Aetiology of Molar-Incisor Hypomineralisation: A systematic review

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Abstract
AIM: This was to review and assess the studies on aetiology of Molar-Incisor Hypomineralisation (MIH) or, as a proxy, of demarcated opacities in permanent first molars and to consider the potential factors involved with findings obtained in animal experiments. METHODS: A systematic search by Medline® online database was performed. Abstracts behind appropriate titles were studied and finally the full articles were evaluated for their strength of evidence in the aetiology of MIH. RESULTS: From a total of 1,142 articles 28 were identified and selected for review. The selected papers covered medical problems in prenatal, perinatal and postnatal period, medication of the child during the first years of life, and exposure to fluoride or environmental toxicants (dioxins and PCBs) in the early childhood. Based on the assessment of the articles it was still not possible to specifically name those factors causing MIH although correlations between several potential factors and MIH were presented. Among the factors suggested and found to cause enamel defects in animal experiments were: high fever, hypoxia, hypocalcaemia, exposure to antibiotics (amoxicillin, a macrolide), and dioxins. CONCLUSION: Despite increased knowledge on the aetiology of MIH insufficient evidence to verify the causative factors exists. Further studies, especially prospective ones, are needed to improve the level and strength of evidence of the role of the present putative factors and to reveal new factors that may be involved. Any combined effect of several factors should be taken into account. Experimental dose/response studies and research on the molecular mechanisms causing the abnormal function of the ameloblasts are also necessary to deepen our knowledge of MIH.

Introduction
Amelogenesis has been divided into three major stages of the ameloblast life cycle, namely secretory, transition, and maturation.

Stage 1. At the secretory stage, ameloblasts secrete large amounts of enamel matrix proteins within which long thin ribbons of enamel mineral, mainly hydroxyapatite, are formed almost immediately as the enamel matrix is laid down. The formation of enamel starts at the cusp tips and extends in a cervical direction (Fig. 1a, b). Throughout the secretory stage enamel crystals grow primarily in length and enamel layer thickness. The mineral phase of secretory enamel is approximately 10–20% by volume, with the remaining portion occupied by matrix protein and water.

Stage 2. Once the full thickness of enamel has been deposited, the secretory ameloblasts transform through a short transitional phase into maturation stage ameloblasts responsible for enamel matrix degradation accompanied by massive mineralisation of the enamel (Fig. 1c).

Stage 3. The mature ameloblasts regulate the final mineralisation of enamel. The enamel layer hardens as the crystallites grow in width and thickness resulting in a mineralised tissue that contains more than 95% mineral by weight.

Tooth development is strictly genetically controlled but sensitive to environmental disturbances. Once teeth have been formed, they do not undergo remodeling. Therefore, the effects of any insult to the ameloblasts are detectable as defects in the mature enamel. In general, systemic factors that disturb the ameloblasts during the secretory stage cause restriction of crystal elongation and result in pathologically thin, or hypoplasic enamel. Disturbances during the transitional and maturation stage of amelogenesis result in pathologically soft (hypomaturated, hypomineralised) enamel of normal thickness. At the early stage of the maturation, ameloblasts are highly sensitive to environmental disturbances [Suga, 1989].

The first permanent molars (FPM) start to develop during the fourth month of gestation. Documents on the mineralisation of FPM rely on histological and radiographic studies and they show that the first signs of mineralisation are seen in the cusp tips around or soon after birth (Fig. 1A) [Hess et al., 1932; Logan et al., 1933]. Around the age of six months the four cusps become united (Fig. 1B) [Logan et al., 1933]. In the end of the first year deposition of the enamel matrix is completed in the occlusal half of the crown and maturation is ongoing (early maturation phase, Fig. 1C). Enamel formation as a whole takes approximately one thousand days [Reid and Dean, 2006] and two thirds of this time is devoted to the maturation stage of amelogenesis.

Enamel hypomineralisation of systemic origin of 1-4 FPMs and frequently also of incisors is known as Molar-Incisor Hypomineralisation (MIH), [Weerheijm et al., 2001]. While the enamel is affected to an extent ranging from mild to severe, changes in dentine seem to be mild. In a study by Heij et
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al. [2007], no morphological changes in the dentine were found by polarized light microscopy except for the presence of interglobular dentine under the affected enamel. Also an overall reduction of about 5% was measured in the mineral concentrations of both the apparently normal enamel and dentine within the MIH teeth compared with those of control teeth studied by an x-ray microtomography [Fearne et al., 2004].

It has been suggested that the most critical period for enamel defects of FPM and incisors is the first year of life coinciding with early maturation. However, as enamel maturation in the FPM takes several years (later maturation stage), hypomineralisations may develop later.

The aim of the present paper was to assess the literature on potential systemic factors of MIH. Because in humans only clinical observations can be made, controlled animal experiments are included in this review on possible aetiological factors that have been suggested on the basis of clinical studies. However, applicability of animal experiments to humans has to be assessed critically.

Methods
A systematic search on Medline® online database was performed using the words molar incisor hypomineralisation and aetiology. The titles were first assessed and then abstracts appropriate titles were studied and finally the full articles were evaluated for their strength of evidence. Case reports, studies on inherited conditions, trauma, rare medical conditions, syndromes and studies exclusively concerning fluorosis, hypoplasia, discoloration, prevalence, or primary teeth were excluded.

Results
A total of 1,142 articles were identified among which there was one critical review [Crombie et al., 2009]. For a detailed evaluation the 28 articles were selected according to the criteria above. Most of the studies were retrospective, cohort or case-control studies. A wide variety of factors were analysed. The articles were grouped by age periods (prenatal, perinatal or postnatal) and by the putative factors likely to be present during those periods.

Pre- Peri- and Post-natal periods
Prenatal period. There was some evidence that medical problems during pregnancy were associated with MIH. In one study a specific illness, urinary infection, during the last trimester was associated with MIH-like lesions [Fredén et al., 1980]. In two other studies specific diseases were not associated with MIH but the authors reported that medical problems were more common in mothers of MIH children than in those mothers whose children did not have MIH [Whatling and Fearne, 2008; Lygidakis et al., 2008].

Perinatal period. In the perinatal period different medical conditions alone or in combination may affect the welfare of a child. In a Greek study, where the most common perinatal problems/conditions were Caesarian section, prolonged delivery, premature birth and twining, MIH was more frequently seen in the study than in the control group children.