Developmental Lead Exposure and Alzheimer's Disease

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Alzheimer's Disease (AD) is the most common neurodegenerative disorder among our elderly but scientists are still not sure when the disease process starts or how long the neurodegenerative processes take before AD manifests. An estimated 5.3 million people have the disease and this number is expected to triple by 2050 (Hebert *et al.* 2003). Early-onset AD has been genetically linked (Campion, *et al.*1999) but the etiology of late-onset AD (LOAD), which affects the majority of individuals continues to be largely misunderstood (Lahiri, *et al.*2008).

Historically scientists have used a 'protein only' explanation for the etiology of LOAD (Lahiri, *et al.*2007). The blame is placed on the plaques and protein tangles caused the amyloid-β peptide which is derived from β-amyloid precursor protein or AAP. The buildup of the peptide plaque causes the symptoms characterized by LOAD (Hardy and Higgins, 1992; Selkoe, 2003; Hardy and Selkoe, 2002). Researchers have also cited oxidative stress and inflammation as links to LOAD (Bellingham, *et al.*2004) but none of these theories has been able to explain the sporadic nature of the disease, nor an exact causal relationship between known risk factors and LOAD. Because of this scientists have begun looking at environmental causes, including developmental exposure to lead (Lahiri, *et al.*2008).

This shift in approach has its basis in the 'Barker Theory', which associates metabolic changes as a result of low birth weight and subsequent rapid childhood weight gain to increased risk of coronary heart disease, hypertension and diabetes later in life (Barker, *et al.*2002; Cheung; *et al.*2000; Eriksson, *et al.*2000, Osmand and Barker, 2000). Barker's theory implies that environmental exposures during developmental stages have a role in the risk of disease as individuals age.

There have been recent animal studies conducted to address the early exposure to lead and latent effects on genetic patterns associated with AD. Bolin and colleagues exposed rat pups

to lead acetate (Bolin, *et al.*2006). There were two experimental groups, those exposed at birth through weaning, those exposed late in life (20 months) and a control group. The animals with early exposure had increased levels of genetic by-products associated with AD and increased oxidative DNA damage when compared to the other groups, suggesting that neurodegeneration in the aging brain is impacted by lead exposure early in life (Bolin, *et al.*2006). In an attempt to link Bolin's results with pathological evidence of AD and to obtain results more homologous to humans, Wu and colleagues examined brain tissue of 23 year old monkeys who were exposed to lead in infancy (Wu, *et al.*2008). Their results showed that when compared to controls, the exposed monkeys had increased levels of amyloid-β and oxidative DNA damage biomarkers. The researchers concluded that developmental exposure to lead increased susceptibility to AD (Wu, *et al.*2008).

Lahiri and associates have proposed the Latent Early-Life Associated Regulation (LEARn) model to explain the relationship between genetics and the environment and how they relate to disease expression (Lahiri, *et al.*2007). LEARn specifically addresses how early exposure to environmental agents can alter the systems that regulate AD associated genes in the long-term (Lahiri, *et al.*2008).LEARn proposes that the overproduction of APP and amyloid-β are triggered during developmental stages by environmental exposures. This mechanism continues throughout life via DNA methylation (Lahiri, *et al.*2008).So because of environmental exposure, any genes that may have AD protective factors have altered methylation processes. Lahiri *et al.* propose that these disturbances coupled with the normal genetic changes that occur during the aging process, like increased inflammation, result in AD (Lahiri, *et al.*2008).

Lead exposure was greatly restricted by the Clean Air Act of 1970 which mandated the reduction of ambient air levels of lead and subsequently required that leaded gasoline be phased

out by the mid-1980s. To protect those most at risk, the U.S. Department of Housing and Urban Development enacted the Residential Lead-Based Paint Hazard Reduction Act of 1992. In December 2008, the Environmental Protection Agency's "Renovation, Repair and Painting Rule" went into effect. The rule requires any contractors that perform renovations to child-care facilities built prior to 1978, must distribute the lead hazard pamphlet to occupants of facilities and caregivers of children who attend these facilities (EPA, 2008).

In the short-term the best interventions are to first establish a nationwide AD registry, fostering collaboration among agencies and tracking AD incidence more closely (Landrigan, *et al.*2005). Second is to improve and expand toxicity testing measures. This would involve changing and extending research protocol to include *in-utero* exposure and life-long follow-up, incorporating neurologic testing and neuropathology (Landrigan, *et al.*2005). Currently the majority of research exposes animals in adolescence with testing conducted 12 to 24 months later (Landrigan, *et al.*2005). In the long-term prospective epidemiologic and genetic studies should be conducted to assess the effects of environmental factors on neurodegeneration (Landrigan, *et al.*2005).

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