Possible involvement of overexposure to environmental selenium in the etiology of amyotrophic lateral sclerosis: a short review

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Summary. Excess exposure to the metalloid selenium (Se), a trace element with both toxicological and nutritional properties, has been implicated in the etiology of a human motor neuron disease of unknown origin and extremely severe prognosis, sporadic amyotrophic lateral sclerosis (ALS). This relation has been suggested on the basis of two epidemiologic investigations which found an increased risk of ALS associated with residence in a seleniferous area or with consumption of drinking water with unusually high levels of inorganic hexavalent Se, in South Dakota and in northern Italy respectively. Biological plausibility to a Se-ALS relation is provided by veterinary medicine observations and toxicological studies, showing that Se, particularly the inorganic forms, has a selective toxicity to motor neurons in swine and in cattle. Neurotoxic effects of Se species have also been demonstrated in laboratory studies and, for the inorganic forms, even at very low concentrations. Selenium has also been shown to affect muscle function in experimental animal models. Overall, these findings from the epidemiologic and the toxicological literature indicate that environmental Se, particularly in its inorganic forms and at unexpectedly low levels of exposure, might be a risk factor for ALS, suggesting the opportunity to further investigate this issue.

Key words: selenium, amyotrophic lateral sclerosis, water, environment, epidemiology.

INTRODUCTION

Despite the several studies carried out so far, the search for environmental risk factors of amyotrophic lateral sclerosis (ALS), a degenerative disease of the motor neurons of unknown origin and extremely severe prognosis, has been so far unable to provide substantial evidence for any causal association. To some extent this is also true for the potential genetic alterations involved in this disease. However, some epidemiologic trends indicate that ALS etiology may be linked to environmental factors, despite other inconsistent observations [1]. Among the environmental factors investigated to date, strong interest has been devoted to neurotoxic chemicals, including heavy metals, metalloids, pesticides and cyanobacteria toxins [2, 3]. Here we present an analysis of the evidence supporting an association between excess exposure to one of these substances, the trace element selenium (Se), and ALS risk.
HUMAN SELENIUM EXPOSURE

The metalloid Se is a trace element characterized by a strong biological reactivity. Wide consensus exists on the fact that Se has both toxic and nutritional activities in the human and a very narrow safe range of exposure, with biological effects largely depending on its chemical forms (i.e., inorganic/organic status and oxidation state) [4, 5]. On the contrary, conflicting opinions exist as to which human diseases are really associated with excess or deficient exposures to this element and the exact boundaries of the safe range of intake [6]. Most recent studies indicated that the safe range of intake is considerably lower than previously believed [6-9], along with Se inability to reduce cancer risk as previously hypothesized [9].

In humans, Se exposure generally occurs through diet, whilst drinking water and occupational environments are rarely a source of exposure [10]. In foodstuffs, Se is generally in the form of organic Se, whilst in occupational settings and in groundwaters Se is generally found in its inorganic hexavalent and tetravalent forms, selenate and selenite, or as volatile Se compounds [6, 11, 12]. Compared with the organic forms, inorganic Se is considerably more toxic, with an increase in toxicity in the order of fifty times for some of the adverse effects of the metalloid. Exposure to Se in humans is generally assessed in two different ways. One is the estimate of Se intake through food frequency questionnaires or other dietary assessment methods, the other is the use of biological indicators such as blood, toenail and hair Se content. Both approaches have important strengths and limitations, discussed elsewhere [10]. The activity of the Se-containing enzymes of the glutathione-peroxidases family has also been widely used to assess overall Se exposure, but the ability of Se to enhance antioxidant enzymes activity [13-15], most likely through its pro-oxidant effects [14, 15], makes it difficult to understand if a rise in Se-induced glutathione peroxidases is either due to the increased nutritional availability of the metalloid or to its pro-oxidant effects [6].

EPIDEMIOLOGIC EVIDENCE

The epidemiologic evidence suggesting a causal relation between exposure to environmental Se and ALS is mainly based on two studies, one carried out in the US and the other in Northern Italy [16, 17]. The first investigation was carried out by Kilness and Hochberg, who reported in 1977 a cluster of four ALS cases in a “sparsely populated county”, with a population of around 4000, located in west-central South Dakota [16]. All these cases were male farmer/ranchers, with a age range between 57 and 66, living a few km away from each other. The investigators noted that the area was known to be affected by naturally occurring selenosis, as demonstrated by cases of Se intoxication in farm animals, and they hypothesized that the association between the high Se environment and the ALS cluster could be causal.

The second study was performed by Vinceti et al. in a Northern Italy municipality, Reggio Emilia, taking advantage of a so-called natural experiment, i.e. the distribution in a small area of that municipal territory of public tap water with unusually high Se content, 7-9 µg/L, compared to the remaining part of the municipal territory where tap water Se levels were lower than 1 µg/L (Figure 1) [17]. The high Se
content in this “exposed area” was due to the high levels of Se in the waters of the two wells which were the source of municipal tap water in that area from 1972 to 1988. The origin of such high concentrations of Se were almost certainly natural, since no anthropogenic source of the metalloid in that area was ever identified. Selenium was almost entirely present in the inorganic hexavalent form, selenate [18, 19]. An eleven-years follow-up study of a cohort of 5182 residents who consumed for at least five years the high-Se tap water, including a subcohort of 2065 individuals characterized by long-term exposure (Figure 2), showed an excess ALS risk, based on four newly diagnosed ALS cases, compared the 0.64 expected ones. The relative risk of ALS was 4.2 (95% confidence limits 1.2-10.8) in the overall exposed population and 8.9 (95% confidence limits 2.4-22.8) in the subcohort with the highest cumulative exposure. All cases were comprised in the subcohort of residents having the longest duration of consumption of tap water with high Se content, in which the number of expected cases was 0.31. Since there were no other distinctive chemical characteristics of the high-Se drinking water, nor evidence for confounding due to life-style or occupational factors, these results suggested an etiologic relation between long-term exposure to inorganic hexavalent Se and ALS.

Further support to an association between Se and ALS comes from two surveys carried out by Yang et al. [20] and by Fordyce [21]. They documented in Se-contaminated areas of China the occurrence of neurological signs and symptoms which indicate that Se may adversely affect motor function in humans, though these studies included neither a detailed report of risks of these neurological effects according to the degree of Se exposure, nor a more in-depth investigation of these pathological conditions. However, these observations are of interest since they confirm that the nervous system is a target organ in Se human intoxication and that motor abnormalities are among the neurological effects induced by excess Se exposure.

Finally, a number of case-control studies have examined the body tissue levels of Se in ALS patients compared with controls [6, 22]. Results of these investigations are conflicting, and this may depend on several factors, such as cases and controls selection bias, effects of disease status on Se status, and inability of peripheral tissues Se concentrations, such as blood, hair and toenails content, to reflect long-term Se exposure. Investigations focusing on spinal cord Se content, however, have shown an excess Se concentration among patients compared with controls, and a lack of relation with disease severity, yielding additional support to the hypothesis of a Se-ALS relation [23, 24].

**BIOLOGICAL PLAUSIBILITY**

Selenium at very low concentrations is considered an essential element for the body but chronic exposure and/or high doses can show toxic effects [6]. The nervous and muscle functions are among those affected by Se in experimental and laboratory models thus yielding biological plausibility to an association between Se and ALS risk [6]. In particular, inorganic and less frequently organic Se forms have been shown to interfere with several pathogenetic mechanisms potentially related to neurotoxicity, such as inhibition of prostaglandin D synthase in the brain, inhibition of squalene monooxygenase, increase in dopamine and its metabolites, inhibition of succinic dehydrogenase, acetylcholine esterase and Na+/K+ ATPase, and induction of seizures [25-31]. Neurotoxic effects have been observed at concentrations of inorganic (tetravalent) Se even lower than the one found in the Reggio Emilia tap water and than the drinking water upper standard of 10 µg/L [6, 32]. Selenium has also been shown to induce toxic effects in rabbit vascular muscle, in rat heart muscle and in chick muscle, and in addition to inhibit axonal conduction and excitatory postsynaptic potentials, indicating the capacity of this metalloid to alter both nervous and muscle function [6, 33-38]. Organic Se species have generally been shown to be far less effective in inducing neurotoxic effects compared with inorganic ones [27, 29-31, 39].

Recently, another mechanism possibly linking Se to ALS etiology has been considered. Bell reviewed the possible association between exposure to L-alpha-gamma-diaminobutyric acid and the so-called ALS-Parkinsonism-dementia complex, and he sug-
ggested a link between non-protein amino acids incorporation into proteins and neurological disease
[2]. Among these non-protein amino acids with potential toxicity, Bell mentions the Se-analogues of the protein amino acids cystine and methionine [2].

However, the most convincing “biological evidence” supporting a Se-ALS relation comes from veterinary medicine observations, which have demonstrated that Se at least in swine and possibly in cattle has a specific toxicity to motor neurons, a property apparently not shared by any other naturally occurring or synthetic chemical, to the best of our knowledge. In fact, several studies have documented selective damage of motor neurons following accidental Se intoxication in swine receiving excess doses of inorganic Se, the main and consistent lesion being bilaterally symmetrical focal poliomyelomalacia of spinal cord ventral horns [40-43]. This poliomyelomalacia has been experimentally reproduced in swine by Panter et al. [44], who also showed the superior toxicity of inorganic Se species despite the higher body levels of Se achieved after supplementation with the organic forms of the metalloid. A number of motor abnormalities has also been recognized in cattle feeding on seleniferous areas, ranging from walking disturbances such as wandering and stumbling, to paralysis and death from respiratory failure [12]. The complex of these motor abnormalities, originally named “blind staggers” [12], has been experimentally reproduced, showing the occurrence of polioncephalomalacia in some of the Se-exposed steers [45].


CONCLUDING REMARKS

Overall, the epidemiologic evidence linking Se exposure to ALS risk, associated with the biological evidence, indicate that Se at least in its inorganic forms may actually represent a risk factor for ALS and suggest the need to further investigate this issue. Some settings might offer unique opportunities for investigating such an association, among which the occupational environments characterized by exposure to Se compounds and the seleniferous areas where naturally-occurring high levels of Se in the environment are found [6]. An interesting opportunity would also be to investigate ALS incidence in subjects consuming drinking water with unusually high concentrations of Se in the inorganic, soluble forms [46-49].

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Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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