J Neurol (2012) 259:2723–2725
DOI 10.1007/s00415-012-6640-1

LETTER TO THE EDITORS

Amyotrophic lateral sclerosis/frontotemporal dementia with predominant manifestations of obsessive–compulsive disorder associated to GGGGCC expansion of the *c9orf72* gene

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Received: 29 May 2012 / Revised: 23 July 2012 / Accepted: 24 July 2012 / Published online: 24 August 2012

Dear Sirs,

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease involving upper and lower motor neurons. Up to 50 % of ALS cases have cognitive and/or behavioral impairment falling into the spectrum of frontotemporal dementia (FTD) [1]. Approximately 10 % of cases are familial (FALS), while the others are considered sporadic, as their occurrence seems to be random throughout the population. Recently, a GGGGCC hexanucleotide repeat expansion in the first intron of *c9orf72* gene on chromosome 9p21 has been related to familial and sporadic cases with ALS, ALS-FTD, or FTD. [2–4].

We describe a 52-year-old man carrying the GGGGCC expansion in the *c9orf72* gene. At 50, he developed muscle weakness and wasting at the right hand. Soon after he developed intrusive thoughts of urine loss, not supported by clinical evidence. After a pantoclastic episode characterized by aggressiveness towards objects and auditory hallucinations due to an obsessive impulse to urinary stimuli, he was admitted to our hospital. He had muscle weakness and atrophy of upper limbs (predominantly right) and spasticity of upper and lower limbs, hyperactive deep tendon reflexes, hyperactive jaw jerk, and fasciculations at limbs and trunk muscles. Bulbar and respiratory muscles were spared. Needle EMG showed a diffuse pattern of chronic and active denervation, with normal nerve conduction studies. Motor-evoked potentials demonstrated increased central motor conduction time. Psychiatric evaluation was consistent with obsessive–compulsive disorder (OCD) with predominantly Obsessional Thoughts or Rumination (ICD-10 code F42.0), with psychotic manifestations. The patient's father died at 42 years old from spinal amyotrophic lateral sclerosis (ALS); he had no cognitive or behavioral impairment. The patient's sister and a paternal uncle had a depressive disorder. The patient was found to carry a hexanucleotide repeat expansion in *c9orf72* gene (>50 repeats); no other mutations of major ALS-FTD related genes were found. Magnetic resonance imaging (MRI) revealed bilateral reduction of fractional anisotropy along the corticospinal tract (predominantly right). Brain positron emission tomography (PET) with ^{18F}FDG presented reduced hypometabolism in the motor cortex bilaterally, in the fronto-mesial cortex bilaterally between the anterior and the middle cingulate gyrus (predominantly right) and in the postero-lateral occipital cortex bilaterally (Fig. 1). The neuropsychological assessment was consistent with a diagnosis of behavioral FTD, associated to OCD, hallucinations, and depressive mood disorder. In the following months, the patient developed dysarthria, dysphagia, tongue atrophy with fasciculations, lower limb weakness and hypotrophy, and worsening of spasticity at the upper and lower limbs.

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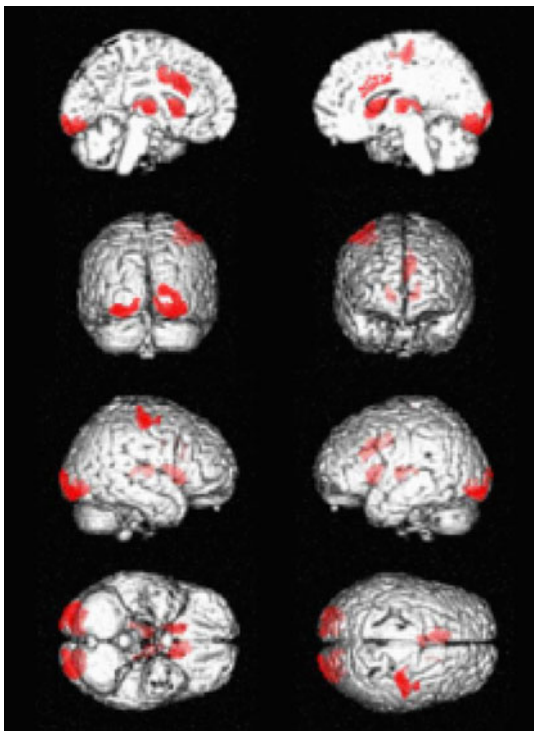

Fig. 1 Three-dimensional rendering of voxels reflecting hypometabolism in our patient as compared to normal controls ($n = 40$). The significant statistical differences are *highlighted*. The first row represents the medial aspect of left (on the *left*) and right (on the *right*) hemispheres; the second row represents the posterior (on the *left*) and anterior (on the *right*) aspect on the brain; the third row represents the lateral aspect of the right (on the *left*) and of the left (on the *right*) hemispheres; the fourth row represents the inferior (on the *left*) and the superior (on the *right*) aspects of the brain. The patient showed no cortical atrophy. The comparison was performed with SPM2 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 6.5 (MathWorks, Natick, MA, USA)

C9orf72 hexanucleotide repeat expansion accounts for one-third of Italian FALS [4] and 4–5 % of Italian SALS [5]. The phenotypic spectrum of patients carrying *c9orf72* hexanucleotide repeat expansion is wide, even within the same family pedigree [6, 7]. In our family, the father was affected by a classic ALS phenotype, without any apparent cognitive impairment. Our patient developed ALS-FTD, associated to psychiatric manifestations including depressive mood disorder, OCD, and psychotic symptoms. Obsessive manifestations have been described in FTD-ALS with *c9orf72* mutations [6, 8]. ^{18F}FDG PET studies in OCD patients have documented relative hypermetabolism in the orbitofrontal cortex [9–11], the anterior cingulate gyrus [11, 12], and the head of the caudate nucleus [9, 13], and relative hypometabolism in the prefrontal lateral cortex in OCD subjects [14, 15]. These findings were not detectable in our patient. The association of ALS, FTD, depression, psychotic manifestations, and OCD could set up a distinctive phenotype related to *c9orf72* gene expansion, which, however, needs to be confirmed by further observations.

Acknowledgments This work was funded in part by Federazione Italiana Giuoco Calcio, Fondazione Vialli e Mauro per la SLA onlus. The research leading to these results has received funding from the European Community's Health Seventh Framework Programme (FP7/2007–2013) (grant agreements 259867 and 278611).

Conflicts of interest None.

Ethical standard All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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