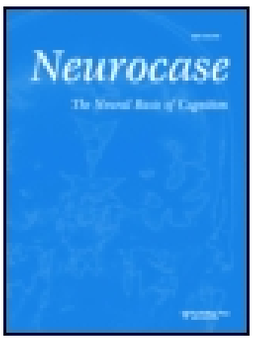

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REPORT

C9ORF72 G_4C_2-repeat expansion and frontotemporal dementia first reported case in Argentina

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ABSTRACT

We present a female patient aged 51 who developed behavioral disorders followed by cognitive impairment over 3 years. Neuropsychological, neuropsychiatric, and radiological features suggested a probable behavioral variant of frontotemporal dementia (bvFTD). A family history of amyotrophic lateral sclerosis and parkinsonism suggested the hexanucleotide repeat expansion G_4C_2 in *C9ORF72* . We set up a two-step genotyping algorithm for the detection of the expansion using fragment-length analysis polymerase chain reaction (PCR) and repeat-primed PCR with fluorescent primers. We confirmed the presence of an expanded G_4C_2 allele in the patient. This represents the first documented case of bvFTD due to a *C9ORF72* expansion in Argentina.

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Frontotemporal dementia; motoneuron disease; amyotrophic lateral sclerosis; *C9ORF72*

Introduction

Frontotemporal lobar degeneration syndrome accounts for the second cause of degenerative presenile dementia after Alzheimer's disease. The behavioral variant of frontotemporal dementia (bvFTD) is a neurodegenerative disorder responsible for a significant percentage of cases of dementia under the age of 65. The syndrome is described by behavioral changes followed by cognitive decline, evolving to dementia and death with an average survival rate of 7 years. About 40% of these cases have a family history with an autosomal dominant inheritance pattern (Goldman et al., 2011). The amyotrophic lateral sclerosis (ALS) is also a neurodegenerative rapidly progressive disease, with an average survival rate of three years. Only 5% of ALS cases show an autosomal dominant inheritance (Rademakers & van Blitterswijk, 2013; Rezania & Roos, 2013).

Regarding bvFTD, pathogenic mutations in genes *MAPT* ("Microtubule-associated protein tau") and *GRN* ("granulin"), both located on chromosome 17, have been described in a significant proportion of these patients (Goldman et al., 2011).

Moreover, the existence of families with frontotemporal dementia (FTD), ALS, or an overlap of both disorders, which showed linkage to a region on chromosome 9p2 is also well known (Shatunov et al., 2010). In 2011, a hexanucleotidic repetition expansion GGGGCC (G4C2) was identified in the intron 1 of the *C9ORF72* gene but with an unknown function. In the general population, the number of G4C2 repetitions at this locus is 2–20. However, in patients with FTD or ALS associated with chromosome 9p, the hexanucleotide could have a greater number of repetitions between 30 and 1600 (DeJesus-Hernandez et al., 2011; Renton et al., 2011). The tracking of this mutation among familiar and sporadic cases of FTD has shown that the expansion G4C2 represents indeed the most common molecular alteration (Majounie et al., 2012) in this particular group of patients.

There is no epidemiological data of FTD in Argentina, for no large-scale studies have been carried out on this disease; in addition, the study of *C9ORF72* is not stablished as a routine test in diagnosis. So far, there have been no cases of FTD due to G4C2 expansion in *C9ORF72* reported in Argentina. Thus, there might be an underestimation of the frequency of this mutation in our population. Later, we describe the first case confirmed in our country. The patient in question also has an atypical clinical presentation, with/including unusual neuroimaging abnormalities and features that are distinctive of *C9ORF72*.

Clinical case

We present a female patient aged 51 who developed behavioral disorders followed by cognitive impairment over 3 years before evaluation. She complained of progressive difficulties in speech, permanent anxiety, and outbursts of verbal and physical aggression at people in public places. These episodes were unleashed by the feeling of being attacked or not respected, e.g., pushed while in public transportation, witnessing someone littering in inappropiate places, racist comments, etc. Her behavior was secondary to a "vindicatory" type of delusion. The patient perceived such episodes as egodystonic and had partial awareness of her abnormal behavior. At the same time she suffered of "prejudice" (people "do things on purpose to harm her") delusional ideas; this idea affected even those she loved like her husband and family. The episodes of aggression were experienced as a sudden and

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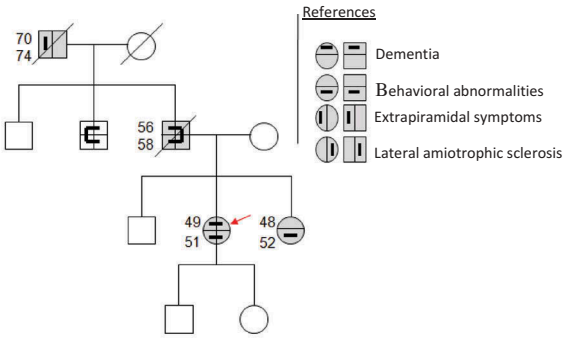

Figure 1. Pedigree. Circles represent females, and squares represent males. Lines represent clinical manifestations according to the reference table. Two-digit numbers represent the age of onset of symptoms (upper) and actual or death ages. Diagonal lines across figures indicate death.

incontrollable feeling ("I had an impulse, and I pruned all the plants in my garden, I couldn't avoid destroying my loved plants"). Past medical history was unremarkable.

Neurologic examination showed mild facial hypomimia, difficulties naming low-frequency used words, and some difficulty in verbal comprehension. The osteotendinous reflexes were brisk and symmetrical, but otherwise there were no release signs or primitive reflexes; no spasticity or stiffness was observed. Formal neurocognitive assessment detected a dysexecutive, anomia, and attention deficit syndrome. Evaluation of theory of mind ("Mind in the Eyes" and "Faux pas Test") showed alterations in social cognition (failure in recognition of negative emotions, inability to distinguish between the situations of "social blunders" by attributing them to a nonexistent intentionality of the participant's story).

We reevaluated the patient 9 months later and found a further deterioration in attentional and executive functions.

Family history shows many cases of neurological diseases. Her father had ALS preceded by mayor depression that began in his 50s. A paternal uncle was diagnosed of Pick's disease at the age of 60. The patient's sister had a diagnosis of bipolar disorder and mild mental retardation and refused to perform further studies. Her brother has multiple sclerosis. Her Russian-born paternal grandfather also had parkisonism (see Figure 1).

Genetic studies

G_4C_2 expansion of C9ORF72 *analysis*

Genomic DNA from the index case extracted from peripheral blood leukocytes was obtained using "Wizard Genomic DNA Purification Kit" (Promega). Initially, 30 ng of genomic DNA were used in polymerase chain reaction (PCR) adapted from DeJesus-Hernandez (DeJesus-Hernandez et al., 2011). Subsequently, a reaction called "Repeat-primed PCR" was performed according to previous publications (DeJesus-Hernandez et al., 2011; Renton et al., 2011). After fluorescent PCR products were detached by capillary electrophoresis, the analyses of these amplicon sizes were performed using the program Peak Scanner (Applied Biosystems). The index case presented one allele with two replicates G4C2 and another allele with pathological expansion (Figure 2(b,c)). Using this technique, the number of repetitions found is 2 and >50 for each allele.

It was thus possible to characterize the mutation in our patient. According to Rascovsky's criteria, the case is defined as a "Definite behavioral variant of FTD (bvFTD)" (Rascovsky et al., 2011).

Cerebrospinal fluid (CSF) analyses

CSF showed a normal physical–chemical and cytologic results. Oligoclonal bands (imnuofixation IgG and isoelectro focusing) were negative.

Alzheimer's disease (AD) biomarkers were performed to rule out an atypical presenile presentation of this disease; the results showed: Ab1-42: 1101.4 pg/mL (normal value: >532.5 pg/mL), total Tau: 224.90 pg/mL (normal value: <100 pg/mL), hyperphosphorylated Tau: 45.6 pg/mL (normal value: <26.5 pg/mL), and were interpreted as not compatible with AD. We used cutoff values set in our laboratory and published in 2013 (Surace et al., 2013).

Imaging studies

Brain magnetic resonance imaging (MRI) was performed (T1, T2, FLAIR, GRE sequences); diffuse brain and cerebellar atrophy was detected (Figure 2(a)).

Brain Tc99 SPECT showed hypoperfusion in anterobasal, polar, and lateral temporal lobe in the left hemisphere; in the right hemisphere, a frontal-orbitary hypoperfusion was observed.

Discussion

This is the first patient in Argentina described with FTD carrying a *C9ORF72* repeated expansion, a family history positive for ALS, dementia, and psychiatric disorders. The paternal branch of the pedigree starts with the grandfather, who as mentioned earlier was born in Russia. Cases of ALS–*C9ORF72* have been recently described in Russia, although with low prevalence (Abramycheva et al., 2015).

From the clinical point of view, this patient represents an atypical case of bvFTD. We consider relevant to point out some peculiarities. First, our patient suffers from psychotic ideation and delusions that are not common in bvFTD patients but which have been recently described as a feature suggestive of *C9ORF72* expansion. A recent work of Snowden et al. in 2012 (Snowden et al., 2012) highlights a powerful association between *C9ORF72* mutations and psychosis and suggests that the behavioral characteristics of patients with the expansion are qualitatively distinct. These findings were replicated by other authors (Arighi, Fumagalli, & Jacini et al., 2012; Kertesz et al., 2013). Furthermore, psychosis as the only initial symptom in G4C2 expansion carriers had also been described (Arighi et al., 2012). Secondly, the patient showed partial awareness of the abnormality of her symptoms (Arighi et al., 2012), being also repeatedly conscious of her misbehavior and showing anxiety and regret when realizing what is happening; this feature is atypical for bvFTD, which in general has a profound anosognosia (O'Keeffe et al., 2007) described as a

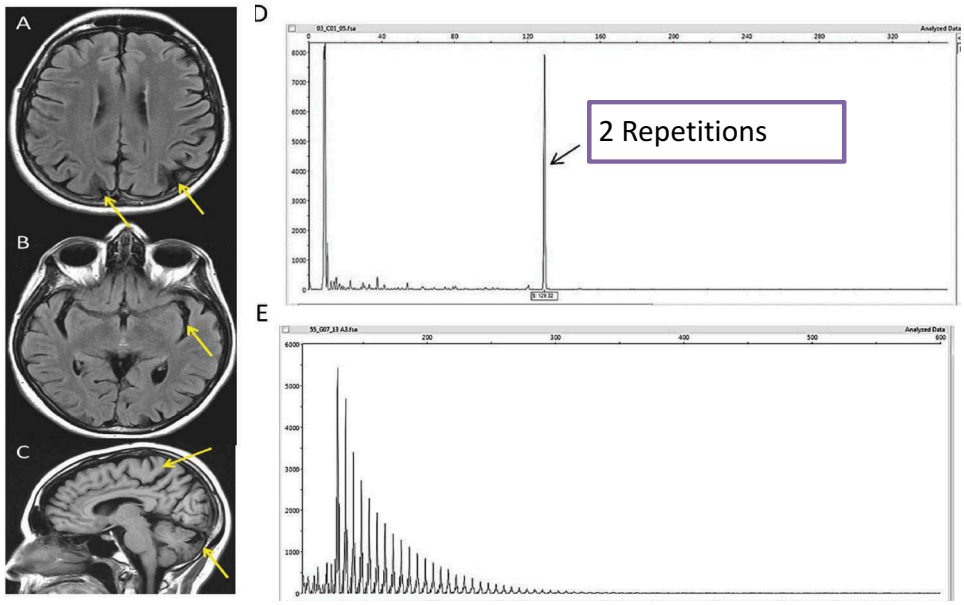

Figure 2. Imaging and genetics studies: Brain MRI. (a) and (b). Flair sequence. Axial view. (c) T1 sequence. Sagital view. Yellow arrows show mild and generalized atrophic changes that include symmetric atrophy in both parietal and frontal lobes, cerebellar hypotrophy is also evidenced. (d) PCR. The electropherogram displays only one allele with two repetitions of the G4C2 hexanucleotide. (e) "Repeated primed PCR", with the characteristic stutter amplification pattern.

core feature of this entity. From the neuropsychological testing results, a profile with abnormalities of language and a dysexecutive syndrome with a relatively good preservation of verbal memory was compatible with bvFTD; also the alteration of the social skills and functions related to "theory of mind" are considered an early and sensitive abnormality of bvFTD and could be useful for diagnosis (Kipps & Hodges, 2006; Wittenberg et al., 2008).

Regarding imaging findings in *C9ORF72*-bvFTD patients, a widespread pattern of gray matter loss compared with controls was described. However, the most noticeable loss is observed in frontal lobes, involving orbitofrontal, medial, and dorsolateral regions followed by temporal lobes. Gray matter loss was observed in parietal and occipital lobes and cerebellum. In comparison with other mutations, *C9ORF72* shows a greater loss in parietal and occipital lobes, particularly medially as well as lateral inferior frontal lobe and cerebellum (Whitwell et al., 2012; Yokoyama & Rosen, 2012). Some studies have also suggested cerebellar and thalamic involvement in *C9ORF72*-associated disease (Souza, Pinto, & Oliveira, 2015). On the other hand, consistently with the behavioral and language abnormalities suffered by the patient, the Tc99 SPECT showed hypoperfusion in the right frontal and left temporal regions.

According to DeJesus et al., who analyzed 909 healthy controls with the described two-step algorithm, the maximum size of the GGGCC repeat length was 23 units whereas our patient has a normal allele with two copies and an expanded one with more than 50; Figure 1 shows the typical hexanucleotide expansion pattern.

Finally, despite the atypical clinical and radiological findings, the family history of psychiatric illness, ALS, and dementia were suggestive of a *C9ORF72* mutation, and was demonstrated to be the genetic cause of the disorder in our case.

Disclosure statement

The authors declare that there are no conflicts of interest.

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