Amyotrophic Lateral Sclerosis (ALS): Research Directory

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease or Lou Gehrig's disease, is a rare neuromuscular disease with an incidence rate of about 1 in 100,000. It is characterized by muscular weakness from the degeneration of motor neurons, and like PD, intellect and personality is often unaffected. The National Institute of Neurological Disorders and Stroke reports that only 5-10% of all ALS cases can be traced to genetics, particularly to a mutation related to the superoxide dismutase 1 enzyme. This leaves the vast majority of cases without a known etiology, with the potential for environmental association briefly outlined below.

Far fewer studies have examined the association of pesticides and ALS than for both AD and PD. McGuire et al. (1997) found that agricultural chemicals have a significant association with the development in ALS, with a stronger association for men than for women.

Metals may play a role in the development of ALS. Some studies have observed an association with occupation in welding or soldering (Armon et al. 1991; Gunnarsson et al. 1992), but not all have found metals to be related to ALS (Gresham et al. 1986; McGuire et al. 1997). More specifically, an association has been observed with exposure to lead (Armon et al. 1991; Chancellor et al. 1993; Felmus et al. 1976; Kamel et al. 2002), but no association was observed between ALS and lead levels in various tissues (Kapaki et al. 1989; Stober et al. 1983) or toenails (Bergomi et al. 2002); however, these studies had limited numbers of study participants. No association was observed between exposure to zinc and ALS (Vinceti et al. 2002), and the evidence from biomarker studies is inconclusive, with an increased (Gellein et al. 2003), decreased (Yasui et al. 1993), and no association observed for levels in brain tissue (Kapaki et al. 1997; Nagata et al. 1985) or toenails (Bergomi et al. 2002) compared with controls. However, these studies may have had limited power based on the size of the study population. Although one epidemiologic study showed no association between exposure to copper and ALS (Vinceti et al. 2002), there was decreased copper concentration observed in both cerebrospinal fluid and blood (Kapaki et al. 1997), and no association in toenails (Bergomi et al. 2002) among patients with ALS versus controls. Mercury was associated with ALS risk (Felmus et al. 1976) but was found in lower concentrations in the blood of ALS patients versus controls (Moriwaka et al. 1993).

Case-control studies examining biomarkers of iron, manganese, selenium, and Al and risk of ALS were found. Increased iron levels have been observed in brain tissue (Kasarskis et al. 1995; Yasui et al. 1993), although not in blood (Nagata et al. 1985) or toenails (Bergomi et al. 2002). An increase of manganese was observed in cervical cords (Miyata et al. 1983), both an increase (Kapaki et al. 1997) and decrease (Nagata et al. 1985) in blood levels, and no difference in toenail concentration (Bergomi et al. 2002) among cases versus controls. Selenium was found to be increased (Nagata et al. 1985) and decreased (Moriwaka et al. 1993) in blood cells, but no association was observed in toenails (Bergomi et al. 2002) of patients with ALS versus controls. An increase was observed in Al in central nervous system tissue (Yasui et al. 1991a, 1991b) and cerebrospinal fluid (Sood et al. 1990), yet others observed no association in spinal cords (Kasarskis et al. 1995) or toenails (Bergomi et al. 2002). However, the latter two studies had small numbers of study participants, possibly limiting the power to detect an association.

A few studies found a relationship between other exposures and ALS. Gunnarsson et al. (1992) found a nonsignificant association with solvents, but the association was stronger and statistically significant for males with family history of neurodegenerative disease or thyroid disease. Others found conflicting results (Chancellor et al. 1993; McGuire et al. 1997). One study found that those with a history of occupation in the manufacturing of plastics have a significant association with the development of ALS (Deapen and Henderson et al. 1986). Occupations in electrical work have been implicated in the development of ALS in a few studies (Deapen and Henderson 1986; Gunnarsson et al. 1992).

Conclusion

Epidemiologic evidence for an association between environmental agents and neurodegenerative disease is inconclusive. The amounts of xenobiotics released into the environment are huge by any measure, and the paucity of information about their effects on various physiologic systems, including neurodevelopmental processes, represents a major gap in knowledge. To close this gap, the following broad areas of research topics need attention: a) better health tracking and monitoring data for chronic diseases, b) more comprehensive and longitudinal biomonitoring of environmental agents that can be linked with specific molecular/biochemical markers of exposure and subsequent health outcome data, and c) more epidemiologic research and testing of environmental agents to better define their effects on the adult and developing brain, as well as other critical organ systems.

Until such time that ethically and scientifically well-designed epidemiologic studies can provide a reasonable certainty that specific environmental agents, either alone or in combination with other agents, cause a given neurodegenerative disease, research on the environmental contribution to neurodegenerative disease needs to continue.

This article is part of the mini-monograph "Early Environmental Origins of Neurodegenerative Disease in Later Life: Research and Risk Assessment."

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A Phase I safety study of hyperbaric oxygen therapy for amyotrophic lateral sclerosis

ALS
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BACKGROUND: Vascular endothelial growth factor and mitochondrial abnormalities have been described in ALS and its animal models. We have reported that hyperbaric oxygen (HBO) treatment delayed the onset of weakness in the wobbler mouse. OBJECTIVE: To perform a Phase I safety study of HBO in patients with ALS.

METHODS: Five patients with ALS were treated for 60min with 100% oxygen at 2 atmospheres pressure daily for five days a week for four weeks. The patients reported any deterioration in their condition after each treatment, and their neurological condition was measured serially during the four weeks of the treatment, and for four further weeks.

RESULTS: Four patients reported decreased fatigue, while one patient dropped out at three weeks because of increased fatigue. Maximum isometric voluntary contraction (MVIC) of all muscle groups except right hand grip improved significantly by up to 97%. Most improvement occurred during the four weeks after treatment. It is possible that the improvement in muscle strength was a placebo or a learning effect, though no such effects have been detected in prior therapeutic trials in ALS using MVIC. No change was detected in other measures of neuromuscular function.

CONCLUSIONS: A longer duration, placebo controlled trial in a larger number of patients is needed to determine the safety and efficacy of HBO. Until that is completed, it is not recommended that ALS patients should be treated with HBO.

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