C9orf72-associated Frontotemporal Dementia and psychosis

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A B S T R A C T

Frontotemporal dementia (FTD) is a progressive neurodegenerative disease. About 30-40% of the cases have a positive family history, and genetic mutations are identifiable in an increasing proportion of cases. Although psychosis in FTD has been recognized for many years, it has not been taken as a key feature, and has not been included in the clinical diagnostic criteria.

This paper assesses the prevalence and characteristics of psychotic symptoms in FTD, comparing cases with (FTD-C9+) and without (FTD-C9-) the *C9orf72* pathologic expansion, analyzing also the impact of psychosis in the misdiagnosis of FTD. For this purpose a literature review was carried out.

Psychotic symptoms may occur in FTD and should not exclude the diagnosis. In addition these are more frequent in FTD-C9+ as compared to FTD-C9-, and may be the first clinical manifestation of the disease, often leading to a psychiatric diagnosis years before the diagnosis of FTD is defined. There is no conclusive evidence on the neuroanatomical basis of psychotic symptoms in FTD, although an association with pathological changes of the right hemisphere seems apparent. Given that psychotic features may be the first manifestation of FTD, a differentiation from other psychiatric disorders is essential. Further studies are needed to better characterize psychotic symptoms in FTD-C9+ and understand its pathophysiology, in order to devise better therapeutic strategies.

Key words: Frontotemporal dementia; Frontotemporal lobar degeneration; *C9orf72*; TDP-43; psychosis; neuropathology.

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Abbreviations:

bvFTD- behavioral variant Frontotemporal dementia
C9orf72- Chromosome 9 open reading frame 72
CBD- Corticobasal degeneration
CBS- Corticobasal syndrome
CHMP2b- Charged Multivesicular Body Protein 2B
FTD- Frontotemporal dementia
FUS- Fused in sarcoma
GNR- Progranulin
MAPT- Microtubule associated protein tau
MND- Motor neuron disease PNFA- Progressive Non-Fluent Aphasia
PSP- Progressive supranuclear palsy
SD- Semantic dementia
TARDBP- Transactive response DNA binding protein
TDP-43- Transactive response DNA binding protein 43 kDa
VCP- Valosin-containing protein

INTRODUCTION

Frontotemporal Lobar Degeneration (FTLD) encompasses a set of neurodegenerative diseases associated with prime involvement of frontal and temporal brain regions.[1] The clinical syndrome Frontotemporal Dementia (FTD) is the second leading cause of dementia in patients younger than 65 years[2], corresponding to 5-15% of all dementias3. Predominant symptoms include progressive changes in behavior and personality, as well as dysfunction of executive abilities and linguistic capacities.[1,4,5]

FTD is clinically and pathologically heterogeneous, so that several syndromes are described in the literature as being part of the FTD complex[1,3]: a) behavioral variant FTD (bvFTD), where there is a change of behavior, with progressive personality deterioration, loss of social decorum, apathy, loss of empathy, and hyperorality; b) Primary Progressive Aphasia, further subdivided into Semantic Dementia (SD), in which there is a loss of linguistic abilities related to the comprehension of single words and objects; and Progressive Non-Fluent Aphasia (PNFA), characterized by difficulties with word evocation, non-fluent effortful speech and a progressive loss of fluency. Corticobasal syndrome (CBS) and Progressive Supranuclear Palsy (PSP) syndrome are two other related disorders. In addition, it should also be noted that there is a well-established association between FTD and motor neuron disease (MND), which may coexist in the same patient (FTD-MND).[2,6]

Neuropathologically, FTD is divided into three subgroups, based on the main pathological protein found in neuronal and glial inclusions[1], namely tau, transactive response DNA binding protein 43 kDa (TDP-43), and fused in sarcoma (FUS).

Like many other neurodegenerative diseases, FTD can present either sporadically or in hereditary forms. There is a positive family history of dementia in 40% of patients[1], and autosomal dominant mutations are now known in several genes[3]: Microtubule associated protein tau (*MAPT*), Charged Multivesicular Body Protein 2B (*CHMP2b*), progranulin (*GNR*), chromosome 9 open reading frame 72 (*C9orf72*), valosin-containing protein (*VCP*), transactive response DNA binding protein (*TARDBP*), and *FUS*. Thus, 30-50% of patients with bvFTD have a positive family history, whereas patients with SD and PNFA have a much lower frequency of family history.[4]

The *C9orf72* expansion is often found in Caucasian patients, and it is the mutation most frequently found in FTD, accounting for around 25% of familial cases and 6% of sporadic cases.[3] The *C9orf72* mutation is associated with 12-19% of bvFTD cases, and the second most common cause of PNFA, after GRN mutations.[3]

The wide variety of symptoms in FTD, including exuberant neuropsychiatric symptoms, often mimics psychiatric illnesses, and these patients are commonly diagnosed with schizophrenia, delusional somatoform disorders, bipolar disorder or major depressive disorder.[7] Although psychotic symptoms are not part of the diagnostic criteria, recent studies have shown a considerable prevalence (10 to 32%) in FTD over the course of the disease, which may often precede the dementia itself, bringing additional diagnostic difficulties.[1] This study reviews the literature on the prevalence of psychotic symptoms and their characteristics in FTD associated with mutation of the *C9orf72* gene, as well as neuroimaging and histopathological correlations.

MATERIALS AND METHODS

A review of the literature was carried out, using the PubMed database, and the following search terms in various combinations: "Frontotemporal dementia; Frontotemporal lobar degeneration; *C9orf72*; Psychotic symptoms; Neuropathology". The review covers the last 10 years of human research in this area. After obtaining the references, the relevance of the studies was assessed, and the information retrieved.

PSYCHOTIC SYMPTOMS

Several studies have demonstrated a high prevalence of psychosis in FTD-C9+ versus FTD-C9-. In a study conducted in Finland2, with a sample of 73 patients diagnosed with FTD, 46 patients with bvFTD (63%), 20 with PNFA (27%), and 7 with SD (10%), the *C9orf72* pathologic expansion was present in 22 of the 73 patients. Most (70%) presented with bvFTD and 30% with PNFA. Although there was a higher frequency of psychotic symptoms in FTD-C9+ patients compared to FTD-C9- (21% versus 10%), the difference was not statistically significant, which could be due to the relatively small population numbers involved in the study. In the FTD-C9+patient group, psychosis was the main symptom and the diagnosis of bvDFT was performed 1-5 years after the onset of psychosis. With regard to psychotic symptoms, delusions and auditory hallucinations were mainly reported, with no reference to visual hallucinations. In addition, the age at onset of the disease and gender distribution were similar between the FTD-C9+ and FTD-C9- groups. It should be noted that the frequency of the *C9orf72* expansion in Finland is among the highest in the world.

In an Australian study10, in which 89 patients with a diagnosis of clinically proven FTD and 22 cases with neuropathologically proven FTD-TDP-43, the *C9orf72* expansion was detected in 15.7% throughout the sample and more specifically in 10% of the cases of patients with a clinically proven FTD diagnosis, rising to 28.6% (6/21) in those with a positive family history for early onset dementia or MND.

In the neuropathologically proven FTD-TDP-43 group, the expansion was present in 40.9% (9/22). In cases with positive expansion the most common diagnoses were bvFTD (58.8%) and FTD-MND (23.5%). The prevalence of psychotic episodes was significantly higher in cases of FTD-C9+ (56% versus 14%), however, there was no significant difference between FTD-C9+ and FTD-C9- cases, regarding age at death, disease duration, or the amount of cerebral atrophy.

In the study by Waldo et al.[1] involving 97 patients with neuropathologically confirmed FTD, psychotic symptoms were present in 32% (n=31). However, there were no

significant differences between patients with and without psychotic symptoms, referring to age at onset of disease, disease duration or gender. In this study, the predominance of visual hallucinations (14.4%) and paranoid type delusions (20%) was observed. Auditory hallucinations were present in 3.1%, tactile in 2.1%, gustatory/olfactory in 1.0%, and erotomaniac delusions in 1.0%, somatic in 3.1% and unspecified in 2.1%. the The *C9orf72* expansion was not sought for in this study. Psychotic symptoms appeared at the beginning or only later in the course of the disease, in contrast to another study[11] that reported these symptoms throughout the course of dementia. Of note, in the initial phase, only 14.4% of the affected patients were diagnosed with FTD, increasing to 78% as the disease progressed, and patients with a family history of psychiatric illness were more likely to receive a psychiatric diagnosis rather than a diagnosis of FTD. The mean time between the onset of symptoms andl the diagnosis of FTD was 4 years. In this study, a strong association was found between psychotic symptomatology and predominantly right brain degeneration; in addition most patients (77.4%) were tau-negative on pathological examination.

Kertesz et al.[9] carried out a study with 62 patients diagnosed with FTD (23 with bvFTD, 18 with SD, 6 with PNFA, 7 with FTD-MND, 5 with corticobasal degeneration (CBD) and 3 with PSP). The authors found that the *C9orf72* expansion was present in 8 patients, with a higher incidence of psychotic symptoms (21% in FTD-C9+ vs 10% in FTD-C9-). Initially 6 of these patients were diagnosed with bvFTD, 1 with PNFA and 1 with depressive disorder. The presence of hallucinations in 50% of cases of FTD-C9+ versus 5% in cases of FTD-C9- was observed, and the presence of delusions was more prevalent in patients with (25%) than without (18%) the pathological expansion.

Snowden et al.,[6] carried out a study with a sample of 398 patients diagnosed with bvFTD (53%, n=211), PNFA (17%, n=66), SD (13%, n=53) or with one or more of these disorders (17%, n=68). The C9orf72 expansion was detected in 8% (n=32) of all patients, distributed as follows: bvFTD 59% (n=19), FTD-MND 28% (n=9), PNFA 9% (n=3), and SD 3% (n=1). Psychotic symptoms were seen in 38% (n=12) of patients with *C9orf72* expansion, in contrast with less than 4% of FTD-C9- patients, with more than 28% displaying paranoid thoughts. These patients had no history of psychiatric disorder and delusional symptoms were typically unresponsive to antipsychotic therapy. Of note, the FTD-C9- patients who reported psychotic symptoms had a previous depressive disorder or another long-standing psychiatric disturbance.

In a study by Galimberti and collaborators[13] 651 patients with FTD were enrolled, and the *C9orf72* expansion was found in 6% (n=39) of cases. Twenty-nine patients had bvFTD (5.2% of all bvFTD cases), FTD-MND was seen in 8 patients (32% of FTD-MND cases), and 2 patients had SD (5.9% of all SD cases). Psychosis manifested initially in 30.3% of patients with FTD-C9+ compared to 8.1% of FDT-C9- cases. Delusions were present in 50% (especially of the mystical and megalomaniac types) and hallucinations were present in 40%, with predominance of visual hallucinations in consonance with the results of other studies.

A recent study[14] enrolling FTD patients with *MAPT*, *GRN* and *C9orf72* gene mutations found that patients with FTD-C9+ had greater co-occurrence with MND, and higher prevalence of psychotic symptoms and bizarre behavior, although they were often considered socially adequate. There was a greater clinical overlap between *C9orf72* and GRN as compared to *MAPT* cases. Psychotic symptoms occurred in both patients with and without MND, although they were more frequent in their absence, suggesting the inexistence of a direct relationship between psychosis and MND.

NEUROIMAGING FINDINGS

The literature does not point to solid evidence concerning the anatomical correlations between psychotic features and FTD. However, brain regions such as the thalamus and cerebellum have been associated with psychotic symptoms in FTD.[18] These brain areas also appear to be involved in FTD-C9+ cases, thus raising a few interesting questions. On the other hand, other studies propose a possible association between psychotic symptoms and cerebral pathology predominantly of the right hemisphere.[1, 11, 15-17]

PATHOLOGICAL FINDINGS

In the various studies, reference has been made to several histopathological backgrounds for psychotic symptoms in FTD. In some studies, a high prevalence of psychotic symptoms was observed in Tau-negative[1,19-21] patients, while in other studies, similar prevalence of both tau-negative and tau-positive11 was reported. In several studies, the pathological examination of patients with FTD-C9+ revealed FTD-TDP-43 type B pathology in most cases.[6,10,22]

CONCLUSIONS

The recently published literature strongly suggests that psychosis may be the first symptom in FTD-C9+. It may even arise years before other symptoms and lead to the initial diagnosis of a psychiatric disorder.[2,19,23]

Some authors have drawn attention to the possibility that might FTD develop in people with a previous psychiatric disorder. In such cases, the clinical change may be misinterpreted and patients may be considered to have become resistant to treatment, and the correct diagnosis will ultimately be achieved as the typical FTD features emerge.[25]

Current therapeutic interventions for the treatment of FTD are very limited, aiming at symptomatic control only, and no specific treatment for FTD-associated psychosis is available.[21] The high rate of psychotic symptoms in patients with FTD-C9+ suggests that these might be a clinical marker for the presence of the *C9orf72* expansion.24 Screening for the mutation should probably be considered in patients with late-onset psychotic symptoms, especially in those without a previous history of a psychiatric disorder, and in those with a clinical diagnosis of FTD in which psychotic symptoms co-exist.[26]

Understanding how FTD may manifest as a neuropsychiatric condition is critical to avoid the occurrence of misdiagnoses and to inform the best clinical management options. Further research is warranted in order to better characterize the neuropsychiatric symptoms associated with the *C9orf72* expansion, as well as to elucidate its pathophysiological mechanisms. In addition, this line of research could provide valuable novel clues into the pathogenetic mechanisms of psychosis in the human brain, ultimately leading to the design of effective therapies.

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