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Correlation between aerosol therapy in early childhood and Molar Incisor Hypomineralisation

ABSTRACT

Aim *To evaluate the correlation between the use of aerosol therapy in early childhood and the presence of Molar Incisor Hypomineralisation (MIH).*

Materials and Methods *Study design: a retrospective case-control study in which a group (cases) consisted of children from 6 to 13 years with MIH visited at the unit of Pediatric Dentistry of the Policlinico Tor Vergata (Rome, Italy), and a group (controls) consisted of an equal number of children of the same age without MIH. Data about the aerosol therapy and the presence of MIH were obtained respectively by medical history and intraoral clinical examination. Collected data underwent statistical analysis using mainly non-parametric tests ($p < 0.05$).*

Results *In the study were included 182 patients, of which 91 (46 males, 51%) were children with MIH (cases), and 91 (46 males, 51%) were children without MIH (controls). In the group of patients with MIH, in the early childhood, 12 (13.1%) never had aerosol therapy, 6 (6.6%) underwent aerosol therapy less than 7 days per year, 22 (24.2%) from 8 to 15 days per year, 22 (24.2%) from 16 to 45 days a year, and 29 (31.9%) more than 45 days per year. In the control group, in the early childhood, 9 (9.9%) never had aerosol therapy, 29 (31.9%) underwent aerosol therapy less than 7 days per year, 26 (28.6%) from 8 to 15 days per year, 20 (22.0%) from 16 to 45 days a year and 7 (7.6%) more than 45 days per year. Statistics: the risk of developing MIH in children undergoing intensive use of aerosol therapy with respect to those receiving a less intensive use resulted in an odds ratio of 3.19 ($p < 0.001$) in the general population, 4.83 ($p < 0.001$) in males and was not statistically significant in females ($p = 0.132$). The Spearman correlation between aerosol therapy and MIH was 0.278 ($p < 0.001$) in the general population, 0.372 ($p < 0.001$) in male, and it was not statistically significant ($p = 0.08$) in female subjects.*

Conclusion *Aerosol therapy carried out in early childhood appears to be a risk factor for the development of MIH, particularly in male subjects.*

Keywords *Aerosol therapy, Molar incisor hypomineralisation.*

Introduction

Molar Incisor Hypomineralisation (MIH) is a developmental disorder of the enamel, characterised by hypomineralisation of systemic origin of 1–4 permanent first molars (PFM), frequently associated with affected incisors [Weerheijm et al., 2001]. Clinically, hypomineralisation can be seen as an abnormality in the translucency of the enamel (opacity). The opacities can be of different colours, depending on the severity of the MIH and they may undergo post-eruptive enamel breakdown (PEB) due to soft and porous enamel [Weerheijm, 2003].

In the literature, the prevalence of MIH in economically advanced countries varies from about 3% to about 20% [Jälevik et al., 2001; Leppäniemi et al., 2001; Zagdwon et al, 2002; Onder Kuscu et al., 2008; Lygidakis et al., 2008a]. A study carried out at the Unit of Pediatric Dentistry of Policlinico Tor Vergata (Rome, Italy) showed a prevalence of 7% [Condò et al., 2012].

Clinical management includes several steps: risk identification, early diagnosis, remineralisation and desensitisation, prevention of caries formation and PEB, restorations and extractions with orthodontic assessment and treatment [William et al., 2006; Williams and Gowans, 2003].

The aetiology is multifactorial and postnatal factors are often involved [Lygidakis et al, 2008b; Jälevik and Noren, 2000; Ford et al, 2009]. The most common postnatal aetiological factors are respiratory diseases such as asthma, pneumonia and respiratory infections [Lygidakis et al, 2008b; Jälevik and Noren, 2000; Ford et al, 2009; Guergolette et al., 2009]. The standard treatment for these diseases includes the use of aerosol. The aerosol devices most commonly used are nebuliser, pressurised Metered Dose Inhaler (pMDI) and Dry Powder Inhaler (DPI). However, all devices have an important percentage of oropharyngeal deposition of drugs; although the change from Chlorofluorocarbon (CFC) to Hydrofluoroalkane (HFA) as propellent in pMDI reduced the amount of drug in the oral cavity, it is still higher than 30% with all devices [Rau, 2005; Berger, 2009; Leach, 2005; Newman

et al., 1981; Ziment, 1973].The use of a spacer associated with a pMDI significantly reduces oral drug deposition and increases pulmonary drug deposition [Newman et al., 1986; Newman, 2004; Rau, 2005]. The drugs most often used in aerosol therapy are corticosteroids, β2 agonists, anticholinergics and mucolytics. Studies in mice have demonstrated that corticosteroids interfere woth amelogenesis, in the same way in which disturb bone formation [Pawlicki et al., 1992; Rehman and Lane, 2003]. In addition, both corticosteroids and β2 agonists, especially in powder formulations, have an acid pH that can damage the enamel already suffering from MIH [Kargul et al., 1998; O'Sullivan and Curzon, 1998].

The aim of our study was to correlate the frequency of use of aerosol therapy and MIH in permanent teeth, and to assess whether the aerosol may be a risk factor for MIH; the secondary aim was to evaluate if use of pMDI with spacer and if rinsing of the mouth after aerosol may represent protective factors.

Materials and Methods

We conducted a retrospective case-control study, of two groups of patients aged 6 to 13 years visited at the Department of Paediatric Dentistry at the Policlinico Tor Vergata in Rome. One group consisted of patients with MIH in permanent dentition (cases), and the control group consisted of an equal number of patients with the same age without evidence of MIH (controls). We excluded patients with known risk factors for MIH.

Information about the presence of concomitant diseases and the diseases for which patients most frequently were prescribed aerosol were obtained from their medical history. Information about the frequency of use of the aerosol therapy, the age of start of the aerosol therapy, the drugs administered by inhalation, the device used, the possible use of the spacer and rinsing of mouth after therapy were obtained from the drug history. Data on dental treatments and any dental trauma were obtained from the dental medical history.

Data on the site, number and severity of enamel lesions, quality of oral hygiene and the presence of carious disease were obtained from intraoral clinical examination.

A descriptive statistics to evaluate the distribution of cases by sex, age, site and number of lesions was performed.

Each group was divided into five subgroups based on the use of the aerosol and its frequency in the first few years of life: Use 0: children never treated with aerosol; Use 1: children treated with aerosol with frequency up to 7 days per year; Use 2: children treated with aerosol >7 days/year and ≤ 15 days/year; Use 3: children treated with aerosol > 15 days/year and ≤45 days/ year; Use 4: children treated with aerosol > 45 days/ year.

For each group, we assessed the distribution of patients in the subgroups, stratified by sex.

For the calculation of risk, each group was stratified into two subgroups larger than the previous ones:

- low frequency of aerosol therapy (including subgroups Use 0, Use 1, Use 2; ≤ 15 days/year);
- high frequency of aerosol therapy (including subgroups Use 3 and Use 4, >15 days/year).

For the calculation of risk, a contingency table stratified by sex was obtained and the odds ratio (OR) with 95% confidence intervals (95% CI) was calculated. For the calculation of statistical significance, we used the Fisher's exact test, considering statistically significant values with $p < 0.05$.

In order to compare the different distribution of aerosol start's age in the two groups, we used the Student's t test.

Furthermore, we calculated the statistical correlation between the use of aerosol and the onset of MIH and between the use of the spacer and the occurrence of such lesions, calculating the correlation coefficient of Spearman.

Statistical analysis was performed using SPSS 20, IBM.

Results

The study included 182 patients, of which 91 (46 males, 51%; mean age 7.99± 1.72 years) were children with MIH in permanent teeth (cases), and 91 (46 males, 51%; mean age 7.99± 1.70 years) were children without MIH (controls).

Comparing the baseline characteristics of patients, as shown in Table 1, it can be seen that in the MIH group there is a higher prevalence of inadequate oral hygiene, although there is not a statistically significant difference; we can also notice that there is a statistically significant difference in the distribution of carious disease, more common in patients with MIH.

MIH lesions were observed in the following teeth: first molars in 35 children (38.5%, 19 males and 16 females), incisors in 26 children (28.6%; 7 M and 19 F), generalised MIH (involving both molars and incisors in 25 children (27.5%, 16 9 M and F), the second molar in 5 children (5.4%, 4 M and 1 F), as shown in Figure 1.

Data on the use of aerosol in the two groups are reported in Table 2. Data about the age of start of aerosol therapy, the use of the spacer, rinsing the mouth after inhalation therapy, the use of most common inhaled are shown in Table 3.

Characteristics	Presence of MIH	Absence of MIH	p value
Age (years; mean±DS)	7,99±1,72	7,99 ±1,70	1,00
Male sex (n, %)	46 (51%)	46 (51%)	1,00
Inadequate oral hygiene (n, %)	37 (41%)	29 (32%)	0,17
Presence of carious disease (n, %)	30 (33,0%)	15 (16,5%)	< 0,05

TABLE 1 Baseline characteristics of the population in the two groups.

We can observe that in the group of patients with MIH, in the early childhood, 12 (13.1%) never did aerosol therapy, 6 (6.6%) underwent to aerosol therapy less than 7 days per year, 22 (24.2%) from 8 to 15 days per year, 22 (24.2%) from 16 to 45 days a year and 29 (31.9%) more than 45 days per year, as reported in Figure 2.

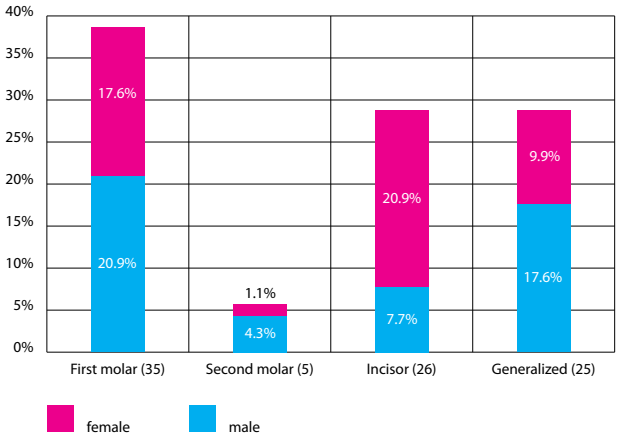

FIG. 1 Distribution of MIH lesions in permanent teeth, stratified by sex.

In the control group, in the early childhood, 9 (9.9%) never did aerosol therapy, 29 (31.9%) underwent aerosol therapy less than 7 days per year, 26 (28.6%) from 8 to 15 days year, 20 (22.0%) from 16 to 45 days a year and 7 (7.6%) more than 45 days per year, as shown in Figure 3.

Diseases for which patients with MIH had been treated with aerosol were, in descending order: pharyngitis (37; 46.8%), bronchitis (20; 25.3%), asthma (17; 21.5%) and bronchiolitis (5; 6.4%). Among patients without MIH, diseases for which they had been treated with aerosol were, in descending order, pharyngitis (52; 63.4%), bronchitis (16; 19.6%), asthma (9; 11.0%), bronchiolitis (3; 3.6%), otitis (1; 1.2%), tracheitis (1; 1.2%). For each child, we considered the condition for which most frequently he underwent aerosol.

The analysis of the risk of developing MIH in children with high frequency of aerosol therapy (>15 days/year, use 3 and 4) than children with low frequency of aerosol therapy (≤15 days/year, use 0, 1 and 2) showed the

Group	Use 0	Use 1	Use 2	Use 3	Use 4
Presence of MIH	12(13,1%) 4M 8F	6 (6,6%) 2M 4F	22 (24,2%) 11M 11F	22 (24,2%) 15M 7F	29 (31,9%) 14M 15F
Absence of MIH	9 (9,9%) 2M 7F	29 (31,9%) 15M 14F	26 (28,6%) 16M 10F	20 (22,0%) 9M 11F	7 (7,6%) 4M 3F

TABLE 2 Frequency of use of aerosol (n,%) in the group of patients with MIH and in the group of patients without MIH, stratified by sex. Use 0: children never treated with aerosol; Use 1: children treated with aerosol with frequency up to 7 days per year; Use 2: children treated with aerosol >7 days/year and ≤15 days/year; Use 3: children treated with aerosol >15 days/year and ≤45 days/year; Use 4: children treated with aerosol >45 days/year.

Characteristics	Presence of MIH	Absence of MIH	P Value
Age of starting aerosol (months)	14,7±10,8	18,9±12,0	< 0,05
Use of pMDI with spacer (n, %)	9 (11,4%) 4 M 5 F	28 (34,1%) 12 M 16 F	< 0,01
Rinse of mouth (n,%)	9 (11,4%) 4 M 5 F	23 (28,0%) 15 M 13 F	< 0,05
Corticosteroids (n, %)	79 (100%) 42 M 37 F	82 (100%) 44 M 38 F	1,00
β2 agonists (n,%)	56 (70,9%) 27 M 29 F	34 (41,5%) 17 M 17 F	< 0,05
Mucolytics (n,%)	41 (51,9%) 24 M 17 F	30 (36,6%) 16 M 14 F	0,056

TABLE 3 Age of starting aerosol in the two groups (mean±SD), distribution of the use of the spacer, rinsing the mouth after aerosol therapy, the use of corticosteroids, β2 agonists and mucolytics in the two groups. Absolute numbers and percentages refer to patients who underwent aerosol therapy (respectively 79 and 82 patients in the two groups).

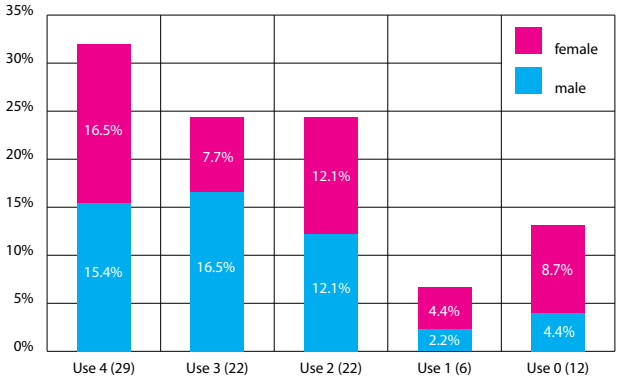

FIG. 2 Histogram that represents the frequency of use of aerosol (n,%) in the group of patients with MIH, stratifled by sex.
Use O: children never treated with aerosol; Use 1: children treated with aerosol with frequency up to 7 days per year; Use 2: children treated with aerosol >7 days/year and ≤15 days/year;
Use 3: children treated with aerosol >15 days/year and ≤45 days/year; Use 4: children treated with aerosol >45 days/year.

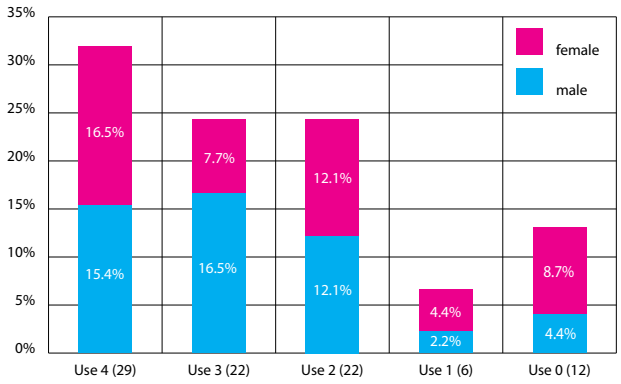

FIG. 3 Histogram that represents the frequency of use of aerosol (n, %) in the group of patients without MIH, stratified by sex.
Use 1: children treated with aerosol with frequency up to 7 days per year; Use 2: children treated with aerosol >7 days/year and ≤15 days/year; Use 3: children treated with aerosol >15 days/year and ≤45 days/year; Use 4: children treated with aerosol >45 days/year.

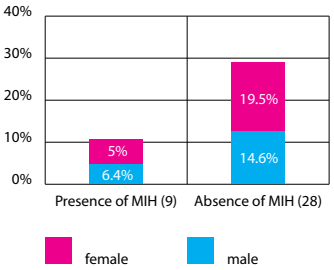

FIG. 4 Use of pMDI with spacer in the two groups, stratified by sex.

following results.

- Odds ratio of 3.19 (IC 95%; 1.72 – 5.90; p <0.001) in the general population.
- Odds ratio of 4.83 (IC 95%; 1.99 – 11.77; p < 0.001) in men.
- Odds ratio of 2.12 (IC 95%; 0.90 – 5.01; p = 0.132) in women.

The study of the correlation between the use of aerosol in early childhood and the onset of MIH shows a Spearman correlation coefficient of 0.278 (p <0.05) in the general population, 0.372 (p <0.05) in male and 0.181 (p = 0.08) in female subjects.

Observing the data of Table 3, we note that patients with MIH began aerosol therapy before those without MIH, with a statistically significant difference. There are no statistically significant differences between the two groups regarding the use of corticosteroids (always used in the aerosol) and mucolytics. Instead, there is a statistically significant difference in the use of β2 agonists between the two groups, with a more frequent use in the MIH group. Furthermore, among patients without MIH there is a higher frequency of rinsing the mouth after aerosol therapy.

Among the children of the case group who underwent aerosol therapy (79), 9 (11.4%) used the pMDI with spacer, while in the control group 28 children (34.1% of those who underwent aerosol therapy) used the pMDI with spacer, as shown in Figure 4.

the risk of developing MIH in children using pMDI with spacer for aerosol therapy with respect to those not using this device resulted in an odds ratio of 0.25 (p <0.01) in the general population, 0.28 (p < 0.05) in males and 0.21 (p < 0.01) in female subjects. The Spearman correlation between use of a pMDI with spacer and MIH was -0.27 (p < 0.001) in the general population, -0.228 (p < 0.05) in males and -0.381 (p < 0.001) in females.

Discussion

This study indicates that the frequent use of aerosol therapy in early childhood is a risk factor for the development of MIH, especially in males. Also, there is a mild-to-moderate correlation between aerosol therapy and the onset of MIH, as indicated by the Spearman coefficient.

Literature reports that MIH has often a systemic aetiology and the diseases of the upper and lower respiratory tract are often implicated [Lygidakis et al, 2008b; Jälevik and Noren, 2000; Ford et al., 2009; Guergolette et al., 2009].

One of the most important routes of drug administration for these diseases is aerosol therapy, and all aerosol devices are associated with an important amount of oral depositions of drug [Rau, 2005; Berger, 2009; Leach, 2005; Newman et al., 1981; Ziment, 1973]. Furthermore, it has been shown that corticosteroids can disrupt amelogenesis [Pawlicki et al., 1992]. It has been clearly shown that ameloblasts are among the most sensitive cells of the human body. If their function is disrupted, either temporarily or permanently, depending upon the tooth development stage, enamel hypoplasia or hypomineralisation are produced [Simmer and Hu, 2001; Fearne et al., 2004].

On the basis of these findings and the results of our study, our interpretation is that the aerosol therapy may represent the true risk factor associated with respiratory disease or otherwise one independent risk factor, in addition to respiratory disease. According to some studies [Lygidakis et al., 2008a], the main risk factor associated with respiratory diseases is hypoxia; this hypothesis has solid bases, however, we believe that the action on active amelogenesis of corticosteroids accumulated in the mouth after aerosol therapy may play a role in the formation of enamel lesions. A Danish study investigated the association between the use of inhaled asthma drugs and the prevalence of MIH, concluding that the use of inhaled medications for asthma is a risk factor for severe lesions with loss of substance, and is not a risk factor for demarcated opacities [Wogelius et al., 2010]. Therefore, further and larger studies will be needed to confirm our hypothesis.

The spacer is, instead, as assumed on the basis of the mechanism of action [Newman et al., 1986; Newman, 2004; Rau, 2005], a protective factor for MIH, particularly in women; therefore, it would be preferable that the inhalation therapy in children is administered with a pMDI with a spacer rather than a nebuliser.

Our study showed that children with MIH begin aerosol therapy before than those without MIH. An early age of initiation of inhalation therapy is a risk factor for the occurrence of such lesions, due to the increased susceptibility of the enamel, in the initial stage of its formation, to environmental factors.

Our data also shows that rinsing the mouth after therapy is a protective factor, removing the drug particles deposited in the mouth that cause injury to ameloblasts.

This study confirms that children with MIH are more susceptible to carious disease; therefore, as a first step in the management of MIH, an early diagnosis and a preventive protocol are essential as suggested by the Italian guidelines for prevention of caries in paediatric age [Accogli et al., 2014], which consider MIH as a high-risk condition.

Conclusion

Children with MIH underwent aerosol therapy more frequently than those without MIH, and the frequent use of aerosol therapy in early childhood is a mild-to-moderate risk factor for the onset of this disease, particularly in males.

The use of a pMDI with spacer and rinsing of the mouth after aerosol therapy are instead protective factors.

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