ELSEVIER

Clinical Neurology and Neurosurgery 109 (2007) 880–883

Clinical Neurology and Neurosurgery

www.elsevier.com/locate/clineuro

Case report

ALS and mercury intoxication: A relationship?

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Received 4 April 2007; received in revised form 12 July 2007; accepted 13 July 2007

Abstract

We report the case of an 81-year-old woman in whom clinical signs and features of electromyographic activity patterns were consistent with amyotrophic lateral sclerosis (ALS). Increased blood level and massive urinary excretion of mercury proved mercury intoxication. Despite a chelation treatment with Meso 2–3 dimercaptosuccininc acid (DMSA), she died after 17 months.

The pathophysiology of sporadic ALS remains unclear. However, the role of environmental factors has been suggested. Among some environmental factors, exposure to heavy metals has been considered and ALS cases consecutive to occupational intoxication and accidental injection of mercury have been reported. Although no autopsy was performed, we discuss the role of mercury intoxication in the occurrence of ALS in our case, considering the results of experimental studies on the toxicity of mercury for motor neuron.
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Keywords: Amyotrophic lateral sclerosis; Mercury intoxication; Motor neuron disease; Mercury; Heavy metal poisoning

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease involving primarily the motor neurons of the cerebral cortex, brainstem and spinal cord. It is one of the most common neurodegenerative disorders of adult onset. The incidence of ALS in the general population ranges about 1.5 new cases per year per 100,000 inhabitants. Usually sporadic, this pathology is encountered in all ages of adult life. At this time, even in cases with mutations in Superoxide Dismutase 1 (SOD1) gene, the pathogenesis remains unclear. Several facts suggest the involvement of environmental factors as the existence of conjugal ALS or cluster of ALS cases [1], the similarities with lathyrism and konzo [2] and the results of epidemiologic studies [3]. Furthermore, in the Chamorro population, the ALS-parkinsonism dementia complex (Guam disease) is linked to the consumption of cycad nuts, either as a component of cycad flour or indirectly through consumption of fruit bats [4]. Exposure to agricultural chemicals seems to be a risk factor for ALS [5].

Heavy metals have been suspected because of their proved neurotoxicity. Some metals are key constituents of metalloproteins and their accumulation lead to systemic disease with neurologic symptoms. For example, Wilson disease and hemochromatosis are linked to copper and iron accumulation, respectively. Other metals without known physiological function but with described neurotoxicity are mercury and lead [6]. Among all metals implicated in environmental or occupational intoxication, mercury appears as one of the most neurotoxic [7]. Neurological clinical features suggestive of mercury intoxication comprise peripheral and central nervous system signs as erethism, tremor, peripheral neuropathy or cortical blindness [8]. ALS cases related to mercury intoxication [9–13] and professional exposure have been reported [14].

We describe the occurrence of ALS in an 81-year-old woman who also presented mercury intoxication after

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doi:10.1016/j.clineuro.2007.07.008

chronic exposure related to pressure therapy in bath of mercury.

2. Case report

An 81-year-old woman was first seen in March 2004 for a progressive weakness of the right hand. She had no familial neurological history and her past medical history was dominated by a right breast neoplasm treated in 1975 by mastectomy and axillary lymph node dissection without any adjuvant therapy as radiotherapy and chemotherapy complicated by a lymphoedema treated twice a year, from 1987 to 2004 (last treatment in January 2004), by pressure therapy.

At that time, clinical examination revealed a slight dysphonia and dysarthria without choking. Amyotrophic Lateral Sclerosis Functional Rating Scale (ALS-FRS) was graded 36. There was a muscular atrophy of the both hands, the right scapular girdle and the lower limbs and slightly in the tongue. Fasciculations were present in spinal and bulbar territories. Muscle testing was graded from 2 to 3 at the right upper limb and from 3 at the left upper limb (MRC scale). Deep tendon reflexes were brisk at the four limbs. Plantar responses were both extensor. There was no oculomotor, sensory or sphincter disturbances. She had no cognitive impairment.

Brain and cervical MRI were normal as was nerve conduction studies without conduction blocks. Myography revealed diffuse denervation at all limbs and the tongue. Cerebral spinal fluid analysis was normal. There was no monoclonal gammopathy, no anti Hu, Ri, Yo antibodies and all serologies were negative.

Despite the absence of the usual local and systemic clinical signs, mercury intoxication was investigated in June 2004 as the tank used for the pressure therapy contained mercury. A slight increase of mercury concentration was found in blood (13.4 μg/L; $N < 10$ μg/L). In urine, mercury excretion was massive (7282 μg/gCreatinine; $N < 5$ μg/gCreatinine). In spinal fluid, the concentration of mercury was 2 μg/L. Right upper limb X-ray disclosed no infiltrated particles in soft tissues. A treatment with Meso 2–3 dimercaptosucininc acid (DMSA) for 4 weeks (30 μg/kg per day) was initiated in July 2004. The disease continued to progress slowly despite an important decrease of the urinary excretion to 2.9 μg/Creatinine without change of blood and spinal fluid levels. In February 2005, she complained of choking and weight loss; ALS-FRS was graded 34. Motor weakness progressed in bulbar and spinal territories as showed clinical examination. She died in June 2005 from respiratory insufficiency. No autopsy was performed.

3. Discussion

Clinical examination and ENMG results were both consistent with a diagnosis of ALS according to World Federation of Neurology [15]. A paraneoplastic syndrome was ruled out based on the delay between the onset of ALS and the diagnosis of neoplasm, the absence of local and regional recurrence and anti-neuronal antibodies [16].

Despite the absence of usual clinical signs of mercury intoxication, the both increased blood level and especially urinary excretion of mercury proved the intoxication [17]. The persistence of a massive urinary excretion 5 months after the last session of pressure therapy was strongly suggestive of insidious and chronic mercury intoxication [18].

The contamination was certainly the pressure therapy as no other source was identified and her husband was unaffected (data not shown). Pressure therapy is based on the properties of mercury to realize a compressive and progressive cast [19]. The arm is placed vertically in a rubber tank inside of which mercury is introduced. Mercury is pumped between the mold and the limb, exerting then a pressure gradient of the extremity equal to the hydrostatic pressure of the mercury column.

Motor neuron disorders following mercury intoxication have already been reported [9–12]. Sometimes, ALS followed accidental mercury injection [13]. These case reports led to consider occupational exposure to mercury as a risk factor for ALS [14]. This relationship between mercury intoxication and motor neuron disease was also underscored through neuropathological examination that showed accumulation of mercury within cortical and spinal motor neurons in a patient after a suicide attempt with mercury injection [20]. Finally, experimental studies based on autometallography analysis demonstrated an accumulation of metallic mercury in motor neurons in mice or rats after blood [21] or peritoneal [22] injection of mercury or after exposure to vapours of mercury [23]. Another experience showed that mercury is transported retrogradely from muscular nerves terminals to spinal and brainstem motor neurons in rats or mice following intramuscular injection of inorganic mercury [24,25].

To date, the exact mechanism of mercury neurotoxicity remains unknown. Nevertheless, it has been demonstrated that mercury reacts and depletes free sulfhydryl groups and causes a reduction in the activity of SOD [26]. Thus the presence of mercury into motor neurons may lead to the formation of an oxidative stress which is implicated in the pathophysiology of ALS [27]. To date, mutations of the SOD1 gene are the most frequent cause of familial ALS and some susceptibility genes such as SMN1 have been described in sporadic ALS [28]. Experimental studies with animal models have shown that mutations of SOD1 gene lead to modify cellular metabolism and develop multiple pathogenic processes including oxidative stress, protein aggregation and mitochondrial dysfunction [27]. Furthermore, the tubulin which is a kinesin protein of microtubule is disintegrated after mercury exposure in an experimental study and this phenomenon lead to neurofibrillary aggregates [29]. In mice, acute mercury vapour exposure led to atrophy of large myelinated motor axons and irregularity in axon shape which may be caused by damage of cytoskeletal components [30]. Abnormal axonal transport is another suspected mechanism

implicated in pathophysiology of ALS. Indeed, accumulation and abnormal assembly of neurofilaments are common pathological hallmarks of ALS [27].

Toxicity of mercury depends on its molecular forms (metallic mercury, ethyl-mercury or methyl-mercury), the source of contamination, the mode of exposure and the timing of the exposure during life stages. As mercury used for pressure therapy was metallic mercury which is volatile, we can suppose that the vapours of mercury were inhaled and absorbed into the bloodstream. We can also presume that the later age of our patient lead her to be more susceptible to mercury toxicity and less responsive to chelation treatment.

Once accumulated into terminal axons in the right upper limb because of the slowing down of the blood stream caused by the lymphoedema, mercury was transported retrogradely within axons to the cellular bodies of motor neurons. This hypothesis also explains the onset at the right upper limb. An alternative hypothesis might be that of a crossing of the metallic mercury through the rubber and then the skin. This hypothesis appeared less likely given the absence of infiltrated particles in soft tissues on the right upper limb X-ray as previously described in such intoxication [13].

Finally, considering that the cumulative lifetime risk of ALS in an 80-year-old woman is around 1/500 [31], a chance association cannot be ruled out.

Although none of the usual clinical signs of mercury intoxication were noticed in our case and the motor neuron disorder was the sole neurological manifestation, it was difficult to exclude an association. Indeed, this hypothesis would signify that the massive mercury intoxication might be asymptomatic. We considered this hypothesis unlikely.

The absence of efficacy of the chelation treatment cannot challenge the relationship between ALS and mercury intoxication. As already reported, DMSA must be initiated shortly after exposure to prevent accumulation and to avoid toxicity [13]. Furthermore, in our case, the data suggested chronic and slow intoxication.

Unfortunately, autopsy was not performed in our case. Thus, it is not possible to conclude that mercury was the causal agent in our case. A previous metabolic, environmental or genetic factor determining motor neuron dysfunction can be considered. Vapours of mercury might not be a causative factor but probably have exacerbated or promoted motor neurons disturbances leading to manifestations of ALS.

Consequently, this case underlie that mercury exposure should be suspected in patients with motor neuron disease. Biological metal analysis should be performed individually when exposition is suspected [18].

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