

Acute onset of bulbar amyotrophic lateral sclerosis after flu – look at the differential diagnosis: A case report

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Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder affecting upper and lower motor neurones. It can be either familial (fALS) or sporadic (sALS). ALS is characterized by muscle weakness and atrophy that can involve the limbs and trunk (i.e. the spinal form of the disease) or speech and swallowing (i.e. the bulbar form). The aetiology of sALS remains unclear although a gene–environment interaction has been proposed as a concomitant trigger for the neurodegenerative process together with viral infections, smoking, heavy metals and pesticide exposure. Herein, we report the case of a 67-year-old woman who experienced an acute onset of bulbar ALS with an atypical clinical course that was probably triggered by a bout of influenza.

Keywords

Familial amyotrophic lateral sclerosis, sporadic amyotrophic lateral sclerosis, bulbar amyotrophic lateral sclerosis, acute onset, differential diagnosis

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Introduction

Amyotrophic lateral sclerosis (ALS) is a complex and progressive neurodegenerative disorder, affecting upper and lower motor neurones in the brain and spinal cord, which is sometimes associated with

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cognitive impairment or frontotemporal dementia.^{1,2} ALS has an incidence of 2–3/100 000 and a prevalence of 6–7/100 000 in Europe, thus being the most common motor neurone disease in human adults.^{3,4} In 90%–95% of cases there is no apparent genetic link (sporadic ALS, sALS), while the remaining 5%–10% of cases have a positive family history (familial ALS, fALS). ALS onset may involve mainly the limbs and trunk (i.e. the spinal form of the disease), causing muscle weakness and atrophy; or speech and swallowing abnormalities (i.e. the bulbar form), causing dysarthria, dysphagia and dysphonia, together with a respiratory involvement.⁵ Bulbar ALS is considered the most devastating variant of the disease, characterized by a rapid decline and the shortest survival (less than 2 years from disease onset).^{6,7} Herein, we report a case of a 67-year-old woman who experienced an acute onset of bulbar ALS.

Case report

A 67-year-old woman, affected by type 2 diabetes mellitus, hypertension and depressed mood, presented at the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Centro Neurolesi Bonino-Pulejo, Messina, Italy in October 2016, because of a history of speech difficulties lasting 1-year, which suddenly appeared during a bout of influenza and a stressful period. Her husband reported that before these events, no speech difficulties were noted and that the patient started having the speech-related symptoms 3–5 days after the bout of influenza. Moreover, her previous comorbidities (i.e. type 2 diabetes mellitus and hypertension), did not influence her quality of life, apart from the presence of depressed mood due to familial difficulties. She also complained of fatigue, sleep disorders (i.e. difficulty resting and frequent nocturnal awakenings) and an unsteady gait. Because of these symptoms, she was initially

admitted to the Ospedale Papardo, Messina, Italy in May 2016, where they performed: (i) brain and cervical magnetic resonance imaging, which showed gliotic lesions and cervical arthrosis; (ii) electromyography, which showed a slight denervation with a neurogenic pattern at the first dorsal interosseous and tibialis anterior muscles, bilaterally; and (iii) motor evoked potentials of the upper and lower limbs, which were normal. Because of this clinical picture, a diagnosis of “dysarthria in patient with subcortical leukoencephalopathy” was proposed. After 1 year from the disease onset, the patient was referred to the IRCCS Centro Neurolesi Bonino-Pulejo because the dysarthria had worsened with mild feeding difficulties. Her neurological examination showed dysarthria, a hypomimic face, tongue and muscle fasciculations (mainly at the right triceps, glutei and left biceps femori muscles); the first interosseous muscle was slightly hypotrophic, bilaterally; deep tendon reflexes were brisk and spreading, Epstein sign was present, as well as the grasping and palmomental reflex. No respiratory involvement was present at the time of this initial evaluation. During neurophysiological evaluations (i.e. electromyography and motor evoked potentials), a massive denervation with a neurogenic pattern was found at the genioglossus muscle, sternocleidomastoid, first dorsal interosseous of the hand, tibialis anterior and gastrocnemius medialis muscles bilaterally. The study of motor evoked potentials from the lower limbs and sternocleidomastoid muscles showed an abnormal central motor conduction time. Thus, the patient was diagnosed with ALS, and 50 mg riluzole, oral administration, twice daily, and 500 mg L-acetylcarnitine, oral administration, six times daily, were prescribed; this treatment is still ongoing.^{8–10} At 6-month follow-up, there was a worsening of motor function, with gait impairment and difficulty in swallowing.

Discussion

To the best of our knowledge, this is the first report on the acute onset of bulbar ALS. To date, the aetiology of sALS remains unclear. A gene–environment interaction has been proposed as a concomitant trigger for the neurodegenerative process.¹¹

There is increasing evidence from post-mortem and biochemical investigations that demonstrates the prominent role of oxidative stress, based on mitochondrial dysfunction, as one of the principal molecular mechanisms for motor neurone degeneration in sALS.^{12,13} Moreover, mitochondrial dysfunction may have a role to play in other reported causes of ALS, including protein misfolding and aggregation, endoplasmic reticulum and cytoskeleton alterations, oxidative stress, glutamate-mediated excitotoxicity, aberrant axonal transport, neuromuscular junction abnormalities, altered RNA metabolism, dysfunction of the ubiquitin proteasome pathway, immune system deficiency and neuroinflammation.¹³ Other causes of oxidative stress seem to be associated with physical activity,¹⁴ viral infections,^{15–17} smoking,¹⁸ heavy metals¹⁹ and pesticide exposure;²⁰ all of which lead to neurodegeneration. In fact, any factor that favours a pro-oxidative state could contribute to oxidative stress, and there are many indicators that oxidative stress is one of the central pathways in motor neurone disease.¹²

Among these different hypotheses, we would suggest that the effects of oxidative stress and viral infection were the triggers for sALS development in this current patient, given that other possible triggers were ruled out. Notably, although influenza is a very common illness, especially in the elderly, ALS related to virus-induced oxidative stress is rare, and this could be because such a trigger may act only in predisposed individuals. In 1975, reverse transcriptase activity was found in the cytoplasmic

fraction of the brain of two ALS patients but not in controls, suggesting a viral involvement in the ALS neurodegenerative process.²¹ Subsequently, enteroviruses (EV) were found to be involved in ALS pathogenesis. For example, a study of 242 ALS patients demonstrated that 14.5% were positive for EV RNA in the cerebrospinal fluid compared with 7.6% of the controls; no EV RNA was found in the fALS group.¹⁵ EV infection may have contributed to the disease onset in a small subgroup of patients in this study, even though the authors did not find any clinical peculiarities in the group positive for EV RNA when they evaluated initial clinical presentation, duration of disease between onset and diagnosis or between first clinical sign and death.¹⁵

More recently, other research has demonstrated that human endogenous virus may be involved in ALS pathogenesis since transgenic animals expressing the *env* gene developed progressive motor dysfunction.¹⁶ Influenza virus is an RNA-virus that belongs to the family of *Orthomyxoviridae*, which uses host cell structures and metabolic pathways for its own life cycle. During influenza virus infection, there is glutathione depletion and an increase in reactive oxygen species, which suggests that influenza virus may increase oxidative stress contributing to neuronal damage.¹⁷ Positron emission tomography has shown that the cellular redox state, specifically an increase in oxidative stress, is involved in ALS.²² A marker of oxidative stress, ⁶²Cu-diacetyl-bis (N4-methylthiosemicarbazone), was found to be reduced in cell lines with mitochondrial respiratory failure and in specific brain areas of patients with ALS, showing a correlation between its retention rate and the clinical severity estimated using the revised ALS Functional Rating Scale score.²² These findings were also confirmed by studies that demonstrated increased oxidative damage in post-mortem tissues from

patients with ALS, such as high levels of protein carbonyls in the spinal cord and motor cortex of the affected patients compared with the control group.^{23,24} Unfortunately, the current patient refused to undergo a lumbar puncture, so it was not possible to present her cerebrospinal fluid data. Whether or not oxidative stress pathways are activated by viral infections remains to be demonstrated.

A peculiarity of this current case was that the clinical course was atypical for bulbar ALS, with dysarthria being the only acute onset symptom, together with depressed mood.

In conclusion, these findings suggest that influenza infection was the trigger for the acute onset of bulbar ALS in the current patient. We recommend comprehensive examination of patients for motor neurone disease in cases of sudden onset of dysarthria, even with the presence of an underlying leukoencephalopathy as a potential cause of the symptoms.

Declaration of conflicting interests

The authors declare there are no conflicts of interest.

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