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Original article

Early-life metal exposure and schizophrenia: A proof-of-concept study using novel tooth-matrix biomarkers

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ABSTRACT

Background: Despite evidence for the effects of metals on neurodevelopment, the long-term effects on mental health remain unclear due to methodological limitations. Our objective was to determine the feasibility of studying metal exposure during critical neurodevelopmental periods and to explore the association between early-life metal exposure and adult schizophrenia.
Methods: We analyzed childhood-shed teeth from nine individuals with schizophrenia and five healthy controls. We investigated the association between exposure to lead (Pb^{2+}), manganese (Mn^{2+}), cadmium (Cd^{2+}), copper (Cu^{2+}), magnesium (Mg^{2+}), and zinc (Zn^{2+}), and schizophrenia, psychotic experiences, and intelligence quotient (IQ). We reconstructed the dose and timing of early-life metal exposures using laser ablation inductively coupled plasma mass spectrometry.
Results: We found higher early-life Pb^{2+} exposure among patients with schizophrenia than controls. The differences in log Mn^{2+} and log Cu^{2+} changed relatively linearly over time to postnatal negative values. There was a positive correlation between early-life Pb^{2+} levels and psychotic experiences in adulthood. Moreover, we found a negative correlation between Pb^{2+} levels and adult IQ.
Conclusions: In our proof-of-concept study, using tooth-matrix biomarker that provides direct measurement of exposure in the fetus and newborn, we provide support for the role of metal exposure during critical neurodevelopmental periods in psychosis.

1. Introduction

According to the neurodevelopmental model of schizophrenia, psychotic symptoms emerge as a result of interactions between brain abnormalities established in early development and brain maturational events that occur much later [1]. Metals have well-known effects on neurodevelopment in children, some acting as essential nutritive elements and others as neurotoxicants [2–8]. For example, zinc (Zn^{2+}) is essential in development of the nervous system, and is involved in neuronal proliferation and migration as well as modulation of synaptic activities and intracellular signaling pathways [9]. Lead (Pb^{2+}) interferes with intraneuronal gene transcription, affects hippocampal neurogenesis, and causes glial dysfunction in developing brain [10]. Furthermore, many essential elements, such as copper (Cu^{2+}), manganese (Mn^{2+}), and Zn^{2+}, might exert toxic effects on brain at higher doses [11–14]. The link between exposure to different metals and adverse early neurodevelopmental outcomes is well known [2,4,6–8,15–22]. However, the effect of metals on later developmental outcomes, such as schizophrenia, is still debated.

Beyond the general effect of metals on neurodevelopment, there are multiple intriguing links between several metals and schizophrenia (Table 1). Lead (Pb^{2+}) and manganese (Mn^{2+}) have been shown to cause alterations in neurotransmitters in the same manner that is often observed in patients with schizophrenia

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Table 1
Clinical and neurobiological similarities of schizophrenia and altered balance of metals.

Schizophrenia	Pb^{2+} (excess)	Cd^{2+} (excess)	Mn^{2+} (excess)	Cu^{2+} (excess)	Mg^{2+} (deficiency)	Zn^{2+} (deficiency)
Core neuropsychological dysfunctions (IQ, working memory, attention, processing speed)	**	**	*	**	*	*
References	[15,16]	[6–8]	[8,56]	[29,57,58]	[59–63]	[18,19]
Core neurotransmitter disturbances						
• Dopamine	+	+	+	+	+	+
• Serotonin	+	+	+	+	+	+
• Glutamate	+	+	+	+	+	+
References	[64–66]	[67–69]	[14,24]	[70]	[71–73]	[74–76]
Clinical evidence of association with psychosis	+	+	+	+	+	+
References	[35,36]	[30,77]	[44,45]	[12,30]	[78,79]	[30]

+ Evidence of association; * moderate association; ** strong association.

[23–25]. For example, strong evidence links developmental exposure to Pb^{2+} with disrupted N-methyl-D-aspartate (NMDA) receptors function [25], which can lead to NMDA receptor hypofunction with subsequent dysregulation of brain-derived neurotrophic factor (BDNF) signaling, synaptic function, and long-term potentiation [23,25]. Furthermore, NMDA receptors, partly regulated by the tryptophan–kynurenine pathway, are essential during in utero brain development and influence synaptic formation and plasticity, cell proliferation, and cell migration during prenatal period [26–28].

Of note, individuals exposed to heavy metals or deficient in nutrient metals frequently experience neuropsychological deficits also observed in schizophrenia [5–7,18,19,29]. Wilson's disease, caused by a hereditary excess in Cu^{2+}, frequently manifests with psychosis [11]. Multiple reports have found different concentration of various metals, such as Cu^{2+}, Mn^{2+}, Zn^{2+}, and cadmium (Cd^{2+}) between patients with schizophrenia and healthy controls [30–34]. Intriguingly, higher delta-aminolevulinic acid levels (marker of Pb^{2+} exposure) have been detected in mothers whose children later develop schizophrenia [35,36].

The debate on the potential role of metals in schizophrenia is further complicated by methodological limitations of available studies. Importantly, metal exposure is mostly measured after disease development and is seldom determined during critical developmental periods. Studies that did measure metal exposure during critical developmental periods usually used indirect measures, such as maternal blood samples [35,36]. Moreover, most studies relied on samples that do not reflect exact timing of exposure during the high-risk developmental period, and fall short of tracking change in exposure over time. To our knowledge, no prior studies have robustly studied the link between fetal or early childhood metal exposure and risk of psychotic illness in adulthood. Our primary objective was to determine whether the timing and dose of prenatal and early childhood metal exposure influences later development of schizophrenia and psychotic experiences.

2. Methods

In a proof-of-concept study, we analyzed shed deciduous teeth from nine individuals from the Genetic Risk and OUtcome of Psychosis (GROUP) [37] study with a DSM-IV diagnosis of schizophrenia and five healthy controls. GROUP is a prospective cohort of 1120 patients with psychotic disorders and 1648 controls and aims to investigate the genetic and environmental risk factors of psychosis in the Netherlands. A total sample size of 14 was estimated to be sufficient to detect a large effect size in the difference in mean log concentrations between cases and controls.

We investigated the association between exposure to metals, including manganese (Mn^{2+}), lead (Pb^{2+}), cadmium (Cd^{2+}), copper (Cu^{2+}), magnesium (Mg^{2+}), and zinc (Zn^{2+}), and intelligence quotient (IQ), syndromal schizophrenia as well psychotic experiences (as assessed by the Community Assessment of Psychic Experiences (CAPE) scale) [38]. Deciduous teeth from each subject were evaluated for pre- and postnatal metal exposure. We reconstructed the dose and timing of fetal and childhood metal exposures using a novel biomarker method named laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS), which has been described and validated in detail elsewhere [39–45]. All teeth collected in the study were shed naturally and kept by the parents at home, as is often the case in some cultures. Teeth were stored dry in sealed containers of various types. The method for tooth analysis in this study excludes the external layers to avoid any contamination. Importantly, all analytical methods used here have been extensively validated and applied to samples stored over decades and archeological samples that are thousands of years old [44,46]. Briefly, the method combines sophisticated histological and laser-based chemical analyses to precisely sample dentin layers corresponding to specific life stages, generating integrated, longitudinal, 1- to 2-week metal exposure estimates in pregnancy and during early childhood [39]. The time-varying difference between early-life (−4 to 6 months) metal concentrations, as measured in the tooth biomarker, and case/control designation was evaluated using a distributed lag model (DLM).

3. Results

Characteristics of the study participants and of the GROUP cohort are presented in Table 2. Mean [standard deviation, (SD)] age for the patients was 25.2 (1.9) years, and mean (SD) age for the control group was 28.0 ± 8.4 years. Mean (SD) duration of disorder was 3.8 (2.5) years.

After stringent statistical correction, the longitudinal differences in log Pb^{2+} were generally estimated above zero, showing statistically significant higher early-life intake of Pb^{2+} among patients with schizophrenia compared with controls (Fig. 1A and B). The differences in log Mn^{2+} and log Cu^{2+} changed relatively linearly over time to postnatal negative values, indicating lower postnatal exposure to Cu^{2+} and Mn^{2+} in patients with schizophrenia than controls (Fig. 1A). The largest between group perinatal difference in Cu^{2+} and Mn^{2+} was observed six months postnatally (log difference case–control for Cu^{2+}, −0.52, case/control ratio of 59% corresponding to 41% lower Cu^{2+} concentrations in cases compared to controls; log difference case–control for Mn^{2+}, −0.42, case/control ratio of 66% corresponding to a 34% lower Mn^{2+} concentrations in cases compared to controls). There was a positive correlation between pre- and postnatal Pb^{2+} levels and CAPE score in adulthood (Fig. 1C). There was a negative correlation between Pb^{2+} levels and adult IQ (Fig. 1D), which was strongest during the second trimester of pregnancy ($r = -0.39$) and decreased gradually