Lead Exposure & Alzheimer's Disease: Is There A Link?

A factsheet for medical professionals

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Alzheimer's disease (AD), or simply Alzheimer's, is the most common form of dementia. This incurable, degenerative, and terminal disease was first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906 and was named after him. *(1)* Generally it is diagnosed in people over 65 years of age, although the less-prevalent early-onset Alzheimer's can occur much earlier. An estimated 26.6 million people worldwide had Alzheimer's in 2006; this number may quadruple by 2050. *(2, 3)*

The term "Alzheimer's" is rapidly being used by the general public to refer to any elderly person suffering from dementia. Everyone who suffers from Alzheimer's disease has dementia. However, not everyone with dementia has Alzheimer's disease. Dementia may be caused by several other diseases.

History:

Alzheimer's disease, the chronic decline in intellectual capabilities, was recognized by the ancient Greek physician Hippocrates. At the time "senility" was thought to be simply a normal part of aging *(4)*. Alois Alzheimer, better defined the disease in a speech given in November 1906. Dr. Alzheimer examined the brain, after her death, of a woman who died at the age of 56, after having paranoid delusions, hallucinations, and a loss of memory, and noticed senile plaques and neurofibrillary tangles in the neurons (brain cells) *(5)*. Alzheimer wrote, "*On the whole, it is evident that we are dealing with a peculiar, little known disease process.*" Up until 1970 the diagnosis of Alzheimer's disease was restricted to patients less than 65 years old*(4).* Alzheimer's disease is no longer defined by age with between 50% and 75% of all dementia cases now being diagnosed as Alzheimer's disease, with the proportion increasing with age *(6,7)*.

Overview of Changes in the Brain:

Alois Alzheimer was able to describe two of the major changes in brain structure caused by Alzheimer's disease. In addition to the neurofibrillary tangles and neuritic plagues, AD also results in granulovascular degeneration, brain shrinkage, and decreased amounts of neurotransmitters (brain chemicals involved in communication). All of these changes impair the function of brain cells (neurons) and eventually lead to cellular death. Unlike many other cells, the brain is unable to regenerate new neurons. The gradual and progressive death of neurons is mirrored in specific behaviour changes. *(4)*

Phases of Alzheimer's

Mild dementia

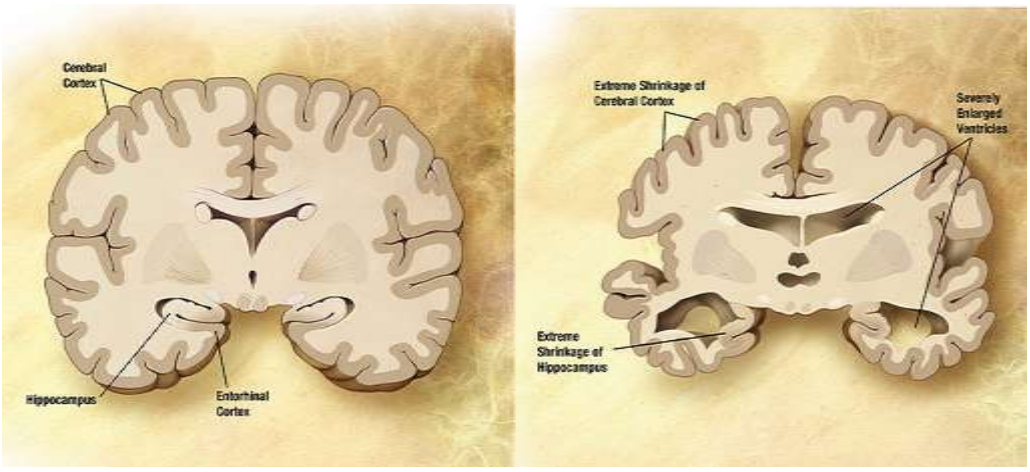
The chief characteristic of mild Alzheimer's disease is forgetfulness. Not only will the individual misplace items but will start to place them in unusual locations (e.g. keys in the freezer). The decline may be so gradual that it may take family members years to notice since some forgetfulness is a natural part of aging. Loss of a sense of time and direction greatly interferes with the ability to navigate and are important components of a "sense of direction." The characteristic of becoming lost, especially in unfamiliar territory is a common hallmark in mild AD. *(4)*

Moderate dementia

Once Alzheimer's disease deteriorates to the moderate stage; profound memory loss that interferes with daily activities characterizes the disorder. The AD patient in the moderate stage is dependent upon others. The sufferer becomes lost even in familiar surroundings and has lost the ability to learn any new material. *(4)*

Severe dementia

Once the disease progresses to the severe stage the patient suffers from severe impairment of mind (cognitive functions) and body. The subject has reached the point they may no longer recognize their spouse and children. The AD patient no longer has any sense of time or current location. Verbal communication has decreased to the point of phrases, words, or merely syllables are constantly repeated. Eventually, even this simple communication degenerates to a complete inability to speak. The overall loss of coordination and body control means the patient may require help dressing, bathing, grooming, eating, and toileting. *(4)*



Description: **Combination of two diagrams of the brain in one for comparison. Left: A normal brain. Right: The brain of a person with Alzheimer's disease showing extreme shrinkage of the cerebral cortex and hippocampus and enlargement of the ventricles.** *(8)*

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Although Alzheimer's disease (AD) is a progressive neurodegenerative disorder whose clinical manifestations appear in old age, the initial events that trigger this disease may begin very early in life.

In consequence of the "Barker hypothesis", which links early life experiences and adult diseases, there is a new concept regarding certain adult diseases that emphasizes the role of environmental factors operating during the preconceptual, fetal, and infantile phases of life. *(9)*

The sporadic nature of most AD cases strongly argues for an environmental link that may accelerate normal age-related processes in the brain. Due to the widespread occurrence of AD, such environmental agents (risk factors) would have to be widespread and persistent, and chronic human exposure to them very common. Although few environmental agents may fit this description, the heavy metal Pb is widespread and is known to produce permanent behavioral and cognitive perturbations. *(10, 11)*

Lead (Pb) poses widespread public concern. Humans can be exposed to Pb through paint, glazed earthenware, lead piping, solder in food containers, moonshine whiskey, and automobile battery casings. Occupational exposure to Pb can come from smelters, battery manufacturing, welding, automobile radiator repair, and production of Pb-based paints. Although organic forms of Pb have been removed from gasoline, inorganic Pb still remains the number one environmental hazard facing humans today. *(12)*

Occupational lead exposure may have long-term effects and dramatically increase the risk of developing Alzheimer's disease in later years, according to research presented during the American Academy of Neurology's 52nd Annual Meeting in San Diego, CA, April 29 -- May 6, 2000. Researchers believe that people who have worked in jobs with high levels of lead exposure are up to 3.4 times more likely to develop Alzheimer's disease. Dr Koss of the American Academy of Neurology quotes: "Although lead has long been known to be toxic -- and is believed to have affected the brains of some of the rulers of the Roman Empire, thereby causing its downfall -- its long-term damages are difficult to measure, and thus, the extent of its negative effects have been largely overlooked." *(13)*

The pathogenesis of Alzheimer's disease: Evidence for an environmental link:

AD pathology is characterized by senile plaques and neurofibrillary tangles (NFTs), combined with massive neuronal loss. The major constituents of senile plaques *(or amyloid plaques)* are 39–42 residue peptides (Aβ) snipped from a larger protein called the amyloid precursor protein (APP). Current studies indicate that APP is processed by a group of secretases. Cleavage of APP by β-secretase produces sAPPβ and C99 fragments. C99 is then cleaved by γ-secretase to release Aβ. However, prior processing of APP by α-secretase precludes the formation of the neurotoxic Aβ. Inhibiting α- secretase activity predisposes the processing of APP via the β-secretase pathway, which ultimately leads to neurotoxicity. On the other hand, suppression of β-secretase or γ-secretase activity prevents the formation of the neurotoxic Aβ molecule. *(14,15)*

Aβ processing and aggregation are thought to be critical events in the etiology of neurodegenerative diseases such as AD. Mutations in APP have been shown to promote AD

pathogenesis in familial AD by altering its proteolytic processing, which results in an increased production of Aβ. *(16)*

Recent studies in rodents have shown that exposure to lead (Pb) during brain development predetermined the expression and regulation of the amyloid precursor protein (APP) and its amyloidogenic β-amyloid (Aβ) product in old age. It is also reported that the expression of AD-related genes [APP, BACE1] as well as their transcriptional regulator (Sp1) were elevated in 23-year-old monkeys exposed to Pb as infants leading to an Alzheimer's disease (AD)-like pathology in the aged monkeys. *(17, 18)*

Chronic lead (Pb) exposure also affected granule cell morphology in Pb-exposed rats. Dendrites frequently appeared dystrophic, similar to those present in Alzheimer's disease. Dendrites play an essential role in neuronal signaling and aberrations in dendritic morphology are likely to alter their functional characteristics. *(19)*

These data suggest that AD pathogenesis is influenced by early life exposures and argue for both an environmental trigger and a developmental origin of AD. The findings implicate an environmental agent (Pb) in the pathogenesis of AD and demonstrate that development is an important period of vulnerability, which could increase future susceptibility to neurodegeneration and AD pathology.

Therapeutic proof of heavy metal implication:

Clioquinol, a chelating agent used in heavy metal toxicity, is under investigation for the treatment of Alzheimer disease. A pilot phase 2 study with clioquinol showed that the effect of the treatment was significant in the more severely affected group and supports further investigation of this novel treatment. Clioquinol is a chelator that crosses the blood-brain barrier and may diminish the accumulation of amyloid beta in plaques. Clioquinol was shown to produce a significant reversal of amyloid-beta plaque deposition in vitro as well as in vivo in a clinical trial. *(20, 21)* Another pilot study has shown the efficacy of the chelating agent ***d-penicillamine*** in reducing oxidative stress in Alzheimer disease patients. *(22)*

In conclusion, lead (Pb) is a xenobiotic metal with no known essential function in cellular growth, proliferation, or signalling and there is compelling evidence that exposures to Pb have adverse effects on the nervous system. *(23)* The sporadic nature of Alzheimer's disease (AD) and a number of studies suggest that AD pathogenesis is influenced by early life exposures and argue for both an environmental trigger and a developmental origin of AD. Recent research presents novel findings that implicate lead (Pb) in the pathogenesis of AD and demonstrate that development is an important period of vulnerability, which could increase future susceptibility to neurodegeneration and AD pathology.

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