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LETTER TO THE EDITORS

Frontotemporal dementia with psychosis, parkinsonism, visuo-spatial dysfunction, upper motor neuron involvement associated to expansion of C9ORF72: a peculiar phenotype?

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Dear Sirs,

From 2006, a locus on chromosome 9p21 has been associated with a large proportion of ALS and FTD [1–3]. Recently, two independent groups have identified a hexanucleotide repeat expansion in noncoding region of the *C9ORF72* gene as the cause of chromosome 9p21-linked ALS-FTD [4, 5].

We report the case of a 64-year-old man who presented with a 3-year history of delusional mystic thoughts, auditive, visual, and olfactory hallucinations, and hyperreligiosity. The patient later developed progressive apathy, dysphoric mood, hyperphagia, self-care reduction, and progressive cognitive decline with motor retardation. The man's father had died at age 68 after committing suicide, and his older brother developed parkinsonism associated with behavioral disturbances at age 60 and died 2 years later. Neuropsychological assessment of this patient, performed 3 years after the onset of neurological symptoms, demonstrated bradyphrenia, marked impairment of attention and executive functions, marked constructional apraxia, mild visual and verbal long-term memory deficit, mild anomia, emotional lability, fatuity, and mild utilization behavior. Blood exams, thyroid antibodies and hormones, vitamin B12, folic acid, and TPHA were all normal. Neurological examination revealed symmetric akinetic-rigid syndrome characterized by hypomimia, dysarthria, camptocormia with anterocollis, and diffuse bradykinesia. Brain MRI documented atrophy mainly frontotemporal but with consistent posterior region involvement (Fig. 1). Perfusion SPECT with ^{99}Tc-ethylene cystine dimer (ECD) showed a marked reduction of the uptake in the frontotemporal and parietal regions bilaterally (Fig. 1). A few months after the first neurological assessment, the patient had a rapid progression to a severe dementia and developed marked pyramidal involvement of upper and lower limbs with an inability to walk. The patient became anarthric, dysphagic, and developed constipation. The nature of the dysarthria was both pseudobulbar and extrapyramidal. Lower motor neuron signs or symptoms were not present. Later the patient was admitted to a surgical department for intestinal sub-occlusion; during the hospitalization, a pulmonary embolism (PE) occurred. The patient died 4 years

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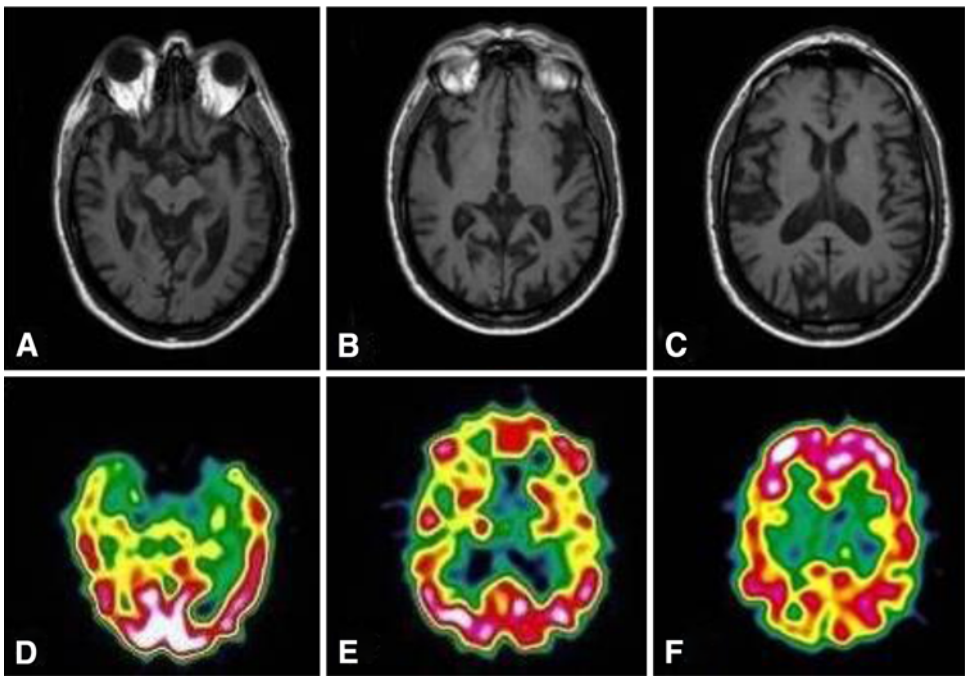

Fig. 1 **a–c** Brain MRI T1-weighted transversal scans showing bilateral frontotemporal and posterior cerebral areas atrophy. **d–f** Perfusion single-photon emission computed tomography (SPECT) with ^{99}Tc-ethylene cystine dimer (ECD). The transversal scans show a marked reduction of the uptake in the frontotemporal regions bilaterally and in the parietal lobes

after the first neurological manifestations. Mutations of *TARDBP*, *MAPT*, and *PGRN* genes were excluded. The patient has been found positive for a GGGGCC hexanucleotide repeat expansion in the first intron of *C9ORF72* gene (>50). Our patient developed a dementia with prominent behavioral disturbances at presentation, characterized mostly by psychosis with mystic themes. The neuropsychological evaluation demonstrated a marked cognitive impairment with predominant frontal syndrome. An important involvement of visuo-spatial functions was also found (Fig. 2). This cognitive impairment, associated with multimodal hallucinations and parkinsonism, which presented before the onset of upper motor neuron signs, raised a differential diagnosis between FTD and dementia with Lewy bodies (DLB). A few cases have been reported with similar diagnostic difficulties [6]. The parkinsonism was not drug-induced. The dementia profile of our patient was consistent with a behavioral variant of FTD. He presented a positive family history for similar disturbances. Some features of our case are atypical for FTD, like psychosis, constructional apraxia associated with the frontal syndrome, atrophy, and perfusional deficit extended to posterior cortical areas. Hallucinations are possible but not common in FTD [7], whereas they are a core clinical feature in the diagnostic criteria of DLB [8]. Of note, some clinical aspects of our case have been reported in patients with ALS-FTD linked to the locus 9p21, such as the presence of parkinsonism, psychosis, visuo-spatial impairment, and brain atrophy with parietal and occipital lobe involvement [9, 10]. We propose that delusions with multimodal hallucinations at presentation, visuo-spatial dysfunction, and frontotemporal brain atrophy also involving posterior areas could be aspects of a possible distinctive phenotype of FTD-parkinsonism-upper motor neuron disease linked to the C9ORF72 gene hexanucleotide expansions.

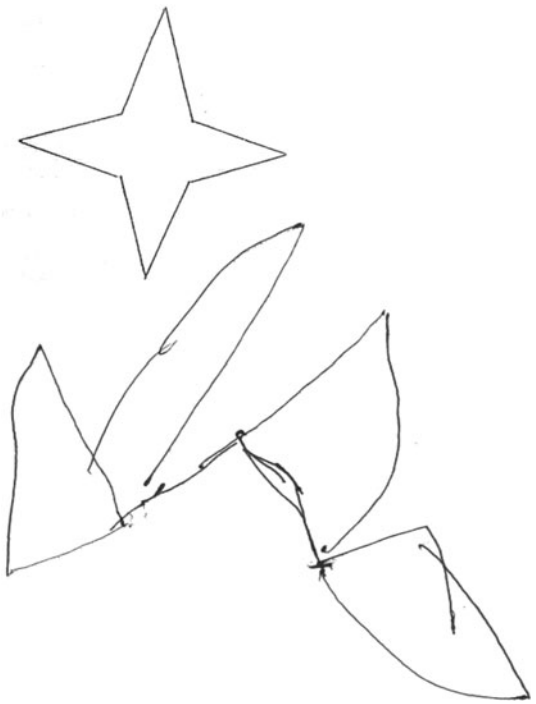

Fig. 2 Severe constructional apraxia demonstrated by the copy of a simple drawing

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Conflicts of interest The authors have no conflicts of interest.

Ethical standards The patient and his family gave their informed consent prior to their inclusion in the study.

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