ORIGINAL RESEARCH

Correlation between Aerosol Therapy and Other Associated Factors in Early Childhood with Molar Incisor Hypomineralization

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Abstract

Context: The etiology of molar incisor hypomineralization (MIH) has been extensively explored. Recently, the effect of drugs used in aerosol therapy in childhood has been implicated as a possible factor in the development of MIH.

Aim: A case-control study was conducted in children aged 6–13 years to determine the association between aerosol therapy and other factors in the development of MIH.

Materials and methods: A total of 200 children were examined for the presence of MIH according to the European Academy of Paediatric Dentistry (EAPD) criteria (2003). Their mothers or primary caregivers were interviewed regarding the preterm history and perinatal, and postnatal history of the child up to 3 years of life.

Statistical analysis: The collected data were subjected to statistical analysis using descriptive and inferential analyses. The *p*-value ≤ 0.05 was considered statistically significant.

Results: Statistically significant association was observed between the development of MIH and exposure to aerosol therapy in childhood and the use of antibiotics before 1 year of life.

Conclusion: Exposure to aerosol therapy and antibiotics before 1 year of age are risk factors in MIH. Children who had aerosol therapy and antibiotics are 2.01 times and 1.61 times more prone to MIH.

Keywords: Aerosol therapy, Antibiotics, Molar incisor hypomineralization.

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Introduction

The term MIH was introduced in 2001 to describe the clinical appearance of enamel hypomineralization of systemic origin affecting one or more first permanent molars that are frequently associated with affected incisors.[1] Clinically, hypomineralization is seen as an abnormality in the translucency of the enamel (opacity), which can be of different colors ranging from white, cream, and yellow to dark brown. Depending on the severity of the MIH and they may undergo posteruptive enamel breakdown due to the soft and porous nature of enamel.[2] Several studies have explored the multifactorial etiology of MIH.[3–5] Prenatal factors such as maternal illnesses and medication, perinatal factors such as preterm birth and low birth weight, and postnatal factors, including diseases during the first 3 years of life such as fever, respiratory infections, and use of antibiotics were implicated as the most common risk factors.[6–9] A systematic review conducted in 2010 concluded that there was insufficient evidence supporting the etiology of MIH.[10] However, a recent systematic review in 2016 suggested that early childhood illness is a probable factor in causing MIH.[11] The most common childhood illness likely to be associated with MIH are respiratory diseases and/or infections such as asthma, pneumonia, and fever.[12–14] In respiratory illness or infections, the frequently used drug administration method is through aerosols since it is an easy, safe, and effective way to deliver the drug in small quantities.[15] A study by Arlene et al. showed that 33–71% of parents of children under 12 years of age reported that children preferred aerosol as a mode for drug delivery.[16] Loli et al. evaluated the association between a history of aerosol therapy with MIH and reported a positive association.[17] However, there is limited research done in this aspect. Hence, we conducted a case-control study primarily to evaluate the use of aerosol therapy in the first 3 years of life and the development of MIH in 6–13-year-old children. The secondary aim was to evaluate the other associated prenatal, perinatal, and postnatal factors in the development of MIH.

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Materials and Methods

A case-control study was conducted to assess the correlation between aerosol therapy and other associated factors with MIH in children between 6 and 13 years of age residing in Navi Mumbai, India. This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

All children between 6 and 13 years of age visiting the outpatient department of Pedodontics and Preventive Dentistry were screened for the study. The study was conducted between November 2018 and August 2019. A total of 200 children have selected for the study, out of which 100 children had MIH. Around 100 children with no evidence of MIH of similar age and sex were selected as controls.

The study was conducted by a single examiner. A total of 10 children between 6 and 13 years of age, who reported to the Department of Pediatric and Preventive Dentistry, were examined by the principal examiner and a gold standard. The same children were reexamined after 1 week to assess the intraexaminer agreement. The κ-statistic was used to determine the intraexaminer agreement (κ = 0.74). The examined children were not included in the main study.

The research protocol of this study was approved by the University Ethical Committee (FRC/2018/Pedo/11). The EAPD criteria were employed to diagnose the presence or absence of MIH. Children with any physical or mental disability, other defects like amelogenesis imperfecta, dentinogenesis imperfecta, tetracycline staining, or diffuse hypoplastic lesions (i.e., fluorosis) were excluded from the study. A face-to-face interview was conducted by the principal investigator (M.S.) with the parents of the children, which included detailed past medical history.

The factors assessed in prenatal history were maternal illness and medication during pregnancy. The factors assessed in the perinatal period were the gestational trimester, nature of delivery, complications during delivery and birthweight of the child. The postnatal factors assessed were a history of fever, respiratory diseases, and/or infection, chickenpox up to 3 years of age, and exposure to antibiotics and aerosol therapy upto 3 years of age. The use of aerosol therapy was divided into five subgroups, as given by Loli et al.[17] Group I—children never treated with aerosol; group II—children treated with aerosol with frequency up to 7 days/year; group III—children treated with aerosol >7 days/year and ≤15 days/year; group IV—children treated with aerosol >15 days/year and ≤45 days/year; group V—children treated with aerosol >45 days/year.[17]

The defect of MIH was examined on 12 index teeth in wet conditions by the M.S. using the EAPD criteria.[18] The conditions recorded were: demarcated opacity, posteruptive enamel breakdown, atypical restoration, extraction because of MIH, and unerupted tooth. Demarcated opacities with a diameter of <1 mm were not included.[19]

Data Analysis

Descriptive and inferential statistical analyses were carried out in the present study. The level of significance was fixed at $p = 0.05$, and any value ≤0.05 was considered to be statistically significant. Chi-square analysis was used to find the significance of study parameters on a categorical scale. Student *t*-tests (two-tailed and unpaired) were used to find the significance of study parameters on a continuous scale between the two groups. The association between selected variables and MIH prevalence was assessed in terms of odds ratio (OR) and 95% confidence intervals using multivariable logistic regression models. The statistical software IBM Statistical Package for Social Sciences statistics 20.0 (IBM Corporation, Armonk, New York, United States of America) was used for the analyses of the data and Microsoft Word was used to generate tables.

Results

The mean age of children at the time of examination was 9.6 years. Table 1 summarizes the variables, including pre, peri, and postnatal factors, and their association with MIH. Considering child-related factors, aerosol therapy ($p = 0.062$) and antibiotics given before 1 year of age ($p = 0.030$) showed statistically significant differences. The results of the logistic regression model for selected variables are presented as crude OR for univariate analysis in Table 2. It is seen that MIH was 2.020 (1.122–3.640) times more likely in children who had aerosol therapy as compared to children who had not taken it. Furthermore, it was seen that MIH was 1.611 (0.462–5.618) times more in children who had antibiotics compared to children who did not consume antibiotics.

Discussion

A global increase has been seen over the past two decades in the number of defects affecting enamel mineralization, which are referred to as MIH.[20] The prenatal, perinatal, and postnatal factors and their association with MIH have been assessed in various studies.[19–23] A recent research by Loli et al. established a positive association between aerosol therapy and MIH.[17] However, there is sparse literature in this regard. Hence, a case-control study was conducted to assess the correlation between aerosol therapy and MIH in 6–13-year-old children. The study also assessed the relation of other associated factors with MIH among these children.

A case-control study was designed since it helps to assess the multiple exposures of different risk factors in both the diseased and non-diseased groups.[24] Children between 6–13 years were selected for the study, as the first permanent molars erupt in the arch by 6 years of age. Children older than 13 years of age were excluded as the severity of MIH increases with age, and severely decayed teeth may be misdiagnosed as posteruptive breakdown due to MIH.[6] According to Garg et al., the optimum age for diagnosis of MIH is 8 years since all permanent first molars, and most of the incisors are erupted by this age.[25] We attempted to keep an equal number of male and female children in our study. Previous studies by Durmus et al.,[26] Allazzam et al.,[27] Mishra and Pandey[22] have stated no difference in the prevalence of MIH in males and females. Socioeconomic status was not included as a variable in the study. Previous studies by Allazzam et al.[27] and Wuollet et al.[28] showed no association between socioeconomic status with MIH. In the present study, we used the EAPD criteria for the diagnosis of MIH (2003).[18] This index is considered to be most acceptable for clinical screening of MIH.[29]

In the present study, 72% of children in the MIH group and 56% of children in the non-MIH group were exposed to aerosol therapy, and this difference was statistically significant. This is in accordance with findings reported by Loli et al.[17] The most commonly used drugs are corticosteroids, β2 agonists, anticholinergics, and mucolytics through aerosol therapy. It has been demonstrated that corticosteroids interfere with amelogenesis, similar to a disturbance in bone formation.[30] Experiments have shown that conditions affecting the enamel matrix pH, that is, respiratory acidosis and abnormal oxygen levels resulting from hypoventilation in various respiratory diseases such as asthma or adenoid infections, inhibit the action of the proteolytic enzymes and the development of the

crystal hydroxyapatite resulting in enamel hypomineralization.[29] In addition, both corticosteroids and β2 agonists, especially in powder formulations, have an acidic pH that can damage the enamel already suffering from MIH.[30]

There was no significant difference between the groups in the prenatal history of the child, which included maternal illness and medication during pregnancy, and perinatal history, which included nature, type, and complication of delivery, gestational week of the mother, and birthweight of the child. Crombie et al., in a critical review and Alaluusua et al., in a systematic review, concluded that there is insufficient evidence to determine the causative factor for MIH.[10,31] Similarly, Silva et al. found that there is limited evidence of a significant association between pre and perinatal factors with MIH.[11]

There was no significant difference in the history of fever, chickenpox and respiratory diseases and/or infection in early childhood between the two groups. Similar results were shown by Whatling and Fearne[32] and Kuscu et al.[33] However, Crombie et al. and Alaluusua et al. found weak evidence showing an association between early childhood illness with MIH.[10,31] A systematic review by Silva et al. concluded early childhood illness was likely to be associated with MIH.[11] Similarly, Lee et al., in a case-control study, concluded that respiratory infections suffered within 3 years after birth are factors associated with MIH among Korean children.[23]

In the present study, 72% of children in the MIH group and 58% of children in the non-MIH group had exposure to antibiotics before

Table 2: Logistic regression model for pre, peri, and postnatal variables and MIH

Variable	*p-value*	*OR (95% confidence ratio)*
Prenatal factors (during pregnancy)		
Illness during pregnancy	0.651	0.660 (0.108–4.036)
Medication during pregnancy	0.733	0.792 (0.206–3.039)
Perinatal factors		
Gestational age	0.602	0.761 (0.272–2.130)
Method of delivery	0.278	0.713 (0.387–1.314)
Birth weight of the child	0.358	0.913 (0.417–2.000)
Birth complications	0.868	0.946 (0.492–1.819)
Postnatal factors		
Aerosol therapy	**0.018***	**2.020 (1.122–3.640)**
Fever	0.211	0.519 (0.188–1.413)
Respiratory diseases and/or infections	0.322	0.755 (0.433–1.317)
Chickenpox	0.336	0.863 (0.453–1.642)
Antibiotics	**0.030***	**1.611 (0.462–5.618)**

**p*-value ≤0.05 was considered to be statistically significant

Table 1: Association between IH and pre, peri, and postnatal conditions (univariable analysis)

Variable	*MIH (n = 100) Yes in percentage*	*Control (n = 100) Yes in percentage*	*p-value*
Prenatal (during pregnancy)			
Illness during pregnancy	3	2	0.651
Medication during pregnancy	5	4	0.733
Perinatal			
Gestational age			0.602
Preterm (<37 weeks)	9	7	
Normal (≥37 weeks)	91	93	
Method of delivery			0.278
Vaginal delivery	67	74	
Cesarean delivery	33	26	
Birthweight of the child			0.358
<2.5 kg	23	20	
2.5–3 kg	43	53	
3 kg	34	27	
Birth complications	24	23	0.868
Postnatal (during first 3 years of life)			
Aerosol therapy	72	56	**0.018***
Fever			0.211
Before 1 year of age	65	53	–
After 1 year of age	28	36	
Respiratory diseases and/or infections	53	46	0.322
Chickenpox			0.336
Before 1 year of age	18	11	
After 1 year of age	25	30	
Antibiotics			**0.030***
At birth	8	4	
Before 1 year of age	72	58	
1–2 years of age	16	27	
2–3 years of age	4	11	

**p*-value ≤0.05 was considered to be statistically significant

1 year of age, and this difference was statistically significant. Similar results were seen by Laisi et al.[34] and Ghanim et al.[21] However, it is unclear whether the medicine or the disease is the cause of the enamel defect.[33] Similarly, other studies by Pitiphat et al.[35] and Allazzam et al.[27] evaluated the use of antibiotics up to 3 years of age and found a significant association with MIH.

This study shows exposure to aerosol therapy and antibiotics before 1 year of age as significant risk factors in the development of MIH. Thus, further studies exploring the various agents used in aerosols and their effect on developing tooth buds are required.

Conclusion

From the results of the present study, it can be concluded that exposure to aerosol therapy and antibiotics before 1 year of age are risk factors for MIH. Aerosol therapy was 2.01 times more likely to cause MIH, whereas antibiotics were 1.61 times more likely to cause MIH in children. Healthcare providers, including pediatric dentists, obstetricians, and pediatricians, should be aware of the postnatal health care of children as it is related to their oral health.

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