Occupational Mercury Neurotoxicity

Subjects: Others

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Elemental (metallic) mercury is an industrial product whose neurotoxicological properties have been known for hundreds of years. Not all workers exposed to this metal develop neurotological damage and this testifies the importance of genetic factors, i.e. polymorphisms.

Keywords: elemental mercury ; polymorhism ; neurotoxicology

1. Introduction

Elemental mercury (Hg) is a naturally occurring toxic heavy metal[1]. It constitutes an important occupational risk by causing neurological, neuropsychological, cardiovascular, and other adverse effects in exposed workers [2]. This occupational risk has been well known for many centuries [3] and is still relevant for certain categories, such as dental technicians [4], miners [5][6], and other industrial workers [7][8][9][10][11][12][13][14]. Mercury is also an environmental toxicant whose effects on cell membranes have been well documented [15]. Global mercury production has steadily increased to reach approximately 4000 tons/year. In 2019, China was the world's largest producer, with a mine production volume of 3500 metric tons [16][17]. Disease-associated with occupational mercury exposure is increasing globally, mainly as a consequence of small-scale mining activities [18].

Neurobehavioral deficits, including memory loss, mood changes, depression, anxiety, and motor dysfunction, have been associated with chronic occupational exposure to both high [19] and lower levels of Hg [20]. According to the literature, the neurotoxic effects of mercury are mainly due to alteration of the antioxidant system. Several mechanisms, including signalling transduction, protein and/or enzyme activity, and gene regulation are involved in mediating the toxic and adaptive response to mercury exposure [21].

Elemental Hg, mainly found in the form of Hg vapour at room temperature, is absorbed via the lungs and distributed in the body via the blood, predominantly to the kidneys and the central nervous system. In the bloodstream, Hg is oxidized to its mercuric ion (Hg2+) by the catalase enzyme. However, before oxidation, elemental Hg easily and rapidly passes through most cell membranes including the blood-brain barrier and the placenta. The urine and faeces are the main excretory pathways of Hg in humans [22].

Although understanding of Hg toxicokinetic has improved, further studies are needed as regards its metabolism, interaction with other metals, distribution, internal doses and targets, and reservoir organs [23][24][25][26]. The influence of genetic factors on mercury toxicokinetic has been extensively studied and available research suggests that polygenic traits may contribute to the adverse Hg-mediated effects and the variability in Hg-associated risk [27][28]. Indeed, as molecular genetic techniques have advanced, DNA sequence variants referred to as polymorphisms (single nucleotide polymorphism SNP, deletion, insertion, copy number variations) have been increasingly recognized as important factors influencing human susceptibility to Hg-related outcomes. Allelic variations may determine functional differences in the level of activity of gene products involved in Hg toxicokinetic, as well as neurotoxic effects, thus potentially playing a role in Hg risk assessment.

Occupational risk prevention is based on the adoption of good working practices [29][30] and the biological monitoring of workers. Mercury in whole blood (B-Hg) or urine (U-Hg) are commonly used to indicate exposure in occupational cohorts [31][32][33], while hair samples are preferred in general population studies [34]. B-Hg is considered a good indicator of recent exposure. U-Hg is an indicator of average exposure during the past month rather than exposure at the time of urine collection when mercury burden has reached the steady-state in occupationally exposed cohorts [32]. The American Conference of Governmental and Industrial Hygienists (ACGIH) recommends a biological exposure index (BEI) of U-Hg in urine <20 µg/g creatinine [35]. The knowledge of genetic determinants that could increase sensitivity to mercury could be very useful for detecting hypersensitive subjects.

2. Studies on Occupational Mercury Neurotoxicity

Taken as a whole, polymorphisms in candidate genes may affect susceptibility for specific neurobehavioral functions associated with occupational Hg exposure. Occupational findings add to existing evidence indicating genetic determinants of mood and behaviour that potentially increase susceptibility to Hg toxicity in human subjects. However, occupational studies have made only a modest contribution to understanding the adverse effects of elemental mercury. To date, no studies have investigated the role that genetic factors may play in the absorption, distribution, and excretion of mercury and most genes are selected by authors based on criteria of biological plausibility and their role in neurological outcomes. The body burden of mercury in workers has been estimated based on the duration and time of exposure, mainly by integrating these data with the Hg dosage in a single urine sample. No studies have measured mercury in tissues. The demonstration of an association between a polymorphism and neurobehavioral alterations, mood, or potentially neurotoxic symptoms cannot be considered evidence if it has not been confirmed by other studies replicating previous observations on the same genetic variant.

Since the studies mostly attempted to identify new variants instead of examining previous findings from other candidate gene studies, it was not possible to pool results to categorically ascertain the influence of a genetic variant. Most of the studies were performed in Caucasian, or predominantly Caucasian populations, or did not report the ethnicity of participants. Consequently, the frequency of allele variations across ethnic groups could not be evaluated [36]. An evaluation of the findings was further limited because the studies retrieved did not always consider the same confounding factors and included factors potentially influencing the results, such as ethnicity, alcohol, health status, as well as diet; this is a further limitation to the evaluation of the findings. Furthermore, published studies were not of high quality, particularly when specific methods for genetic studies were used for assessment [37]. Research findings demonstrate the difficulties encountered in reproducing behavioural or symptomatic results for very low exposures in different populations and with changing explanatory variables. Clearly, further studies are needed to confirm or disprove the associations observed and to investigate numerous other genetic factors that could be associated with the toxic effects of mercury in workers.

However, adverse neurobehavioral effects may be associated with occupational elemental mercury exposures similar to those experienced by the general population due to mercury amalgam dental fillings, or other environmental pollution sources. Occupational studies, therefore, have an important significance for public health.

Studies on occupational cohorts, such as workers exposed to mercury in the same workplace, could easily be carried out by an occupational health and safety service. The medical health surveillance of workers and their biological monitoring would be much more efficient if they could incorporate elements of genetics to promptly identify polymorphisms that increase the risk of neurological damage. Employers may have a legitimate interest in funding studies on the genetic status of their employees, to limit the exposure of hypersensitive individuals, who could be harmed even if exposed to levels not exceeding the permissible standard. Concern for both occupational and public health should encourage governments to intervene to fund or promote prevention in this area. Studies conducted by the United Nations on gold-working artisans in the Philippines, Indonesia, Tanzania, and Zimbabwe point in the right direction and should be followed by interventions to improve the conditions of these workers.

Unfortunately, the increase in occupational exposure to mercury, as recorded throughout the world, principally involves developing countries or those in which industrial development takes place without due regard for Western health and safety standards. In such countries, the clinical and genetic evaluation of workers is undoubtedly difficult, as is demonstrated in Siberia where even the type of work activity is unknown.

The difficulty of being able to study an occupational cohort exposed to significant levels of mercury vapour, added to the complexity, invasiveness and cost of the tests required have limited research. Dental workers, who were willing to undergo the complex analyses needed to identify pre-clinical alterations, have gradually adopted measures to reduce their occupational exposure. Dental exposure to mercury has fallen significantly over the last few decades. Consequently, mean urinary mercury concentrations in dentists are currently approaching levels observed in the general population. The difference between the positive findings of the Washington cohort, recruited in 1999, and the negative results in the more recent Michigan sample, indicates the current difficulty in obtaining a sample of high-dose exposed and available workers in Western countries.

Previous studies in non-occupational settings have provided sufficient evidence of the role of SNPs in Hg toxicity. These studies, however, focus mainly on organic mercury that has a different toxicological profile from that of the elemental metal. For example, maternal polymorphisms in glutathione-related genes were associated with maternal mercury concentrations and early child neurodevelopment in a population with a fish-rich diet [38]. Genetic polymorphisms of catechol-O-methyltransferase were found to modify the neurobehavioral effects of mercury in children [39], and increased

susceptibility to the adverse neurobehavioral effects of Hg was found among children with relatively common genetic variants of metallothionein [40]. While levels of mercury exposure have fallen in industries (at least in developed countries), the accumulation of Hg in biota and its biomagnification in aquatic food chains pose a real threat to public health [41][42]. Recent studies have shown that increasing concentrations of inorganic Hg may be present in the brain of relatively low exposure subjects as they get older and that the pattern of Hg deposition in the brain tissues of individuals exposed to environmental pollution is different from that of workers with acute or subacute exposures to lethal or significantly higher concentrations in workplaces [43]. The spread of this neurotoxic metal in the environment and its bioaccumulation in the food chain are leading to epigenetic consequences [44]. Other neurotoxic metals, such as aluminium, may be present in the environment [45], and this can definitively increase the risk for occupationally exposed workers. Future occupational studies will need to take these important factors into account.

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