On the Etiology of Molar-Incisor Hypomineralization

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MIH was originally described as an idiopathic defect [Weerheijm, 2003] and a clear etiology for the condition is yet to be defined [Alaluusua, 2010]. This condition has been associated with a variety of etiological factors but, according to the results of two systematic reviews [Crombie et al., 2009; Alaluusua, 2010], none of the potential risk factors analyzed presented convincing causality. Crombie et al. [2009] stated that most of the papers they evaluated provided a low level of evidence for associations. Moderate evidence was found for exposure to polychlorinated biphenyl/dioxin and weak evidence for the role of nutrition, birth and neonatal conditions, and acute or chronic childhood illness and associated treatments. Evidence implicating fluoride or breastfeeding as a risk factor for MIH was considered very weak. Alaluusua
[2010] concluded that it was still not possible to specify causal factors for MIH, even though correlations between several potential factors and MIH have been reported. Animal models suggested preceding events such as hypoxia, high fever, hypocalcaemia, exposure to antibiotics (amoxicillin), and dioxins as possible causes of MIH. When rats were exposed to a daily low dose of bisphenol A (BPA), an endocrine disrupting chemical, the exposed rats developed an enamel hypomineralization condition very similar to the human MIH [Jadeon et al., 2013]. BPA mainly targeted two genes (kallikrein-related peptidase 4, Klk4, and enamelin, Enam), which are responsible for enamel matrix protein secretion and enamel matrix degradation (to allow enamel mineral crystal growth), respectively. It was found that modulation of the expression of these genes led to enamel hypomineralization. BPA stimulates activity on ameloblast proliferation and gene transcription and provides evidence for a hormonal influence on amelogenesis, demonstrating that dental epithelial cells are estrogen targets [Jadeon et al., 2014]. We were the first to suggest that a genetic component involving genes that contribute to enamel formation may be playing a role in MIH [Jeremias et al., 2013].

One question we find intriguing is how can the phenotype have such a peculiar preference for two specific tooth types? Here we present two lines of thought. The suggestion that the development of different types of teeth (incisors, canines, premolars, molars) is influenced by unique factors is not new. The anteroposterior morphogenetic ‘field’ concept was first suggested in 1939 [Butler, 1939, 1978] and was used to justify the preferential association of agenesis of maxillary lateral incisors and maxillary canine-first premolar transposition (anteriort field), agenesis of mandibular second premolars and positional canine anomalies (intermediate field), and agenesis of third molars and palatally displaced canines and mandibular lateral incisor-canine transposition (posterior field) [Peck et al., 1996, 2002]. Concomitant disturbances of molars and incisors are therefore plausible based on these data.

We also have original data that support the preferential occurrence of developmental disturbances in incisors and molars. From a cohort of 116 cases with tooth agen-
ness (excluding third molars), 16 cases had a concomitant dental anomaly [Vieira et al., 2004]. Among these, the cases that had molar agenesis ($n = 11$) had a 4-fold increased likelihood of having an anomalous maxillary lateral incisor, typically microdontia (odds ratio = 4.0; 95% confidence interval: 0.99–16.15) [Barbosa et al., 2004]. Data also exist showing that individuals with third molar agenesis have smaller maxillary lateral incisors compared with individuals with normally formed third molars [Oliveira et al., 1991]. Based on these data, it appears that the concomitant preferential involvement of incisors and molars can involve agenesis and microdontia, disturbances that are related to the earlier stages of dental development. These localized clinical presentations involving incisors and molars remind us of preferential enamel hypomaturation affecting incisors and molars.

The exclusive affection of permanent first molars and incisors suggests a specific window of time for the disturbances to occur during the maturation stage of the affected teeth. However, it is possible that primary second molars can be affected, which is considered a predictive factor for MIH [Elfrink et al., 2012]. Similarly, there are reports that suggest primary canines can also be affected [Dietrich et al., 2003; Bhaskar and Hegde, 2014; Schmalfuss et al., 2015]. These suggest that this window of time can start during the maturation stage of primary second molars and ‘stay open’ while the enamel of permanent canines is maturing.

The localization of the hypomineralization in molars and incisors is a remarkable aspect of the clinical presentation. Hence, another way of thinking about this problem is that it is not that the timing of the disturbances of enamel maturation is the most critical factor but that enamel maturation disturbances are localized and that the factor causing disturbances can be so strong as to affect adjacent teeth. Support from this argument comes from two other craniofacial disturbances: oral clefts and tooth agenesis. Individuals born with oral clefts are up to 12 times more likely to have tooth agenesis outside the cleft area (posterior teeth, mandibular teeth) [Tanndure et al., 2012]. The remaining teeth of individuals born with clefts generally have smaller tooth sizes for both arches compared with individuals born without clefts [Rawashdeh and Bakir, 2007; Akcam et al., 2008; Walker et al., 2009; Sabóia et al., 2013]. When we evaluated the tooth dimensions of individuals born with clefts with concomitant dental anomalies, evidence of sitespecific tooth reductions emerged [Sabóia et al., 2013]. As an example, a case with agenesis of the right first maxillary premolar exhibited reduced dimensions of the permanent teeth anterior to the agenesis (maxillary right central and lateral incisors and canines). This pattern of reduced tooth sizes of the remaining teeth in cases with dental agenesis was reported in a family with a missense mutation in $PAX9$ and oligodontia [Brook et al., 2009]. $PAX9$ mutations lead to an interesting phenotype of oligodontia with preferential agenesis of permanent molars [Vieira, 2003]. These data suggest that a $PAX9$ protein alteration may result in the development of phenotypes ranging from agenesis to smaller tooth dimensions.

Along the same lines, MIH in some instances may not exclusively affect first permanent molars and incisors, but can also alter primary second molars and/or permanent canines and could extend further to affect premolars (fig. 1). This argues for a genetic alteration causing MIH, which most typically leads to alterations confined to the enamel of first permanent molars and incisors, but on occasion can affect the enamel of adjacent teeth. The geographic differences in disease prevalence [Alaluusua et al., 1996; Dietrich et al., 2003; Kukleva et al., 2008; Wogelius et al., 2008; Soviero et al., 2009; Schmalfuss et al., 2015] and the lack of clear associations with environmental risk factors [Alaluusua, 2010; Serna et al., 2016] further support the idea that a genetic component is the best explanation for the occurrence of such interesting clinical presentation. Therefore, we propose that MIH is not an idiopathic but a genetic condition related to disturbances in the maturation stages of enamel, which in most instances in localized to first permanent molars and incisors. On occasion, second primary molars and permanent canines and premolars can also be affected. The involvement of additional teeth may be due to the influence of additional gene variants in any of more than 100 genes expressed during late enamel development (http://bite-it.helsinki.fi/).

Disclosure Statement

The authors declare that there are no conflicts of interest.

References


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