

C9orf72 hexanucleotide expansion and parkinsonism: weak link, innocent bystander, or central player in neurodegeneration?

F. Cavallieri¹, J. Mandrioli¹, N. Fini¹, S. Contardi¹, A. Fasano¹, E. Menozzi¹, P. Nichelli¹, A. Chiò², F. Valzania¹.

1: Department of Neuroscience, S. Agostino-Estense Hospital and University of Modena and Reggio Emilia, Modena, Italy.

2: ALS Center, 'Rita Levi Montalcini' Department of Neuroscience, Neurology II, University of Torino, Turin, Italy; Azienda Ospedaliero-Universitaria Città della Salute e della Scienza, Torino, Italy.

Introduction: C9orf72 expansion is the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Although few case reports have been described, an increasing role of this hexanucleotide expansion in parkinsonism and related disorders has been recently suggested.

Case report: A 60 years-old woman was admitted with a 3 years history of progressive gait disturbance with frequent falls, urinary incontinence, bradykinesia and rigidity with a positive family history of ALS (the mother and two sisters).

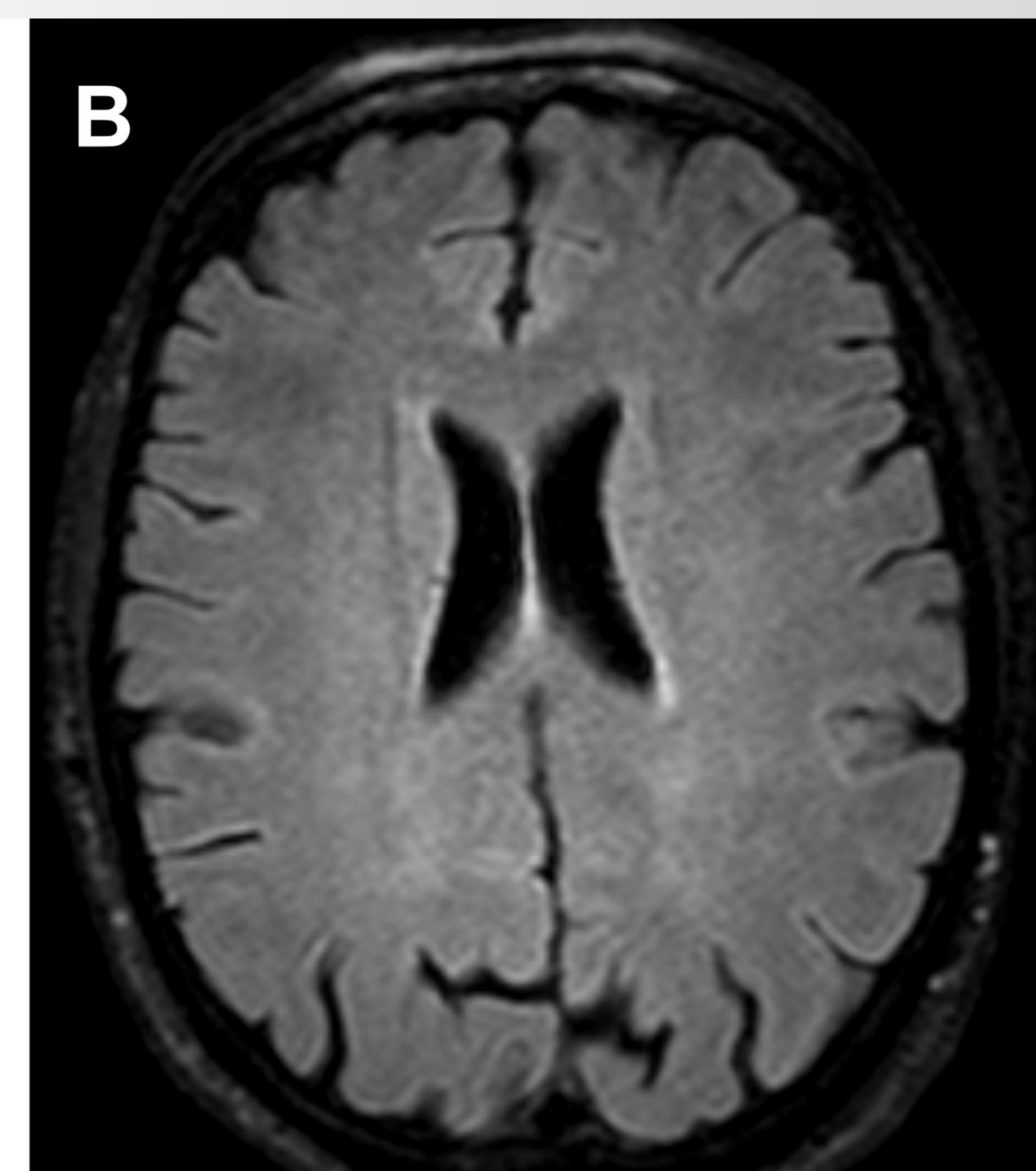
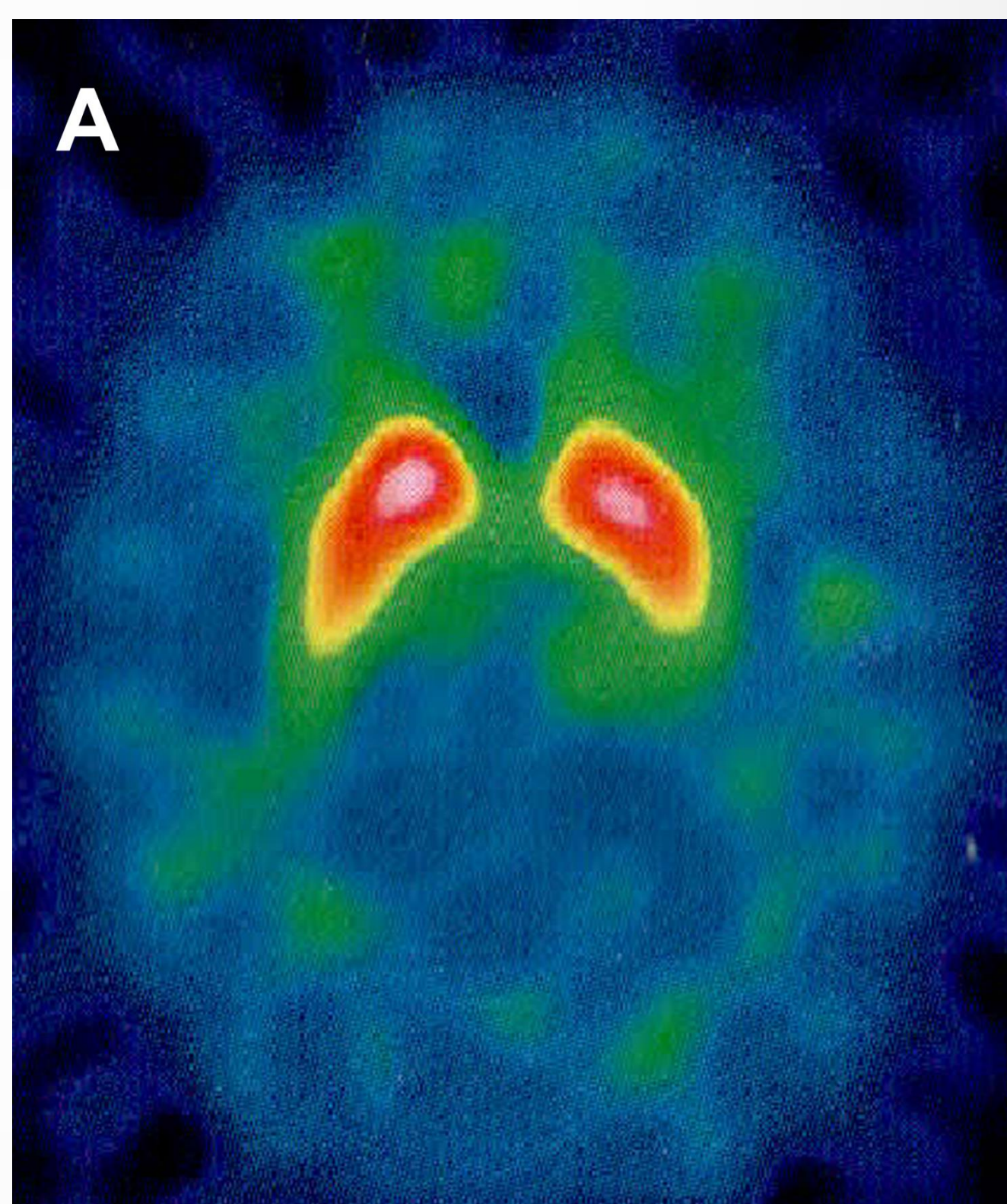
- *Neurological examination:* dysarthric speech, hypomimia, slowness of vertical eyes movements, frontal release signs, symmetric akinetic-rigid parkinsonism, hyperreflexia, slow, wide-based, apraxic gait, anterocollis and camptocormia.
- *Neurophysiological studies:* increased motor central conduction time with normal needle electromyography.
- *DAT-SPECT:* symmetrical mildly reduction of striatal uptake prevalent in left posterior putamen (figure, A).
- *Brain and spine MRI:* normal (figure, B).
- *Neuropsychological assessment:* impairment in executive functions and praxis abilities.
- *Acute levodopa test:* improvement of 45% in UPDRS part III score, mainly on limbs bradykinesia and rigidity.

Genetics: pathological expansion (37 repeats) of the GGGGCC hexanucleotide in C9ORF72 gene



Therapy with levodopa-carbidopa (300 mg/day) and 4 mg rotigotine transdermal patch led to a stable motor response with development of levodopa-induced oro-buccal dyskinesia.

At 7 years from onset, she did not develop lower motor neuron, cerebellar signs or further cognition involvement.



Discussion: As already described, C9orf72 associated parkinsonism is frequently characterized by atypical features, concomitant motor neuron signs and cognitive impairment. In this case, the onset could be compatible with a Progressive Supranuclear Palsy-like phenotype, but the association of autonomic dysfunction, anterocollis, pyramidal signs and levodopa-induced oro-buccal dyskinesia may be more suggestive of Multiple System Atrophy. The significant and stable L-DOPA response together with a very mild progression may move towards the evolution of Idiopathic Parkinson's Disease. This apparent discrepancy is similar to what is observed in genetically determined parkinsonism, in which clinical profile, progression and L-DOPA responsiveness not always meet the paradigms of idiopathic forms. Indeed, while in the last few years some case reports enlarged the clinical spectrum of C9ORF72-associated parkinsonian syndromes without ALS or FTD, 2 studies on different populations of patients affected by atypical parkinsonian syndromes or PD, did not show an increased incidence of G4C2 hexanucleotide repeats expansion. These data suggest that the pathogenic role of C9orf72 hexanucleotide expansion should be considered with caution in such pathologically and clinically different diseases. 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.

Conclusion: This case report highlights some important elements connected to C9orf72 expansion to bear in mind when dealing with patients: incomplete penetrance, complex genotype-phenotype correlations, wide range of clinical manifestations and overlapping, different response to treatments and prognosis. 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 cautiously interpretation of its role with patients and their families. These considerations may be useful in clinical practice for patients counselling and prognosis.

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