

CONJUGAL AMYOTROPHIC LATERAL SCLEROSIS IN BRAZIL

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Abstract – The origin of amyotrophic lateral sclerosis (ALS) remains unknown, although it seems to be multifactorial. The role of environmental factors has been frequently investigated and suspicion of its influence can be obtained when clusters of a rare disease are described. **Objective:** To describe conjugal cases of ALS in Brazil. **Method:** We describe 2 couples in which both spouses were affected by ALS. Both couples had lived in southeast Brazil and were married for at least 20 years. **Results:** There was a great variability in clinical presentation of ALS in our patients. In both couples the interval between disease onsets was short. No precise environmental factors could be identified at the origin of these conjugal cases. **Conclusion:** The occurrence of ALS in couples living in the same area may be epidemiologically important, but we cannot exclude that cases may be due to a chance association.

KEY WORDS: amyotrophic lateral sclerosis, conjugal, environmental factors, etiology.

Esclerose lateral amiotrófica em casais no Brasil

Resumo – A origem da esclerose lateral amiotrófica (ELA) permanece desconhecida. O papel de fatores ambientais tem sido frequentemente investigado e a suspeição de sua influência pode ser obtida quando são descritas salvas de casos de uma doença rara. **Objetivo:** Descrever casos de ELA em casais no Brasil. **Método:** Apresentamos dois casais em que ambos os cônjuges foram acometidos pela ELA. Ambos os casais residiram na região sudeste do Brasil e estiveram casados por pelo menos 20 anos. **Resultados:** Houve grande variabilidade na apresentação clínica da ELA em nossos pacientes. Em ambos os casais, o intervalo de início da doença foi curto. Nenhum fator ambiental foi identificado na etiologia destes casos conjugais. **Conclusão:** A ocorrência de ELA em casais que habitam a mesma região pode ser epidemiologicamente importante, mas não podemos excluir que estes casos tenham sido mera associação.

PALAVRAS-CHAVE: esclerose lateral amiotrófica, casais, fatores ambientais, etiologia.

The etiology of amyotrophic lateral sclerosis (ALS) remains largely unknown, but seems to be multifactorial and probably multigenic¹. The role of environmental factors has been frequently investigated and suspicion of its influence can be obtained when clusters of a rare disease are described. Environmental factors may be involved in the development of ALS based upon several factors: geographic clustering of sporadic cases, cases in common occupational environments, endemic areas of particular forms such as the Guam complex, and conjugal cases².

The occurrence of ALS in both a husband and wife suggests either an environmental factor or consanguinity as the cause of the disease. Herein, we report two Brazilian

married couples who have developed ALS, and discuss some epidemiological aspects of this disease.

We obtained informed consent from the patients or their relatives for publication

METHOD

All four patients presented herein were referred to our Muscle Disorders Unit, at Federal University of São Paulo, in which the diagnosis of ALS was established, according to revised El Escorial criteria³.

Family 1

In 2004, a 68-year-old woman, housewife, noted speech

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difficulty. She did not complain of any sensory or motor abnormalities in her limbs or bladder dysfunction. The symptoms progressed rapidly, and after 18 months, she presented frank dysphagia and dysarthria. On neurological examination, we observed distal weakness in the upper limbs alongside muscle atrophy and fasciculations. The strength on the lower limbs was normal. Deep tendon reflexes were brisk and Babinski sign was present bilaterally. Gag reflex was reduced and tongue was atrophic. Electromyography (EMG) disclosed diffuse involvement of motor neurons in the four limbs and tongue characterized by spontaneous activity (positive waves, fibrillations, and fasciculations), with normal sensory and motor nerve conduction velocities and without conduction blocks. Brain and cervical magnetic resonance imaging (MRI) were unremarkable. Laboratory testing (hematological and biochemical screening, thyroid and parathyroid function, serum immunofixation electrophoresis) was also normal. She was considered to have progressive bulbar palsy, a variant of ALS. In July 2008, she had an acute respiratory arrest secondary to hypersecretion and has remained in coma since then.

In March 2007, her husband, a 71-year-old retired college professor, started to notice weakness in his left upper limb. The symptoms progressed over the next 7 months involving the distal part of his limb, followed by fasciculation and muscle atrophy. He came to the medical office in panic due to his wife past medical history. His own medical record was unremarkable, except for bone fractures in his arms when he was young. On neurological examination, we observed distal and proximal weakness in the upper limbs (left > right) associated with atrophy of left arm and diffuse fasciculation. Deep tendon reflexes were abolished and Babinski sign was not present. EMG revealed abnormal spontaneous activity and chronic denervation in the four limbs. He was diagnosed with ALS. He is still on follow-up.

Curiously, both patients had an identical surname while they were single, but there was no known consanguinity. They do not belong to a common ethnic group. They were born and grew up in the city of Sao Paulo, and were not regularly exposed to known environmental toxins. They were married for more than forty years and had two children, both healthy.

Family 2

In March 2000, a 52-year-old librarian woman, noticed progressive symmetrical weakness in her upper limbs associated to dysarthria and dysphagia. Over the next 08 months, the symptoms progressed to the lower limbs. On neurological examination, we observed global muscle atrophy (distal >> proximal) and fasciculations in the four limbs. She was tetraplegic and deep tendon reflexes were brisk. Babinski and Hoffman signs were presented bilaterally. Her speech was unintelligible. She also presented fasciculation and atrophy of her tongue. Sensations were preserved. Her past medical history was unremarkable. EMG revealed a denervation pattern with fasciculations in the four limbs and tongue. Laboratory studies (as performed in

family 1) were normal. She was diagnosed with ALS. She died of respiratory arrest 08 years after diagnosis.

One month earlier, in February 2000, her husband, a 54-year-old engineer, started to complain of fluctuating weakness in his upper limbs. He also noticed progressive difficulty to write, to shave and to put clothes on. He was also presenting cramps during sleep. On neurological examination, we observed mild dysphagia and dysarthria and distal weakness in the upper and lower limbs. Deep tendon reflexes were abolished. There were no fasciculations or amyotrophy. Sensation and coordination were preserved. First EMG revealed fatigability (Myasthenic phenomenon) with decrement of 40%. He was initially diagnosed as Myasthenia Gravis and was put on treatment with azathioprin 150 mg/day. He did not notice any improvement after one year of treatment. In February 2001, he presented distal and proximal weakness associated with fasciculation and amyotrophy in four limbs. He could not walk without assistance. Deep tendon reflexes were still abolished. Bulbar involvement was present with dysarthria, dysphagia, emotional lability, amyotrophy of the tongue. A new EMG disclosed diffuse denervation in the four limbs. He was diagnosed with the Progressive Muscular Atrophy variant of ALS. Nowadays, he is restricted to bed and needs continuous respiratory support.

These patients were born and lived in the countryside of the state of Sao Paulo. There was no known history of consanguinity or toxic exposure. They were divorced by the time they developed their diseases. They had two children, and both are healthy.

RESULTS

In both families, wives were first affected and presented a worst prognosis. There was a great variability in clinical presentations of ALS in our patients. In both couples the interval between disease onsets was short. No precise environmental factors could be identified at the origin of these conjugal cases. Table summarizes the clinical characteristics of both couples.

DISCUSSION

There are few data on the epidemiology of ALS in Brazil. Regional published data concerning ALS mortality in Brazil, where it is fairly reliable (São Paulo and Rio de Janeiro cities), infers an incidence rate of 0.3–0.5/100,000 inhabitants. Considering the mean duration of the disease to be 3 years, this yields a disease prevalence of about 1,440 to 2,400 cases in Brazil (0.9 to 1.5/100,000 inhabitants), lower than that described in Europe and USA⁴. Most cases of ALS are sporadic and more frequent in men than women (3:2). The onset is generally in the late fifties and early sixties, although rarely symptoms begin before 20 years of age the mean survival ranges from 3–4 years, with survival after diagnosis being approximately two years⁵. To the best of our knowledge, there are no previous reports of conjugal ALS in Brazil. We present ALS in two couples,

Table. Characteristics of conjugal ALS cases described.

| | Family 1 | | Family 2 | |
|------------------------------|----------|----------|-------------|-------------|
| | Wife | Husband | Wife | Husband |
| Onset age (yr) | 68 | 71 | 52 | 54 |
| Duration (yr) | 4 | 1.6 | 8 | 8 |
| Interval between onsets (yr) | 3 | 3 | <1 | <1 |
| Period lived together (yr) | 40 | 40 | 20 | 20 |
| Site of onset | Bulbar | Left Arm | Upper Limbs | Upper Limbs |
| Lower Motor Neuron Signs | Yes | Yes | Yes | Yes |
| Upper Motor Neuron Signs | Yes | No | Yes | No |
| Bulbar Signs | Yes | No | Yes | Yes |
| El Escorial criteria | Definite | Definite | Definite | Probable* |

*Laboratory supported.

which is an atypical situation and may reveal some clues for the understanding of this disease.

The multifactorial etiology of ALS lies on a complex interplay between genetical and environmental causes. A clue for the genetical cause came from reports of families with ALS. A positive family history for ALS is found in 5–10% of patients autosomal recessive and dominant pattern of inheritance were already described. Between 10 to 20% of autosomal-dominant patients have mutations in superoxide dismutase (SOD1) gene on chromosome 21. Generally, the clinical features of patients with SOD1 ALS are indistinguishable from those of patients without a mutation⁶. Although previous reports on conjugal ALS in Brazil have not been described, cluster of ALS in certain regions of our country were reported. Eight families, comprising more than 1,500 individuals of whom about 200 are affected, are now known to carry the P56S mutation in the VAPB gene, which causes ALS. Seven are of Portuguese-Brazilian ancestry and one of African-Brazilian ancestry. Haplotype analysis shows a common founder for all families regardless of ancestry, with a founding event 23 generations ago, consistent with the Portuguese colonization of Brazil⁷. In our cases, there is no history of consanguinity between spouses or any clue of familial ALS. However, the variable clinical presentation of genetic forms of ALS does not permit that this etiology be ruled out.

A host of environmental factors have been investigated as potential risk factors, ranging from heavy-metal toxic effects to occupational exposures¹. Spencer and co-workers⁸ have proposed the role of environmental factors based on ALS-parkinsonism-dementia cases in the Pacific island of Guam, possibly linked to excessive consumption of cycad, a B-methylaminoalanine (BMAA)-containing seed, which act as N-methyl-D-aspartate agonist. BMAA, produced by symbiotic cyanobacteria present in the cycad rooth, was first proposed as contributor to the ALS-Par-

kinsonism-Dementia Complex (ALS/PDC) that has been remarkably prevalent amongst the Chamorro people of Guam. However, this concept remains in dispute, as other environmental toxins have recently been implicated, and a role of genetic factors as well has also been proposed for the occurrence of ALS/PDC cases⁹. Protein-bound BMAA has been found in millimolar concentrations in brains of Chamorros dying from ALS/PDC and North American ALS and Alzheimer's disease patients, but not in control brains. Cyanobacteria that produce BMAA and other neurotoxins are ubiquitous, particularly in water resources associated with animal deaths¹⁰. This could represent a direct link between environmental risk factor and ALS.

Specific association of ALS with different occupation has appeared in some case-control studies. Thus, ALS has appeared associated with heavy manual work, electric trauma, and employment in the plastic industry, exposure to heavy metals, acids and animal carcasses, high increased exercises as seen in soccer players in Italy^{11,12}. Besides genetic and environmental factors, the existence of a yet-unidentified transmissible agent cannot be excluded. Enteroviral nucleic acids in motor neurons were detected in more than 80% of the ALS patients¹³ and individuals infected with human immunodeficiency virus may present a rapidly progressive form of ALS¹⁴. We did not seek for enteroviral viruses in the motor neuron of our patients, but HIV infection was excluded.

In literature, there are previous reports of couples with ALS. Conjugal ALS was noted in 10 couples on Guam, where ALS was 50 to 100 times more common¹⁵. Since then there were other reports outside the Western Pacific¹⁶⁻²⁵. Except in Guam, where an environmental factor was considered, none of the previous reports pointed out a clear explanation for appearance of these clusters. All measured the question "Environmental or genetic factor?"; but the conclusion in most of them was that these clus-

ters of conjugal ALS were mere coincidence. In one report of conjugal ALS, both patients have been exposed to aluminum and manganese, the husband for occupational reasons and the wife through environmental exposure. It is noteworthy that aluminum and manganese are suspected of playing a role in ALS. However, this was an isolated observation and it does not permit a definite conclusion. The largest series on conjugal ALS²⁴ observed that the long period of conjugal life is more compatible with environmental factors, but concluded that the possibility coincidence cannot be rejected.

In the cases that we have described it was not possible to identify an environmental clue between the married couples pointing out for their neurodegenerative disorder. However, we must highlight that wives were committed before husbands in both couples, and they had different clinical presentation. In women, the upper motor neuron was more involved, while in men was the lower one. But, we did not find a reasonable explanation for this distinctiveness.

In conclusion, the occurrence of ALS in couples living in the same area may be epidemiologically important, but we cannot exclude that cases may be due to a chance association.

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