Does epilepsy contribute to the clinical phenotype of C9orf72 mutationin fronto-temporal dementia?

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C9orf72 mutation is the most common genetic cause of frontotemporal dementia (FTD) and amyotrophiclateral sclerosis (ALS) worldwide.

Recently, several reports of patients with FTD who carried the C9orf72 mutation and also manifested epilepsy have been published, since seizures occur in FTD at a higher ratethan in the general population, the possible association between epilepsy and C9orf72 mutation remainsto be clarified. In the attempt to understand whether epilepsy contributes to the phenotype of the C9orf72 mutation, we compared epilepsy occurrence in patients with FTD who carried the C9orf72 mutation and those who did not. In our sample of 84 patients with FTD, 7.1% of cases reported epilepsy, with no significant differences between subsamples of patients with FTD stratified according to the presence ofthe C9orf72 mutation or to family history of FTD/parkinsonism/motor neuron disease. Our findings did not support to the possibility that epilepsy represents a characteristic feature of the C9orf72 mutation, as suggested by recent case reports published in the English literature.

1. Introduction

C9orf72 mutation is the most common genetic cause of fron- totemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) worldwide [1]; its clinical phenotype is wide and pleiotropic, also including parkinsonism and dementia [2]. Recently, several reports of patients carrying the C9orf72 mutation, associated with FTD or motor neuron syndrome, who also manifested epilepsy, have been published [3–6]. These observations raised the possibil- ity that epileptic manifestations are part of the clinical spectrum of the C9orf72 mutation. Since seizures occur in FTD at higher rates than in the general population [7,8] the possible association between epilepsy and C9orf72 mutation remains to be clarified. In the attempt to understand whether epilepsy contributes to the phenotype of the C9orf72 mutation, we assessed epilepsy occur- rence in patients with FTD who carried the C9orf72 mutation and those who did not.

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https://doi.org/10.1016/j.yebeh.2022.108783

2. Methods

Patients were recruited among those followed up between 2013 and 2019 in the outpatient department of the Neurologic Clinic of the University Hospital of Cagliari. All patients were Sardinian fromat least three generations. FTD was diagnosed according to the Ras- covsky criteria for the behavioral variant FTD (bvFTD) and the Gorno-Tempini criteria for the variants included in primary pro- gressive aphasia (PPA) form (semantic variant PPA (svPPA), logope- nic PPA (lvPPA), and nonfluent/agrammatic variant PPA (nfaPPA)) [9,10]. Positive family history was diagnosed when FTD and/orparkinsonism and/or motor neuron disease were observed in a first-degree relative of studied patients. All patients underwent genetic screening for theC9orf72 mutation.

Patients with FTD were checked for seizures and epilepsy according to established clinical diagnostic guidelines [11]. Infor- mation on epileptic manifestations was confirmed by informed rel- atives and medical records. Patients with seizures provoked bycortical lesions, acute metabolic disorders or subdural hematomas, and patients taking antipsychotic drugs or other medication lower- ing seizure threshold at the time of their first unprovoked seizure were excluded.

Data were expressed as mean and standard deviation (SD) unless otherwise indicated. Statistical analysis was performed by

STATA 11 package using *t*-test, Chi-square test, and Fisher's test, as appropriate.

3. Results

During the study period, 84 patients were diagnosed with FTDand checked for the C9orf72 mutation. Forty-nine men and 35women were identified, aged 64.1 ± 9.8 years at the onset of FTD.PPA was diagnosed in 23 patients (5 lvPPA, 9 svPPA, and 8 nfaPPA)while bvFTD was diagnosed in 61 patients. Frontotemporal demen-tia was associated with signs of parkinsonism in 30 patients andsigns of motor neuron disease in 10; these two phenotypes coex-isted in 3 patients. Family history of FTD, parkinsonism, or motorneuron disease was reported by 30/84 patients (36%). TheC9orf72 mutation was detected in 20/84 (23%) patients, including20/61 patients with bvFTDA and 0/23 patients with PPA (p = 0.001).

Epilepsy was diagnosed in 6 patients (3 men and 3 women aged 64.5 ± 6.1 years at the onset of FTD) and considered symptomatic according to the ILAE Classification. Generalized tonic-clonic sei- zures were observed in all patients, with focal motor manifesta- tions being evident in one of them. All patients underwent antiepileptic drug treatment. In the six patients with epilepsy, FTD started at 54.2 ± 15.8 years while new-onset seizures appeared 5.8 ± 3.9 years later (range 1–11 years).

Prevalence rate of epileptic manifestations in all patients with FTD was 7.1% (6/84). Epilepsy was more frequent in patients with PPA than in patients with bvFTD (4/23 vs. 2.61, p = 0.045), while the frequency of the condition did not differ between patients with positive and negative family history (3/30 vs. 3/54, p = 0.6). When we stratified the sample by C9orf mutation, epileptic manifesta- tions were present in 2/20 (10 %) patients who carried the C9orf72 mutation and in 4/65 patients (6.2%) who did not (p = 0.6). Disease duration did not significantly differ across sub-groups (Table 1).

4. Discussion

In our sample of patients with FTD, 7.1% of cases reported epi- lepsy characterized by unprovoked seizures that lacked distin- guishing clinical features. Epilepsy was more frequent in patients with PPA than in patients with bvFTD. By contrast, distribution of epilepsy did not significantly differ between patients with or with- out family history of FTD/parkinsonism/motor neuron disease, or between patients who carried the C9orf72 mutation and those who did not.

The 7.1% frequency of new-onset seizure found in our sample is higher but not far from the 2.6% prevalence of new-onset seizures recently reported in FTD by a larger clinic-based study [7]. Both estimates are greater than those observed in the healthy adult and elderly population, where the prevalence of epilepsy has been reported to be 0.7% in the age ranges 55–65 years and 1.2% in the age range 85–94 years [12]. The higher rate observed in our clinic probably resulted, at least in part, from being a referral center for both epilepsy and FTD/ALS. Regardless of the explanation, our find- ings confirmed recent reports which suggested that epilepsy is part of the clinical spectrum of FTD. The lack of differences in the fre- quency distribution of epilepsy between subsamples of patients with FTD stratified according to the presence of the C9orf72 muta- tion or family history of FTD/parkinsonism/motor neuron disease, however, did not support the possibility that epilepsy represents a characteristic feature of the C9orf72 mutation, as recent case reports would have suggested [3–6]. In agreement with recent data indicating that the prevalence of epilepsy is greater in PPA than in the bvFTD [13], we observed a statistically significant association between epilepsy and PPA. Although the finding has no obvious explanation, it is nevertheless in line with the reported differences in susceptibility to network hyperexcitability in specific types of dementia.

This study has some limitations. It was a clinic-based study and incomplete case ascertainment might have occurred. Owing to the rarity of FTD, however, a population-based survey is difficult to perform. Nevertheless, our patient sample was similar to the gen-eral population for most demographic and clinical features (includ- ing men preponderance, age at onset, frequency of clinical phenotypes, and the relationship between C9orf72 mutation and the bvFTD phenotype), which further supports the accuracy of the measurement. Also consistent with previous observations in the Sardinian population, our cohort reported a high rate of family history of FTD and related conditions, and a high frequency of C9orf72 mutation [13]. Since we assessed epilepsy in FTD but not in ALS, another condition associated with the C9orf72 mutation, our results only apply to the C9orf72-associated FTD. Low statisti- cal power might have also been responsible for the lack of differ- ence in the frequency of epilepsy between patients who carried the C9orf72 mutation and those who did not. Assuming the C9orf72+/C9orf72 ratio in FTD as 1:3, about 1000 patients withFTD (of whom 250 should carry the C9orf72 mutation) would be needed to observe a two-fold difference in epilepsy frequency between groups as statistically significant (p < 0.05, two-sided) with 80% study power. Owing to the rarity of both FTD [14] and C9orf72 mutation (1.5/100,000 in the Sardinian population) [15],such sample size is difficult to reach, even in a multicenter setting. Finally, we did not assess whether sub-clinical epileptiform activ- ity was present even in patients with no history of overt clinical seizures.

Despite of the mentioned limitations, this study provided novel information about the occurrence of epilepsy in FTD and its rela-tionship with FTD phenotype and C9orf72 mutation. Power calcu- lation indicated that the contribution of C9orf72 mutation to seizure development in FTD, if any, is probably low. In conclusion,

Table 1
Distribution of epilepsy according to the clinical form of fronto-temporal dementia (FTD), the presence of family history of FTD/parkinsonism/motor neuron disease, and thedetection of the C9orf72 mutation.

	Frontotemporal dementia diagnosis			Family history of frontotemporal dementia/parkinsonism/motor neuron disease			C9orf72 mutation		
	bvFTD	PPA	*P* value	Y	N	*P* value	Y	N	*P* value
N. patients	61	23		30	54		20	64	
N. patients									
– with epilepsy	2	4	0.045	3	3	0.6	2	4	0.6
– without epilepsy	59	19		27	51		18	60	
FTD duration	4.1 ± 3.8	3.9 ± 2.5	0.45	4.2 ± 4.1	3.7 ± 3.1	0.2	4.1 ± 4.1	4.1 ± 3.3	0.5

FTD = fronto-temporal dementia; bvFTD = behavioral variant fronto-temporal dementia; PPA = primary progressive aphasia.

the recently reported association between C9orf72 mutation and epilepsy seems to be explained by the recognized association between epilepsy and FTD, rather than the C9orf72 mutation itself.

Declaration of Competing Interest

The authors declare that they have no known competing finan- cial interests or personal relationships that could have appeared to influence the work reported in this paper.

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