Gene-environment relationships in dento-alveolar complex: The tooth as an early marker of exposure to environmental pollutants

Sylvie Babajko’s team
High prevalence of enamel pathologies associated to environmental conditions

The prevalence of enamel pathologies associated to environmental conditions has been listed as one of the most frequent inflammatory pathologies. Dental decay, for example, has been included in the Global Burden of Chronic Disease 2010, along with MIH, fluorosis, and caries as the most common environmental enamel defects.

### Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence (both sexes)</th>
<th>Male prevalence</th>
<th>Female prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (thousands)</td>
<td>Total (thousands)</td>
<td>Total (thousands)</td>
<td>Total (thousands)</td>
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<tr>
<td>------------------------------------------------</td>
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</tr>
<tr>
<td>Dental caries of permanent teeth</td>
<td>2,410,928</td>
<td>1,271,987</td>
<td>1,138,941</td>
</tr>
<tr>
<td>Tension type headache</td>
<td>2,110,687</td>
<td>1,121,537</td>
<td>989,150</td>
</tr>
<tr>
<td>Migraines</td>
<td>1,431,544</td>
<td>717,182</td>
<td>714,362</td>
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<tr>
<td>Fungal skin diseases</td>
<td>975,667</td>
<td>518,367</td>
<td>457,300</td>
</tr>
<tr>
<td>Other skin and subcutaneous diseases</td>
<td>813,327</td>
<td>427,520</td>
<td>385,807</td>
</tr>
<tr>
<td>Chronic periodontitis</td>
<td>243,187</td>
<td>121,807</td>
<td>121,380</td>
</tr>
<tr>
<td>Mild hearing loss with peripheral onset due to other hearing loss</td>
<td>214,189</td>
<td>105,12</td>
<td>109,069</td>
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<tr>
<td>Acne nodules</td>
<td>648,488</td>
<td>312,349</td>
<td>336,139</td>
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<tr>
<td>Low back pain</td>
<td>621,945</td>
<td>314,793</td>
<td>307,152</td>
</tr>
<tr>
<td>Dental caries of baby teeth</td>
<td>619,978</td>
<td>314,793</td>
<td>305,185</td>
</tr>
<tr>
<td>Moderate iron-deficiency anemia</td>
<td>602,925</td>
<td>301,463</td>
<td>291,462</td>
</tr>
<tr>
<td>Other musculoskeletal disorders</td>
<td>560,378</td>
<td>283,729</td>
<td>276,649</td>
</tr>
<tr>
<td>Noise-related due to sensoric vision loss</td>
<td>493,646</td>
<td>231,952</td>
<td>261,694</td>
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<tr>
<td>Mild iron-deficiency anemia</td>
<td>375,428</td>
<td>187,572</td>
<td>187,856</td>
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<tr>
<td>Asthma</td>
<td>214,189</td>
<td>105,129</td>
<td>109,069</td>
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<tr>
<td>Neck pain</td>
<td>132,049</td>
<td>66,023</td>
<td>66,026</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>128,615</td>
<td>64,308</td>
<td>64,307</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>115,892</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Major depression disorder</td>
<td>190,441</td>
<td>111,641</td>
<td>78,800</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>283,229</td>
<td>147,378</td>
<td>135,851</td>
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<tr>
<td>Anxiety disorders</td>
<td>327,777</td>
<td>168,731</td>
<td>159,046</td>
</tr>
<tr>
<td>Mild uncontrolled diabetes melitus</td>
<td>261,758</td>
<td>139,572</td>
<td>122,186</td>
</tr>
<tr>
<td>Osteoarthritis of the lower limbs</td>
<td>297,785</td>
<td>156,885</td>
<td>140,900</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>218,366</td>
<td>114,077</td>
<td>104,289</td>
</tr>
<tr>
<td>Esophageal reflux</td>
<td>159,781</td>
<td>81,065</td>
<td>78,716</td>
</tr>
<tr>
<td>Uncomplicated diabetes mellitus</td>
<td>227,858</td>
<td>114,821</td>
<td>113,037</td>
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<tr>
<td>HIV-related disorders</td>
<td>235,259</td>
<td>123,589</td>
<td>111,670</td>
</tr>
<tr>
<td>Sexually transmitted chlamydial diseases</td>
<td>235,675</td>
<td>123,589</td>
<td>112,086</td>
</tr>
</tbody>
</table>

Dental decay has been listed at the most frequent inflammatory pathology.

Global Burden Chronic Disease 2010 WHO
MIH « Molar Incisor Hypomineralization »
HSPM «hypomineralized second primary molar »

**MIH definition and prevalence**

**Prevalence**
- MIH prevalence varies between 2 and > 40% depending on studies
- Mean prevalence turns around 15-18% children 6 to 9 years old worldwide according to the most recent published data

**Diagnosis**
- Well demarcated creamy white to brown lesions on one to four permanent first molars
- Associated with affected incisors
- Hypoplasia / Substance loss / enamel breakdown
- Atypical caries and restoration
- Sensitive teeth
MIH « Molar Incisor Hypomineralization »

AN EMERGING PATHOLOGY

with a similar prevalence than other pathologies associated to exposure to EDCs

A link with exposure to endocrine disruptoring chemicals?

SELECTIVE DENTAL DEFECTS
Specific window of time

<table>
<thead>
<tr>
<th>Mineralization of permanent first molars and incisors</th>
</tr>
</thead>
<tbody>
<tr>
<td>birth</td>
</tr>
</tbody>
</table>

years
Xeno-estrogens: PCBs (polychlorinated biphenyl), PBDE (polybromated biphenyls ether), phthalates, alkylphenols, bisphenol A, genistein, UV filters, pesticides, conservatives, cadmium nanoparticles, diesel nanoparticles

Xeno-androgens: PCBs, UV filters (benzophenone-4)

Anti-estrogens: PBDE, flavones and isoflavones (phytoestrogens), UV filters (benzophenone-4), insecticides, phthalates

Anti-androgens: PCB#138, organochlorinated pesticides, UV filters (benzophenone-4), bisphenol A, vinclozolin, diesel nanoparticles

Disruption of thyroid axis: PCBs, dibutylphthalate, bisphenol A, pesticides, triclosan, perfluorated compounds, UV filters, PBDEs, DEHP

Disruption of corticoid axis: hexachlorobenzene

Aryl carbon receptor (AhR) activation: dioxins (TCDD)
Comparison between human MIH affected teeth and BPA treated rat incisors

Control - Score: 0   BPA - Score: 1S   BPA - Score: 1S   BPA - Score: 2S   BPA - Score: 3 AS   BPA - Score: 3b AS

D30

Control - Score: 0   BPA - Score: 0   BPA - Score: 0   BPA - Score: 0   BPA - Score: 0   BPA - Score: 0

D100

MIH - Score: 1AS   MIH - Score: 1AS   MIH - Score: 2b AS   MIH - Score: 3AS

Jedeon et al., Am J Pathol, 2013
The time-window of sensitivity to low-dose BPA

Jedeon et al., Am J Pathol, 2013
- The prismatic structure of enamel is hidden by a magmatic organic layer.
- The surface of enamel is rough.
BPA increased the level of enamelin adsorbed to crystal

Jedeon et al., Am J Pathol, 2013
Amelogenesis in control rats

SECRETION STAGE AMELOBLASTS  MATURATION STAGE AMELOBLASTS

Amelogenesis in rats exposed to BPA

SECRETION STAGE AMELOBLASTS  MATURATION STAGE AMELOBLASTS

- Increased enamelin expression
- Decreased Klk4 expression
- Albumin accumulation
- Enamelin accumulation
- Increased carbon content

Hypomineralized enamel characterized by opaque spots

Jedeon et al., Am J Pathol, 2013
ENAMEL DEFECTS, EARLY MARKER OF EXPOSURE TO EDCs

Cell proliferation ++

EDCs, BPA, substitutes and metabolites

1.25(OH)2 vitamin D3 steroid hormones

1.25(OH)2 vitamin D3 steroid hormones

Cell metabolism and cancer

Epithelial pathophysiology

Interactions with CRC teams

BREAST I. Cremer
LIVER S. Colnot
CRC platforms
INTESTINE S. Tenet
RETINAL-EYE F. Behar-Cohen
RENAL G. Crambert

MI

EDCs, BPA, substitutes and metabolites

1.25(OH)2 vitamin D3 steroid hormones

genomic pathways

non genomic pathways

Epithelial functions - mineralization

Cell Proliferation

inhibition

++

ERα

ERβ

AR

VDR

ERRγ

GPCR30
BPA disrupts amelogenesis preferentially in male rats

Jedeon et al., Endocrinology, 2014
Expression of sex steroid receptors in rat dental epithelium

- AR was the most highly expressed in ameloblasts involved in the enamel terminal mineralization

Houari et al., Front Physiol, 2016

Jedeon, et al., Endocrinology, 2016
Amelogenesis in control rats

PRE-AMELOBLASTS → SECRETION STAGE AMELOBLASTS → MATURATION STAGE AMELOBLASTS

Amelogenesis in rats exposed to anti-androgenic EDCs

PRE-AMELOBLASTS → SECRETION STAGE AMELOBLASTS → MATURATION STAGE AMELOBLASTS

EDCs, as BPA and Vinclozolin, may disrupt amelogenesis through AR pathway

- ANDROGENS MODULATE ENAMEL QUALITY

SECRETION STAGE AMELOBLASTS

SECRETION STAGE AMELOBLASTS

SECRETION STAGE AMELOBLASTS

SECRETION STAGE AMELOBLASTS
Uncharacterized enamel hypomineralizations

Increasing fluorosis prevalence

Interference between various environmental pollutants including endocrine disruptors?
Complementary hypomineralizing effects of NaF and BPA

Jedeon, et al., JBMR, 2016
Exposure to BPA weakens enamel making it more susceptible to frequent mineralization defects, Molar Incisor Hypomineralization and Dental Fluorosis.

Increased prevalence of DF and increased susceptibility to fluoride.

Our study identifies a small group of genes involved in systemic enamel hypomineralization, some of them also reported in genetic enamel pathologies.

**ENAMELOME**
The crucial role of save environment to keep a nice smile and a good health

Environmental pollutants
BPA, anti-androgenic EDCs, Phthalates, Fluoride ...

Metabolism-cancer .... MIH, fluorosis, caries

Ethics
EDC-free Reconstruction

Dental prevention products, medical devices, resins, materials

Leaching of monomers (Bis-GMA, Bis-EMA, Bis-DMA), Mercury, Triclosan, Fluoride ...

Indirect exposure

Direct exposure