Atypical motor neuron disease with bent spine clinical onset and long survival carrying C9orf72 expansion

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Dear Editor,

The pathological repeat expansion in the C9ORF72 gene is observed in about 10% of patients with amyotrophic lateral sclerosis (ALS) of European ancestry; it accounts for 30% of familial ALS and it is typically associated with a worse prognosis [1]. Recently, Quattrone et al. described a case of frontotemporal dementia (FTD) and ALS characterized by a dropped head syndrome [2]; authors therefore suggested an expansion of pathological phenotypes of FDT-ALS associated to C9orf72. In keeping with this idea, we describe the first case of ALS due to C9ORF72 mutation with long disease duration and an isolated camptocormia at disease onset.

In January 2014, a 65-year-old man came to our attention for a 2-year progressive difficulty in maintaining the erect posture associated with irascibility. He had previously been diagnosed as Parkinson's disease and had been treated with LDOPA without benefit. Neurological examination at first access to our clinic showed absence of cognitive decline at MMSE test, camptocormia during walking or standing, anserine gait, nystagmus, normal deep reflexes (Fig. 1A and video S1 in supplemental material). We found an increase of transaminases and creatine kinase level. We prescribed a DAT-SPECT scans that excluded a Parkinson disease. Electromyography showed myopathic changes in proximal muscles of limbs, without fibrillation/fasciculations; the lung function test showed light dysventilation. The repetitive stimulation at EMG examination, motor-evoked potentials, brain magnetic resonance imaging (MRI), and whole body computer tomography (CT) were normal; muscular CT and MRI showed paraspinal atrophy and adipose tissue substitution in dorsal-lumbar muscles (Fig. 2). A biopsy of a paraspinal muscle showed a mixed feature with the presence of increased variability in fiber size, a high number of internal nuclei, and neurogenic atrophy with target fibers. No necrosis, increase of connective tissue, or significant inflammatory infiltrates has been seen (Fig. S2 in supplemental material). The immunostaining for dystrophin and sarcoglycans were normal. The pathogenic variants of SMN1, TTN, ACTA1, and Ryr1 genes and the mutations for FSHD1, myopathic conditions possibly associated to this phenotype, were excluded by gene-specific analysis and NGS panel on congenital myopathies.

The weakness progressed to the proximal and distal muscles of upper limbs and to the respiratory muscles leading to progressive respiratory insufficiency and mechanical ventilation 24/24 h at the end of 2014. Later, weakness progressed to proximal and distal muscles of legs; in late 2015, we found that Babinski sign and prolonged central motor conduction time (CMCT) have also been documented on motor-evoked potential. A diagnosis of atypical motor neuron disease was formulated, and the analysis of ALS-associated genes ALS (SOD1, TARDBP, FUS, and C9ORF72) was performed.

We found a pathological GGGGCC expansion in the first intron of the C9ORF72. In 2017, about 5 years after the onset

of symptoms, he became wheelchair-dependent and dysphagic; the EMG showed an acute and diffuse denervation; the patient started therapy with riluzole without modification of disease course.

Finally, we learned that patient' sister presents a Pisa syndrome; unfortunately, she rejected clinical and genetic study (Fig. 1B); nevertheless, she performed an EMG that showed signs of chronic denervation at lower limbs. The parents of the patient have never shown any correlated symptom; unfortunately, they died before the appearance of the disease in our patient and the performance of genetic tests was not possible.

The patient is still alive even if substantially restricted to bed and dependent in most activities of daily life.

We acquired informed consent to publicize the photos and the videos of cases enclosed in the paper and in the supplementary materials. We describe the first patient with C9ORF72 mutation in which camptocormia and paraspinal muscular atrophy were the early and for long time the unique manifestations of motor neuron disease. Camptocormia, or "bent spine syndrome", is an abnormal posture characterized by flexion of the thoracolumbar spine that appears upon standing, increases in walking, and disappears in supine position. [3, 4] Camptocormia is recognized as a feature of central or peripheral nervous system, or of muscle disorders [4]. The causes of bent spine are still debated and several genetic mutations have been associated with this syndrome.

In our case, the diagnosis was delayed by 4 years because the disease progressed without signs of clinical or electrophysiological denervation for years and only at a later time caused active neurogenic EMG findings. Muscular biopsy findings were consistent with neurogenic alterations with some characteristics of myogenic disease, such as internal nuclei and rounded shape of muscle fibers. The presentation led to an extensive differential diagnosis including Parkinson's disease, myasthenia gravis, and myopathy. Some aspects of the posture may initially suggest motor-induced dystonia, because the patient displayed nearly normal posture on start of gait that progressively became kyphotic during the walk.

The presence of C9ORF72 mutation is considered an independent negative factor for prognosis [1]; conversely, in our patient, the disease had more favorable course: we observed a duration of disease free from mechanical ventilation of 36 months and a total disease duration of 92 months to date. Furthermore, differently from Quattrone et al. [2], we did not observe dementia or cognitive deterioration throughout the long follow-up neither in the patients nor in his sister. Taking together these two data, we can speculate that several similar cases could be unrecognized at disease onset and that the genetic diagnosis can be missed in most of them.

Finally, the presence of the posture problems in the sister of our patient suggests that she could have the same mutation; unfortunately, we could not confirm this suspect. In any case, the clinical evolution of the sister's disturbances was slower. It is possible that patient occupation, he worked as a gardener, with forced posture and exposition to toxicants, has played a role in the clinical presentation [5].

Our observation further extends the clinical presentation and the disease duration of pathological phenotypes associated to C9orf72 gene mutations and suggests that the diffusion of those mutations could be underestimated.