Chronic Exposure to Toxic Metals as a Risk Factor for Alzheimer’s Disease: A Review

Leah Elizabeth Yang

Citation: UBCMJ. 2019: 11.1 (11-13)

Abstract
Alzheimer’s disease (AD) is an age-related neurodegenerative disease characterized by progressive memory loss, decline of cognitive functions, and, eventually, the inability to communicate or perform daily life tasks. Despite the fact that researchers have made significant progress regarding the etiology of AD in recent years, the environmental risk factors involved in the pathogenesis of the disease still remain unclear. One widely known hypothesis that deals with environmental risk factors is the biometal dyshomeostasis hypothesis, which claims that the accumulation of toxic metals in the body over time is positively associated with the stages of neurodegeneration observed in AD. While many studies have produced results in support of this hypothesis, others have found no significant relationship between exposure and disease outcomes. This review will focus on elucidating contentious areas in the existing body of knowledge surrounding AD by examining the evidence behind the biometal dyshomeostasis hypothesis.

Introduction
In 2017, Alzheimer’s Disease International estimated that roughly 50 million people worldwide were living with some form of dementia, and that roughly two-thirds of those cases had AD.¹ That year, AD was responsible for an estimated 1.54 million deaths worldwide, and AD-related mortality is predicted to increase significantly as the global population ages.² Currently, there is no known cure, and out of over a hundred clinically-tested drug treatments, only five have been approved for use as AD treatments in Canada.³ These drugs may help in managing common symptoms, but they often have little to no effect on life expectancy, as the typical life expectancy after being diagnosed with AD ranges from four to eight years regardless of medications.⁴ In Canada, the national prevalence of AD and other forms of dementia is rising, and the Alzheimer Society of Canada estimates that there are over 564,000 Canadians living with dementia today.⁵ In addition to that, an excess of 25,000 new cases are being reported each year, and by 2031, the national prevalence of dementia is projected to rise up to 937,000 cases.⁶ This increase in cases would put a significant strain on Canada’s economy, as it would increase national dementia healthcare costs from $10.4 billion per year to $16.6 billion per year—an upsurge that Canada’s health care system is ill-fit to handle.⁷ Hence, it is imperative that Canada enacts primary prevention methods to decrease the incidence of dementia in the near future. The purpose of this review is to identify and explore the relationship between environmental exposures and the pathogenesis of AD. Once the relationship between exposure and disease is established, that information can be used to promote better health outcomes by guiding policy decisions related to environmental and occupational health and safety.

The Biometal Dyshomeostasis Hypothesis
The biometal dyshomeostasis hypothesis attempts to explain environmental risk factors for neurodegenerative disorders based on the fact that toxic metals can promote aggregation of β-amyloid clusters in the brain, which is a biological hallmark of AD.⁸ While there are a multitude of risk factors that may contribute to the pathogenesis of AD, the most prominent risk factors are aging, genetic predispositions, previous traumatic brain injuries, and environmental exposures.⁹ Out of those, the only factor we can actively change is the exposure to environmental hazards, with the main exposure of concern being toxic metals.

People are mainly exposed to toxic metals in the environment by soil and water contamination, as well as airborne pollutants generated by industrial waste from mining operations, mills, and battery factories.¹⁰ For instance, lead, aluminum, mercury, and cadmium are heavy metals that are utilized extensively in industrial processes. While acute exposures may generate little to no risk, the bioaccumulation of these toxic metals over time can lead to effects such as permanent brain damage, which may be associated with the pathogenesis of AD.¹¹ Thus, workers in industrial facilities are at a high risk for developing AD later in life.² Of course, all people are at risk due to the ubiquitous nature of airborne pollutants and soil and water contamination, but occupational exposures tend to be far more significant.⁶ Workers in battery factories are often exposed to much higher levels of heavy metals compared to the general population, and one meta-analysis showed that being chronically exposed to aluminum increased lifetime risk of developing AD by nearly 70%.¹² This phenomenon makes sense from a biological perspective, as the cellular damage inflicted by the bioaccumulation of toxic metals can result in a number of neurological impairments, including memory loss, tremors, and changes in sensory perception, all of which may be correlated with the development of neurodegenerative diseases such as AD.⁶

Review of the Evidence
Multiple epidemiological studies have already linked chronic exposure to heavy metals with neurodegenerative effects such as memory loss and reduction of brain volume, which sets the foundation for the biometal dishomeostasis hypothesis. Until the early 2000s, this hypothesis was highly contentious among researchers, for although the majority of studies had observed higher blood levels of heavy metals in AD patients compared to healthy patients, there were also studies with no statistically significant difference between groups.⁷ For example, one cohort study observing the effects of aluminum exposure on workers in the automobile industry found that there was no significant difference in brain function compared to unexposed workers of the same age range, and two cross-sectional studies conducted in a similar occupational setting reached the same conclusions.⁹¹⁰
In recent years, however, findings from key studies have started to become more consistent, and researchers seem to be nearing an agreement about the potential risks of environmental and occupational exposure to heavy metals.11 In 2018, a meta-analysis of 42 studies showed that blood levels of mercury, aluminum, and cadmium were significantly higher in AD cases than in controls.4 Furthermore, a report from a hospital in Seoul revealed that blood levels of lead, copper, and mercury were significantly higher in patients who had AD compared to those with no neurodegenerative diseases, which suggests that not only may the same concept also hold true with other toxic metals, but there also may be synergistic effects associated with exposure to multiple metals.12

Many studies observing the development of AD narrowed their focus to a singular toxic metal. For instance, one post-mortem case-control study of a family in China that had been exposed to high levels of mercury throughout their lives showed that the accumulation of mercury in the brain can inflict significant neurodegenerative damage, as all members of the family had experienced a degree of neurodegeneration not typical of their age groups.13 Another post-mortem case-control study in California analyzed the results of 99 MRI brain scans and found higher levels of iron and lower tissue integrity in the hippocampus of subjects who had died of AD.14 Both of these examples illustrate the potential neurodegenerative effects of long-term exposure to toxic metals. Moreover, a meta-analysis of case-control studies observing lead as a risk factor for AD found that there was a significant difference in lead exposure between disease groups, though the researchers also recommended prospective studies to be conducted in the future.15 While there are limited prospective studies involving human subjects, one retrospective cohort study conducted in Thailand showed that long-term exposure to arsenic in early stages of childhood development significantly impaired brain growth in a group of children, which led to them having lower brain weights at maturity.16

**Methodological Flaws in Past Studies**

Many of the observational studies reviewed here focused on isolating one specific heavy metal to explore its neurotoxic effects, but restricting the scope of observation to individual exposures has some noteworthy limitations. Having a single-metal study design is not representative of reality, as people are often exposed to multiple different metals at the same time, and combining exposures may have synergistic or antagonistic effects on neurotoxicity. In fact, one rodent study reported that the administration of a mixture of metals decreased the rodents’ neural functions much more than any single metal did.17 That is likely because multiple metals enter the body through the same biological pathways and share the same ion transporters in circulation, which means that any change in the circulatory level of one metal may have unintended effects on the circulatory level of others.5 By only specifying one toxic metal as an exposure of interest, many of the observational studies reviewed here failed to account for the effects of other toxic metals in the environment. Having this uncertainty present, there is a clear need for more comprehensive studies exploring the effects of chronic exposure to multiple metals in order to reveal their combined effects on the pathogenesis of AD.

Additionally, many studies found it challenging to account for all sources of bias. A few of the studies reviewed did not adjust their results for extraneous variables, which could have introduced confounding bias into their conclusions. Some potential confounding factors include variations in exposure time, variations in the concentrations of toxic metals that individuals were exposed to, and genetic predisposition to AD. As well, there may have been information bias in some of the cohort studies, as participants did not always know their own exposures, so self-reported data on exposure status may have been inaccurate.

**Future Research Directions**

In many of the papers reviewed here, researchers emphasized the need for longitudinal cohort studies to further support their conclusions, and they recognized that larger sample sizes would be needed in order to attain generalizable results.4,11 These claims have substantial implications for future research, prescribing that in order to fully confirm the role of toxic metals in the pathogenesis of AD, future research should involve more prospective studies in order to track lifetime environmental exposures and to determine how different combinations of toxic metals in the brain can affect the severity of neurodegenerative damage. Theoretically, a prospective cohort study could observe lifetime toxic metal exposure and accumulation of toxic metals in the brain by having participants receive MRI scans on a yearly basis. That would decrease the potential bias associated with self-reporting exposure status, increasing the internal validity of the study. Knowing the true association between exposure to toxic metals and risk of developing AD will help decision-makers determine whether any environmental interventions are needed in order to mitigate health risks.

**Conclusion**

Overall, there is already a fair amount of existing evidence to establish a positive relationship between exposure to toxic metals and the pathogenesis of AD, as the accumulation of toxic metals in the brain has been shown to lead to neurodegenerative effects.13 However, more studies are needed in order to understand the complex interactions between exposures and how chronic exposure to multiple metals may affect one’s lifetime risk of developing AD. Clearly, there is a gap in the research regarding how chronic exposure to mixed metals affects the development of AD. This is important as AD is both a disease that inflicts a heavy burden on individuals and their communities, and one where therapies to reverse the effects of neurodegeneration have been elusive. Providing long-term care for people with AD is an extremely costly expense for the Canadian healthcare system, and since there are no effective AD treatments on the market, it is time to focus on research efforts that can inform environmental and occupational health and safety policies in order to mitigate the risk of AD.

**References**

6. Martin S, Grwisold W. Human health effects of heavy metals [Internet].

UBCMJ Volume 11 Issue 1 | Fall 2019


