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Blood lead level and seizure: a narrative review

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ABSTRACT

Environmental pollution is one of the most serious and fast-growing problems in the world of today. Lead poisoning is a threatening environmental situation with the potential of causing irreversible health issues and serious negative consequences in adults and children. Lead proves to have almost no clear biological function. However, once it enters the body, it is known to cause severe health effects, which might be irreversible. In this article, we aimed to review the related literature to find evidence concerning the effect of lead toxicity on CNS, particularly its role in febrile convulsion. In this review, PubMed database was searched using MeSH terms. One hundred and fifty seven articles were retrieved, most of which were irrelevant to the topic. After a thorough search in PubMed and Google Scholar, seizure was shown to be one of the consequences of lead toxicity, but there was no evidence of epilepsy or febrile convulsion, induced by this metal contamination.

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Introduction

Environmental pollution and the continuous exposure of people to toxic heavy metals such as lead are among the most serious and fast-growing problems in the world of today (1). Over the past fifty years, because of an exponential increase in the use of heavy metals, the exposure to metals has dramatically soared.

Lead poisoning is a threatening environmental situation with serious and negative consequences on adults and children. Moreover, the working class and those living in developing countries are more prone to lead toxicity. Studies on children's blood lead levels (BLLs) have shown cognitive impairments at increasingly lower BLLs. This mainly indicates that lead contamination can negatively affect one's health from the prenatal period till adulthood (1).

The sources of lead exposure vary in different countries. Historic contamination, recycling old lead products and manufacturing new products account for the main lead sources (2). In developing countries, lead poisoning has been known as one of the major public health concerns. Although various health measures have been taken for controlling the amount of lead exposure, cases of lead poisoning continue to emerge (3). In fact, no level of lead exposure appears to be necessary or useful for the body and no level of safe exposure has been yet determined.

Lead toxicity has the potential of causing irreversible health issues and is known to interfere with various body functions, particularly the nervous system, hematopoietic system, liver and kidney (4). Occupational exposure leads to acute toxicity and is less common than other factors. On the other hand, chronic toxicity is much more prevalent, occurring at BLLs of about 40–60 µg/dl. This type of toxicity can become even more se-

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vere if not treated on time.

The main clinical manifestations of lead poisoning are persistent vomiting, coma, encephalopathy, lethargy, delirium and convulsions (5,6). In this article, we aimed to review the related literature to find evidence concerning the effect of lead toxicity on CNS, particularly its role in febrile convulsion.

In this review, PubMed database was searched, using MeSH terms including "lead poisoning", "nervous system" and "childhood". Overall, 157 articles were retrieved, most of which were irrelevant to the topic. Therefore, Google Scholar was also searched using keywords such as "lead", "seizure", "epilepsy" and "convulsion". We used various Boolean modifiers, as well. Finally, 25 articles were found eligible and were included in the current study. These articles included descriptive studies, reports, reviews and epidemiologic studies.

Literature review

Mechanism of toxicity

Lead has been extensively evaluated in various studies. According to previous research, various cellular, intracellular and molecular mechanisms are caused by lead exposure in the body. Oxidative stress has been reported as a major mechanism of lead-induced toxicity (7,8) by substituting other bivalent cations (e.g., Ca^{2+}, Mg^{2+}, and Fe^{2+}) and monovalent cations (e.g., Na^{+}) (9-12).

History of studies

Lead poisoning has been known to have harmful effects on one's health. Albert performed one of the first related studies in 1975. In this study, deleterious health effects were reported in children who were treated for severe lead poisoning and undiagnosed cases with elevated BLL (≥0.06 mg) (13).

Epidemiology

Various studies have demonstrated the high risks of lead exposure. A survey of school children in an isolated community revealed that 59% of subjects had decreased erythrocytic delta-amino levulinic dehydratase (ALAD) activity, which was highly correlated with a prior history of gasoline sniffing; only 5% of children had BLLs > 40 µg/dL. The reported survey suggested that a large number of children living in isolated communities might be suffering from lead poisoning due to gasoline sniffing. This is in fact a major public health concern and a social problem (14).

The effect of lead exposure on central nervous system (CNS)

Compared to other organs, CNS appears to be a chief target for lead-induced toxicity (12). In fact, both CNS and peripheral nervous system are affected by lead exposure, but the impacts on the peripheral nervous system are more pronounced in adults (15,16).

Encephalopathy is directly caused by lead exposure and its major symptoms include dullness, irritability, poor attention span, headache, muscular tremor, loss of memory and hallucinations. At very high exposures, more severe manifestations including delirium, lack of coordination, convulsions, paralysis, coma and ataxia may occur (5).

Fetuses and young children are highly vulnerable to the neurological effects of lead since the developing nervous system absorbs a higher lead fraction. In fact, the amount of systemically circulating lead, gaining access to children's brain, is significantly higher than that of adults (17). Children may appear inattentive, hyperactive and irritable even at low levels of lead exposure and those with greater exposure to lead might suffer from delayed growth, decreased intelligence, short-term memory and hearing loss (18). Moreover, lead can cause irreversible brain damage and even death at higher levels (19).

Lead poisoning has been reported to cause persistent seizures, requiring ventilator support when BLL exceeds 244 µg/dL. In a case report, a child suffered from global developmental delay and the CT scan of the brain revealed cerebral atrophy. The mother of this patient had high BLL and lead line in the radiograph of long bones. Therefore, it seems that lead poisoning has significant effects on CNS (20-22).

Lead exposure-induced seizures

Seizures have been described as the endpoint of lead intoxication in both humans and animals. Lead-induced seizures can occur in the absence of changes in blood-brain barrier. In a study, exposure of rats to two different levels of lead (below the level producing overt encephalopathy) sensitized the rats to the behavioral effects of convulsant agents including picrotoxin, isoniazid, mercaptopropionic acid and strychnine but not pentylenetetrazol.

Lead exposure affects several aspects of regional GABAergic function (23). Moreover, the results of this study indicated that lead exposure increased glutamine acid decarboxylase (GAD) activity, decreased GABA-T activity and elevated the apparent rate of GABA synthesis. Lead exposure also inhibited the uptake and release of [^{14}C] GABA (unstimulated and K-stimulated). This effect was observed in both treatment groups and all brain regions, except the cerebellum. These findings support the hypothesis of a neurochemical basis for lead-induced seizures, involving inhibition of GABAergic neurotransmission (23). It seems that motor impairments and seizures are

frequent neurologic sequelae of excess lead exposure in children.

Given the difficulty of studying the effect of such exposures in humans, animal models have been employed. In a study performed by Overmann et al. which aimed to evaluate the relative significance of symptoms in an animal model, long-Evans rats were exposed to lead from parturition to weaning by the adulteration of dams' drinking water (with 0.02% or 0.2% lead acetate). The findings of the mentioned study showed that prenatal and postnatal lead exposure did not alter electro-shock seizure thresholds in rats, tested at 8-20 days of age. The results suggested that lead exposure levels were at or near a no-effect level for several common neurobehavioral tasks. Moreover, kidney weight might be a more discriminative index of excess lead exposure compared to some simple neurobehavioral indices (24). Therefore, it seems that laboratory tests could be better indicators of lead exposure level compared to late-onset clinical manifestations.

Age and convulsion

Moreover, the effects of body lead burden on slow cortical potentials were studied in 63 children, aged 13-75 months. Slow wave (SW) voltage during sensory conditioning varied as a linear function of BLL. The slope of this function changed systematically with age. In children under 5 years of age, SW voltage tended to be positive at low BLLs and negative at > 30 µb/dL.

In children over 5 years of age, SW voltage tended to be negative at low BLLs and less negative (or positive) at >30 µb/dL. These results provided evidence of altered CNS function at the lowest reported lead exposure (25). These differences show that susceptibility to convulsion varies by age and the level of exposure.

Lead exposure and febrile convulsion

In a study by Farhat et al. BLLs were randomly measured in 206 children, referring to a University Hospital in Iran. Among these subjects, 95 cases presented with convulsion and 111 cases had no convulsions. This study showed that BLL in convulsive patients was not at a statistically significant level compared to the non-convulsive group and routine measurement was not advised. Therefore, we cannot confirm the association between lead poisoning and epilepsy, nevertheless the findings showed a marginal correlation (P=0.7), which indicates the need for larger-scaled studies with better sampling methods (15). As previous case reports and studies have indicated, lead exposure is significantly correlated with future nervous complications in children including susceptibility to convulsion (26,27).

Conclusion

Lead proves to have almost no clear biological function. However, once it enters the body, it is known to cause severe health effects, which might be irreversible. This metal affects almost all major body organs, particularly the CNS. Various molecular, cellular and intracellular mechanisms including the generation of oxidative stress, ionic mechanism and apoptosis have been proposed to explain the toxicological profile of lead.

Although animal studies have suggested risky BLLs in human studies, there are controversies regarding the relationship between lead poisoning and CNS manifestations, seizure and epilepsy. Besides, there are debates about the association between lead poisoning and development of epilepsy. Our literature review indicated that larger cohort studies are essential for clarifying this issue.

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Conflict of Interest

The authors declare no conflict of interest.

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