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The Association of Exposure to Lead, Mercury, and Selenium and the Development of Amyotrophic Lateral Sclerosis and the Epigenetic Implications

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Amyotrophic lateral sclerosis · Lead exposure · Environmental risk factors

Abstract
Metal exposures are an intriguing potential culprit in the cause of sporadic amyotrophic lateral sclerosis (ALS). For one, there are numerous case reports linking different metals to an ALS phenotype. Furthermore, some investigators have demonstrated higher levels of certain metals in the blood, bone, cerebrospinal fluid, urine, or spinal cords of patients with ALS compared to controls. There are also many case-control studies looking at the possible association of certain metals with the development of ALS. We have reviewed the relevant literature regarding metal exposures and the risk of developing ALS. We found that many different metals have been implicated as having a role in ALS, but there is more literature investigating the role of lead than any other metal. Despite many studies, the role, if any, of this metal in the pathogenesis of ALS remains unclear. Similarly, other metals either have inconclusive, conflicting, or insufficient results in order to make a definitive conclusion. One explanation for these findings is that metal exposures alone are insufficient for the development of ALS. Perhaps an interaction between the metal exposure and an individual's genetic makeup is required to produce epigenetic changes that ultimately lead to ALS.

Amyotrophic Lateral Sclerosis (Background)

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disease that occurs in sporadic (90%) and familial forms (10%) [1]. The cause of sporadic ALS remains unknown, and only a small percentage of familial cases have an identified genetic abnormality [1]. ALS is characterized by motor neuron degeneration which leads to progressive muscle weakness, swallowing difficulties, and respiratory failure. An aggressive disease, ALS is usually fatal within 3–5 years after the onset of symptoms [1]. The devastating nature of this condition combined with an incidence of approximately 2 per 100,000, makes ALS a pressing target for investigation [2].

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Metals and Trace Elements

Abnormal exposure to metal ions may be a risk factor for ALS. Overexposure to any of several metal ions, including lead, mercury, selenium, cadmium, manganese, arsenic, copper, aluminum, and zinc, is known to be neurotoxic [3]. Specifically, motor neurons appear to be susceptible to metal ion toxicity. Lead toxicity, for example, is known to mimic motor neuron disease [4]. Motor symptoms are also associated with selenium toxicity [3]. Similarly, iron supplementation decreases motor activity in animals [5]. Furthermore, oxidative stress is hypothesized to play a role in the pathogenesis of ALS which may be one mechanism by which metals cause neurotoxicity. The role of oxidative stress is supported by evidence of oxidative damage to proteins, lipids, and DNA in postmortem tissue samples of both familial and sporadic forms of the disease [6, 7]. Additionally, evidence of oxidative stress is present in the sera and spinal fluid of living ALS patients [7]. Metal ions are suitable mediators of oxidative insults due to their propensity to catalyze oxidation and reduction reactions. Several transition metals are known to cause neurotoxic effects by generating reactive oxygen species. Examples include lead, mercury, manganese, cadmium, and copper. We will focus on the three metals with the most literature to support their role in the development of ALS, namely lead, mercury, and selenium.

Lead

Lead exposure is among the most studied environmental risk factors in ALS. The association between the two dates back to 1850, when Aran first described motor neuron disease in the context of lead exposure. Three of his 11 patients with progressive muscular atrophy had been exposed to lead, 2 of them having suffered from outright lead poisoning [8]. In 1907, Wilson reported 4 additional cases of ALS associated with chronic lead poisoning [9]. There are also modern case reports that describe ALS in the setting of acute lead exposure [10]. Since the second half of the twentieth century, these associations have been examined in much greater detail.

Several early studies investigated lead levels within different body compartments of ALS patients compared to controls. Such studies focused on the abnormal turnover, tissue distribution, detoxification, and excretion of lead. Abnormal lead levels were thought to result in subsequent lead uptake by neurons, eventually manifesting in toxic neurodegeneration [11]. Conradi et al. [9] reported increased levels of lead in the cerebrospinal fluid of ALS patients and confirmed this finding again in 1980. Meanwhile, Kurlander and Patten [12] measured elevated levels of lead in spinal ventral horn tissue. These values directly correlated with the duration of the illness. Whereas Conradi et al. [9] found significantly elevated plasma lead levels in ALS patients, whole blood lead levels did not appear to differ between cases and controls in an earlier study [9]. In other pathologic states related to lead toxicity, such as acute lead intoxication, the hypothesis is that plasma lead levels are more meaningful than levels found within whole blood [13]. In contrast to many of these early findings, a small study consisting of only 9 patients found no association between ALS and lead levels in whole blood, plasma, erythrocytes, or CSF [14]. However, one must consider the possibility of drawing erroneous conclusions from such a small sample of ALS subjects. There is also conflicting evidence as to whether elevated levels of lead in skeletal muscle are present in ALS patients [11, 15]. Lastly, the administration of a metal chelating agent to ALS patients did not lead to detectible mobilization of lead stores [16]. Admittedly, however, the amount of lead excreted in the urine may not accurately depict the amount of lead that has accumulated in neurons.

More recently, investigators began to consider lead levels as surrogates for prior lead exposure, which is now viewed as a potential risk factor for ALS in susceptible patients. Consistent with previous data, Vinceti et al. [17] found no abnormalities in whole blood lead levels during early stages of the disease. However, they noted a positive correlation between whole blood lead levels and the progression of the disease, measured in this case by worsening functional impairment. Thus, elevated whole blood levels appear in later stages of the disease, similar to observations made by Kurlander and Patten [12] with respect to lead levels in the spinal cord. Since blood levels rise only after the onset of clinical symptoms, this abnormality likely reflects changes associated with disease progression rather than continued accumulation of lead in response to exposure. Interestingly, a more recent study found ALS patients to have elevated whole blood lead levels with a dose-response relationship between lead levels and risk of ALS [18]. Additionally, they found weaker, less consistent correlation between ALS and elevated bone lead levels. Because patients in the study were not stratified based on the stage of their disease, one might argue that, in light of the findings of Vinceti et al. [17] and Kurlander and Patten [12], this patient population might have been biased towards end stage patients, who would be more likely to have elevated lead levels. However, after

excluding all patients who were diagnosed more than 1 year prior to enrolling, their findings were unchanged. Furthermore, neither blood nor bone levels correlated with the time since diagnosis. It is also worth noting that several patients who met this study's inclusion criteria elected not to participate because they were too sick or because travel was too difficult, implying that end-stage patients self-selected out of the case population. One potential limitation is the low participation rate for the controls in this study, which brings up the possibility of selection bias.

Clearly, these findings are insufficient to make any convincing arguments regarding the role of lead as a risk factor in the pathogenesis of ALS. In response, a number of additional case-control studies have compared self-reported histories of lead exposure between ALS patients and controls. Overall, we have identified 10 case-control studies investigating the possible pathogenic role of lead [18–27]. These studies are summarized in table 1. Conclusions clearly vary from study to study. Several factors influence the findings in these studies. One factor is the number of cases within each study, which varied from 25 to 518. Thus, smaller studies may be inadequately powered to detect an association between exposure and disease. Another factor is the inherent recall bias associated with case-control studies. This point is emphasized in McGuire et al. [20], which show that self-reported exposure to lead is exaggerated in comparison to the level of exposure determined by a panel of 4 industrial hygienists based on self-reported job descriptions. Such overestimations of past exposures may lead one to erroneously identify associations when, in fact, no such association exists. Overall, most of the studies showed an association between lead exposure and risk of ALS, but a few did not, including the study that assessed the largest sample size.

An epidemiologic investigation conducted in Jefferson County, Missouri, reveals a small but statistically significant standardized prevalence ratio of ALS (6.4, $p = 0.0437$) within proximity of a lead smelter known to be responsible for local atmospheric and soil contamination [28]. Recently, Kamel et al. [29] were able to follow up on 91% of the cases included in their previous case-control trial that confirmed an increased risk of ALS associated with a history of lead exposure [18]. Unexpectedly, they now note that lead exposure appears to be directly correlated with disease survival among the ALS cases. Though unintuitive, this finding is consistent with some previous reports. For example, one study showed a greater 5-year survival rate among ALS cases with a history of high lead exposure compared to cases with no history of lead exposure [8]. Kamel et al. [29] postulate that, together, the evidence implies that lead exposure promotes disease onset, but delays disease progression. They argue that the possibility that lead exposure is simply a marker associated with a different factor is unlikely since the findings were unchanged after adjusting for age, sex, smoking, education, BMI, physical activity, bulbar onset of symptoms, diagnostic delay, family history of ALS, and respiratory dysfunction. However, the mechanism by which lead could slow disease progression is unclear and makes definitive conclusions from this study difficult. Although there is evidence to suggest that lead exposure may be associated with ALS, and may even affect disease progression, the specific role of lead in the pathogenesis of ALS remains poorly defined and deserves further study.

One potential explanation for these conflicting results is that lead exposure is only part of the equation. Recent evidence has shown that lead exposure can cause epigenetic changes, which are DNA modifications that do not cause a change in the DNA sequence [30]. In this case, these changes are modifications in the methylation patterns that can subsequently lead to alterations in the transcription and subsequent translation rates of genes and proteins throughout the genome. Pilsner et al. [30] showed that maternal lead exposure as determined by patella lead levels was inversely correlated with methylation levels of her child's DNA in cord blood. These results indicate that even maternal lead exposure can alter the epigenome of her offspring, which may have implications for subsequent disease susceptibility. Given the fact that lead can cause significant epigenetic changes, perhaps the reason that so many studies have been unrevealing is that we are missing the essential interaction of lead with the epigenome.

Further evidence that epigenetic changes are involved in the pathogenesis of ALS comes from studies of genes known to cause familial ALS. Two of these genes, FUS and ELP3, encode proteins that can cause alterations in histone acetylation [31]. Histones are an essential component of the organization of DNA within the cell. DNA wraps around an octamer of histones to form a nucleosome, which is the fundamental building block of the chromosome. However, histones are not merely a scaffold for the organization of our genetic material, but also undergo modifications that can have a profound influence on the transcriptional activity of nearby genes [31]. The best studied modifications are acetylation by histone acetyltransferases (HAT) and deacetylation by histone deacetylases. In regard to ALS, FUS interacts with the CREB binding protein decreasing this protein's HAT ac-

Table 1. Case control studies investigating the association between lead exposure and the risk of developing ALS

Reference	Location	Time period	ALS cases	Conclusions	Limitations
Felmus et al. [22]	Methodist Hospital in Houston, Tex.	Not specified	25	Self-reported lead exposure is a risk factor for ALS in predisposed individuals.	Small number of cases.
Pierce-Ruhland and Patten [23]	Houston, Tex.	Not specified	80	In genetically susceptible individuals, lead exposure is a possible antecedent event in ALS pathogenesis.	Exposure to lead alone was not significantly associated with increased risk. Only in conjunction with past mercury exposure was there a statistically significant association.
Gresham et al. [19]	San Diego, Calif.	1985	66 males	No association between self-reported occupational exposure and risk of ALS in males.	11.6% of cases had a family history of ALS. 39% of cases had traveled to the Marina islands. Possible overmatching of controls.
Deapen and Henderson [24]	United States (nationwide)	1977–1979	518	No relationship exists between self-reported lead exposure and the risk of ALS.	Study was not designed to investigate lifetime lead exposure in detail.
Armon et al. [21]	Mayo Clinic in Rochester, Minn.	Not specified	47 males	Among men, there is an association between ALS and self-reported exposure to lead vapor, although true etiology appears to be multifactorial in nature.	Small number of cases.
Gunnarsson et al. [25]	Southern Sweden	1990	92	A non-significant increased risk for ALS is associated with self-reported occupational lead exposure.	Possibility of confounding variables: lead exposure highly correlated to solvent exposure and the occupation of welding.
Chancellor et al. [26]	Scotland	Disease diagnosed 1990–1991	103	Occupational lead exposure is a risk factor for ALS.	Selection and recall bias. The patients included in the study had a trend towards longer survival.
McGuire et al. [20]	Western Washington State	1990–1994	174	An apparent association exists between self-reported lead exposure and ALS. No association between estimate of lead exposure by expert panel based on job description and ALS.	Findings suggest that marked recall bias may plague case-control studies.
Kamel et al. [18]	New England	1993–1996	109	An increased risk of ALS is associated with self-reported occupational lead exposure in a dose-dependent pattern. No increased risk of ALS associated with residential or recreational exposure.	Possibility of recall bias.
Qureshi et al. [27]	Massachusetts General Hospital, Boston, Mass.	1998–2002	95	A significant association exists between self-reported lead exposure and risk for ALS.	Failed to demonstrate smoking as risk factor contrary to most of the literature on this subject.

tivity, thus downregulating CREB target genes that may be involved in the pathogenesis of ALS [31]. Similarly, ELP3 is able to alter the expression of HSP70 through its HAT activity [32]. Interestingly, overexpression of HSP70 has been shown to decrease the amount of insoluble SOD1 in a SOD1 mouse model of familial ALS as well as prevent neuronal cell death in a mammalian cell model [33, 34]. These findings are the first glimpse that epigenetic changes are involved in the pathogenesis of ALS and open up a whole new avenue for potential experiments and perhaps future treatments of this devastating condition.

Mercury

There is a large amount of evidence suggesting that mercury is toxic to motor neurons. In animals, mercury accumulates in motor neurons following its injection into blood [35]. In humans, Pamphlett and Waley [36] report the preferential uptake of mercury by cortical motor neurons over other cerebral neurons following a suicide attempt involving intravenous injection of mercury. Arvidson [37] theorizes that mercury enters the CNS from peripheral exposure through uptake at neuromuscular junctions, which is followed by retrograde axonal transport. Mercury may mediate its neurotoxicity through one or more of several theorized mechanisms. These include inhibition of the activity of superoxide dismutase, damage to microtubules or other cytoskeletal components, and impairment of axonal transport [38].

A case report from 1996 [39] describes the onset of ALS in a 38-year-old woman 3.5 years after accidental injection of mercury into her hand. Importantly, mercury (and lead) concentrations in her blood, urine, and hair were not elevated at the time of diagnosis. Regardless of whether or not mercury exposure was responsible for the development of ALS in this patient, this finding is significant in that it shows that detection of body levels of a particular toxin via these methods may not account for previous exposure. Also of note, despite the fact that urinary mercury excretion increased dramatically after chelation treatment with dimercaptosuccinic acid (DMSA), symptoms failed to improve, and actually worsened. Praline et al. [40] report a more recent case of ALS in an 81-year-old woman following chronic exposure to mercury vapor from a tank used for pressure therapy to treat lymphadenopathy in her left arm. The patient had only slightly elevated mercury levels in her blood, but enormous levels were detected in her urine, even though her last exposure had taken place 5 months before. Despite the fact that urinary levels of mercury decreased significantly in response to 4 weeks of DMSA therapy, her symptoms, like those of the previous case, continued to worsen. This failure to clinically respond to chelation therapy is consistent with findings from animal studies that show that DMSA is unable to decrease the brain burden of mercury [41]. Paradoxically, DMSA might inappropriately increase the exposure of motor neurons to mercury as a result of redistribution of mobilized ions [41]. Other case reports describe similar examples of the onset of ALS preceded by mercury exposure [42, 43]. In the cases described by Adams et al. [42] and Barber [43], symptoms resolved once the exposure was removed.

A study that investigated urinary excretion of mercury and lead after administration of a chelating agent found no difference between ALS patients and controls in the amount of background excretion of mercury or excretion 48 h after chelation therapy [16]. Similar results were reported with respect to lead with the exception of background urinary lead excretion in males, which was significantly elevated in male ALS patients compared to controls. This is attributed to the combination of the fact that ALS males were significantly more likely to have possible occupational lead exposure than control males with no such difference among females. The fact that urinary mercury excretion increased only slightly after chelation is inconsistent with the above case reports, in which patients had known histories of significant mercury exposure [39]. The authors conclude, however, that the amount of mercury available for excretion may not represent the amount which has accumulated in motor neurons. Alternatively, the neurotoxic amount of mercury accumulated in neurons may indeed be mobilized by chelation, but is too small to be detected in the urine.

Most case-control trials that studied mercury as a risk factor for ALS investigated exposure to several other neurotoxic agents at the same time. Some of these trials were mentioned above as they pertained to lead. In short, mercury was not associated with an increased risk of ALS in two studies [19, 20] but was associated with an elevated risk in a third [23]. A cohort study amongst 83 Japanese mercury miners poisoned by or exposed to mercury vapor failed to identify any cases of ALS in 18 years of follow-up. No cases were reported among the 65 controls either. Overall, there is no conclusive evidence to suggest increased mercury exposure is associated with ALS but the literature on this subject is limited.

Selenium

As previously mentioned, selenium is neurotoxic in humans [3]. Suspicion regarding a link between selenium

exposure and ALS was described in a 1977 report of 4 sporadic cases occurring among unrelated farmers living within a 15-km radius of each other in a selenium-rich region of South Dakota [44]. These reports are consistent with those of ALS-like syndromes associated with nearby livestock also exposed to toxic levels of selenium [45]. Not only did these animals show signs of progressive motor neuron disease culminating in respiratory failure, but degeneration of the ventral horns of the spinal cord was also present upon postmortem examination of some of the swine, further indicating motor neuron degeneration.

Vinceti et al. [46] studied a population that was also exposed to high levels of environmental selenium in Rivalta, Italy, where the municipal tap water contained elevated levels of selenium between 1972 and 1988. A cohort of residence living in Rivalta between 1980 and 1985 were found to have a standardized incidence ratio of 4.22 (95% CI: 1.15–10.8) compared to the unexposed population of the municipality. Moreover, a cohort of residence living in Rivalta since 1974 was found to have a higher standardized incidence ratio of 8.90 (95% CI: 2.43–22.79). Comparing these findings, this study demonstrates a higher incidence ratio of ALS in those Rivalta residents with a longer exposure to tap water with elevated selenium.

Several case-control trials examine the role of selenium exposure and diagnosis of ALS. Many of these trials use selenium levels in various body compartments as markers of selenium exposure. Early work from Nagata et al. [47] reveals a statistically significant elevation in erythrocyte selenium levels of ALS patients when compared to controls. However, more recent findings challenge these data. For example, Moriwaka et al. [48] found an inverse relationship between disease progression and both serum and erythrocyte selenium levels. Vinceti et al. [17] report a similar pattern with serum selenium levels. When they restricted their analysis to ALS patients with only a limited degree of disability, they found no difference in serum selenium levels compared to matched controls. This suggests that as the disease progresses, selenium levels in the blood fall. This relationship is believed to reflect the poor nutritional status associated with advanced disease. Most recently, Pamphlett et al. [49] observed no difference in whole blood, plasma, and erythrocyte selenium levels between ALS patients and controls, further confirming previous findings. Together, these data suggests that acute exposure to selenium does not necessarily precede disease onset, and that selenium levels change throughout the course of the disease. In order to study the influence of chronic selenium exposure on the risk of ALS, Bergomi et al. [50] used toenail metal concentrations, which reflects selenium exposure roughly over the prior 12–15 months. This study also failed to uncover an association between selenium exposure and risk of ALS. Their findings do, however, offer further support for the inverse relationship between selenium levels and disease progression.

Neurologic tissue has also been studied for associations between ALS and selenium. Mitchell et al. [51] report a significant elevation of selenium within the cervical cords (as well as livers and bones) of motor neuron disease patients. However, a similar trend is absent in the thoracic and lumbar spines. Kurlander and Patten [12] found elevated selenium in the anterior horn cells of only one of 7 motor neuron disease patients, but in 3 of 12 controls. In a larger study, Ince et al. [52] report significantly elevated levels of selenium in the lumbar spine of ALS patients, where there is also significantly elevated selenium-dependent glutathione peroxidase activity. Increased lumbar spine selenium levels appear to be independent of duration of disease, disease severity, and L_4 segment lower motor neuron count, suggesting that its accumulation is unlikely to be a consequence of disease progression, but rather an earlier event in the course of the disease [53]. Ince et al. [52] caution, however, that the elevated selenium levels may be secondary to increased glutathione peroxidase enzymatic activity in response to oxidative stress from another source. Given all of the studies, there is very little data to suggest that selenium has a major role in the pathogenesis of ALS.

Epigenetic Changes

For many years, the dogma in biology was that DNA sequence-specific transcription factors were the only regulatory elements dictating gene expression. In the last decade, the field of epigenomics has emerged, revealing that DNA modifications, including DNA-bound histones, DNA methylation, and chromatin remodeling also provide levels of gene regulation and alter gene expression [31]. Epigenetic factors are probably much more suited than genetic factors to explain disease onset and progression in ALS, since aberrant epigenetic patterns may be acquired throughout life. One hypothesis is that environmental life exposures result in a failure to maintain epigenetic homeostasis in the nervous system which in turn leads to aberrant gene expression, contributing to nervous system dysfunction and in some cases the development of ALS. Metals are one of the most likely culprits to be a key

exposure risk factor in the development of ALS given their well-documented potential for neurotoxicity and involvement in oxidative mechanisms of injury. However, to date the epidemiologic literature supporting the role for metals in ALS pathogenesis has been disappointing. One potential reason for this discrepancy is the failure to understand the importance of the epigenomic background of patients and its interaction with exposures. Future studies are needed to investigate this relationship.

Conclusions

The role of metal exposures in the pathogenesis of sporadic ALS is unclear. There have been many studies investigating the role of metals such as lead, mercury, selenium, and cadmium. Unfortunately, many of the studies have had contradictory or indefinite findings. However, given the potential neurotoxicity of metals and their ubiquitous nature, further large-scale studies with rigorous epidemiologic designs are needed to reach more definitive conclusions. Furthermore, the interaction of lead and other metals with the epigenome of patients needs to be investigated to determine if epigenetic changes are the missing link between exposure and disease. Establishing or excluding the role of metals in the development or progression of ALS could lead to new insights into the cause of this devastating condition and potentially long overdue therapeutics. Moreover, the field of epigenetics has the potential to cause a major change in our current understanding of the pathogenesis of ALS and therefore new therapeutic targets.

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