Neurological Sciences (2020) 41:1919–1921
https://doi.org/10.1007/s10072-020-04317-5

BRIEF COMMUNICATION

Altered sensory-motor plasticity in amyotrophic lateral sclerosis and complex regional pain type I syndrome: a shared mechanism?

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Received: 20 December 2019 / Accepted: 24 February 2020 / Published online: 5 March 2020

Abstract

Besides the prominent motor syndrome, some patients affected by amyotrophic lateral sclerosis (ALS) complain of many non-motor symptoms during the disease course, in particular chronic pain that significantly reduces the patients' quality of life. Complex regional pain syndrome (CRPS) is a rare painful condition, rarely described in ALS patients. We present the clinical case of a patient affected by spinal-onset ALS, who developed a type I CRPS (CRPS-I) at the upper limbs. To the best of our knowledge, only five cases of ALS-CRPS-I have been reported and they share some peculiar features: ALS spinal-onset with classic phenotype, rapid deterioration of quality of life, and a poor prognosis. Different mechanisms have been supposed in the pathogenesis of both CRPS and ALS, resulting in distinctive clinical presentations. Altered plasticity of brain sensory and motor areas might represent a common feature that seems to influence negatively ALS progression and prognosis.

Keywords Amyotrophic lateral sclerosis · Chronic pain · Complex regional pain syndrome · Altered plasticity

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disorder of the upper and lower motor neurons, with unknown pathogenesis, poor prognosis, and fatal outcome [1].

Besides the prominent motor syndrome, chronic pain, an underestimated and neglected symptom, significantly reduces the patients' quality of life, is less frequently reported in the bulbar form of ALS, and correlates to motor dysfunction [2]. Mechanisms of chronic pain in ALS are largely unknown and might be the consequence of the maladaptive synaptic plasticity of spinal/supraspinal nociceptive systems, inducing central sensitization as a secondary effect of motor neuron degeneration [3].

Complex regional pain syndrome (CRPS) is a rare condition with obscure pathogenesis characterized by spontaneous or evoked regional pain with allodynia or mechanical hyperalgesia, autonomic dysfunction (temperature changes, edema, hyperhidrosis), sensory-motor signs and symptoms, often triggered by traumas, fractures, surgery, or drug injection [4]. Current diagnostic criteria have been validated in 2010 (IASP diagnostic criteria) [5]. Accordingly, CRPS is classified in type 1 (CRPS-I) or type 2 (CRPS-II) with the absence or presence of peripheral nerve lesions, respectively.

We aim to describe the rare case of a ALS-CRPS-I patient, proposing a new intriguing pathogenetic hypothesis based on common mechanisms.

Case report

A 64-year-old man presented with a 10-month history of weakness of the upper limbs. His familial and medical history was unremarkable. Neurological examination revealed weakness and atrophy of proximal (MRC 2–3/5) and distal muscles (MRC 4/5) of the upper limbs, with diffuse fasciculations. Deep tendon reflexes were diffusely brisk, with bilateral Hoffman and Babinski signs. Routine blood and chemistry laboratories and brain and spinal magnetic resonance imaging (MRI) were unremarkable. Motor and sensory nerve conduction was normal. Needle EMG demonstrated neurogenic active remodeling of motor unit potentials, with diffuse muscular rest activity (fibrillations/sharp waves and fasciculations),

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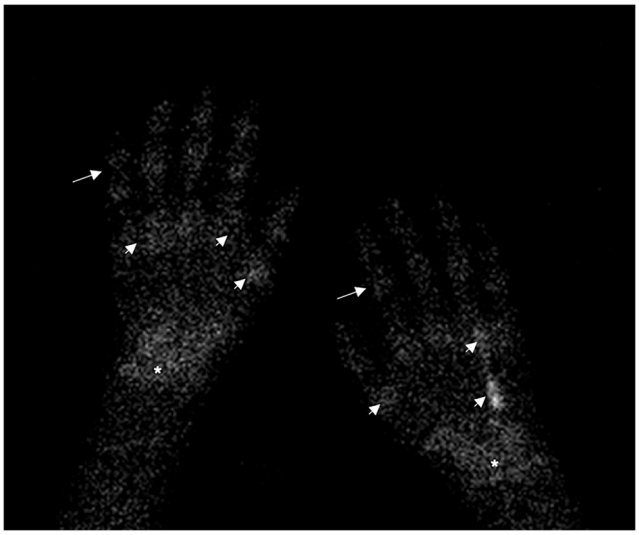

Fig. 1 Three-phase bone scintigraphic scan, showing increased uptake of the radiotracer (99mTc-MDP) in carpal (asterisks), metacarpo-phalangeal (arrow-heads), and inter-phalangeal joints (arrows), bilaterally

leading to the diagnosis of definite ALS. Patient started pharmacological (riluzole 100 mg/day) and physical therapy but 3 months later complained of severe hand pain with bilateral warm, swelling, sweating, and hyperalgesia. A diagnosis of CRPS-I was suspected and supported by hands radiography (severe osteopenia) and three-phase bone scintigraphic scan, with increased uptake of the 99mTc-methylen-diphosphonate in carpal, metacarpo-phalangeal, and inter-phalangeal joints, bilaterally (Fig. 1). Deflazacort (6 mg/day) and neridronate (100 mg/week) significantly improved the syndrome; however, for rapid deterioration of clinical conditions, the patient died of ventilatory failure after 6 months.

Discussion

To the best of our knowledge, the association between ALS and CRPS-I has been only reported in five patients (Table 1) with spinal disease onset, classic phenotype, and poor prognosis.

The association of such two rare conditions prompts us to suppose common and shared physiopathological mechanisms. Experimental genetic models of ALS investigate how mutations induce motor neuron degeneration; however, none replicates the human disease that is the result of many interacting mechanisms (genetic mutations, altered protein homeostasis, altered RNA/DNA metabolism, intracellular dysfunction, excitotoxicity, neuroinflammation, altered synaptic plasticity) that finally lead to the motor neuron degeneration, with changes of the synaptic homeostasis, failure of rescue mechanisms, and disruption of the brain/spinal networks [6, 7].

CRPS results from the interaction of many pathophysiological mechanisms (release of inflammatory mediators and glial activation, uncontrolled activity of afferent fibers and nociceptors, nerve fiber degeneration, motor neuron hyperexcitability, and maladaptive synaptic plasticity) with external triggers and genetic factors [8]. In CRPS patients, altered central plasticity has been demonstrated through advanced MRI techniques, showing dysregulation of pain processing–related brain networks (such as

Table 1 Main clinical features of ALS patients affected by CRPS

Features	De Carvalho et al.[1]			Shibata et al.[2]	Park[3]	Our case
	Patient 1	Patient 2	Patient 3			
Gender	M	F	F	M	M	M
Age at onset	74 years	49 years	63 years	65 years	60 years	64 years
Disease onset	Spinal (upper limbs)					
Phenotype	Classic					
Disease duration	Unknown	Unknown	> 24 months	9 months	26 months	20 months
CRPS type	I	I	I	I	Recurrent, I	I
Cause/trigger	Trauma	None	Frozen-shoulder	Trauma	Adhesive capsulitis	Frozen-shoulder
Therapy	Calcitonin, steroid, propranolol	Calcitonin NSAIDs, GB	Calcitonin, NSAIDs	GB	Steroid	Steroid, neridronate

M/F, male/female; *NSAIDs*, non-steroidal anti-inflammatory drugs; *GB*, ganglion block

[1] De Carvalho M, Nogueira A, Pinto A, et al. (1999) Reflex sympathetic dystrophy associated with amyotrophic lateral sclerosis. J Neurol Sci 169:80–83. https://doi.org/10.1016/S0022-510X(99)00220-8 [13]

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dorsal insula, orbitofrontal, and cingulate cortex) but also other motor, autonomic and affect systems (amygdala, putamen, hypothalamus, hippocampus) [9].

Evidence from neurophysiological techniques supports a functional reorganization of the sensory-motor networks and dysregulation of the pain processing [10]. Somatosensory evoked potentials (SEPs) demonstrated changes of somatosensory processing at cortical level [11]; transcranial magnetic stimulation (TMS) studies showed maladaptive plasticity changes in motor cortex excitability and brain mapping [12] in CRPS-I patients.

In conclusion, despite different mechanisms in the pathogenesis of ALS and CRPS resulting in distinctive clinical presentations, these morpho-functional data highlight the alterations of central plasticity of sensory-motor networks as a key role in the pathophysiology of both diseases. This might explain the bilateral spreading of CRPS-related symptoms.

Pain and other CRPS symptoms might induce long-lasting changes and altered sensory-motor plasticity, which seems to influence negatively ALS progression and prognosis. Wherever in these cases the altered plasticity is a consequence or a leading mechanism of the neurodegenerative process needs to be clarified.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval None.

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