interval; *Statistically Significant.

Discussion

The hipomineralized enamel results from amelogenesis disruption during the late maturation stage [8]. During this phase, which starts in the last pregnancy trimester and finishes around three years postnatal [12], the degradation of enamel matrix proteins by proteolytic enzymes and the development of crystal hydroxyapatite contribute to enamel mineralization [18]. Therefore, adverse health events during prenatal, perinatal and postnatal periods may result in a dental structural defect [7].

During the prenatal period no association was found between MIH and the systemic factors, corroborating with other findings [16,19,20]. Literature reports that fewer MIH cases are related to systemic disorders in this period [8,19,21] when compared with the subsequent periods. It could be explained by the fact that the fetus is probably protected in utero [21]. However, a systematic review with meta-analysis found that children whose mothers had health problems during prenatal period had 40% higher odds of MIH than children whose mothers had no problems during this same period [7]. Another study observed that some mother's conditions during pregnancy were associated with a higher prevalence of hypomineralization in the primary molars [22]. There is no information about the mechanisms involved in the presence of illnesses and enamel defects. However, a study suggested that some maternal illnesses during pregnancy, as gestational diabetes, hypocalcemia, hypertension, and preeclampsia, are more frequent in women who present low vitamin D levels [23]. This micronutrient has the main function of maintaining constant plasma calcium concentrations, playing an important role in stimulating mineralization of tooth enamel [24]. Thus, this may be a possible explanation for the association between MIH and some pregnancy health problems.

No association was found between MIH and perinatal factors, which corroborates the findings of other studies [16,19]. Other studies have reported some perinatal factors associated with MIH, as cesarean section [2,7,18,20], delivery complications [7,8], premature birth [2,10,12,25,26], low birth weight [10,12], twinning [2,18] and breastfeeding period [26]. Nevertheless, it is difficult to analyzes these factors separately since they are often coexisting [11]. For example, preterm birth is frequently associated with low birth weight, and caesarean section is commonly performed in cases those pregnancy presents risks [7].

Breastfeeding was one of the perinatal factors not associated with MIH in the present study. The literature does not clear regarding breastfeeding and the occurrence of MIH. Some studies reported that long breastfeeding with environmental contaminants in the human milk increases the risk for enamel opacities [27,28], resulting in disturbances of amelogenesis [27]. In contrast, more recent studies suggest that breastfeeding presents a protective effect against the occurrence of developmental dental defects due to the human milk nutritional content, which avoid malnutrition includes calcium and phosphorous, minerals that contributes for enamel mineralization [29]. Besides that, adequate breastfeeding practice can protect children against respiratory infection, otitis media and malnutrition [30] – illnesses related to be associated with a higher risk for MIH development [8].

The use of medication during the first three years of children's life was the only factor during postnatal period that showed association with MIH. A systematic review [9] evaluated the medications related to MIH in studies that were classified as high-quality studies and observed that antineoplastic [31-34], antibiotics [15,35,36] and asthma medications [37] were reported to be associated with MIH. However, there are controversies in this context, since children who use medications for a long period had also illnesses. Thus the medication or the disease could be involved in the etiology of the enamel defect [9].

In contrast to our results, a recent study [29] has found that the recent use of anti-infection medications had a protective effect on DDE. It can be considered that these medicaments are used to treat

infections and reduce sequelae, as high fever, and consequently, reduces the risk of DDE. However, it is necessary to take into account that the study in question evaluated the use of anti-infection medications only in the last two weeks before the interview, which didn't represent enough time to cause DDE. Such finding leads the authors to suggest that the act of medicating the child could reflect a profile of care and attention to the child's health rather than the protective effect of the medication itself [29].

Although the non-association between MIH and health problems during the postnatal period in this study, respiratory problems and fever are reported to be associated with MIH by previous studies [7,12,19,26]. It is known that oxygen shortage, associated with respiratory diseases, as asthma, can affect ameloblasts activity and affect enamel matrix pH [26]. In this line, persistent high fever episodes can disturb the enamel matrix formation stage, resulting in enamel defects [38]. A recent cohort study [39] assessed all permanent teeth of children at the age of 10 years for 5 years. The authors found after 5 years, an increased odd of MIH between asthmatics children who did not receive metered-dose inhaler (MDI) medication, which can suggest that the defects are associated with the disease itself, and not with its treatment [37]. These differences between the present results and other findings can be explained by the fact that despite the sample of this study being representative, the prevalence of MIH found (12.1%) [13] was lower than other studies, which may be a limitation.

Information about systemic factors should be interpreted with caution, given the limitations of retrospective designs regarding the risk of memory bias [21]. Another possible limitation of this study was the categorization of the use of medications during the first three years of life as "yes" or "no"; thus, neither the duration of medicament uses nor the medication classes were considered, which can overestimate the role of this factors in enamel development. Moreover, it is recommended larger sample size for studies on possible MIH etiological factors [40].

The knowledge about the etiology of MIH is important to identify children groups at risk, to establish an early diagnosis [12], and consequently, to allow the early treatment of these defects. Furthermore, the prevention of possible injuries is an important aspect to be considered since children with teeth affected by MIH have 10 times more treatment when compared to children without this defect [41]. Despite the association between MIH and medication use during the three years of children's life found in this study, the need for well-design prospective studies is reinforced. In addition, as several factors can be interacted, making it difficult to assess their isolated effects, experimental studies should be performed to understand the influence of these factors on enamel development.

Conclusion

The use of medications during childhood is associated with higher MIH prevalence.

Authors' Contributions

GFS	https://orcid.org/0000-0002-8040-8553	Investigation, Data Curation and Writing - Original Draft.
ALF	https://orcid.org/0000-0002-8910-4417	Methodology, Formal Analysis, Investigation and Data Curation.
FCF	https://orcid.org/0000-0001-5290-7905	Writing - Review and Editing.
LRSA	https://orcid.org/0000-0002-7380-8583	Writing - Review and Editing, Supervision and Project Administration.
JFS	https://orcid.org/0000-0001-9969-3721	Conceptualization, Writing - Review and Editing, Supervision and Project Administration.

All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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