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Letter to the Editor

C9ORF72 and parkinsonism: Weak link, innocent bystander, or central player in neurodegeneration?

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Dear Editor,

C9ORF72 expansion is the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) [1]. Although few case reports have been described [2,3], an increasing role of this hexanucleotide expansion in parkinsonism and related disorders has been recently suggested.

We describe a 60 years-old woman admitted with a 3 years history of progressive gait disturbance with frequent falls, urinary incontinence, diffuse bradykinesia and rigidity. The mother and two sisters of the patient died at 57, 59 and 66 years, respectively, due to ALS with bulbar onset. Neurological examination showed mild dysarthric speech, facial hypomimia with astonished expression, slowness of vertical pursuit eyes movements without supranuclear gaze palsy, frontal release signs (snout reflex and glabellar tap) and symmetric akinetic-rigid parkinsonism without resting, postural or action tremor. Bilateral symmetric brisk reflexes without clonus, spreading or Hoffman and Babinski signs were also seen; the jaw jerk reflex was normal. She had a slow, wide-based, apraxic gait, bilateral decreased arm swing, anterocollis and camptocormia with abnormal "pull" test (Video 1). We did not detect neither lower motor neuron signs, nor cerebellar or sensory deficits. In particular no fasciculations, cramps, hyporeflexia, or muscular atrophy were seen in upper and lower limbs. Careful examination of bulbar region did not reveal the presence of fasciculations or wasting of the tongue. There was not limbs hypotonia or muscle weakness.

Neurophysiological studies showed increased motor central conduction time while needle electromyography was normal. Brain and spine MRI did not reveal abnormalities. DAT-SPECT showed symmetrically mildly reduced striatal uptake prevalent in left posterior putamen. Neuropsychological assessment showed impairment in executive functions and praxis abilities. Standard blood examinations, infection markers, autoimmune and neoplastic investigations resulted normal. In order to quantify the motor response to levodopa, an acute drug test was performed by oral administration of 200/50 mg of levodopa-carbidopa with an improvement of 45% in Unified Parkinson's Disease Rating Scale (UPDRS) part III score (from 37/108 in Off-drug condition to 21/108 in On-state), mainly on limbs bradykinesia and rigidity. Levodopa's effect was not detected neither on gait impairment nor on postural instability.

Genetic tests were performed: all the coding exons and 50 bp of the flanking intron-exon boundaries of SOD1, VCP, of exon 6 of TARDBP, of exons 14 and 15 of FUS, of exons 2, 11 and 12 of the MATR3, and exons 5, 9, 12, and 14 of OPTN have been polymerase chain reaction (PCR) amplified, sequenced using the Big-Dye Terminator v3.1 sequencing kit (Applied Biosystems Inc.), and run on an ABI Prism 3130 genetic analyzer [4–6]. Repeat-primed PCR (RP-PCR) analysis revealed a heterozygous pathological expansion (37 repeats) of the GGGGCC hexanucleotide in C9ORF72 gene (Fig.

1) [4]. We then discovered further information about one of the patient's sisters that has been followed up in another Italian Centre, which confirmed us the presence of segregation: she was affected by bulbar ALS and had a heterozygous pathological GGGGCC hexanucleotide expansion in C9ORF72 gene. Therapy with

levodopa-carbidopa (300 mg/day) and then with 4 mg rotigotine transdermal patch led to a stable motor response with subsequent de-velopment of levodopa-induced oro-buccal dyskinesia (Video 2). At subsequent follow-ups, treatment was slightly adjusted. At 8 years from onset, she did not develop lower motor neuron/cerebellar signs or further cognition involvement.

This case underlines the widening spectrum of C9ORF72-associated diseases ranging from ALS-FTD complex, psychiatric manifestations, to the broad .eld of movement disorders [7]. As already described, C9ORF72 associated parkinsonism is frequently characterized by atypi-cal features, concomitant motor neuron signs and cognitive impairment [2]. In this case, the onset, characterized by postural instability, gait dis-turbance and parkinsonism could be compatible with a Progressive Supranuclear Palsy (PSP)-like phenotype, but the association of autonomic dysfunction, anterocollis, pyramidal signs and oro-buccal dyskinesia without supranuclear vertical gaze palsy may be more suggestive of Multiple System Atrophy (MSA) with predominant parkinsonism. Indeed, our patient meets all of the criteria for a possible diagnosis of MSA, PSP and perhaps also Cortico-Basal Degeneration, but does not ful.l criteria for a probable diagnosis [8]. Furthermore, the signi.cant and stable L-DOPA response together with a very mild progression may move towards the evolution of Idiopathic Parkinson Disease (PD). This apparent discrepancy is similar to what is observed in genetically determined parkinsonism, in which clinical pro.le, pro-gression and L-DOPA responsiveness not always meet the paradigms of idiopathic forms. Despite family history, MND or marked cognitive impairment has not emerged, thus con.guring an isolated L-DOPA re-sponsive atypical parkinsonism till now. This case highlights some im-portant elements connected to C9ORF72 expansion to bear in mind when dealing with patients: incomplete penetrance, complex geno-type-phenotype correlations, wide range of clinical manifestations and overlapping, different response to treatments and prognosis. Indeed, while in the last few years some papers, mainly case reports, enlarged the clinical spectrum of C9ORF72-associated parkinsonian syndromes without ALS or FTD [2,7], studies on different populations of patients affected by atypical parkinsonian syndromes or PD, did not show an in-creased incidence of G4C2 hexanucleotide repeats expansion [9]. These data suggest that the pathogenic role of C9ORF72 expansion should be

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Letter to the Editor

Image of Fig. 1

considered with caution in such pathologically and clinically different diseases [10]. In fact, while there was no evidence for over-representa-tion of C9ORF72 expansions in patients with PD and con.rmed a-synucleinopathy, neurodegeneration was shown in the substantia nigra of C9ORF72-related ALS cases [10]. Therefore, it is possible that de-spite the fact that C9ORF72 expansions are not a cause of classical PD, the neuropathology associated with C9ORF72-expansion can affect the substantia nigra and cause parkinsonism. Thus, C9ORF72 expansions can affect multiple brain areas which lead to different clinical conse-quences [11].

This opens also the question concerned to the repeat size at which the mutation becomes pathogenic in different clinical syndromes. The GGGGCC expansions have been described as pathogenic if they are N30 repeats. However, the clinical phenotype of ALS cases with 20–30 repeats are similar to those with N30 repeats [12], suggesting that the minimum number of repeats needed for pathogenicity may be smaller than the currently accepted cut-off. On the other hand, mutations with N30 repeats have also been reported in healthy individuals, as well as in those affected by other neurodegenerative diseases [11]. In our patients with parkinsonian features we found a relatively small expansion that may suggest a relationship with the relatively mild disease phenotype; nevertheless this correlation between expansion size, disease phenotypes and disease severity is still greatly controversial in literature and large cohort studies are needed to bring clarity on this topic.

In conclusion, in our case (as well as in the previously reported ones) we cannot exclude a fortuitous combination of parkinsonism and C9ORF72 intronic expansion (with possible future development of ALS-FTD), with a C9ORF72 role of “innocent bystander”, although the “atypical” phenotype could suggest a genetic imprint.

Therefore, genetic testing for C9ORF72 mutations should be considered in presence of pure atypical parkinsonism and a family history of ALS or FTD, with a cautious interpretation of its role with patients and their families. These considerations may be useful in clinical practice for patients counselling and prognosis.

Author contributions

Dr. F. Cavallieri: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Dr. J. Mandrioli: conception and design of the study, acquisition of data, analysis and interpretation of data, revising the manuscript for important intellectual content, final approval of the version to be submitted.

Dr. F. Rosa: acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Dr. S. Contardi: acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Dr. A. Fasano: acquisition of data, analysis and interpretation of data, final approval of the version to be submitted.

Dr. E. Menozzi: acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Dr. C. Caponnetto: acquisition of data, analysis and interpretation of data, final approval of the version to be submitted.

Prof. A. Chiò: conception and design of the study, drafting the article, revising the manuscript for important intellectual content, final approval of the version to be submitted.

Dr. F. Valzania: conception and design of the study, analysis and interpretation of data, drafting the article, revising the manuscript for important intellectual content, final approval of the version to be submitted.

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Con.ict of interest

The authors report no con.icts of interest.

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