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Case Presentation

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A Case of C9orf72-Associated Behavioral Variant of Frontotemporal Lobe Degeneration Presenting with Multiple Suicide Attempts

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Introduction

Frontotemporal lobe degeneration (FTLD) comprises a spectrum of clinical syndromes that includes multiple neurodegenerative disorders with different neuropathological pathways that lead to a common frontal and temporal lobe degeneration and share a similar complex phenotype, consisting of early-onset dementia with progressive deficits in behavior, language, motor and executive functions. Behavioral variant of frontotemporal lobe degeneration (bvFTLD) usually presents with disinhibition or apathy, loss of empathy, perseverative/compulsive behaviors, hyperorality and executive dysfunction, thus mimicking many psychiatric disorders, such as schizophrenia, schizoaffective disorder, major depressive disorder, bipolar disorder, obsessive-compulsive disorder or personality disorders, as there is a significant symptomatic overlap with these entities [1].

Mutations in the chromosome 9 open reading frame 72 (C9orf72) gene have been linked to FTLD, amyotrophic lateral sclerosis (ALS) and the mixed overlap phenotype FTLD-ALS [2], and is the most common genetic cause of bvFTLD [1].

We report the case of a 43-year-old man with C9orf72-associated bvFTLD with an atypical clinical presentation, consisting of recurring suicidal ideation and multiple high-lethality suicide attempts, initially misdiagnosed with several psychiatric disorders, including major depressive disorder, bipolar disorder, schizophrenia and personality disorder. We then review the existing literature regarding C9orf72-associated bvFTLD and its differential diagnosis with psychiatric disorders.

Case Presentation

In 2017, a 43-year-old man, with no family or personal neuropsychiatric history, presented to the emergency department with self-inflicted cervical and thoracic trauma using a knife. He was in hypovolemic shock, unresponsive, and was admitted to the intensive care unit, where he gradually improved over the following week with supportive care only. The patient reported depressed mood, anhedonia and suicidal ideation starting 2 months prior to this episode, which he attributed to several adverse life events, including being fired from his long-term job and a recent divorce. He had no relevant medical history and the only previous consultation with a psychiatrist occurred 1 month before this episode, when he reported the same symptoms and was started on escitalopram. Upon observation, the patient presented with psychomotor retardation, depressed mood with feelings of hopelessness and suicidal ideation. The laboratory testing, CT scan and electroencephalogram were normal. The patient was admitted to the psychiatry department and was initially diagnosed with major depressive disorder and treated with venlafaxine and mirtazapine. Upon starting this medication, he had a rapid mood elevation, with increased energy and pressure of speech. The patient's family reported an episode suggestive of hypomania in his recent past, consisting of mood elevation, increased activity and energy, decreased need for sleep and irritability. Considering this new data on the clinical history and evolution of symptoms, the diagnosis of bipolar disorder was suspected. The antidepressant therapy was suspended, and the patient was started on sodium valproate and quetiapine. He then showed progressive improvement and was discharged from the hospital to follow-up outpatient clinic.

He maintained good treatment adherence and moderate clinical improvement. However, the patient stated that he "didn't feel like himself", and reported a loss of emotional resonance, apathy and fatigue. He was started on bupropion but reported no clinical improvement.

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During 2018, the patient was hospitalized 3 times, once for suicidal ideation and twice for new suicide attempts, one of which by means of self-inflicted trauma using a knife, that led to hemorrhagic shock and the need for urgent surgical intervention. Throughout the multiple hospitalizations in this one-year period, the patient reported feeling depressed and frustrated due to difficulties performing his work-related tasks, and he also started displaying some signs of impulsive behavior, disinhibition and periods of dysphoria, hostility and coprolalia. A rigid personality with inflexibility to changes in routine was also apparent and the patient displayed some obsessions in the form of recurrent and intrusive thoughts of suicide. The family also reported difficulties in short-term memory, planning and performing daily life tasks. On observation, the patient presented with affective flattening, aprosodia, poverty of speech, agrammatism, concrete thinking, and over inclusive thinking, in addition to the previously described symptoms.

Several psychopharmacological strategies were attempted, including increasing the dosing of sodium valproate and introducing lamotrigine and lithium, but little improvement was seen.

During his hospitalization in the psychiatry ward, due to the patient's unusual clinical presentation, significant functional impairment and cognitive decline, a brain magnetic resonance imaging (MRI) was carried out but was unremarkable and a neuropsychological assessment revealed deficits in cognitive and executive functions. The diagnosis of frontotemporal lobe degeneration was considered, and a neurological consultation was performed during the patient's hospitalization. On neurologic examination, the patient exhibited psychomotor retardation, decreased speech rate, thought perseveration and dyscalculia, with no other deficits being detected. A set of exams were carried out to assess medical causes, all of which showed negative results, namely autoimmunity study, with antinuclear antibodies (ANA) and antineutrophil cytoplasmic autoantibodies (ANCA), extractable nuclear antigens (SSA, SSB, Sm, RNP, Jo1, Scl70), viral encephalitis (Herpes simplex type 1, Herpes simplex type 2, Herpes hominis type 6, Herpes hominis type 7, Cytomegalovirus, Epstein-Barr Virus, Varicella Zoster Virus, Enterovirus, Parechovirus and Adenovirus), autoimmune encephalitis (anti-NMDA, anti-AMPA1 and 2, anti-GABA-b, anti-CASPR 2, anti-LGI1, anti-mGluR5, anti-Hu, anti-Ri, anti-Yo, anti-Tr, anti-Ma, anti-Ma 2, anti-CV2/CRMP5 antibodies) and cerebrospinal fluid proteins (Tau, and beta-amyloid).

The patient was discharged from the hospital after mild improvement and transferred to an inpatient rehabilitation facility. He was also referred to a behavioral neurology consultation for further investigation. At this setting, a couple of months after the previous observation, the neurologist reported bradykinesia with hypomimia, sialorrhea, short-stepped gait and decreased eye blinking, which were interpreted as iatrogenic effects of the antipsychotics. Due to previous periods of symptomatic improvement, the presence of depressive symptoms and the correlation between the beginning of the symptoms and adverse life-events, it was considered that the psychiatric etiology was the most probable one.

In 2019, the patient abandoned the inpatient rehabilitation facility and got lost for a few days. He was later found after a new suicide attempt with self-inflicted trauma using a knife, admitted in the ICU and then transferred to a psychiatric ward for clinical stabilization, after which he went to a convalescence unit.

During 2020, the patient had multiple visits to the ER due to depressive symptoms and suicidal ideation. Sertraline was introduced but showed no clear benefit. The patient's symptoms were similar to previous descriptions, consisting of affective flattening, alogia, apathy and anhedonia, deficits in executive functioning, reasoning, social cognition, attention and memory. In addition to this, he started mentioning auditory hallucinations, consisting of voices instructing him to harm himself. The diagnosis of schizophrenia was considered. Several psychopharmacological approaches were attempted, including paliperidone, haloperidol and clozapine, with no significant symptomatic improvement, and exuberant sensitivity to extrapyramidal effects. After one of his visits to the ER, the patient was hospitalized again due to a high suicide risk. During hospitalization, the diagnosis of frontotemporal lobe degeneration was considered once again. Screening for cognitive impairment revealed a Mini Mental State Examination (MMSE) of 23/30 and a Montreal Cognitive Assessment (MoCA) of 15/30. A new brain MRI was performed, which revealed bilateral cortical atrophy, predominantly in the external parietal region, symmetrical, with no other relevant changes. A new observation by a neurologist was requested and revealed, in addition to the previously described symptoms, a bilateral palmomental reflex and a glabellar reflex. However, it was once more considered that the condition was likely to be of psychiatric etiology, for the same previously described reasoning. Due to the persistence of bradykinesia, tremor and rigidity, a DatScan was performed, which was negative for neurodegenerative parkinsonism, and an iatrogenic cause was admitted. A genetic testing for Huntington's Disease was also performed and had a negative result. The patient was discharged from inpatient treatment and, due to persisting doubts about his diagnosis, was referred to a neuropsychiatry consultation.

In 2021, the patient attended a neuropsychiatry consultation, performed simultaneously by a psychiatrist and a neurologist. He displayed the same clinical picture described above, which led to the decision to request a genetic study for FTLD. This study revealed a heterozygotic GGGGCC expansion in the C9orf72 gene, with more than 90 repetitions of this hexanucleotide, confirming the diagnosis of C9orf72-associated bvFTLD.

Discussion

The case report presented above depicts a case of C9orf72-associated bvFTLD. Mutations in the C9orf72 gene can lead to repeat expansions of the hexanucleotide GGGGCC (G4C2) located in the promoter or in the intron 1 of this gene [3] and are associated with FTLD, ALS and the overlap phenotype FTLD-ALS [2]. There are also descriptions of other diagnoses associated with this mutation, namely confluent variant primary progressive aphasia, Alzheimer's

disease, parkinsonism, corticobasal degeneration syndrome and ataxia [1]. There is currently no threshold for the number of repetitions needed to cause the disease, but normal individuals have an average of 1-30 and individuals with symptoms can have hundreds or thousands of repeats [4]. Some authors consider that this threshold should be around 30-60 repetitions [2]. There is a marked variation in the number of repetitions found in different cell tissues of the same individual, which may explain the variability found in different studies [2].

This mutation appears to be present in about 0.15% of the general population [5]. It is nowadays considered the most frequent genetic cause of FTLD, and it accounts for about 20-25% of familial forms of FTLD and 2-6% of sporadic cases [1]. It has an autosomal dominant pattern and, on average, individuals begin manifesting the disease around the 5th or 6th decade of life, but some patients may only show the first signs of disease at an older age [2].

The most frequent phenotype is bvFTLD. The International Consensus Criteria for Behavioral Variant FTD states that a diagnosis of "Possible bvFTD" requires the presence of a progressive deterioration of behavior and/or cognition and at least three of the following: early behavioral disinhibition; early apathy or inertia; early loss of sympathy or empathy; early perseverative, stereotyped or compulsive/ritualistic behavior; hyperorality and dietary changes; executive/generation deficits with relative sparing of memory and visuospatial functions; a "Probable bvFTD" diagnosis requires the criteria for "Possible bvFTD" plus significant functional decline and imaging results consistent with bvFTD [6]. Due to its presentation, this condition often mimics many psychiatric conditions, with about 50% of patients having a previous diagnosis of a psychiatric illness [7], as observed in the case report depicted above. Psychiatric symptoms appear more frequently in individuals with C9orf72-associated bvFTLD when compared to individuals with bvFTLD without the mutation [2]. 21-56% of patients with C9orf72-associated FTLD show psychotic features (delusions and/or hallucinations), whereas in the remaining patients with FTLD without this mutation, these symptoms are unusual: 4-18% [3]. Somatic delusions are the most frequently mentioned in the literature, but persecutory, infidelity, grandiose, and mystical delusions may also be present.

Other psychiatric symptoms, such as mania, catatonic symptoms, obsessive-compulsive symptoms, major depressive episodes and anxiety are described in these patients [4]. The existing literature mentions that suicidal ideation and suicide attempts are rare in this population. One of the possible explanations for this finding is that patients are seldom aware of the severity of their symptoms. However, in the case report depicted above, the patient presented with multiple suicide attempts and recurring suicidal ideation, which suggests that these symptoms may also present as a manifestation of this disease in some patients.

Regarding motor symptoms, up to 75% of patients with bvFTLD can display Parkinson's Disease-like symptoms. It is possible that the bradykinesia, rigidity and tremor the patient displayed may be related to this finding, although the simultaneous use of antipsychotics can also cause or aggravate these symptoms [8].

These late-onset psychiatric symptoms (compared to primary psychiatric disorders) depicted above are often the first manifestation of C9orf72-associated bvFTLD and may appear up to 1-5 years before the other symptoms that are usually present, such as apathy, disinhibition, deficits in social cognition, abnormal eating behavior, loss of empathy, repetitive/obsessive/stereotyped behavior, and deficits in executive functions.

Neuroimaging tests are often normal in the early stages of the disease. In more advanced stages, there is no specific imaging finding, but variable patterns of cortical and subcortical atrophy are usually observed. Notwithstanding, these atrophy patterns are not restricted to the frontotemporal region, and often affect the parietal region, cerebellum and thalamus [3]. These findings are consistent with the ones described on this case report.

In patients with primary psychiatric disorders (for example, patients diagnosed with schizophrenia, schizoaffective or bipolar affective disorder), the percentage of patients with the C9orf72 mutation reported is similar to the general population (about 0.1%), and routine testing of these patients is not recommended.

There are currently no official recommendations regarding the diagnostic approach for these patients. Some authors suggest that patients with late-onset symptoms (mania, psychosis, catatonia, cognitive symptoms) should have a complete clinical history, cognitive assessment (MoCA), neurological examination, and brain imaging (MRI should ideally be obtained, but a computed tomography is also acceptable) [4]. Regarding which individuals to test, some authors suggest that patients with the mixed phenotype FTLD/ALS or with familial forms of one of these syndromes should always be tested and that it should also be considered in patients over 40-years-old, with cognitive decline or with a pattern of atrophy on neuroimaging exams, and a family history of FTLD, ALS or other psychiatric disorders [9]. There are also no specific recommendations regarding treatment for carriers of this mutation. Some case reports suggest there may be an increased resistance to antipsychotics in these patients. Some therapeutic strategies are currently under study, including small molecules and gene-silencing tools that inhibit the transcription of C9orf72, antisense oligonucleotides that bind and inactivate RNA with repetition and antibody-based approaches that inhibit the accumulation of related proteins [10].

In summary, the case report depicted above suggests that suicidal ideation and suicide attempts may present as a manifestation of C9orf72-associated bvFTLD. It also highlights the variety of different presentations of this syndrome and the current difficulties regarding diagnosis and treatment of these patients. Further investigations into the relationship between C9orf72 mutation, psychiatric symptoms and the underlying mechanisms may help to clarify our understanding of these phenomena and aid in the diagnostic and therapeutic approach of these patients.

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