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Molar incisor hypomineralisation – aetiological factors and clinical manifestation

Hipomineralizacja trzonowcowo-siekaczowa – czynniki etiologiczne i manifestacja kliniczna

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Abstract

Molar incisor hypomineralisation is described as enamel hypomineralisation of systemic origin involving the first permanent molars. It is also often associated with damage to permanent incisors, which undoubtedly have an important function during developmental age. It is estimated that permanent incisors are involved in approximately 30% of patients with molar incisor hypomineralisation. Early diagnosis of molar incisor hypomineralisation, implementation of appropriate treatment and knowledge of the factors that may contribute to this disorder can reduce the risk of loss of the affected teeth. The aetiology of the disorder has not been fully established. Many studies have shown correlations between molar incisor hypomineralisation and a particular aetiological factor. Research is underway to narrow down this area of consideration, as the aetiology identified to date is very extensive and multifactorial. Both genetic, epigenetic and environmental factors influence the onset of molar incisor hypomineralisation. In the large latter group, a particular role in the aetiology of the disorder is attributed to maternal viral infections during pregnancy, as well as chronic maternal diseases such as hypertension or diabetes, maternal use of certain medications during pregnancy, perinatal complications and diseases of early childhood. Many studies indicate that genetic factors and endocrine disturbances are the most important predisposing factors for molar incisor hypomineralisation. This paper discusses the diagnostic challenges and the most likely aetiological factors of molar incisor hypomineralisation investigated to date.

Keywords: molar incisor hypomineralisation, MIH, aetiology of MIH

Streszczenie

Hipomineralizację trzonowcowo-siekaczową (*molar incisor hypomineralisation*, MIH) opisuje się jako hipomineralizację szkliwa pochodzenia ogólnoustrojowego, obejmującą pierwsze zęby trzonowe stałe. Często jest też związana z uszkodzeniem zębów siecznych stałych, które niewątpliwie pełnią istotną funkcję w wieku rozwojowym. Uważa się, że stałe zęby sieczne są objęte procesem chorobowym u około 30% populacji pacjentów z MIH. Wczesne rozpoznanie zespołu MIH, wdrożenie odpowiedniego leczenia oraz znajomość czynników mogących się przyczyniać do jego powstawania pozwalają zmniejszyć ryzyko utraty zębów objętych zmianami hipomineralizacyjnymi. Etiologia MIH nie została w pełni ustalona. Istnieje wiele badań wykazujących zależności pomiędzy występowaniem MIH a danym czynnikiem etiologicznym. Prowadzone są badania mające na celu zawężenie tego obszaru rozważań, gdyż dotychczas wskazywana etiologia jest bardzo obszerna oraz wieloczynnikowa. Na powstanie MIH mają wpływ czynniki zarówno genetyczne, epigenetyczne, jak i środowiskowe. Spośród licznej grupy tych ostatnich szczególną rolę w etiologii MIH przypisuje się infekcjom wirusowym występującym u matki podczas ciąży, chorobom przewlekłym matki, takim jak nadciśnienie tętnicze czy cukrzyca, stosowaniu przez ciężarną niektórych leków, komplikacjom okołoporodowym oraz chorobom przebytym we wczesnym dzieciństwie. W wielu badaniach wskazuje się, że najistotniejszymi czynnikami predysponującymi do wystąpienia MIH są czynniki genetyczne oraz zaburzenia gospodarki hormonalnej. W niniejszej pracy omówiono problem rozpoznania tej jednostki chorobowej oraz najbardziej prawdopodobne czynniki etiologiczne MIH zbadane do tej pory.

Słowa kluczowe: hipomineralizacja trzonowcowo-siekaczowa, MIH, etiologia MIH

INTRODUCTION

Molar incisor hypomineralisation (MIH) was described as a distinct clinical entity by Weerheijm et al. in 2001[1]. MIH is defined as enamel hypomineralisation of systemic origin that involves 1–4 first permanent first molars; however, permanent incisors may be also involved[2]. Reduced enamel mineralisation and changes in protein composition lead to opacities, discolouration and fractures within the affected teeth[3]. The severity of MIH varies considerably. It may range from mild, demarcated opacity to enamel breakdown (Figs. 1–3). Depending on the severity, appropriate therapeutic measures are taken. MIH can significantly complicate clinical management and the loss of molars at a young age is a major concern. Additionally, the condition is associated with hypersensitivity and reduced response to local anaesthetics[4,5], making it difficult for the dentist to work with a young patient. MIH teeth are more susceptible to caries and post-eruptive enamel breakdown (PEB). MIH is believed to be responsible for a significant proportion of childhood caries disease as it is highly prevalent[6]. Recent data indicate high global prevalence of this developmental defect. Worldwide studies estimate the prevalence of MIH at 3–44%[3]. The role of the dentist should be to detect this condition early enough to implement preventive or therapeutic measures to achieve better outcomes, while preserving the aesthetics and functionality of the affected teeth. To this end, the criteria for the diagnosis of MIH should be used. An important element is to collect patient's history so that MIH can be linked to potential risk factors, knowledge of which will allow for early interventions to slow the progression of the disease. This, however, may pose difficulty due to the unclear and complex aetiology of MIH; therefore research is continued to identify possible causes of the disorder. This review discusses the diagnostic challenges, the most likely aetiological factors investigated to date and possible therapeutic interventions for the different stages of this disease.

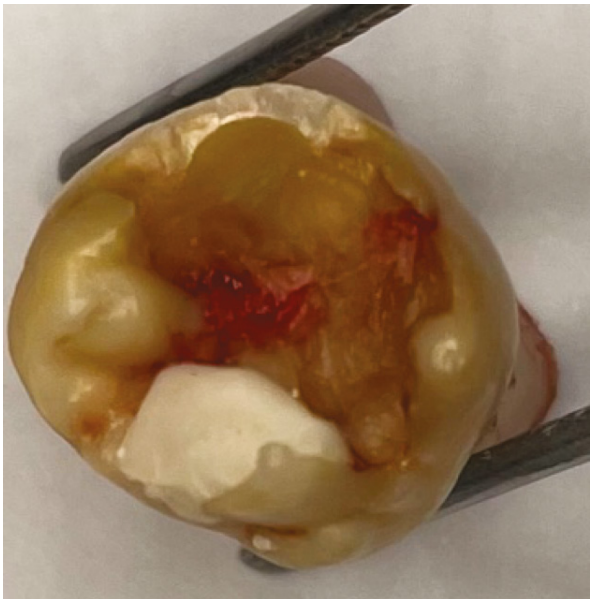

Fig. 1. Tooth 16 with molar incisor hypomineralisation (MIH), MIH-TNI (MIH treatment need index) classification – 2c (condition caused by rapid caries development in the enamel affected by MIH; extraction was performed due to severe destruction of the crown hard tissue and advanced pulp inflammation)

METHODS

This is a review paper. We reviewed the literature on MIH, its aetiology and clinical manifestations. Online databases such as PubMed and Google Scholar were used as search engines. The following keywords were used: MIH, molar-incisor hypomineralization, and MIH aetiology. Publications in English and Polish were included.

AETIOLOGY OF MIH

Establishing the aetiology of MIH is difficult, as there is no single confirmed aetiological factor for this disease. Many

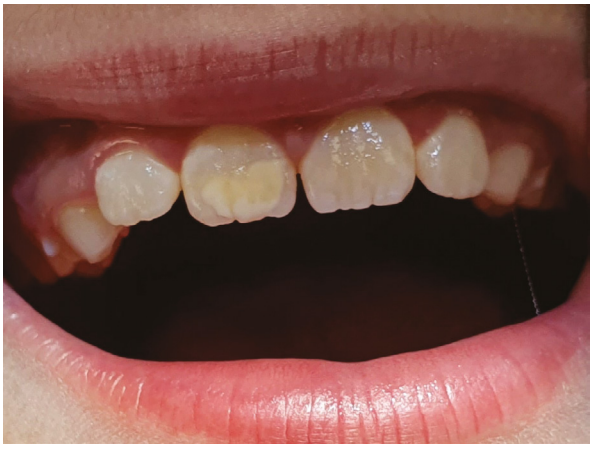

Fig. 2. White-creamy opacities, complete loss of enamel translucency in tooth 11

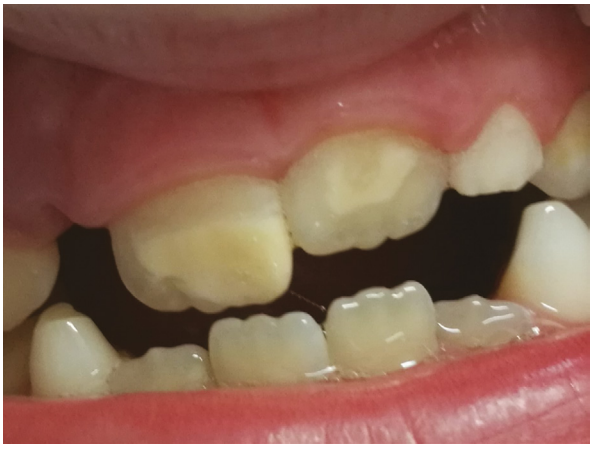

Fig. 3. White-creamy opacities, complete loss of enamel translucency in both central upper incisors

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environmental factors can either additively or synergistically contribute to the development of MIH. An analysis of systemic and environmental determinants influencing dental development in the prenatal, perinatal and postnatal periods was performed. It is presumed that chronic maternal diseases such as hypertension or diabetes, viral infections, malnutrition, renal failure or frequent vomiting can trigger MIH. Certain medications taken by the mother during pregnancy (e.g. antibiotics), as well as preterm birth, caesarean section, complications during delivery, low birth weight or twin pregnancy can also contribute to the development of MIH. These factors can cause ameloblast dysfunction, leading to hypomineralisation[7–9]. Many researchers point to a correlation between MIH and respiratory problems, asthma, bronchitis, otitis, high fever (caused by infections), the use of certain drugs (e.g. amoxicillin, erythromycin) and exposure to compounds that pass into breast milk (dioxins, polychlorinated biphenyls) in the first years of a child's life[7,8,10,11]. In addition, it has been suggested that the development of MIH is influenced by serum vitamin D_3 levels or environmental pollution[12,13]. Some researchers postulate that it is a genetic factor that is primarily responsible for the development of MIH[14].

PRENATAL AND PERINATAL PERIOD

Certain chronic maternal diseases during the prenatal period, particularly during the third trimester of pregnancy, and maternal pharmacotherapy during this time are thought to increase the likelihood of MIH in the child, as is environmental pollution[15].

It has been shown that children whose mothers experienced health problems (e.g. viral infections, hypertension, gestational diabetes, medication use) during pregnancy had a 40% higher risk of MIH compared to children whose mothers were healthy[7,15]. Furthermore, perinatal complications, i.e. complications during delivery, delivery by caesarean section, premature birth or low birth weight, may promote MIH[6].

RESPIRATORY DISEASES

A Dutch pilot study has shown an association between respiratory diseases in the first years of life and MIH[16]. Furthermore, Jälevik et al. showed a high rate of past respiratory disease in children who had one or more first molars removed due to severe hypomineralisation[17]. The relationship between MIH and factors affecting the pH of the enamel matrix, namely respiratory acidosis and abnormal oxygen levels resulting from hypoventilation accompanying various respiratory conditions such as asthma and respiratory infections, was also investigated[18]. Analyses have identified the possibility that respiratory diseases may contribute to MIH. This is supported by the association of abnormal oxygen levels and altered enamel matrix pH with impaired proteolytic enzyme function and hydroxyapatite development.

PHARMACOTHERAPY

Certain medications may promote MIH. Inhaled corticosteroid (CS) therapy, commonly used in children with asthma, inhibits osteoblast formation and activity. As a result, bone metabolism and formation are impaired. A similar effect on ameloblasts could explain the relationship between CS intake and hypomineralisation[19,20].

The relationship between MIH and antibiotic therapy is somewhat unclear, as antibiotics are commonly used to treat respiratory diseases. Therefore, it is not possible to say conclusively whether it was the respiratory disease or the antibiotic taken during the course of the disease that contributed to MIH. An analogous example is another potential aetiological factor for MIH, namely episodes of high fever in children under three years of age, which can interfere with amelogenesis. However, it often accompanies respiratory diseases. Therefore, also in this case, it is difficult to determine unequivocally what actually accounts for the development of MIH[21].

POSTNATAL FEEDING

A Swedish study in 17,000 children found no correlation between the incidence of hypomineralisation of first molars and childhood diseases, maternal medication and socioeconomic or environmental factors. However, a 5-fold increase in the risk of MIH was found in children with two factors: breastfeeding beyond 6 months and late (i.e. after 6 months of age) introduction of gruel and infant formula[22]. These can be considered as further likely causes of MIH.

GENETIC/HORMONAL FACTOR

There have been a number of studies attempting to confirm the genetic as well as endocrine aetiology of MIH. One of these was a study on rats exposed to low doses of bisphenol A (BPA), an endocrine disruptor. Rats exposed to BPA developed enamel hypomineralisation very similar to human MIH. BPA affected two genes (the gene encoding kallikrein-related peptidase 4 – *KLK4* and the gene encoding enamelin – *ENAM*), which are responsible for the secretion of enamel matrix proteins and their degradation (to allow the growth of hydroxyapatite crystals). Modulation of these two genes was found to cause enamel hypomineralisation. This study provided evidence of a potential endocrine influence on the process of amelogenesis by demonstrating that ameloblasts can be affected by oestrogens[23].

Vieira and Kup suggested based on their study that the occurrence of MIH-like lesions mainly on permanent first molars and permanent incisors may indicate the existence of a specific "time window" in which the maturation phase of these teeth may be affected[23]. If this "time window"

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remains open for a prolonged period of time, MIH-like lesions may extend to further teeth that develop later in the child's life, i.e. permanent canines, permanent second molars[23].

Modern gene mapping technologies have allowed German researchers to investigate a potential gene on chromosome 22 responsible for MIH. However, the study sample was too small to unequivocally confirm this theory[14]. What is interesting is the fact that despite the presence of many potential causes of MIH, no specific risk factors have been identified in up to 20% of affected children[7]. Due to both this fact and observations that MIH is more common in siblings, it has been suggested that genes related to the process of amelogenesis may play a key role in the development of MIH[24]. The most convincing evidence for the genetic aetiology of MIH was delivered by studies involving monozygotic and dizygotic twins. Koruyucu et al. found an association between genes such as the gene encoding enamelin (*ENAM*), the gene encoding tuftelin interacting protein 11 (*TFIP11*) and the gene encoding tuftelin 1 (*TUFT1*) and MIH in children[25]. Research is still underway to unequivocally confirm the genetic aetiology of MIH.

CLINICAL MANIFESTATION – THE MIH-TNI CLASSIFICATION

In addition to knowledge on the possible aetiology of MIH, the clinical diagnosis of this disease entity, which often has a varied clinical picture, is also important. In order to determine the severity of the lesions and plan appropriate therapeutic strategy, the MIH treatment need index (MIH-TNI) classification is useful, as it clearly allows the severity of the disease to be determined individually.

The classification is based on two main criteria: the presence of tooth hypersensitivity and destruction of the hard dental tissues. The range of changes for the different grades of the MIH-TNI scale is presented in Tab. 1[3]. The assessment is based on measurements taken in the maxillary and mandibular sextants:

- sextant 1: maxillary right teeth – distal to tooth 14 (tooth 54);
- sextant 2: maxillary anterior teeth – teeth 13–23 (teeth 53–63);
- sextant 3: left maxillary teeth – distal to tooth 24 (tooth 54);
- sextant 4: mandibular left teeth – distal to tooth 34 (tooth 74);
- sextant 5: mandibular anterior teeth – teeth 33–43 (teeth 73–83);
- sextant 6: mandibular right teeth – distal to tooth 44 (tooth 84).

In clinical practice, MIH can manifest in various forms[26]. The clinical assessment takes into account the presence or absence of limited enamel opacities, the presence of atypical fillings (size and shape do not correspond to the typical picture of carious disease) or PEB present on permanent molars and often also on permanent incisors. The presence of white, yellow or brown spots on the tooth surface and increased porosity of the enamel are typical[27]. MIH can affect more than one tooth or be limited to a single tooth[28]. It can be moderate, severe or very severe[8,29,30].

Index	Definition
0	No MIH
1	MIH without hypersensitivity, without defect
2	MIH without hypersensitivity, with defect
2a	<1/3 defect extension
2b	>1/3 to <2/3 defect extension
2c	>2/3 defect extension or/and defect close to the pulp or extraction or atypical restoration
3	MIH with hypersensitivity, without defect
4	MIH with hypersensitivity, with defect
4a	<1/3 defect extension
4b	>1/3 to <2/3 defect extension
4c	>2/3 defect extension or/and defect close to the pulp or extraction or atypical restoration

MIH – molar incisor hypomineralisation; **MIH-TNI** – MIH treatment need index.

Tab. 1. MIH-TNI classification[3]

The MIH-TNI classification allows for a reproducible assessment of lesion severity and specific clinical picture, individually for each patient[31]. Based on this, an appropriately designed therapy can be selected, taking into account all possible findings and complications, as simple and predictable as possible, with clearly defined therapeutic options[7].

PREVENTION AND TREATMENT

The clinical management of MIH poses a considerable challenge for dentists due to the often significantly advanced destruction of hard dental tissues, more rapid loss of properly performed fillings or microleakage and further penetration of the carious process. Studies indicate that children with MIH have a 10-fold higher need for dental care compared to children without MIH[17].

Early introduction of prophylaxis is made possible by an accurate medical history, which provides data on the risk of MIH. Additionally, studies indicate a 5-fold higher incidence of MIH in children who have previously been diagnosed with hypomineralised second primary molars (HSPM)[32]. Involvement of hypomineralised permanent teeth at an early age and their rapid loss can result in the loss of lateral support, alveolar bone atrophy and temporomandibular joint disorders[4,5].

If risk factors are present, clinical management should be limited to controlling hypersensitivity and limiting the formation of early carious lesions by reinforcing dental hard tissue. To this end, age-appropriate fluoride preparations or casein phosphopeptide–amorphous calcium phosphate (CPP-ACP) preparations are used. In addition, it is important to make patients aware of caries-promoting factors, possible home prophylaxis, as well as the need for frequent follow-up visits[33]. Regardless of the aetiology, the therapeutic management of MIH should be selected

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after assessment of the clinical picture, while increased clinician's vigilance for the presence of risk factors is desirable in prevention.

In the case of incompletely erupted teeth or when adequate dryness of the treatment area cannot be achieved, glass ionomer materials are used to restore lost tooth tissue. They also show effectiveness in uncooperative young patients. Disadvantages of these materials include inferior strength and rapid abrasion[34]. On the other hand, in the case of good patient/dentist cooperation, composite materials are used for tooth restoration. Some authors recommend complete removal of the altered enamel. Leaving at least two healthy tooth crown walls ensures good retention of the filling for an average of four years. Moreover, it is the least invasive therapeutic option[34,35].

In the advanced stage of the disease, when the chances of permanent restoration of the tooth using composite material are very low, the use of prefabricated steel crowns is considered. This is a very durable solution that protects the tooth from further progressive changes. The disadvantage of this method, however, is its low aesthetic value. In the case of teeth with severe lesions, whose restoration or prosthetic restoration would not generate the desired outcomes, extraction is considered[36,37].

Before reaching a final decision, an orthodontic consultation is advisable in order to obtain an opinion on the absence of contraindications or the most favourable solution associated with a good prognosis.

CONCLUSION

The aetiology of MIH is still not clear, with many studies pointing to different causes of this clinical entity. Among these are certain chronic maternal diseases and maternal pharmacotherapy (e.g. antibiotics) in the prenatal period, as well as perinatal complications or diseases in the child during the first three years of life. Some publications also consider the length of breastfeeding after birth as an important aetiological factor[22].

Some researchers suggest that the development of MIH may be influenced by serum vitamin D_3 levels or environmental pollution[12,13]. Nowadays, there is a tendency to classify this clinical entity as a predominantly genetic disease, with many authors emphasising the fact that the aetiology of MIH is multifactorial. There is still a need for research to identify specific risk factors for MIH. Furthermore, clinicians' awareness of the clinical recognition of this disease entity and the need for a thorough medical history is important. Since the clinical manifestation of MIH can vary greatly depending on the severity of the lesions, the MIH-TNI classification is helpful to unambiguously categorise a given clinical picture and plan appropriate preventive and therapeutic measures.

Conflict of interest

The authors report no financial or personal relationships with other persons or organisations that could negatively influence the content of the publication and claim rights to this publication.

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