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THE ROLE OF ENVIRONMENTAL MERCURY, LEAD AND PESTICIDE EXPOSURE IN DEVELOPMENT OF AMYOTROPHIC LATERAL SCLEROSIS

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Abstract

Exposure to an environmental toxicant as a risk factor in the development of amyotrophic lateral sclerosis (ALS) was first hinted (demonstrated) in the Chamorro indigenous people of Guam. During the 1950s and 1960s these indigenous people presented an extremely high incidence of ALS which was presumed to be associated with the consumption of flying fox and cycad seeds. No other strong association between ALS and environmental toxicants has since been reported, although circumstantial epidemiological evidence has implicated exposure to heavy metals such as lead and mercury, industrial solvents and exposure to pesticides especially organophosphates and certain occupations such as playing soccer. Given that only ~10% of all ALS diagnosis has a genetic basis, a gene-environmental interaction provides a plausible explanation for the other 90% of cases. This mini-review provides an overview of our current knowledge of environmental etiologies of ALS with emphasis on the effects of mercury, lead and pesticides as potential risk factors in developing ALS. Epidemiologic and experimental evidence from animal models investigating the possible association between exposure to environmental toxicant and ALS disease has proven inconclusive. Nonetheless, there are indications that there may be causal links, and a need for more research.

Keywords

Methylmercury; Lead; Organophosphates; Paralysis; Amyotrophic lateral sclerosis; Gene-environment; Neurodegenerative disease

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a lethal, progressive, adult onset motoneuron disease characterized by disintegration of corticospinal tract neurons and α -motor neurons in the brainstem and spinal cord (Morrison et al., 1995; Sejvar et al., 2005; Schymick et al., 2007). ALS neuropathology is characterized by accumulation of insoluble proteins in the cytoplasm of disintegrating neuronal cells (Leigh et al., 1991). The sequelae of ALS include difficulty in performance of certain tasks within a single limb which progresses gradually to include

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disintegration in other muscle groups leading to loss of limb function, difficulty in speaking or swallowing. It ultimately ends in respiratory failure and death. Once diagnosed with ALS, the survival time is 2 to 5 years making ALS one of the most rapidly progressive and fatal neurological disorders. The worldwide incidence of ALS is ~2–4 /100,000 people affected per year with the exception of some high-risk areas around the Pacific Rim such as Guam or parts of Western New Guinea (Spencer et al., 1987; Iwami et al., 1993; Plato et al., 2003a, b; Waring et al., 2004). Specifically, individuals of the Chamorro indigenous people of Guam had a high incidence rate, and men exhibit a 20–60% increased risk compared to women (Christen et al., 2006; Schmidt et al., 2008). Additionally, 1991 Persian Gulf War Veterans have been reported to have a twofold increase risk of developing ALS, particularly among Air Force and Army personnel (Horner et al., 2008; Miranda et al., 2008). The basis for this enhanced susceptibility is yet unknown, however, several postulated causes have for the most part been ruled out. Age is certainly a risk factor for developing ALS; individuals older than 40 years present higher susceptibility rates, with a median age of 55 years. Moreover, within the last two decades the incidence and mortality rates in the general population have risen (Worms, 2001). However, it is quite striking that in the Persian Gulf War veterans the age of onset of ALS is dramatically earlier (Haley 2003; Kasarskis et al., 2009).

ALS occurs either as a sporadic (sALS) or familial form (fALS); both forms present indistinguishable clinical symptoms. Approximately, 90% of the cases of ALS are of the sporadic (sALS) form with no known etiology, but 10% have a known genetic basis. Approximately, 20% of the familial cases are linked to mutations in Cu/Zn-superoxide dismutase 1 gene (SOD1) (Rosen et al., 1993; Gurney et al., 1997).

Shortly after World War II the Chamorro Guamanians experienced an extremely high incidence rate of ALS or ALS-like condition; in 1954 it was estimated to be 50–100× higher than the worldwide rate (Kurland and Mulder, 1987). Recent investigation suggests that the incidence and prevalence rate has declined precipitously over the last 4 decades to levels that correlate more closely to the rest of the world (7/100,000) and it is found only in older individuals and rarely in persons born after 1960 (Galasko et al., 2002; Plato et al., 2003a, b). The reason for this decline is unknown. Plato et al. (2003a, b), conclude that it was not due to genetic factors, but most likely is the result of ethnographic changes, radical socioeconomic, and ecologic changes brought about by the rapid westernization of Guam. Galasko et al. (2002), conclude that it was due to modifying environmental factors. However, the emerging view seems to suggest that the initially high incidence rate of ALS among Chamorro Guamanians was the result of the cumulative consumption of cycad flour and flying fox (Spencer et al., 1987; Kirsby et al., 1992; Cox and Sacks, 2002). The flying fox which was a regular part of their diet, bioaccumulates toxic substances found in the cycad seed, one of these was identified as β-methylaminoalanine (BMAA) a known neurotoxin (Cox and Sacks, 2002). In addition, cycad flour made from the seed of cycad, *Cycas rumphii*, was well known to the Chamorro as acutely toxic and they detoxified the flour with multiple washing during preparations (Sack 1993; Cox and Sacks, 2002; Murch et al., 2004). Collectively, the consumption of cycad flour and cycad-eating flying foxes which biomagnifies the highly lipophilic BMAA provide causal environmental link to ALS or ALS-like condition in Guam. Additionally, a combination of other environmental factors, superimposed, perhaps on genetic polymorphism yet to be identified may have contributed to the high incidence rate of ALS among indigenous Chamorro of Guam. Due to the relatively high rates of sporadic as compared to familial ALS, the potential role of environmental factors to its etiology is suggestive.

The comparatively high rate of sALS as compared to fALS has led to the postulate that exposure to environmental pollutant is link with potential genetic susceptibility to contribute to the pathogenesis of ALS. A growing list of potential environmental risk factors is proposed for developing sALS (McGuire et al., 1997; Weisskopf et al., 2004; Sutedja et al., 2008; Weisskopf

et al., 2009). However, to date no definitive causal link has been consistently established. The most consistent associations are exposure to pesticides, heavy metals including lead and mercury, intense physical activity including playing professional soccer, head injury, cigarette smoking, and electromagnetic fields-EMF (Nelson et al., 2000; Håkansson et al., 2003; Morahan et al. 2006; Qureshi et al., 2008). Physical activity is reported to have minimal, if any, effect as a risk factor for developing ALS (Longstreth et al., 1998; Veldink et al., 2005). There is some epidemiological evidence of an association between occupational exposure to EMF and the risk of developing ALS (Li et al., 2003, Håkansson et al., 2003). However, these risks have not been confirmed in the experimental mouse model of ALS (SOD1G93A) following exposure to extremely low frequency magnetic fields (Poulletier de Gannes et al., 2008).

Among the many forms of environmental exposure scenarios postulated, agricultural pesticides and heavy metals such as mercury and lead in particular are the most likely toxicants routinely encountered by humans and could potentially be a risk factor in the development of sALS. They are likely candidates because we encountered these toxicants in a plethora of environmental media such as air, water, wind drift, multiple dietary sources and volcanic eruptions. Specifically, the pathophysiology of agricultural pesticides, lead and mercury is not yet known but their human neurotoxicity is well studied, documented and is substantial (Roscoe et al., 2002; Thakur et al., 2008; Albanito et al., 2008; Mutter and Yeter, 2008). Mercury and lead exposure have each been associated with the risk of developing ALS (Praline et al., 2007; Kamel et al., 2008). However, inconsistent results have been reported between the concentration in tissue and cerebrospinal fluids and their correlation with the risk of developing ALS. For example, mercury, lead and other metals were found either in lower concentrations or unchanged in the blood and cerebrospinal fluid of ALS patients versus controls (Pierce-Ruhland, 1980; Foo et al., 1993). Conversely, Kurlander and Patten, (1979), report that even after 1-year of chelation therapy the concentration of environmental metals in tissue after death was significantly increased. Retrospective and prospective epidemiological studies of ALS and environmental factors are also inconclusive. A large prospective study of chemical exposures and ALS did not uncover any evidence for an association with exposure to pesticides/herbicides; however, there was an increased risk of ALS with formaldehyde exposure (Weisskopf et al., 2009). Interestingly, this large prospective study examined many different chemicals but did not include heavy or transitional metals.

LEAD

Metals have been known for sometime to possess the potency to induce pathologic conditions if they accumulate to toxic levels or become deficient. The literature is replete with information demonstrating the efficacy of iron and copper for example, to cause disease in humans. In fact, abnormal increases in copper or iron in the blood cause Wilson's disease and hematochromatosis, respectively. Furthermore, in a rodent model of ALS, exposure to high or low levels of zinc hastens the time of onset of ALS like phenotype (Groeneveld et al., 2003; Ermilova et al., 2005). Currently, some progress has been made in trying to understand the role of heavy metals in neurodegenerative diseases. Johnson and Atchison (2009), recently reported that chronic exposure of mutant human SOD1G93A mice to low levels of methylmercury hastens the time of development of ALS phenotype. However, no evidence has been presented as to the ability of any metal to independently or in concert with a genetic polymorphism to cause or promote the development of neurodegenerative diseases in humans, including ALS.

The association of exposure to lead and development of neurodegenerative diseases is not well studied. Paradoxically, lead is reported to be associated with greater survival in ALS patients and human mutant superoxide dismutase-1 G93A transgenic mice (Campbell et al., 1970; Barbeito et al., 2005; Kamel et al., 2005). Boillee et al. (2006) showed that different cell types

contribute to different stages of ALS onset and progression. This was supported by the observation that greater tibia and blood lead levels increase survival of ALS patients (Kamel et al., 2008). This is somewhat controversial given the plethora of evidence that indicates that lead is a neurotoxicant and not a neuroprotectant (Bins et al., 1999; Albalak et al., 2003; Lindgren et al., 2003; Yan et al., 2008). Further, the basis for this presumably neuroprotective role of lead in ALS patients or transgenic mice is unknown. An abstract published by Barbeito et al. (2005), suggested that exposure to lead causes activation of astrocytes. One of the explanations cited was that lead causes activation of astrocytes which induce increase accumulation of lead by increasing production of antioxidant thereby providing protection to neuronal cells. This hypothesis is still awaiting verification.

MERCURY

Mercury neurotoxicity in humans is well documented, with toxic episodes occurring in Japan and Iraq (Bakir et al., 1973). Mercury, especially methylmercury (MeHg) intoxication is a real concern. However, very few epidemiological studies have examined the relationship between chronic mercury ingestion and its ability to caused neurodegenerative diseases in humans or animals (Zumstein and Regli, 1982; Praline et al., 2007). Epidemiological and case control studies have shown an association between exposure to total mercury and the potential to develop ALS (Provinciali et al., 1990; Praline et al., 2007). Acute or accidental mercury ingestion cases in humans have been reported (Adams et al., 1983; Schwartz et al., 1996). Schwartz et al. (1996) reported that after three years of accidental acute mercury exposure, the clinical symptoms were similar to those observed in ALS patients. Anecdotally, mercury toxicity can cause syndromes similar to those used when diagnosing ALS including tremor, extremity weakness, spasticity, hyperreflexia, fasciculation and ataxia. Conversely, Gresham et al. (1986), using retrospective case control study, reported no association between mercury and other heavy metals in the pathogenesis of ALS. Other similar retrospective studies have confirmed those results (Moriwaka et al., 1991). There have been virtually no animal experiments to test this association. However, in the mouse model of ALS, overexpressing the mutant human SOD1 gene (TgN SOD1G93A), chronic exposure to methylmercury induced early onset of hind limb weakness characteristic of this model (Johnson and Atchison, 2008). This suggests that if an individual has an underlying genetic polymorphism for ALS exposure to a toxic metal such as methylmercury could hasten the onset of ALS

Methylmercury exposure can occur after acute, sub-chronic or chronic episodes and the symptoms are characterized by ataxia, disturbances of sensory and visual function and extremity weakness. In acute accidental exposure such as those observed in Iraq, autopsy of brains of prenatally-exposed infants showed widespread inhibition of cellular processes and deranged brain connectivity (Bakir et al., 1973). Moreover, for some of these patients a neuromuscular disorder resembling myasthenia gravis was reported (Rustam et al., 1975). However, a cause and effect relationship between exposure to MeHg and ALS has never been specifically demonstrated. Nonetheless, evidence following occupational exposure scenarios and animal studies seem to suggest that mercury exposure may play a contributory role in the etiology of ALS (Barber, 1978; Adams et al., 1983; Praline et al., 2007). A single dose of HgCl_2 in mice causes deposition of mercury in localized spinal motor neurons, brainstem motor nuclei and cerebral cortex (Arvidson, 1992; Chuu et al., 2007). Barber, (1978), reported a case of occupational exposure to metals and ALS in which occupational exposure to mercury induces neurologic dysfunction resembling ALS. However, those results were not supported by Pamphlett and Waley, (1998). They found no significant differences in concentration of inorganic mercury in the upper and lower motoneurons of patients with sporadic motoneuron disease and controls. Paradoxically, a report by Sienko, et al. (1990), on a cluster of cases of ALS in families in a Lake Michigan-based city with a history of frequent consumption of fresh-caught fish which lends some credence to the postulate that environmental exposure to an agent

such as MeHg could contribute to the pathogenesis of ALS. Given the clear association of fish consumption with MeHg exposure and the reported levels of Hg in some Lake Michigan fish species this observation provides some basis for suggesting a potential role of metal exposure in ALS.

Humans are potentially exposed chronically to a variety of environmental contaminants. It is therefore plausible, that if an individual has the genetic polymorphism for ALS, they may be at greater risk of developing a disease condition when challenged by one such contaminant. MeHg is one such environmental contaminant that still possesses significant toxicological human health risk, especially in the Great Lakes, to Greenlandic Inuits, the Faroe Islands, and recently in the Brazilian Amazon (Donoghue, 1998; Grandjean, et al., 1999). No association between dietary MeHg exposure and ALS incidence has been reported, but the target populations are sufficiently small that a difference could not be apparent. In terms of human exposure, MeHg is the most important organic mercury compound. Exposure is primarily through the diet, with fish and fish products implicated as the dominant sources. In several minority populations such as American Indians, as well as Alaskan Natives, recreational anglers, and subsistence fishers, blood mercury levels are higher than acceptable levels (Burge et al., 1994). In addition, the 1999 and 2000 NHANES data showed that a significant number of babies in the US may have been exposed *in utero* to MeHg at dosages that were previously thought to be safe (Mahaffey et al., 2004). Thus, exposure to MeHg remains a potential toxicological challenge that could be superimposed on a genetic underlying condition.

PESTICIDES

Pesticides are strong candidates to be examined for their risk of inducing ALS because of their pervasive and ubiquitous nature and their association with other neurodegenerative diseases such as Parkinson and Alzheimers (Elbaz et al., 2007; Stozická et al., 2007). However, few epidemiological or animal studies have examined the relationship between exposure to pesticides and the risk of developing ALS. Pesticide exposure and especially organophosphates gained prominence in their association with ALS following the observation that Persian Gulf War veterans presented an increased incidence of ALS (Horner et al., 2008; Kasarskis et al., 2009). Hitherto, no conclusive epidemiological evidence has emerged to explain this apparent increase in risk of developing ALS in Gulf War veterans. However, it has been reported that returning 1991–1992 Gulf war veterans who were in the conflict arena received prophylactic treatment containing cholinergic inhibitors to guard against nerve gas and insect pests (The Reigle Report, 2003). It is therefore plausible to suggest that these pretreatments could have exacerbated an underlying genetic polymorphism or unmasked other factors that increase risk of motoneuron death.

The organophosphate (OP) class of pesticides is widely used in agricultural and some household settings. OP's accounts for one half of the total pesticide usage annually in the USA (Weiss et al., 2004). OPs have been investigated as a potential risk factor in development of ALS (Morahan et al, 2006, 2007a; Wills et al., 2008). Morahan et al. (2007a) analyzed the potential of pesticides, heavy metals and chemicals to cause sALS and showed that impaired ability of sALS patients to detoxify these toxicants could be related to differences in metallothionein family of genes, metal transcription factor-1 (MTF-1) and glutathione synthetase (GSS). Other studies investigating the likelihood of exposure to organophosphates and the potential for developing ALS have examined paraoxonase genes. Paraoxonase is classified as an A-esterase based on its ability to detoxicate paraoxon; the prototype OP. Paraoxonase (PON1) which detoxifies OPs, has several variants; PON1, PON2 and PON3. It is postulated that a person risk of developing ALS could increase if there is an increase in mutation of PON1 gene and if the body concentration of PON1 is suboptimal (Furlong et al., 2000 and 2005; Landers et al., 2008; Richter et al., 2009). This postulation originates from the

fact that PON1 hydrolyses OPs and its ability to detoxify them is largely determined by different variants of PON1 as opposed as to other variants (Li et al., 2000; Saeed et al., 2006; Valdmantis et al., 2008). For example, genetic variations have been found in the coding and promoter region of the human PON1 locus that determines the catalytic activity and enzyme levels (Adkins et al., 1993; Brophy et al., 2001). Therefore, mutations that impair the ability of PON1 to detoxify OPs could increase the sensitivity of patients to OPs and potentially lead to development of ALS (Slowik et al., 2006; Sirivarasai et al., 2007). However, epidemiological and animal studies have been very inconsistent in establishing a causal link between OP exposure and mutations in the PON1 gene (Simpson and Al-Chalabi, 2006; Wills et al., 2008). Wills et al. (2008), showed that polymorphism of PON1 genes did not reduce enzyme activity and is unlikely to be the cause of sALS. Nonetheless, strong support continues for a causal link between exposure to OPs, some paraoxonase variants and Gulf War syndrome (Martin et al., 1985; Henderson et al., 2002; Saeed et al., 2006; Cronin et al., 2007; Valdmantis et al., 2008; Diekstra et al., 2009). Further study to buttress the apparent association between increase Gulf War Syndrome and exposure to OPs has been reported (Haley et al., 1996; Mackness et al., 2000). Those studies suggest that US veterans with Gulf War syndrome had significantly lower serum concentrations of one form of PON1 allozyme, whereas British veterans with Gulf War Syndrome were found to have lower concentrations of both allozymes (Q and R allozymes) compared with healthy Gulf War veterans.

Summary

It is reasonable that multiple gene-environmental interactions which govern several biochemical pathways are linked to development of ALS. Exposure to heavy metals and pesticides are potential candidates. However, it is still not known which, if any of these environmental exposure scenarios, affect human health risk for development of ALS. The heavy metals are certainly likely candidates because of there proven neurotoxicity, ubiquitous nature and causal epidemiological link that has been established with ALS and other neurodegenerative diseases. Conversely, exposure to OPs, gained notoriety as a risk factor in developing ALS since the end of the first Persian Gulf War. Obviously, more systematic investigation is needed to test whether the pathways associated with motoneuron degeneration can potentially interact with environmental toxicants to contribute to development of ALS.

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