Frontotemporal Dementia in a Brazilian Kindred With the C9orf72 Mutation

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Objectives: To describe the clinical features of a Brazilian kindred with C9orf72 frontotemporal dementia–amyotrophic lateral sclerosis and compare them with other described families with C9orf72 and frontotemporal dementia–amyotrophic lateral sclerosis–causing mutations.


Setting: Dementia center at a university hospital.

Patients: One kindred encompassing 3 generations.

Results: The presence of a hexanucleotide (GGGGCC) expansion in C9orf72 was confirmed by repeat-primed polymerase chain reaction and Southern blot. The observed phenotypes were behavioral variant frontotemporal dementia and amyotrophic lateral sclerosis with dementia, with significant variability in age at onset and duration of disease. Parkinsonian features with focal dystonia, visual hallucinations, and more posterior atrophy on neuroimaging than is typical for frontotemporal dementia were seen.

Conclusions: Behavioral variant frontotemporal dementia due to C9orf72 expansion displays some phenotypic heterogeneity and may be associated with hallucinations, parkinsonism, focal dystonia, and posterior brain atrophy. Personality changes may precede the diagnosis of dementia by many years and may be a distinguishing feature of this mutation.


METHODS

We describe a Brazilian family of Italian and Portuguese origins (kindred UCSFBR1, Table). Two patients were seen at the University of California, San Francisco, and other affected members’ data are summarized based on the information provided by the family and their neurologist (M.L.V.P.). The pedigree (Figure 1) was simplified and anonymized for confidentiality (at-risk individuals were omitted). This report is based on data collected in an institutional review board–approved project, and family members (or their surrogates) signed informed consent. The diagnoses of bvFTD and ALS were made based on current diagnostic criteria.

RESULTS

PATIENT III-1

A right-handed man had behavioral changes beginning at age 38 years, when he became obsessed with preparing for a course he planned to take the following year. Subsequently, his family noticed increased aggression, disinhibition, and
Electromyography did not show signs of motor neuron disease. Gait was also slow, with mild bradykinesia. Tonic posturing of her left hand during gait were the only abnormalities observed. Magnetic resonance imaging of the brain revealed mild atrophy of the anterior temporal lobes, insula, and orbitofrontal region as well as dorsal atrophy (Figure 2B). Electromyographic findings were normal (units were at the upper limit of normal in tongue electromyography), but intermittent tongue fasciculations were noted. She was diagnosed as having bvFTD with concerning signs for concomitant motor neuron disease.

OTHER PATIENTS

Patients I-1, I-3, and I-4 had no history of cognitive or behavioral problems. Patient I-3 had Crohn disease. Patient I-2 was described as having memory problems and personality changes starting in her 40s. She later developed movement problems and further cognitive decline consistent with dementia. She died at age 76 years. Patient I-5 had a history of unspecified late-onset dementia (as did one of her daughters).

Patient II-1 was described as having odd behaviors beginning in his 30s and being a cruel parent. He was diagnosed as having bvFTD in his late 60s, with visual hallucinations and disinhibition as early manifestations followed by memory, language, and further behavioral decline. Later, he developed parkinsonian signs. He died at age 72 years.

At age 57 years, patient II-2 began having difficulty recognizing people and trouble with navigation as well as being less interested in social interactions. Changes in empathy and eating habits 3 years later led to a diagnosis of bvFTD. Twelve years after the onset of symptoms, she was bedridden and almost mute.
Patient II-3 began having cognitive and behavioral problems at age 55 years (although her family reported some degree of social compromise in her 40s) and was diagnosed as having late-onset schizophrenia. She died at age 64 years, 5 months after being diagnosed as having ALS.

**GENETIC ANALYSES**

Samples of DNA were obtained from peripheral blood, and expanded GGGGCC hexanucleotide repeats in C9orf72 were detected in a stepwise fashion according to previously described methods. Samples from individuals II-0, II-1, III-1, II-2, and II-4 were first screened by fluorescent fragment-length polymerase chain reaction analysis to identify a potentially unamplifiable repeat expansion (Figure 3A). The facts that all patients showed a homozygous pattern (single peak) and that the affected son (III-1) did not seem to inherit an allele from his affected parent (II-1) were considered suggestive evidence of a repeat expansion. Repeat-primed polymerase chain reaction analysis was then used to verify the presence of an expansion in all patients, confirmed by the observation of a stutter amplification pattern on the electropherogram (Figure 3B). The presence of expanded alleles was further substantiated by Southern blot (Figure 3C), which showed additional expanded alleles at 5 to 23 kilobases in affected individuals.

**COMMENT**

Similar to previous reports, the main clinical syndromes seen in this family with the C9orf72 mutation were bvFTD and ALS. The phenotypic heterogeneity observed in previously described families thus far was also apparent in this kindred.

Age at onset with the C9orf72 mutation was difficult to precisely ascertain. In many members of the family, subtle personality changes began decades before dementia was diagnosed. In patient II-4, the history behind her hysterectomy—14 years before the onset of symptoms—raises suspicion as to whether she was truly asymptomatic then. Cognitive impairments in presymptomatic mutation carriers have been described in MAPT mutations, but personality changes predating the diagnosis of dementia have not been reported and may be a distinguishing feature of C9orf72 expansions. Also, in generation III, at least 3 individuals were diagnosed as having depression and/or anxiety (not depicted in the pedigree). Those conditions are prevalent in the general population and also have familial aggregation, so it is currently unclear whether they represent a first symptom in the neurode-
generative process or whether other confounding genetic factors are contributing to a higher frequency of psychiatric conditions in this family.

Anticipation is a characteristic of many repeat expansion disorders, although with the massive numbers of repeats present in all patients tested to date it is possible that anticipation will not be a strong feature of the C9orf72 mutation. Patient III-1 was diagnosed as having bvFTD at an earlier age than the previous generation; however, if the onset is considered as the earlier personality changes, his symptoms began at around the same age as his father’s. Further research is necessary to determine whether C9orf72 expansions are associated with anticipation, and developing ways to accurately measure the exact number of repeats may help with this understanding. Although in our study the presence of repeat expansions was confirmed by Southern blot, significant repeat-size heterogeneity resulting in a smear on the Southern blot complicated accurate sizing of the repeat length.

Parkinsonian features, often a finding associated with C9orf72 mutations,2,10,11 were also observed in this family. In addition to parkinsonism appearing in clinical con-

Figure 3. Molecular genetic analyses of C9orf72 repeat expansions in the UCSFBR1 family. A, Fluorescent fragment-length analysis of a polymerase chain reaction fragment containing the GGGGCC repeat in C9orf72 in 4 patients (II-1, III-1, II-2, and II-4) and an unaffected spouse (II-0). A lack of transmission from the affected parent (II-1) to the affected offspring (III-1) is seen. Numbers under the peaks indicate the number of GGGGCC hexanucleotide repeats. B, Polymerase chain reaction products of repeat-primed polymerase chain reactions separated on an ABI3730 DNA Analyzer (Applied Biosystems) and visualized by GeneMapper software (Applied Biosystems). Electropherograms are zoomed to 2000 relative fluorescence units to show stutter amplification. Results from an expanded repeat carrier (II-1) and a healthy control are shown. C, Southern blotting of C9orf72 alleles. Patients with expanded repeats (II-1, III-1, and II-2) show additional alleles ranging from 5 to 23 kilobases, while the unaffected spouse (II-0) shows only the expected approximately 2.3-kilobase wild-type allele.

junction with either motor neuron disease or FTD,1,12 nigral degeneration is a frequent finding in ALS with dementia,13 so this association is not surprising.

Dystonia has rarely been described as an additional sign, and only briefly in a previously described family with a chromosome 9p mutation.11 Parkinsonism with focal dystonia may be seen in atypical parkinsonism14 but is only rarely observed within the bvFTD phenotype. Also, a previous report mentioned parkinsonism with dystonia in a family with FTD-ALS with the MAPT mutation.15 Further observations are needed to ascertain the significance of focal dystonia in C9orf72 mutations.

Mutations in TARDBP have also been associated with parkinsonian or dystonic features in families with ALS.10 Parkinsonism was reported with dementia and upper-limb muscle weakness in 1 individual with a chromosome 9p mutation,11 although the point during the course of disease at which it appeared was not described.12 DCTN1 mutation has been associated with ALS, FTD, and Perry syndrome, but its pathogenicity in FTD-ALS is still not entirely clear.18

Psychosis has been reported in 4 families with chromosome 9p mutations2,10,19,20; hallucinations may be distinguishing symptoms2,10 as they are considered rare in sporadic bvFTD.13 Visual hallucinations are the most commonly reported type (as in patient II-1), but the description of auditory hallucinations in 3 previous reports2,19,20 suggests that they could also be a marker for this mutation. Psychosis was reported in 1 patient with a VCP mutation, although it was not described in detail.17

In this study, a somewhat more posterior pattern of atrophy was observed on neuroimaging. This is similar to a previous report in which C9orf72 bvFTD demonstrated more parietal and occipital and less temporal atrophy compared with sporadic bvFTD.10 This pattern is in line with the finding of more significant visuospatial dysfunction in a subset of patients with the C9orf72 mutation (such as patient II-3),2 which is unusual for bvFTD.12

Finally, the occurrence of inflammatory bowel disease in 2 members of this family is intriguing. Even though no direct associations can be made based on the limited knowledge gathered so far on C9orf72, increasing evidence links neurodegenerative processes and inflammation.21 Although no other previous reports to our knowledge have mentioned inflammatory diseases occurring in families with the C9orf72 mutation, it is possible that they have been overlooked.

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