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Early detection of the low dose of Lead exposure prevents mental disorders using non-invasive fluorescence and multi-omics

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Abstract

Lead poisoning is an epidemic that can affect anyone. Lead toxicity most commonly affects children and causes neurodevelopmental problems chronically. Lead is a heavy metal that alters calcium metabolism and deactivates enzymes essential in activating heme in the blood. Heme is an integral part of homeostasis and body defense in the shuttling of oxygen throughout the tissues, most notably the brain metabolism. The lack of oxygen throughout the brain slows down brain development (e.g., Neuronal cell migration, polarization, neuronal cell differentiation) and leads to lower IQs, learning disabilities, and lifelong ailments. The most common form of lead exposure comes from lead-based paint, toys, cosmetic materials, other household materials, various environments, and occupational pollutants. The current biomarkers used for lead toxicity successfully detect current lead levels in the blood but are not excellent at determining duration. Bone-Pb allows for the detection of lead toxicity duration, but it is not widely accepted throughout the United States. Significant limitations exist because all biomarkers test for lead poisoning after it has already happened which makes it challenging to prevent lead exposure in a clinical setting. Prevention needs to happen at the governmental and, more importantly at the individual levels. The focus of this study is on lead toxicity and prevention followed by reducing risk and improvement of detection utilized tools-driven molecular-based assessment along with visual imaging technique. It examines how lead finds its way into the human body for storage or metabolomic by-products. Identifying the risks of exposure would inform the mechanisms that can be employed to prevent further exposure and toxicity in other organs or intervene with metabolism or biotransformation. It predicts the potential counteract mechanisms through which lead affects the health of pregnant mothers, or interaction between prenatal, ~~or~~ the unborn, and post-natal status, different stages of developmental, and post-menopausal women. The study outlines the various ways of detecting the presence of low levels of lead in the blood and bones using non-invasive fluorescence combined with multidimensional omics such as metabolomic and proteomic by which early detection of organ dysfunction can be used to monitor Ca2+ metabolism in the cell or tissue/organ level before the onset of disease

Keywords: Lead poisoning; Exposure assessment; Environmental injustice; Heme production; Non-invasive X-ray fluorescence

1. Introduction

Lead has been commonly used in construction materials, gasoline and fuel additive, lead batteries, paint, folk medicine, and herbal remedies. These materials have been used for centuries and lead's harmful effects on the human body and brain make this heavy metal a public health concern [1, 15]. The most common source of lead exposure is contact with lead-based paint and other household materials [1,6]. Lead paint, which contains a mixture of household dust and lead-contaminated soil can elevate the blood levels in children by about 70%. These levels with prolonged exposure can cause detrimental effects on the brain and body [1,15]. In addition, 30% of documented lead exposure attributes to

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drinking contaminated water, imported goods, candies, spices, pottery, and herbal remedies. These utilities and goods are commonly found throughout the United States. In 1978, lead-based paint was banned in the United States, but this did not lead to a sudden decrease in exposure and prevalence rates. Instead, it took many years for the prevalence of lead poisoning to decrease because most of the lead paint was already painted on the walls in these homes. In 2019, 3.6 million US families reported having a child under the age of six being exposed to elevated levels of lead [15]. In 2020, the EPA's American Children and Environment report found that the median concentration of lead in the blood of children between the ages of 1-6 has dropped from 15 ug/dL in 1976-1980 to 0.7ug/dL in 2013-2014 since the ban of lead-paint in household items [6,28].

There are some caveats that not all mental and behavioral disorders are associated with lead contamination. An accurate picture of the extent of harm caused by lead would be obtained after examining the other causes of diseases such as environmental factors [8]. Therefore, an in-depth analysis should be done to ensure that the disorders manifested in children do not come from environmental factors alone. Other genetic and epigenetic factors that trigger or intervene with the reward circuit in brain development could be considered covariant or compound factors. For example, the socio-economic environment is emerging as a trigger or risk factor to create vulnerability in children raised under a stressful atmosphere could result in mental deterioration. Some children were raised by abusive parents or guardians, hence growing up with behavioral alteration and mental disorders due to failure of stress management [25, 27]. Thus, it is important to understand these other causes of mental and behavioral disorders and rule them out. Engwa *et al* (2019) found that exposure to lead can result in cognitive and behavioral disorders compared to those resulting from environmental causes [8]. Therefore, it is worth examining the possibilities of exposure to lead and exposure to other stimuli that can trigger similar behavioral and mental disorders.

2. Risk of Exposure

The most common and studied exposure method is through contact with a lead-laced home [6]. One million homes in the United States have lead-based paint, and about 23.2 million homes have at least one or more significant lead-based paint hazards, such as elevated levels of lead in soil and minute levels of lead in hard surfaces [28]. Ab Latif Wani & Usmani (2015) explain that over time, as the paint begins to decompose, this increases the risk for exposure and can go nearly undetected by family members until they start exhibiting symptoms of lead poisoning [1]. Children have a much higher risk when compared to adults and are the most vulnerable population regarding lead poisoning [24]. The most common form of exposure is through the respiratory or gastrointestinal tract. Children between 18 to 36 months have the greatest risk of toxicity due to hand-to-mouth activities, rapid metabolism, and neurodevelopment [15]. Other studies have suggested children who live in environments that are near major busy roads and near domestic waste incinerators have the greatest risk of exposure to lead [16]. Waste management plants, regional airports, and battery manufacturers are some of the most considerable lead contributors to the soil and have the potential to contaminate surrounding communities [15]. These areas show a high prevalence of lead poisoning.

Socioeconomic status directly correlates with lead exposure, and the lower the socioeconomic class, the higher the prevalence of lead exposure [22]. Buildings must be inspected for lead including homes, daycare centers, schools, and other settings where a child may interact. Depending on the age of the buildings and whether it has been renovated, these settings, especially in inner cities, can hold the most prominent risk for lead exposure. The true health disparity lies within minority populations, low-income families, and the communities they live in.

According to Khan *et al* (2010), the nature of one's occupation plays a role in the risk of exposure [13]. Apart from painting work, other occupations are also known to be sources of lead exposure. For example, burning fossil fuels, soldering, mining, and manufacturing. As workers interact with lead while working on the materials in these occupations, they may inhale it and the lead dust settles in the body compartments. Some workers carry their overalls and other occupational clothes for washing, storage, or changing. These clothes can cause lead exposure to those who interact with them in washing or storage [13]. Thus, it is advisable that those whose occupation deals with lead products maintain high levels of hygiene and change their work clothes as soon as they leave the working sites.

Another risk of exposure to lead is where people live near factories that deal with lead. Any industry that deals with lead products emits substances that have led in one form or another. These factories include battery manufacturers, lead smelters, and lead refineries. The gas emitted from such factories might carry with it certain amounts of lead, and inhalation of such gases place the victims at risk of lead toxicity [7]. Similarly, people that live near areas where such factories dispose their wastes are at risk of being contaminated with lead.

3. Health Effects

Lead is a systemic toxicant that affects almost every organ system in the body but primarily targets the central nervous system and leads to neurodevelopmental problems, hypertension, smooth muscle contractility, and kidney dysfunction due to the altering of calcium metabolism [6, 23]. These effects are most prominent during brain development and children are most susceptible to long-term effects [21]. Elevated levels of lead exposure are linked to multiple health deficiencies. Even minute amounts of lead exposure can be extremely dangerous to infants and can lead to long-lasting effects on cognition [17]. When a child has been exposed to lead poisoning it is important to have their blood levels screened to determine the amount of exposure and the duration they experienced. The exposed child can experience symptoms like reduced kidney function, behavioral abnormalities, cognitive impairment, abdomen pain, vomiting, and colic [10]. If high blood lead levels are indicated the child can experience loss of muscle control, convulsions, and even death. It is extremely important to identify the source of lead toxicity and provide appropriate prevention and intervention to better manage the environment and reduce the exposure for children [25].

Regardless of the mode in which lead entered the body, the effects on health are the same [6]. One may have toxicity from swallowing, breathing, or absorbing the lead particles. However, higher levels of lead are achieved when it is absorbed through breathing. Once in the body, lead is stored in tissues, bones, and body. This storage, however, is not permanent. It is a reservoir from where the lead is slowly released into the system for internal exposure [18]. With increasing age, the bones undergo demineralization, further releasing larger amounts of lead from the bone. Similarly, women in their menopause may experience more exposure from bones releasing the stored lead. It has been noted that women have higher blood levels of lead after menopause than before.

Studies have shown that lead can cross the placental barrier [4]. As a result, unborn children can be exposed to lead toxicity when their mothers are exposed. Shukla *et al* (2018) mentioned that exposure can damage the nervous system of the developing baby [25]. In such developing babies, even exposure to minute amounts of lead can affect their intelligence and behavior. Exposure to lead can result in infertility, miscarriages, and even stillbirths [18]. Children are more affected by lead exposure than adults. Intellectual disability and neurological impacts might be observed among children whose parents work in industries that interact with lead.

4. Biomarkers for Lead Poisoning

It was illustrated that "A biologic marker is a robust early perturbation in response to a low-dose lead exposure" [19]. Although the presence of these biomarkers does not mean that there will be adverse effects, it is a good way to calculate the risk of disease and complications. Lead concentration in the whole blood is used to monitor the exposure of this heavy metal in clinical settings. Given the current knowledge, a blood lead concentration should be below 10 µg/dL at any given time. Any level higher than 10 µg/dL likely leads to a lower IQ, neurobehavioral changes, and growth index deficits [19]. Recent studies show that levels lower than 10 µg/dL cause adverse health effects in children [2]. This suggests that there are no safe levels of lead blood concentration. Most biomarkers for lead poisoning are of the body-burden type and it's usually too late when detected in the blood Several molecules were used to determine lead exposure after measuring them in the blood, or hemoglobin concentration and the urine [26]. Lead affects the biological synthesis of heme in the blood and alters essential enzymes, leaving them unable to speed up reactions necessary in heme production. Heme is essential in the shuttling of oxygen throughout the body and without heme necrosis of tissue damage is probable [3].

Over the last decade, a form of non-invasive X-ray fluorescence has been used to measure lead in the bones (bone-Pb, BPb) and has been quite successful. This technique uses fluorescing photons and removes the inner-shell electron from the Pb atom. This leaves the atom in an excited state and emits an X-ray photon that can be measured by the imaging machine [3]. Testing of bone-Pb allows the duration and extent of lead toxicity to be measured directly, which allows for proper intervention and treatment if warranted.

The primary biomarker used to monitor lead exposure is the lead concentration in whole blood. However, BPb is not useful in differentiating high-level short lead exposure from low-level chronic lead exposure using a single measurement of blood lead levels [2]. It is therefore important that serial measurements of blood lead levels be taken to give a better estimation of the possible health concerns that might arise from lead exposure [21]. The challenges faced in the assessment of the actual nature of lead exposure are not so much dependent on problems with the available methods of analysis, but on the complexity of lead toxicokinetics with the various body compartments [5]. In the body, lead is stored in areas such as soft tissues, bone, and blood. To accurately distinguish between lead that has been in the body for many years and that which has come from recent exposure, it is important to have details on other biomarkers of exposure [14]. Currently, none of the existing internal lead biomarkers have been accepted as reliable enough to substitute the measurement of blood lead.

4.1. Prevention

To have the most effective prevention at the community level, there should be an effort to establish a relationship between the city and state. Each state should be aware of the local population most at risk for lead exposure and should work with the individual cities to screen for lead poisoning and to provide prevention techniques. For example, the Center for Disease and Control (CDC) recommends screening for all Medicaid-eligible children at 12 and 24 months of age, at least once between 36 and 72 months, and for every individual living in areas where 27% of housing was built before 1950 [15]. It is also important to engage property owners and private contractors to start partnering with government agencies to develop a plan to prevent lead poisoning in existing buildings and build awareness in the community.

Primary prevention at the individual level can begin with the parents' awareness and occupational guidance in the family. They can start by identifying the risks of early exposure during pregnancy or developmental age, like when the babies are born. Parents should receive lead-prevention counseling from public health officials, have their homes tested for lead-based paint, and regularly practice proper hand hygiene to keep their children from being exposed to lead dust on their hands [15]. Parents should ~~also~~ ensure proper hygiene practices to reduce heavy metal contamination such as regularly cleaning the home, not allowing shoes to be worn in the home, staying informed about products that could contain lead, and always checking medicines received from foreign countries [15]. Clinicians and other public health officials suggest that parents test the amount of lead in household tap water before cooking, bathing, and flushing toilets [16]. Multiple studies have shown that household interventions are the most effective form of prevention of lead poisoning [20]. Individualized interventions and prevention practices can help ~~to~~ reduce lead exposure and better mitigate the extent of lead poisoning [9].

5. Perspective

Current biomarkers are not sufficient to help with the prevention of lead poisoning. Lead (Pb) tests in the blood allow for the detection of Pb at low levels. This is essential in determining exposure for at-risk communities. However, there are many limitations in place and there is no easy way to test Pb toxicity duration, which is one of the most critical factors in heavy metal poisonings [18]. Recent X-ray developments have allowed us the ability to test for the duration of lead exposure, but it is still not a widely accepted practice. For example, Hu H. et al. (2007) reported that lead levels in the bone measured by K-shell X-ray fluorescence can predict an individual's cumulative blood lead index which reflects a relatively new biological marker of cumulative dose and represents covariable factors in a multidimensional preventive study [12]. However, it is still challenging to adapt imaging techniques due to the high application cost of X-rays in large populations of people. Lead toxicity affects the lower socioeconomic class the most, who do not have the resources to pay for imaging. In the future, a systemic approach to Prevention such as integrated multidimensional metabolomics and genomics followed by molecular diagnostic tools such as sequencing, PCR, and protein array depends on disease patterns depending on age, race, and gender in case of kidney dysfunction and hypertension biopsy is a new way to limit lead exposure, susceptibility, and increasing sensitivity. Combinatorial approaches like exploring new molecular markers by visualization molecular behavioral change in an animal model with imaging techniques should be done through screening, monitoring, and surveillance, while a variety of samples might be collected to do lead-prevention counseling, and testing household goods, paint, water quality depends on the geographical and economic~~al~~ isolated region.

6. Conclusion

In conclusion, a future challenge could be demanded on how to detect the effect of a low dose of lead exposure and determine the early onset of its health implication in the gender-specific or developmental age-specific manner. Determination of molecular connectivity between the neural circuit, metabolism or visualization of chromosomal alteration, disease patterning by molecular diagnostic and genetic variants following environmental intoxication such as lead exposure during prenatal period linked with the underlying mechanism of the aging process, can shed light on new avenues on how mental health can prevent disorders such as Alzheimer's disease, a part of neurodegenerative disorders.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there are no conflicts of interest.

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