Review

HEAVY METALS IN PARTICULAR LEAD, NEUROTOXIC EFFECT OF LEAD AND LEAD INTERACTION WITH PARKINSON'S DISEASE

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ABSTRACT

The present study reviewed the literature about heavy metals including lead (pb) from various points of view including chemistry of these heavy metals and their interactions with neurons. We also introduced the concept of neurotoxicity with heavy metals. The role of heavy metals in induction of Parkinson Disease was also discussed, particularly the role of lead (Pb).

KEYWORDS: heavy metals, lead (Pb), neurotoxicity, Parkinson Disease.

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INTRODUCTION :

Metals: on overview

Metals are naturally found in rocks and soils[1]. According to environmental pollution, metals are divided to[2] :

-Not critical metals: (Na, Mg, Fe, K, Ca, Al, Sr, Li, Rb),

-Toxic and rare: (Ti, Zr, W, Ta, Ga, La,Ru, Ba, Rh), and

-Very toxic and available: (Co, Ni, Cu, Zn, Sn, Cr, As,Te, Ag, Cd,Tl, Pb, Bi).

Toxicity of metals pollution is recognized globally[3]. An important sources for heavy metals from ports and harbors, also faced to heavy metal inputs accompanied with commercial, and military shipping activities[4].

An Exposure to Toxic Industrial Metals:

Precise diagnosis of exposure to heavy metals is complex, because these metals have an irregular distribution in the environment and people may exposed in different fractions to them. They are considered as huge of a danger as chemical war materials since they are available and produced in large concentrations[5]. The all population is also at risk for exposure to these toxic metals in the environment or due to occupational dangers. In the period between 1980 and 1983 an international survey worked by the National Institute for Occupational Safety and Health recognized that 727, 240 individuals (most of them are workers) were exposed to nickel metal compounds[6].

The metals nickel (Ni), cadmium (Cd), and copper (Cu) are examples of Toxic industrial heavy metals which have occupational and environmental relationships. Nickel is used in synthesis of batteries and stainless steel, producing an environmental dangers. It has been used by the military forces in tungsten and cobalt as a friend to the environment that replace the uranium, but was stopped when recognized to be carcinogenic to humans[7].

Cadmium is considered as an occupational danger since it is usually used in pigments, and batteries in industry field[8] .

Although Ni, Cd, and Cu are commonly used and well known, little biomarkers exist and their precise mechanism of their toxicity remain unrecognized. These metals are expected to lead to oxidative stress, that cause damage of DNA and protein synthesis[9]. Nickel cause Fenton type reactions producing reactive oxygen species, while cadmium is expected to produce oxidative stress by inhibition of anti-oxidant substrates [10].

Nickel and cadmium are expected to lead to destruction of DNA by inhibition of enzymes that cause repair to DNA[9]. Nickel is the only heavy metal of these three that recognized to resemble hypoxia, induction genes used in cellular processes[10]. Ni, Cd, and Cu are also expected to cause degradation of cell proliferation by a lot of signaling pathways and transcription factors, due to formation of reactive oxygen species (ROS), but these pathways is still not well known[9].

The detection of exposure to these toxic metals is very difficult because of the high variability in response and clinical characteristics between individuals although there are markers that may give diagnostic indicators for identifying the exposure. The Food and Drugs Administration (FDA) considered these biomarkers to be the characteristics that measured as markers of normal biological processes or pharmacologic responses to a drugs intervention[10].

Heavy metals consist of toxic pollutants pervading the environment. They are widely distributed in the environment and poison the living systems, as they accumulate. Mature tissue is protected from metal toxicity by the blood–brain barrier which prevents the movement of heavy metals from the systemic circulation to brain and by the formation of metal-protein complexes rendering metals unavailable to exert its toxic effects. In fetal brain this sequestering mechanism is impaired[11].

Lead (pb)

Lead is released into the atmosphere from natural and anthropogenic sources. Natural emissions are from wind resuspension and from sea salt, volcanoes, forest fires and biogenic sources[12]. (Nriagu, 1989). According to Nriagu[12], these emissions are not entirely natural but contain some contributions from historical depositions of anthropogenic lead. Major anthropogenic emission sources of lead on a global scale include the combustion of fossil fuels from, for example, traffic, non-ferrous metal production and iron and steel production. Some contributions are also made by cement production and waste disposal[13].

The magnitude of anthropogenic emissions in Europe can be obtained from the officially reported data or from expert estimates. The total emissions in Europe, based on a combination of officially reported emissions and expert estimates obtained using the procedure presented by Berdowski et al [14, 15], were about 35 kt/a and 8.6 kt/a in 1990 and 2003, respectively. Expert estimates were used for countries that did not produce official reports regarding their emission data. More details about the combining of official and expert emission data are available in Ilyin and Travnikov[16].

Sources of Blood Lead

Several sources attribute to increase blood lead such as lead paint chip ingestion, lead in paint and gasoline and inhaled air lead[17]. According to Meyer and Mitchell[18], the lead share of USA pigments fell from near100% in 1900 to 35% by the mid-1930s. Furthermore, the USA forbidden lead paint after 1977, but 80% of pre-1940 and 46% of 1940–1959 homes still had some interior lead paint in1999[19].

Blood Lead Levels in Children with Neurological Disorders

Kumar et al[20] evaluated blood Pb levels using atomic absorption spectrometry in 82 children suffering from various neurological disorders (cerebral palsy 42, seizure disorders 35, acute encephalopathy of unknown origin 5) and in 28 healthy children, aged 1 to 12 years. The results showed that mean blood Pb levels were 11.96 ± 10.97 µg/dL in control children and 19 ± 17.65 µg/dL in children with neurological disorders. A significant number of control children as well as those who had neurological disorders were found to have blood Pb concentrations of > 10 µg/dL and >20 µg/dL, the cut-off limits for lead poisoning and medical evaluation, respectively. Blood Pb levels were, statistically, elevated in children with cerebral palsy compared to controls. Children with pica behavior exhibited higher blood Pb concentrations.

Lead Chemistry

Lead (Pb) is one of the oldest known metals. It was used by the ancient Babylonians, Egyptians, and the Romans to make water pipes and solder. Its rank is 36th in abundance in the Earth's crust and it is seldom found alone. Its compounds are largely distributed throughout the world. It is mainly used in the production of storage batteries and in sheathing electric cables. It has useful use as protective shielding from x-rays and radiation from nuclear reactors. The lead compounds are usually used as pigments in paint, putty, and ceramic and as insecticides. It was included as an "antiknock" agent in gasoline, until it was banned as an environmental pollutant[21].

Exposure to Lead

It has been recognized that exposure to lead results in significant health impacts which makes taking consequent policy actions to decrease its levels among population in developed countries[22]. According to Landrigan et al[23], numerous countries did not show commitment to remove lead from gasoline although this process was shown to have a strong effects in reducing blood lead in children.

In their study, Murray and Lopez[24] pointed to various considerations such as that there were increasing evidence on having some milder disease outcomes and physiological changes including loss of IQ points and blood pressure increases. They also pointed that although

these conditions may be perceived as mild at the individual level, but they have significant impacts in population level. Furthermore, it has been recently shown that some of the health effects occur at levels of exposure that were considered safe previously[22].

Murray and Lopez[24] identified large number of sources that could contribute to lead exposure. They also reported that some of these exposures are common among large parts of the world's population, whereas others are more locally or culturally specific.

Lead (pb) is known to occur naturally as a metal. Pb is found in the earth's crust at concentrations about 15 – 20 mg/kg[25]. Several uses have been associated with the use of Pb[26]. Among these uses, Pb additives are included in in gasoline, manufacture and use battery, ammunition, ceramics, cosmetic and soldering of containers[27].

Industrialized countries witnessed an epidemic of lead poisoning following the widespread use of lead salt additive[28]. Various routes have been associated with Pb introduction into the human body from environment including respiratory system and gastrointestinal tract while the lead in gasoline has ability to be absorbed through the skin[29].

Environment and PD

Numerous epidemiological studies have been performed in an attempt to define factors associated with an increased risk of developing PD. Although no specific causative smoking gun has been identified definitively, there are intriguing clues. For example, case-control studies have suggested that i) rural living, ii) farming as an occupation, iii) drinking well water, and iv) pesticide exposure are each associated with an increased risk of PD. Although not all studies have been positive, recent meta-analyses have indicated that the risks associated with these factors are likely to be real[30, 31]. The extent to which these factors are related or independent is not clear, however. An additional environmental risk for PD is occupational exposure to certain metals, most notably manganese[32]. Interestingly, many pesticides and manganese share the common mechanism of causing mitochondrial dysfunction. Such mechanistic commonalities may eventually provide insights into PD pathogenesis. Unfortunately, with the exception of 1-methyl-4-1,2,3,6-tetrahydropyridine (MPTP), no specific environmental agent has been linked conclusively to PD pathogenesis. There are several possible explanations for this. First, chronic low-level environmental exposures may be more relevant to sporadic PD but may be very difficult to detect. Second, acute environmental exposures may produce delayed or slowly progressive degeneration, so that the disease expression (symptom onset) might be remote in time and place from exposure. Indeed, imaging and postmortem studies suggest that exposure to MPTP in the remote past may cause a progressive parkinsonian disorder[33, 34]. Third, individual genetic variations may explain the development of PD only in a subset of individuals exposed to similar toxins. Such genetic variation could involve polymorphic variations in disease-associated genes, such as α-synuclein[35], xenobiotic metabolism[36], mitochondrial function[37], or even blood-brain-barrier function.

In 1982, the product of a botched meperidine synthesis, MPTP, was injected inadvertently by several drug addicts in the San Francisco bay area. This unfortunate event provided direct evidence for the potential role of "environmental" toxins in PD pathogenesis: MPTP caused an acute and permanent parkinsonian syndrome in these individuals[38]. Investigations of the mechanisms through which MPTP exposure resulted in selective dopaminergic cell death have uncovered clues to PD pathogenesis. 1-Methyl-4-phenylpyridinium ion (MPP+), the active metabolite of MPTP, is a substrate for the dopamine transporter, which is selectively expressed in dopaminergic neurons[39]. Once inside these neurons, MPP+ accumulates in mitochondria and exerts its toxicity by inhibiting complex I of the mitochondrial electron transport chain[40]. Importantly, this finding suggested that mitochondrial dysfunction may have a role in PD

pathogenesis. Thus, the epidemiological study that led to the identification of MPTP ultimately suggested a pathogenic mechanism. With an understanding of the mechanism of action of MPTP, several laboratories began to investigate the status of mitochondrial complex I in sporadic PD. These studies demonstrated that PD patients express modest, but reproducible, reductions in complex I activity in tissues including brain and platelets[41-43]. On average, in platelets, there appears to be about a 25% decrease in complex I activity, but current complex I assays are insensitive to subtle defects[44]. Thus, these results suggest that PD patients have a systemic complex I defect, affecting both brain and peripheral tissues. The use of cytoplasmic hybrid (cybrid) cells has suggested that PD patients may harbor mutations in mitochondrially encoded subunits of complex I. Cybrids are created when cells devoid of mtDNA (due to longterm, low-dose exposure to ethidium bromide) are repopulated with mtDNA from platelets of PD patients. These cybrids express mtDNA from PD patients, or age-matched controls, on a uniform nuclear background. This technique has demonstrated that the reduced complex I activity seen in PD platelets can be transmitted stably into cybrid cell lines, which suggests that it may result from mutations in mtDNA[45, 46] . On the other hand, despite intensive efforts, no causative mtDNA mutations have been demonstrated unambiguously.

In summary, PD is associated with a modest, systemic defect in complex I activity, which may result from genetic or acquired alterations in mitochondrial protein subunits, or environmental exposures that inhibit complex I function[37, 47]. Whether or not this complex I abnormality had anything to do with PD pathogenesis, however, remained uncertain.

Various metals such as aluminium, zinc, iron, copper and mercury have been linked with the neurodegenerative diseases. However, in some cases results are controversial and no direct association between these metals and neurological diseases have been demonstrated. For example, high level of aluminum in drinking water has been shown as a risk factor of Alzheimer's disease in some studies while other studies fail to establish any such relation [48, 49]. The reason for such contrary results includes inadequate aluminum analysis methods, improper selection of subjects and matching controls[50].

Transition metals like zinc and copper are other sources of brain toxicity and are believed to results in Aβ aggregation[51]. Like brain, retina is considered to be an immune privileged site due to presence of the blood-retinal barrier and has been found to be sensitive to metal toxicity. Metal exposure and its association with retinal degeneration has been examined in various studies[52-54]. Low and moderate level of gestational lead exposure (GLE) i.e. first trimester results in increased amplitude of a and b waves in 7–10 year old children [55]. Similarly high level of mercury and Pb in umbilical cord blood due to prenatal exposure impaired the visual processing as shown by visual evoked potential measurement in exposed children after 11 years[56].

Toxic effects of heavy metal exposure are also evidenced from animal studies. Long-term potentiation (LTP) which is responsible for enhancing the signal transmission between the neurons is considered as the major mechanism underlying information storage and memory formation, resulting in increased synaptic strength[57]. Enhancement in signal strength is dependent on two factors, one is the presynaptic increase in neurotransmitter release and other is enhanced function of glutamate receptor at the postsynaptic end. NMDA receptor function has been found crucial for the LTP induction in hippocampus[58, 59] .

Neonatal exposure to aluminium chloride has been shown to reduce the LTP amplitude in rats by affecting both presynaptic and postsynaptic signal transmission[60].

Heavy metal exposure such as zinc, copper and Pb have a negative effect on LTP during developmental stage as it reduces the potentiation magnitude and increases its decay time as well as the threshold level for induction in hippocampus[58, 61].

Combined prenatal effects of arsenic, cadmium and Pb in rats exposed to metal mixture have been shown to disrupt blood–brain barrier and cause memory deficit[62]. Although various studies have focused on the role of different metals in pathogenesis of neurological disease, the role of Pb is most widely investigated. The early life exposure of Pb and its effect on adults has thus been a major area of investigation for past few years. Rats exposed to low Pb level during in-utero and lactation period have shown impaired learning and memory, hyperactivity and anxiety in adults[63]. In vivo studies of Pb exposure on various animal models, such as rats and monkeys, have revealed the role of developmental exposure of sub-toxic doses of Pb on neurodegeneration. It is evident from studies that the Pb exposure in developmental stages results in the increased level of beta amyloid in brain causing Alzheimer in later age[64, 65].

In their study, Nadella et al [66] investigated if an association between lead exposure and PD exists. The plasma levels of copper, iron, manganese and lead in PD cases (n = 150) and controls (n = 170) were determined by inductively coupled plasma mass spectrometry (ICP-MS) and correlated with the oxidative stress markers like malondialdehyde (MDA), protein carbonyl and total glutathione. Results indicated significant increase in the levels of copper (17.73 ± 4.48 vs. 13.0 ± 3.22 ng/ml) and iron (554.4 ± 123.8 vs. 421.7 ± 126.1 ng/ml) in PD cases compared to controls, whereas no significant differences in the levels of manganese and lead were observed. Further, the data based on urban or rural residence showed that plasma copper, iron, manganese levels were comparatively higher in rural subjects, whereas plasma lead levels were significantly higher in urban subjects. Increased plasma iron showed positive correlation with marker of lipid peroxidation (MDA), suggesting that increased iron levels induced oxidative stress in PD. These results substantiated the earlier observations about the role of environmental exposure and metal-induced oxidative stress in the etiology of PD[66].

Lead is neurotoxic and known to induce multiple clinical phenotypes, including Parkinsonism in lead-exposed individuals[67]. The mechanisms involved in metal-induced toxicity have one thing in common i.e. increased oxidative stress, either directly or indirectly[68]. Transition metals like copper, iron, manganese and zinc catalyze redox reactions within biological systems and hence mediate the oxidative stress[69]. (Liochev, 1999). Whereas redox inactive metals like lead, chromium etc. are indirectly involved in the production of ROS by depleting glutathione and protein-bound sulfhydryl groups[70].

Palacios et al[71] conducted a study to examine in a large prospective study of female nurses whether exposure to airborne metals was associated with risk of PD. Study findings pointed to limited evidence for the association between adulthood ambient exposure to metals and risk of PD.

Manganese and PD

Manganese intoxication is recognized as a cause of parkinsonism at high levels of exposure[72,73]. However, the pathology of manganese intoxication is distinct from that of PD[73], and the causal association of exposure to manganese with PD continues to be debated74-76. For example, a study that compared the food habits of 250 patients and 388 controls found that a high manganese intake combined with a high intake of iron was significantly associated with PD[77]. In another study in Quebec, Canada, a slightly higher although not statistically significant risk of PD was observed among participants with occupational exposure to manganese, iron, and aluminum[78]. At the same time, many studies of manganese and PD have been null[79-82].

There has also been some evidence of onset of PD following occupational[83, 84] as well as nonoccupational[85] exposure to high levels of lead. Increased brain iron levels have been found in PD patients by some investigators, although this has not been confirmed in all studies[86-88]. Some but not all studies have reported positive associations between PD and exposure to copper[89]. Furthermore, mercury measured in blood, urine, and hair has been positively associated with PD[90].

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