Molar-Incisor Hypomineralization: Positive Correlation with Atopic Dermatitis and Food Allergies

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Aim: *Molar-incisor hypomineralization is a disturbance in dental development that involves first permanent molars as well as permanent incisors with a prevalence that ranges from 2.5% to 40%. The objective of this study was to investigate the etiology of molar-incisor hypomineralization among school children from two randomly selected towns in the province of Barcelona, Spain.* ***Study design:*** *A cross-sectional study was conducted with 705 children ranging in age from six years-old to 14 years and 11 months-old. Full mouth examinations were carried out in accordance with the European Academy of Paediatric Dentistry criteria for the diagnosis of molar-incisor hypomineralization, from April to July 2016.* ***Results:*** *A total of 56 cases of molar-incisor hypomineralization were found in 22 (39.3%) boys and 34 (60.7%) girls. MIH was significantly more prevalent among those who had atopic dermatitis (OR=90.9; 33.4-247.1 CI 95%), food allergies (OR=104.2; 12.2-887.5 CI 95%), bronchitis/asthma (OR=5.3; 2.7-10.1 CI 95%), varicella (OR=96.3; 41.9-221.1 CI 95%), otitis media (OR=12.2; 6.3-23.5 CI 95%), pneumonia (OR=276.7; 35.1-2183.7 CI 95%), and febrile syndrome (OR=7.8; 4.1-14.8 CI 95%).* ***Conclusions:*** *The present research reveals for the first time a statistically significant relationship between atopic dermatitis and food allergies with the presence of molar-incisor hypomineralization.*

Keywords:: *Molar-incisor hypomineralization, Atopic dermatitis, Food allergies,.*

INTRODUCTION

The term "molar-incisor hypomineralization" (MIH) refers to a disturbance in dental development, affecting mineralization from one to four first permanent molars, frequently associated with affected mineralization in one to eight permanent incisors.[1]

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The majority of studies on the prevalence of MIH have been conducted in Europe, although recently this investigation has become globalized with many countries across the world looking after this issue. Currently, figures varying from 2.4% to 40.2% have been suggested,[2] with a large consensus declaring that children with poor general health during the first three years of life have greater probabilities of suffering from MIH.[3,4]

Tooth enamel is a highly mineralized tissue, the hardest of the organism, derived from the oral epithelium that is produced like epidermis from the ectoderm. Amelogenesis is a process of epithelial-mesenchymal interactions in which numerous genes code for growth factors, factors of transcription and proteins of common structures for other processes of embryological development.[5] Ameloblasts have therefore a double embryological epithelial and mesenchymal origin. Defects in the development of enamel may be inherited as a result of mutations in the genes that code for the enamel proteins or as traits of generalized family anomalies that often involve other tissues such as the skin which shares a common embryological origin with the teeth.[6]

Genetic alterations may directly affect the oral epithelium modifying the differentiation or function of the ameloblasts and the cellular support tissue. If the affected genes are expressed mainly in the dental tissues, the result is that the teeth are the principal affected structures resulting in a variety of enamel phenotypes that respond

to a deficiency in the quantity and change in composition and/or structure.[7,8] Dental development is therefore controlled genetically but is also highly sensitive to environmental alterations, thus the effects on ameloblasts may be detectable as defects in the mature enamel. If the function of the ameloblasts is interrupted either temporarily or permanently and depending on the moment of this impact, hypoplasia or hypomineralization shall take place[4].

Despite the fact that histologically the microstructure is maintained indicating the normal functioning of the ameloblasts during the secretion phase[9], it is believed that the root of the problem may lie in the alteration of the resorption power of the organic matrix and the inhibition of the proteolytic enzymes leading to a retention of proteins and interference with the formation of crystals given the lack of space for the mineral deposit.[10] The overall creation of enamel in permanent teeth extends over a period of some one thousand days and two thirds of this time is dedicated to the phase of amelogenesis maturation. For the first molars and the permanent incisors the affected period of the causal agents is considered to most likely be between birth and three years of age. [11,12]

The etiology of the MIH is unknown although it is believed to be of systemic origin. Despite the fact that a large variety of etiological factors have been proposed as mediators in the appearance of MIH, there is still no definitive agreement regarding its etiology.[13] In recent publications examining the potential causes of MIH, the presence of immunological immaturity is beginning to be considered as a relevant factor.[14]

Atopic dermatitis (AD) is a complex condition caused by an interrelation between multiple genetic and environmental factors, being the most frequent chronic inflammatory disorder of childhood. Defects in the skin's barrier permit environmental antigens to enter the skin and interact with natural and acquired elements of the immune system causing a very intense Th2-type allergic response.[15]

AD is often the starting point of the so-called "allergic march", a term that refers to the evolution of atopic manifestations and that is characterized by a typical sequence of immunological responses associated with the production of specific IgE and the early appearance of clinical symptomology of allergic diseases including atopic dermatitis, food allergies, allergic rhinitis and asthma.[16,17] Patients suffering from AD are found to have defects both at a skin barrier level as well as in natural cutaneous defences.[18]

Given that there is no definitive and conclusive data on the etiologic origin of MIH, accepting that the origins of the skin and the enamel are the same and accepting that amelogenesis is under genetic control,[5,8] it can be deduced that alterations or mutations in the responsible genes may be associated with the appearance of atopic dermatitis and deformations in enamel both quantitatively (hypoplasia) as well as qualitatively (hypomineralization). The aim of this research was to study and evaluate the strength of the relationship between diverse etiological factors with MIH in a population of Spanish children.

MATERIALS AND METHOD

The research protocol (P15/022) for this cross-sectional study on the etiology of MIH was approved by the IDIAP Governmental Health Service ethical committee.

A power calculation was used to assess the required sample size with at least 80% power and a = 0.05. A minimum of 600 children were needed. A total of 772 children from six to 14 years and 11 months-old were recruited from two randomly selected towns by the throw of a dice in the central region of the province of Barcelona, Spain, consisting of 51 towns.

Sixty-seven children out of 772 were rejected from the study since it was impossible to ensure the adequate control of the pregnancies and pediatric revisions during the first years.

Finally the study sample consisted of 705 Spanish school children, 375 boys (53.2%) and 330 girls (46.8%). Oral examinations were conducted from January to April 2016 as part of the governmental health control program after informed consent was obtained.

All children were examined by a pediatric dentist following a series of calibration exercises. A chart of 50 clinical pictures of affected teeth covering all degrees of MIH and other lesions such as hypoplasia, amelogenesis imperfecta and fluorosis was used for this purpose. An intra-examiner agreement of 97.6% was found using Kappa factor analysis.

This study applied the criteria recommended by the European Academy of Paediatric Dentistry (EAPD) for MIH studies.[1] Children were examined in a dental office with good lighting under direct vision with the aid of a dental mirror. All teeth had been previously cleaned and were wet. General enamel defects such as opacities of less than 2mm were excluded to avoid overestimation of the frequency of the alteration and to favor the reproducibility and comparison with other studies.

If MIH was diagnosed parents or legal guardians were informed of the need to bring the child back to the dental office for further explanations and relevant actions. Upon informing the parents or legal guardians of MIH characteristics they were asked if they agreed to participate in a study on the potential etiological factors of MIH. After signing an informed consent they were asked to respond to a questionnaire consisting of several topic-based blocks: affiliation and MIH diagnosis; maternal pre-existing medical conditions (heart disease, diabetes, arterial hypertension, allergies and others); diseases suffered by the mother during pregnancy (gestational diabetes, pre-eclampsia, eclampsia or vomiting); number of ultrasound examinations conducted on the mother during pregnancy; toxic habits of the mother (alcohol and smoking); mother's physical activity during pregnancy; type of labor (vaginal, cesarean, single, multiple, full term, premature, with epidural anesthesia); fetal suffering; weight and length at birth; maternal lactation and usual medication received during the first three years of life (antipyretics, antibiotics, anti-inflammatory drugs, bronchodilators, inhaled corticosteroids) and the child and family's dental history (agenesia, supernumerary teeth, traumatisms, infections and alterations in form and color).

As for medical problems, the possible relationship between MIH and the following conditions was studied: acute gastroenteritis, varicella, otitis media, respiratory virosis, pneumonia, bronchitis/asthma, atopic dermatitis, food allergies, frequent appearance of high fevers, acute tonsillitis, vomiting, dehydration and foot hand and mouth disease (table 1).

Data were entered into the IBM SPSS Statistics for Windows, version 22.0. (Armonk, NY: IBM Corp.) and a Chi square (χ^2) test was used to determine associations in MIH etiology.

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RESULTS

Fifty-six cases of MIH in 22 boys (39.3%) and 34 girls (60.7%) with a global prevalence of 7.9%, a gender prevalence of 5.8% for boys and 10.3% for girls and a boy/girl ratio of 1:1.58 were found. Forty-four consents were obtained from the 56 affected children.

No statistically significant correlation was found between the presence of MIH and pre-existing medical conditions of the mother including isolated cases of hypothyroidism, thalassemia *minor* and in vitro fertilization, diseases suffered by the mother during pregnancy, the number of ultrasound examinations conducted on the mother during pregnancy, toxic habits of the mother, mother's physical activity during pregnancy, type of labor and whether there was or not fetal suffering.

No statistically significant correlation was found between weight and height at birth or duration of maternal lactation, medication that was frequently taken by the child during the first three years of life and child/family's dental history.

A statistically significant association has been found (χ^2, $p<0.05$) with varicella, otitis media, pneumonia, bronchitis/asthma, atopic dermatitis, food allergies and febrile syndrome (table 2).

DISCUSSION

The primary rationale for conducting the study was to identify distinct etiological factors associated with the etiology of MIH. This is the first time that AD and food allergies are found to be related with the development of MIH. This study has found a MIH prevalence of 7.9% in its sample which is comparable with the findings from other childhood populations.[2]

There is much speculation regarding the etiological factors of MIH[4,14,19-21] and it has been suggested that there is a greater risk in children who during the first three years of their life have had respiratory diseases, metabolic alterations related to calcium and phosphates, diseases accompanied by high fevers[14,22] and certain environmental pollutants such as dioxins[6] and furans.[23] Given that it is quite clear that children with MIH have more diseases during the first three years of life than children without MIH, we have studied the effects of some diseases mentioned in different articles over the years as potential etiological factors in the appearance of MIH.

Some papers have reported statistically significant associations between MIH lesions and the presence of prenatal medical problems in mothers and perinatal problems in children (low birth weight and

Table 1 – Medical problems studied and their prevalence in children with MIH.

		DISEASES STUDIED											
	ICD-10*[40]	N = 705		n♂ = 375 (53.1 %)		n♀ = 330 (46.8 %)		MIH N = 44		MIH n♂ = 17/44 (38.6)		MIH n♀ = 27/44 (61.3)	
		n	%	n	%	n	%	n	%	n	%	n	%
AGE**	A09	162	22.9	96	25.6	66	20	15	34.1	5	29.4	10	37.1
Varicella	B01.9	42	5.9	18	4.8	24	7.2	29	65.9	12	70.5	17	62.9
Otitis media	H66.9	72	10.2	42	11.2	30	9.1	22	50	7	41.1	15	55.5
ARV †	J00	260	36.8	129	34.4	131	39.6	18	40.9	8	47.1	10	37.1
Pneumonia	J18.9	13	1.8	9	2.4	4	1.2	13	29.5	9	52.9	4	14.8
Bronchitis/asthma	J40/J45.9	192	27.2	93	24.8	99	30	28	63.6	12	70.5	16	59.2
Atopic dermatitis	L20.9	26	3.6	14	3.7	12	3.6	20	45.4	8	47.1	12	44.4
Food allergies	L27.2	7	0.9	4	1.1	3	0.9	6	13.6	4	23.5	2	7.4
Febrile syndrome	R50.9	90	12.7	46	12.2	44	13.3	21	47.7	8	47.1	13	48.1
Acute tonsillitis	J03	8	1.1	7	1.8	1	0.3	9	20.4	4	23.5	5	18.5
Vomiting	T17.91	10	1.4	4	1.1	6	1.8	11	25	5	29.4	6	22.2
Dehydration	E86.0	7	0.9	4	1.1	3	0.9	7	15.9	2	11.7	5	18.5
Foot hand mouth	B99	10	1.4	4	1.1	6	1.8	10	22.7	4	23.5	6	22.2

*ICD-10: International classification of diseases and related health problems[40]; **AGE: acute gastroenteritis; †ARV: acute respiratory virosis.

Table 2 – Positive association. Odds ratio (OR), Confidence interval (CI), Chi-squared test (χ^2) and significant statistical evidence (p<.05).

Diseases	Total (%)	MIH (%)	No MIH (%)	OR	CI	χ^2	p
Varicella	42 (5.9)	29 (65.9)	13 (2.0)	96.3	41.9-221.1	301.1	p<.001
Otitis media	72 (10.2)	22 (50.0)	50 (7.6)	12.2	6.3-23.5	81.1	p<.001
Pneumonia	13 (1.8)	13 (29.5)	0 (0.0)	276.7	35.1-2183.7	198.9	p<.001
Bronchitis /asthma	192 (27.2)	28 (63.6)	164 (24.8)	5.3	2.7-10.1	31.3	p<.001
Atopic dermatitis	26 (3.7)	20 (45.5)	6 (0.9)	90.9	33.4-247.1	230.4	p<.001
Food allergies	7 (1.0)	6 (13.6)	1 (0.2)	104.2	12.2-887.5	76.3	p<.001
Febrile syndrome	90 (12.7)	21 (47.7)	69 (10.4)	7.8	4.1-14.8	51.5	p<.001

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premature births) but other studies have found the associations to be non-statistically significant.[4,14,19,23] It has been suggested that more than birth weight, hypoxia may play a major role as a causal factor in the development of enamel deformations upon acting on the ameloblasts during the active phase.[20] The present study did not find a significant relationship between the presence of MIH and the child's birth weight or the existence of health problems of the mother during pregnancy.

The present investigation did not find a statistically significant correlation between the duration of maternal lactation and the presence of MIH defects. Our findings are not in accordance with those from Alaluusua *et al* [24] who reported a relationship between prolonged lactation and a presence of MIH possibly due to contaminating agents in maternal milk. Ghanim *et al* ,[25] on the other hand, reported that children who had been breastfed for a period of less than six months had three times the possibility of having MIH than those who were breastfed the first year of life.

Our study found a statistically significant correlation between MIH and having had varicella prior to the age of three, coinciding with studies by Silva *et al* [14] and Sonmez *et al* [20] This last study considers that given that the varicella virus attacks the epithelial surfaces and given that ameloblasts are of an epithelial origin MIH lesions shall be due to degenerative changes in the ameloblasts caused by the virus, although there is no evidence existing to this respect.

The role of otitis media is unknown although in our study a correlation was found between MIH and the presence of frequent bouts of otitis media during the first three years of life. We agree with Beentjes *et al* [26] and differ from Sonmez *et al* [20] and Whatling and Fearne.[27]

Different authors have reported about the significant relationship between respiratory diseases and MIH.[14,20,28] Upper and lower respiratory tract infections tend to be accompanied by febrile states which at very early ages and due to the immaturity of the thermo-regulation system tend to cause very high fevers. In our study we have found a significant relationship between MIH and bronchitis/asthma, pneumonia and high fever during the first three years of the child's life.

As a cause of hypomineralization an alteration in the reabsorption of the proteins of the matrix has been suggested due to a lack of oxygen supply.[4] Theoretically, diseases such as asthma or adenoiditis may have an altering effect on the ameloblast activity during the phase of mineralization due to the direct influence of the disease or given the presence of hypoxia, hypocalcemia, fever and/or malnutrition as a result of the disease.[28] Experimental studies reveal that the conditions affecting the pH of the enamel matrix in various respiratory diseases, such as asthma or adenoid infections, inhibit the action of the proteolytic enzymes and the development of hydroxyapatite crystals resulting in the hypomineralization of the enamel.[29]

Atopic diseases have increased their frequency over recent decades until affecting approximately 20% of the global population.[30] In the present study a statistically significant correlation was found for the first time between AD and food allergies with MIH. Food allergies have been described as a known cause of AD and those mediated by IgE are situated at approximately 35% in children affected by AD.[31] It has been suggested that the high incidence of food allergies during childhood is the result of a defect in the skin barrier and in the immaturity of the local and systemic immunology.[32] In any case, the prevailing theory defines AD as a starting point of the allergic march and signals the skin as being mainly responsible for early allergic sensitization that occurs in patients with AD.

Defects in the skin barrier facilitate the entry of pathogens, allergens and other environmental aggressors such as toxins and irritants and are currently considered to be the primary mechanism of development of the AD.[32-34] A dysfunctional skin barrier is a gateway for the entry of environmental and bacterial antigens facilitating the allergic sensitization and promoting a systemic lymphocytic immune response of type Th2.[35]

Jälevik and Norén[36] reported one child suffering from cow milk allergy and presenting MIH. In a recent paper Salem et al.[37] found "dermatitis of allergic origin" a statistically significant predictor for MIH. Not many details about how the study was performed are given and "dermatitis of allergic origin" is an ample term that comprises many medical conditions and not equivalent to a concrete condition such as Chawla *et al* [38] cite the presence of asthma (19 cases) and allergies (22 cases) before age three in 182 MIH cases. Analyzing potentially associated factors, Souza *et al* [19] found no significant statistically association between allergies (medical general term) and MIH. Sönmez *et al* [20] found no association between asthma, pneumonia, bronchitis and MIH. Rhinitis, bronchitis and high fever were more prevalent but not significantly in a group of Brazilian children with MIH.[23]

It has been suggested that maternal diet during pregnancy influences immune development.[39] Further intervention studies are needed to establish whether the modification of maternal nutrient intake during pregnancy can be used as a healthy low-cost public health measure to reduce the prevalence of atopy.

Although there is no specific data regarding the etiology of MIH, a study by Jeremias *et al* [7] was the first to evaluate the possibility that the genetic mutations somehow interact with environmental factors and are associated with the amelogenesis process and the presence of MIH. Genetic variations and agents that act negatively at the skin barrier and its development may be at the root of amelogenesis alterations. Targeting atopy associated pathways may help to reduce molar-incisor hypomineralization prevalence .

CONCLUSIONS

1. The prevalence of MIH in the sample studied was 7.9% with a boy/girl ratio of 1:1.58.
2. This investigation finds out for the first time a statistically significant relantionship between AD and food allergies with MIH.
3. This investigation also found a statistically significant relantionship between varicella, otitis media, pneumonia, bronchitis/asthma, and febrile syndrome with MIH.

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