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EDITORIAL

Lead and Neurotoxicity

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The lead exposure is a public health concern, especially in early childhood as children are more at risk because of increased hand to mouth activity and absorb about half of an oral dose of water-soluble lead [1]. Childhood lead exposure is estimated to contribute to 600,000 new cases of children with intellectual disabilities every year with 99 % of them living in developing countries [2]. The lead exposure in utero, infancy or early childhood can slow mental development and cause lower intelligence later in childhood that can persist beyond childhood. The effects of lead are more toxic on developing nervous system of children than on a mature brain.

Lead-associated deficits have been documented in most fields including verbal intelligence quotient (IQ), performance IQ, academic skills such as reading and mathematics, visual/spatial skills, problem-solving skills, executive functions, fine and gross motor skills, memory and language skills. Meta-analyses have indicated that children's IQ scores decline 2–3 points per 10 ug/dl increase in blood lead level [3] and identified no threshold for the effects of lead on IQ [4]. In fact academic performance of children exposed to lead has been observed to be subservient in comparison to controls. Children (6–10 year old) with blood lead levels of 5–10 ug/dl scored significantly lower than children with levels of 1–2 ug/dl on academic skills such as word reading, reading comprehension, listening comprehension, math reasoning and math calculations [3]. Another large American study documented inverse association between blood lead levels as low as 2 ug/dl, measured up to 5 years of age, and end-of-grade reading and mathematics achievement scores [5]. In National Health and Nutrition Examination Survey (1999–2002), the risk of parent-reported diagnosis of attention deficit hyperactivity disorder increased, in a dose-dependent manner with blood lead level [3]. Similar findings have been reported by a recent Indian study which emphasizes the detrimental effect of lead on executive and attention domain in neurobehavioral function [6].

The mechanisms underlying lead-induced neurotoxicity are complex. Oxidative stress, membrane bio-physics alterations, deregulation of cell signaling, and the impairment of neurotransmission are key aspects involved in lead neurotoxicity. It can cause toxicity by oxidative stress directly or indirectly by lipid peroxidation resulting in the generation of reactive oxygen species (ROS), including hydroperoxides, singlet oxygen, hydrogen peroxide and direct depletion of antioxidant reserves. Lead renders enzymes nonfunctional by binding to their sulfhydryl groups further contributing to an impairment in oxidative balance [7].

The ability of lead to pass through the blood–brain barrier is mainly due to its ability to substitute for calcium ions. Within the brain, lead-induced damage in the prefrontal cerebral cortex, hippocampus, and cerebellum can lead to a variety of neurological disorders, such as brain damage, mental retardation, behavioral problems, nerve damage, and possibly Alzheimer's disease, Parkinson's disease and schizophrenia [8]. Lead substitutes for calcium and to a lesser extent zinc, inappropriately triggers processes dependent on calmodulin. Lead also restricts neurotransmitter release, disrupting the function of GABAergic, dopaminergic and cholinergic systems as well as inhibiting NMDA-ion channels during the neonatal period. Indeed experimental studies have shown that lead activates protein kinase C in capillary cells and inhibits Na+/K+-

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ATPase thus interfering with energy metabolism. Within the cell, lead appears to interfere with calcium release from the mitochondria resulting in formation of permeability transition pore and primes for programmed cell death processes leading to mitochondrial self-destruction [9]. Hence direct neurotoxic actions of lead include apoptosis, excitotoxicity affecting neurotransmitter storage, release and modifying neurotransmitter receptors, mitochondria, second messengers, cerebrovascular endothelial cells, astroglia and oligodendroglia.

Mechanisms underlying cognitive deficits resultant of lead exposure have been reported using cellular models of learning and memory. There is convincing evidence that exposures to lead have adverse effects on the central nervous system (CNS), environmental factors augment lead susceptibility and exposures in early life can cause neurodegeneration in later life. Magnetic resonance spectroscopy (MRS) has revealed reductions in the N-acetylaspartate-to-creatine and phosphocreatine ratios in the frontal gray matter of lead-exposed children, consistent with increased neuronal loss. Similarly in adults an association between greater cumulative lead exposure and higher myoinositol-to-creatine ratios in the hippo-campus, reflecting glial dysfunction has been seen [3].

With the development of molecular biology, the knowledge of genetics has been incorporated into the environmental health research. The individual genetic profile has to be taken into account in investigating the toxic effect of lead. Likewise, the gene encoding δ-amino levulinic acid dehydratase (ALAD), an enzyme actively involved in leadership kinetics, could make a portion of the population with some ALAD genotype more susceptible to lead toxicity [10]. As such, these people need special attention and protection. It is of public health importance to figure out which allele is the susceptible one and how it operates in the human body. The human data available on chelation efficacy suggest that primary prevention of exposure is the best strategy for limiting lead-associated neurodevelopmental morbidity [9].

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