Molar-Incisor Hypomineralisation and Allergic March

Molarno-incizalna hipomineralizacija i alergijska stanja

Abstract

Background: Molar-incisor hypomineralisation 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%. Aim: The objective of this study was to investigate the effect of atopic diseases on the development of molar-incisor hypomineralisation. Material and methods: The study was based on the review of the medical records of a group of 102 children whose age was between eight and 12 years and 11 months and who had previously been diagnosed with MIH. Results: An association (χ²; p<0.05) has been found between molar-incisor hypomineralisation in children's mouths and the existence of: atopic dermatitis (OR=2.504; 1.54-4.05 CI 95%), food allergies (OR=2.171; 1.03-4.56 CI 95%), allergic rhinitis (OR=0.17; 0.02-1.27 CI 95%), and asthmatic bronchitis/asthma (OR=1.707; 1.05-2.76 CI 95%). When analyzing the pathologies by location, we found that atopic dermatitis, food allergies, allergic rhinitis and asthma were more frequent in children who had (p≤0.05) #12, #11, #21, #22, #36, #31, #41 and #42 affected. Conclusions: The association between molar-incisor hypomineralisation and the presence of atopic diseases in the first 36 months of life underlines the convenience of approaching this problem from a multidisciplinary perspective.

Uvod

Na sastanku Europske akademije za dječju stomatologiju (EAPD), održanom u Ateni 2003., prihvaćena je sintagma molarno-incizalna hipomineralizacija (MIH) koju su Weerheijm i suradnici (1) predložili 2001. godine. MIH se odnosi na poremećaje u razvoju zuba nepoznate etiologije koji utječe na trajne zube, a posebno pogađa prve trajne kutenke i sjekutiće (2).

Istraživanja o MIH-u su česta i ta se tema trenutačno pro- učava u gotovo svim zemljama svijeta. Podatci o učestalosti, koji se danas razmatraju, kreću se između 2,4 i 40,2 % (3). Uz to, stručnjaci se slažu u vezi s činjenicom da će djeca lošijega zdravlja tijekom prvih 36 mjeseci života češće patiti od teškoga MIH-a (4).

Danas znamo više o MIH-u, ali njegova točna etiologija još je nepoznata. Trebala bi biti sistemskog podrijetla, a iako je predložen širok spektar etioloških čimbenika kao posrednika u nastanku MIH-a, konačni dogovor još nije postignut (5).

Među mogućim etiološkim čimbenicima MIH-a jedan od najrelevantnijih uzroka, na temelju nedavnih istraživanja o njezinoj etiologiji, jest imunosna nezrelost pa se čini sve jačijim da uključuje disfunkciju imunosnog sustava tijekom djetetovih prvih godina (6).
singly clear that the immune system dysfunction during the first years of the child’s life is involved (6).

The pathogenesis of atopic dermatitis (AD) – which is the most frequent chronic inflammatory disease of childhood – is not fully understood, but current evidence suggests that AD is characterized by a dysfunction of the skin barrier, (7,8). Skin barrier defects allow environmental antigens to enter the body and interact with elements of the immune system, natural and acquired, causing a very intense Th2-type allergic response, (9).

AD is often the initial step of the “atopic march”. The atopic/allergic march is characterized by a typical sequence of immunological responses associated with the production of specific IgE against allergens. It begins with AD and progresses to IgE-mediated food allergy (FA), asthma, and allergic rhinitis (AR), (10).

Hernández et al (5) reported the significant relationship between MIH and the presence of AD and FA, components of the so-called the atopic march, in a study on the etiological factors of MIH. Suspecting that the presence of MIH could be related to allergic march as a whole, the primary rationale for conducting the study was to analyse a sample of children diagnosed with MIH to determine whether or not there was any relationship with the components of allergic march.

Material and Methods

The study was based on the review of the medical records of a group of 102 children whose age was between eight and 12 years and 11 months. All the children – 55 boys and 47 girls who had participated in the previous study on MIH without significant differences due to sex had the first four permanent molars and the eight permanent incisors erupted and had been previously diagnosed with MIH. When MIH was diagnosed, all the children had been examined by a calibrated pediatric dentist. The dentist had been graded with an intra-examining Kappa factor of 97.6% (5).

The Institutional Review Board (Bioethical Committee, University of Barcelona, Spain) approved the study protocol (IRB00003099) for this study on the etiology of MIH. After informed consent was obtained, the medical records were checked for the presence or absence of AD, atomatic bronchitis, FA, and allergic rhinitis, all components of the allergic march.

Data were analysed using the 24.0 SPSS statistical software (IBM™) and a Pearson’s χ² test was used to evaluate associations in MIH etiology. A level of p≤0.05 was considered statistically significant.

No children participants were excluded from the sample since all of them had been diagnosed with having MIH in their teeth in the previous study by the same author.

Results

A statistically significant association (χ², p≤0.05) was found between atopic dermatitis, food allergies, allergic rhinitis, atomatic bronchitis/asthma and the presence of MIH in children’s mouths (Table 1).

When analyzing the pathologies by location, we realized that AD is more frequent in children who have #31 (OR=2.23; 1.06–4.69 CI 95%), #41 (OR=2.22; 1.04-4.68

Patogeneza atopijskog dermatitisa (AD) – a to je najčešća kronična upalna bolest u djetinjstvu (7) – nije potpuno razjašnjena, ali sadašnji dokazi upućuju na to da AD karakterizira disfunkcija korisne barijere kože. Oštećenja kožne barijere omogućuju okolišnim čimbenicima ulazak u tijelo i interakciju s prirodnim i stečenim elementima imunosnog sustava, što potiče vrlo intenzivan alergijski odgovor tipa 2 (9).

Zapravo, AD je često početak tzv. atopijskoga marša. Ato-pijski/alergijski marš obilježava tipičan niz imunosnih odgovora povezanih s proizvodnjom alergospecifičnih IgE proteina. Počinje s AD-om i napreduje do alergije na hranu posredovanu IgE-om (FA), astme i alergijskoga rinitsa (AR) (10).

Hernández i suradnici (5), u istraživanju o etološkim čimbenicima MIH-a, istaknuli su značajan odnos između MIH-a i prisutnosti komponenta tzv. atopijskoga marša AD-a i FA-a. Sumnja da bi MIH mogao biti povezan s alergijskim maršem u cjelini, osnovni je razlog za analiziranje skupine djece s dijagnosticiranom MIH-om kako bi se doznao postoji li ili ne veza s komponentama alergijskoga marša.

Materijal i metode

Istraživanje se temelji na pregledu medicinske dokumentacije 102 djeteta u dobi od 8 do 12 godina i 11 mjeseci. Sva djece – 55 dječaka i 47 djevojčica – koja su sudjelovala u prethodnom istraživanju o MIH-u (5) bez znatnih razlika ovisno o spolu, imala su prva četiri trajna kutnjaka i osam trajnih sjekućica i već im je bio dijagnosticiran MIH. Kad je dijagnostičan taj poremećaj, svu je djece u sklopu ispitivanja pregledao kalibrirani pedijatrijski stomatolog s čimbenikom Kappa od 97,6% (5).

Mjерodavni odbor institucije (Bioetički odbor Sveučilišta u Barceloni, Španjolska) odobrio je protokol studije (IRB00003099) za ovog istraživanje o etiologiji MIH-a. Nakon dobivanja informiranog pristanka, u medicinskoj se evidenciji provjeravalo postoji li ili ne kod sudionika u studiji AD, astmatični bronhitis, FA i alergijski rinits te sve komponente alergijskoga marša.

Podatci su analizirani statističkim softverom 24,0 SPSS (IBM™), a Pearsonov test χ² korišten je za procjenu povezanosti alergijskih stanja u MIH-ovoj etiologiji. Razina p ≤ 0,05 smatrana je statistički značajnom.

Ni jedno dijete nije isključeno iz istraživanja jer je svim sudionicima isti stručnjak dijagnosticirao MIH na zubima.

Rezultati

Utvrđena je statistički značajna povezanost (χ², p ≤ 0,05) između atopijskog dermatitisa, prehrabene alergije, alergijskog rinitsa i astmatičnog bronhitisa/astme i MIH-a u ustima djece (tablica 1.).

Analizirajući patologije prema mjestu na kojem su se javile, shvatili smo da je AD češći kod djece kojoj su zahvaćeni zubi # 31 (OR = 2,23; 1,06 – 4,69 CI 95%), # 41 (OR = 2,22; 1,04-4,68
CI 95%), and #42 (OR=1.65; 0.86-3.16 CI 95%) affected. Regarding FA, we could see that they were more frequent in children with involvement of #12 (OR=1.94; 1.48-2.54 CI 95%), #11 (OR=3.02; 1.30-7.03 CI 95%), #21 (OR=2.05; 1.53-2.76 CI 95%), #22 (OR=2.06; 1.09-3.90 CI 95%), #31 (OR=2.22; 1.10-4.50 CI 95%), #41 (OR=3.68; 1.19-11.37 CI 95%) and #42 (OR=2.94; 1.04-8.36 CI 95%). Likewise, in our study, allergic rhinitis is related to the presence of MIH in #11 (OR=2.63; 1.85-3.73 CI 95%), #21 (OR=3.47; 1.34-8.99 CI 95%), #31 (OR=1.91; 1.07-3.39 CI 95%), #41 (OR=1.14; 0.73-1.76 CI 95%), and #42 (OR=1.17; 0.82-1.68 CI 95%), while asthmatic processes manifested more frequently in children who had affected #36 (OR=7.48; 2.53-22.24 CI 95%), #41 (OR=3.07; 1.79-5.27 CI 95%), and #42 (OR=2.14; 1.76-2.75 CI 95%).

**Discussion**

Although it was recommended that children be observed at age eight when it comes to MIH studies, our sample ranged from age eight to the day before their thirteenth birthday (11). In this study, this age range was used because it was considered that, once the tooth had erupted, the age at which it had erupted was not so important as whether it was affected by MIH.

Little is known about the etiological factors of MIH (6,12–15). It has been suggested that there is a greater risk in children who during the first three years of their life have had, among others, adenoid infections, tonsillitis, respiratory diseases, diseases accompanied by high fevers and certain environmental pollutants (6,16–19).

Several authors have reported the significant associations between postnatal diseases of atopic origin (AD, asthma, bronchitis or allergic rhinitis) and MIH. The research suggested that respiratory diseases and asthma may be causative factors of MIH (5,6,14,16,19-23).

However, other studies have found the associations not to be statistically significant (12,14,19,24). Analyzing potentially associated factors, Souza et al (13) found no significant statistical association between allergies, and MIH. Sönmez et al (14) found no association between asthma, pneumonia, bronchitis and MIH. Dantas-Neta et al (24) indicate that asthma, bronchitis, sinusitis, and rhinitis, which were more prevalent in the MIH group, but not associated with MIH, were among the variables analysed in the children’s medical history during the postnatal period of life. Rhinitis, bronchitis and high fever were more prevalent but not significantly represented in the group of Brazilian children with MIH (19). In their recent paper Salem et al (25) have found “der-
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matitis of allergic origin” to be a statistically significant predictor for MIH, although not many details about how the study was performed are given.

It has been suggested that 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 (14). Experimental studies reveal that the conditions affecting the pH of the enamel matrix in various respiratory diseases inhibit the action of the proteolytic enzymes and the precursors of enamel affecting ameloblastic activity and altering development of hydroxyapatite crystals resulting in enamel’s hypomineralisation (26).

Atopic dermatitis is a childhood disease with immunological and skin barrier malfunction showing a high degree of comorbidity. The term atopy represents IgE-mediated hypersensitivity reactions (7).

Our environment and lifestyle are changing very rapidly and the appearance of new pollutants that may affect the period of amelogenesis could be an etiological factor to consider in future studies (27).

Endocrine Disrupting Chemicals (EDCs) are exogenous substances that alter functions of the endocrine system and consequently cause adverse health effects in an intact organism (28).

Many of the proposed causal factors for MIH, including EDCs, involve the large family of the steroid receptors. Most of them are expressed in ameloblasts and their levels of expression are dependent on their stage of differentiation (29). Steroid receptors thus appear as the common elements able to modulate the expression of enamel key genes controlling enamel synthesis or leading to enamel hypomineralisation in case of disruption (27).

Exposure to EDCs alters innate and adaptive immune mechanisms interfering with cellular and humoral activities that affect cell maturation and lifespan (30).

Atopic comorbidities (AD, AR, and asthma) are common and often appear together (31). They usually begin early in life with their co-occurrence greater than expected by chance alone, regardless of IgE sensitization (32). 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 (33).

Currently, 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 suggesting a cutaneous and systemic immune activation (34).

Our study found a significant relationship (p<0.05) between having MIH and having or having had atopic dermatitis, food allergies, allergic rhinitis, and asthma.

Today, there is a research path that follows the idea that genetic variations and agents that act negatively on the skin barrier and its development may be at the root of amelogenesis alterations since the enamel formation process is genetically controlled (21).

Jeremias et al (35) were the first to evaluate the possibility that the genetic mutations somehow interact with the envi-

MIH, iako nema mnogo detalja o tome kako je provedeno istraživanje.

Pretpostavlja se da hipoksija može biti važan uzročni čimbenik u razvoju deformacija cakline nakon djelovanja na ameloblaste tijekom njihove aktivne faze (14). U eksperimentalnim istraživanjima otkriveno je da uvjeti koji utječu na pH caklinske matrice, kod različitih respiratornih bolesti, inhibiraju djelovanje proteolitickih enzima i prekurzora cakline koji pak utječu na aktivnost ameloblasta i tako mijenjaju razvoj Kristala hidroksiapatita, što rezultira hipomineralizacijom cakline (26).

Atopijski dermatitis dječja je bolest s poremećajem imunosne i barijere koja pokazuje visok stupanj komorbide- teta. Atopija je zapravo reakcija preosjetljivosti uz posredovanje IgE: protučitjela (7).

Naše se okružje i način života vrlo brzo mijenjaju, pa bi pojava novih onečišćivača koji mogu utjecati na razdoblje amelogeneze mogla biti etiološki čimbenik koji treba uzeti u obzir u budućim studijama (27).

Kernikalije koje potiču poremećaje endokrinog sustava (EDC) vaniške su tvari koje mijenjaju funkciju endokrinog sustava i posljedično uzrokuju štetne zdravstvene učinke u netaknutom organizmu (28).

Mnogi od predloženih uzročnih čimbenika za MIH, uk- ljučujući i EDC, obuhvaćaju veliku obitelj steroidnih receptora. Većina njih je na ameloblastima i njihova razina ekspresije ovisi o stupnju diferencijacije (29). Tako se steroidni receptori pojavljuju kao zajednički elementi koji mogu modulirati ekspresiju ključnih gena cakline koji kontroliraju sintezu cakline ili potiču njezinu hipomineralizaciju u slučaju poremećaja (27).

Izloženost EDC-ima mijenja prirođene i stečene imuno- sne mehanizme koji interferiraju sa staničnim i humoralnim aktivnostima koji, pak, utječu na starenje i životni vijek sta- nica (30).

Atopijski komorbiditeti (AD, AR i astma) uobičajeni su i često se pojavljaju zajedno (31). Obično počinju u djetinj- stvu istodobno s pojavom tih poremećaja većom nego što je očekivano, bez obzira na IgE senzibilizaciju (32). Disfunkcionalna kožna barijera mjerio je ulaska okolišnih i bakterijskih antigena koji olakšavaju alergijsku senzibilizaciju i potiču sistemski imunosni odgovor limfocita tipa 2 (33).

Trenutačno prihvaćena teorija definira AD kao polazište alergijskoga marša i upućuje na kožu kao na glavnu odgovor- nu značajku za ranu alergijsku senzibilizaciju koja se pojavljuje kod pacijenata s AD-om, a pokreće kožnu i sistemsku imunosnu aktivaciju (34).

U našem istraživanju otkrili smo značajnu povezanost (p ≤ 0.05) između MIH-a i atopijskog dermatitisa, prehrambeni alergena, alergijskog rinitisa i astme.

Danas postoji istraživački put koji slijedi ideju da genske varijacije i agensi koji djeluju negativno na kožnu barijeru i na njezin razvoj, mogu biti uzrokom promjena u amelogene- ziji jer je proces stvaranja cakline genski kontroliran (21). Je- remias i suradnici (35) prvi su procijenili da genske mutacije možda djeluju uzajamno s čimbenicima okoliša i da su pove- zane s postupkom amelogeneze i MIH-om.

Razlike između istraživanja o mogućim etiološkim čim-
ronmental factors and are associated with the amelogenesis process and the presence of MIH.
Discrepancies between the studies regarding the possible etiological factors of MIH highlight the importance of conducting more research on this pathology.

Conclusion
The statistically significant and widely demonstrated association between MIH and the presence of atopic diseases in the first years of a child’s life underlines the convenience of approaching this problem from a multifocal perspective.
Pediatric dentists must take into account in their protocols that children with AD and atopic comorbidities are more likely to suffer MIH and that they should advise parents of children with the atopic march about the need for increased oral health care for their children.

Conflict of interest
None declared

Author contributions
MH conceived the idea, collected the data, led the writing, and gave the final approval of the version to be published; JM analysed the data, critically reviewed the manuscript, and gave the final approval of the version to be published.

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