About a case of Frontotemporal Dementia - behavioral variant, with amnesic symptoms and Alzheimer type cerebral images: report of a case.

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Frontotemporal dementia - behavioral variant (FTD-bv) is a significant cause of disability in adults under 65 years of age. It is postulated as a neurological disease with predominantly psychiatric manifestations and, therefore, constitutes a frequent differential diagnosis in psychiatric pathologies of not early onset. Although traditionally, the absence of memory impairment was considered among its diagnostic criteria - as opposed to Alzheimer's disease (AD) -, several studies have found until 15% of prevalence of cases with frank mnemonic deterioration, as well as neuroimaging of one and the other can have overlap. Currently, the presence of "phenocopy syndromes" --clinical pictures similar to FTD-bv but without cognitive impairment-- and cases of AD with disinhibition and behavioral symptoms, make the clinical diagnosis more complex and suggest the insufficiency of the established diagnostic criteria and the necessary adoption of paraclinical criteria. To this purpose, we present an illustrative case of FTD-bv with memory impairment and Alzheimer-like neuroimages, and we review the pertinent bibliography.

Keywords: *Frontotemporal Dementia; Alzheimer's Disease; Memory.*

Introduction

Frontotemporal dementia (FTD) is a group of neurodegenerative disorders of early-onset and considerable heterogeneity, both in its clinical presentation, etiology, imaging, and histopathological findings[(1)]. It is the type of dementia with the most significant genetic component and produces impairment of behavior, executive functions, and language. FTD is the second leading cause of dementia after Alzheimer's disease (AD) in people younger than 65 years; therefore, it has a significant impact on the working-age population[(2)]. Although the first cases were reported by Pick in 1892, research on FTD has only increased recently[(3)].

FTD manifests itself clinically through two major syndromes: Behavioral variant FTD (bvFTD), with predominant changes in social behavior and executive control, and the so-called Primary Progressive Aphasia, with the subtypes: progressive non-fluent aphasia, semantic

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dementia, and logopenic aphasia, where language is most affected. In its evolution, the subtypes manifestations may converge, since tissue degeneration massively affects the frontal and temporal lobes[4]. The evolution from the first symptoms to the patient's death usually ranges from five to seven years[2].

Recent studies find deficits in episodic memory similar to AD in up to 15% of bvFTD, even from early stages[5]. These deficits cannot be explained by alterations in coding and recovery—where the prefrontal cortex intervenes—but in memory consolidation and storage. Furthermore, in bvFTD cases, imaging studies have found deficits in the hippocampal and temporal regions, similar to those seen in AD cases[6]. This contradicts the diagnostic paradigm in which memory was not altered in bvFTD, and further research is required in order to characterize this type of condition better. Another issue pending clarification is the nature of the so-called bvFTD "phenocopies," that is, patients who manifest the same clinical picture but with prolonged evolution, without impairment of daily activities, and without a correlation of cortical atrophy.

With regard to the case of a 68-year-old woman, who, in her evolution, has presented a clinical picture compatible with DFT-vc with marked mnestic alterations, we reviewed the literature and tried to frame the case in the current perspective.

Clinical case

A 68-year-old woman, widow, mother of three children, with ten years of schooling. Seven years ago, changes in her attitude were noted: once kind and restrained, she began treating her grocery shop clients with bluntness. She became progressively more irritable and ruder, even with her relatives, with a tendency towards disinhibition and lack of empathy. After two years, it was observed that she started treating her grandchildren with vulgarity: she accused them of being pestiferous and lousy. She disclosed this to people outside the family, which prompted many discussions. The family took her to a neurologist, who diagnosed her with "senile dementia" and prescribed her with Donepezil, without improvement. She showed erratic behaviors: persistent dromomania and prodigality with strangers. Furthermore, she started having cognitive problems: she would make mistakes when preparing meals, such as adding sugar instead of salt or forgetting to turn off the stove's burner. She was instructed to take care of the housework, and it was observed that she would stereotypically repeat the tasks.

Three years ago, neglect for personal hygiene was evidenced: she refused to shower except for when she was prompted and would burp in public. She presented compulsive hoarding behavior: her room was cluttered with useless objects. If someone confronted her, she would deny it and react with annoyance. In general, though, she tended to react with mutism, prolonged apathy, and immobility.

Two years ago, her deterioration became more apparent: she could not perform any domestic tasks. She started showing mouth movements stereotypical of suckling, sticking out, and inserting her tongue in her mouth. At times she would count, whispering: "1...2...3...4" with her hands behind the back. She presented hyperorality: great appetite for candy and soft drinks. She would get annoyed if these were not provided to her, and she gained weight. Furthermore, she showed impatience: she assaulted people if they did not comply immediately and cried without any apparent cause. Different professionals diagnosed her with "vascular dementia" or "Pick's disease." She was prescribed Quetiapine in increasing doses up to 400mg, as well as 10mg of Memantine and five drops of Haloperidol in case her relentlessness accentuated, thereby partially reducing her irritability and impulsivity. Her requested laboratory tests (hematic biometry, and renal, liver, and thyroid urinogram) showed findings within normal ranges, except for a B12 vitamin deficiency (87 pg/mL).

Today, the patient does not present spontaneous discourse and preserves motor and verbal stereotypes. She can get dressed and eat on her own, and she does not wear diapers. She shows less irritability and aggressiveness, although she demands candy and behaves childishly. In her mental exam, she was found awake, inattentive, and aware of her surroundings. She understood simple and complex orders, with facial hypomimia, and bradykinesia. She is disoriented

in time but oriented in space and person. Her language is plain, non-spontaneous. She seems apathetic, and does not smile.
Sometimes she interrupts, pointing out inappropriately: "my son is a district attorney for the supreme court," which is false. At the end of the interview, she repeatedly asked if her son had paid the appointment and demanded to leave. Her impatience makes a more detailed examination difficult to conduct. She lacks insight or awareness of her illness. The neurological exam did not show any motor or sensitive abnormalities, though the osteotendinous reflexes increased asymmetrically. Babinski and Hoffman were bilaterally negative. Primitive reflexes: digital grasp and sucking; forced palmar grasp reflex was not found. Balance and coordination were preserved. Cranial nerves are normal. Scores: Mini Mental State Examination (MMSE): 20/30. Addenbrooke's Cognitive Examination (ACE): 72/100. INECO Frontal Screening (IFS): 10/30. Clinical Dementia Rating (CDR): 2 (moderate stage). Neuropsychological evaluation: Severe impairment of the executive and attentional functions as well as the social cognition, with a minor impairment of language and visuo-constructive functions; there is also a considerable impairment of verbal memory. Figures 1, 2, and 3 show the NMRIs of the patient's brain.

Discussion

bvFTD represents between 50-60% of FTD cases, and it occurs more in men than women (2 to 1)[2]. In the clinical picture, empathy loss is combined with disinhibition, apathy, emotional flattening, and affective indifference[1]. Likewise, the development of stereotypical and compulsive movements and hyperorality behaviors is frequent. A lack of self-analysis and insight is discernible, as well as a decrease in spontaneous language. Even mutism is observed[3, 7]. There is a percentage in which late-onset movement disorder, such as motor neuron disease, supranuclear palsy, and corticobasal degeneration, also appear[8]. FTD is often confused for a series of different psychiatric disorders: a manic disorder due to disinhibition symptoms, depression due to apathy symptoms, an obsessive-compulsive disorder due to stereotypical symptoms, late-onset schizophrenia in cases with psychotic symptoms. Furthermore, secondary clinical pictures can develop in the early stages of bvFTD, such as ludopathy, compulsive shopping disorder, pathological collecting behavior, addictions, and other psychiatric disorders[9, 10].
According to the International Consensus Criteria (2011), at least one of the three following criterion is required to establish a possible bvFTD diagnosis: disinhibition, apathy or abulia, empathy loss, stereotypical or compulsive behavior, hyperorality or dietary changes, neuropsychological profile with impairment of executive functions but with preservation of memory and visuospatial functions[7]. In this instance, the clinical criteria for a possible FTD case are met.
Regarding neuroimaging, the findings of atrophy and hypometabolism in the frontal lobes and anterior poles of temporal lobes are characteristic of bvFTD. The pattern is non-symmetrical, and predominant in the right hemisphere and areas such as the insula, the cingulate gyrus, and specific frontal areas[1]: the susceptibility of these areas is stipulated due to the existence of Von Economo neurons, essential in the prefrontal cortex function. In our case, neuroimaging shows an evident frontotemporal and insular atrophy, which is predominantly right-sided, and it corroborates this is a probable cause of FTD. Additionally, hippocampal atrophy is evident, a finding similar to the AD one[11].
On a histopathological level, the atrophic impairment of these structures is known as frontotemporal lobar degeneration (FTLD)[12]. It is the dysfunction of lysosomal and proteasomal systems with the corresponding accumulation of neurotoxic aggregates[12]. The current neuropathologic consensus establishes three main groups of protein accumulations: Tau protein, DNA-binding protein, and proteins fused in sarcoma (FUS). The first group corresponds to 30-50% of cases. The second group is predominant, with more than 50% of cases. The third group provides a marginal percentage[13]. At the genetic level, there are three genes involved: C9orf72, MAPT, y GRN: 40% of patients have a family history of dementia; however, only 10% show clear autosomal dominance. Most implicated chromosomes are 3,9, and 17[12]. Di-

Figure 1. Nuclear magnetic resonance imaging, axial-FLAIR brain section: moderate to severe frontal bilateral and insular atrophy, predominantly right-sided. Additionally, hyperintensities of white matter are observed at the periventricular level and at the level of the anterior part of the corpus callosum with dilation of lateral ventricles.

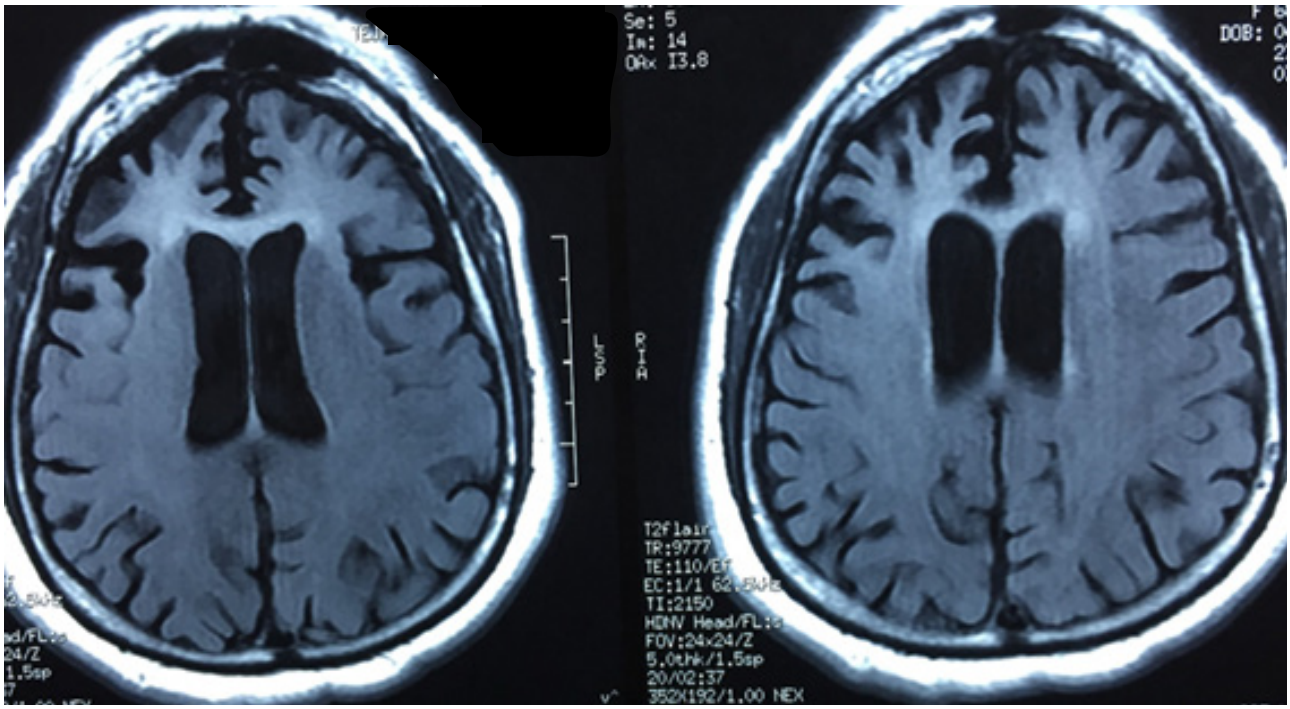


Figure 2: Nuclear magnetic resonance imaging, sagittal-T1 brain section: moderate to severe frontal cortical atrophy compared to posterior lobes.

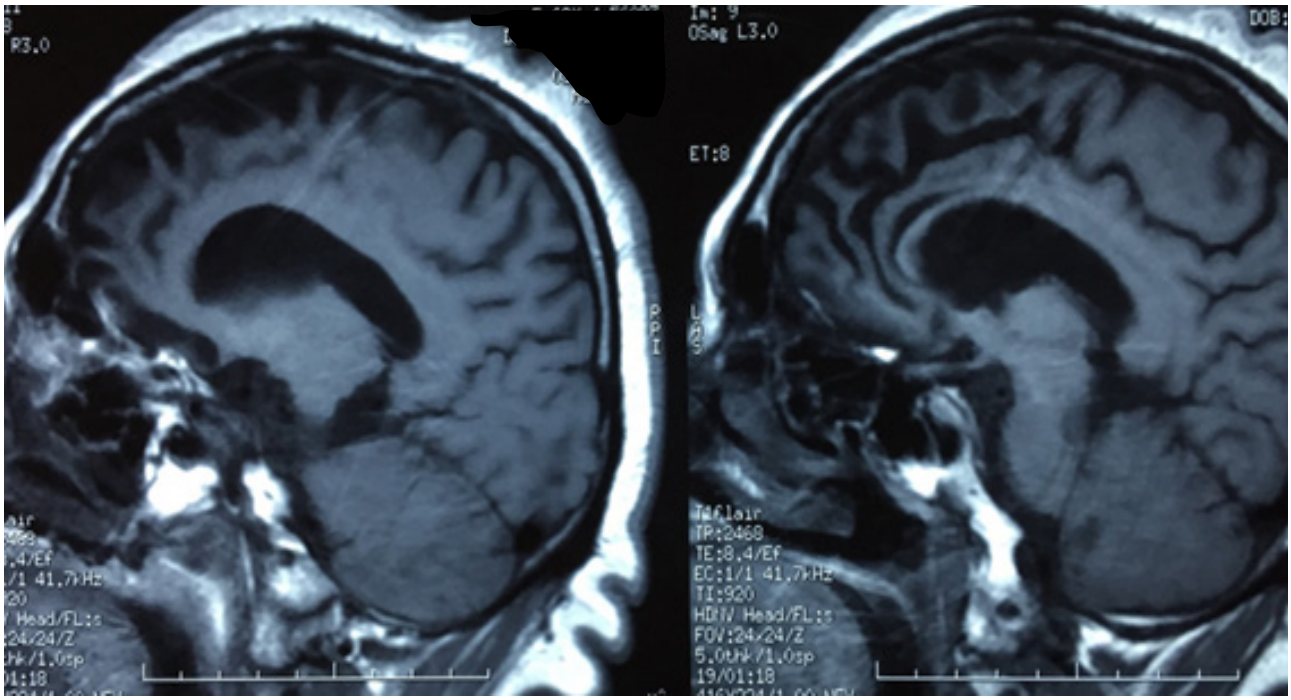
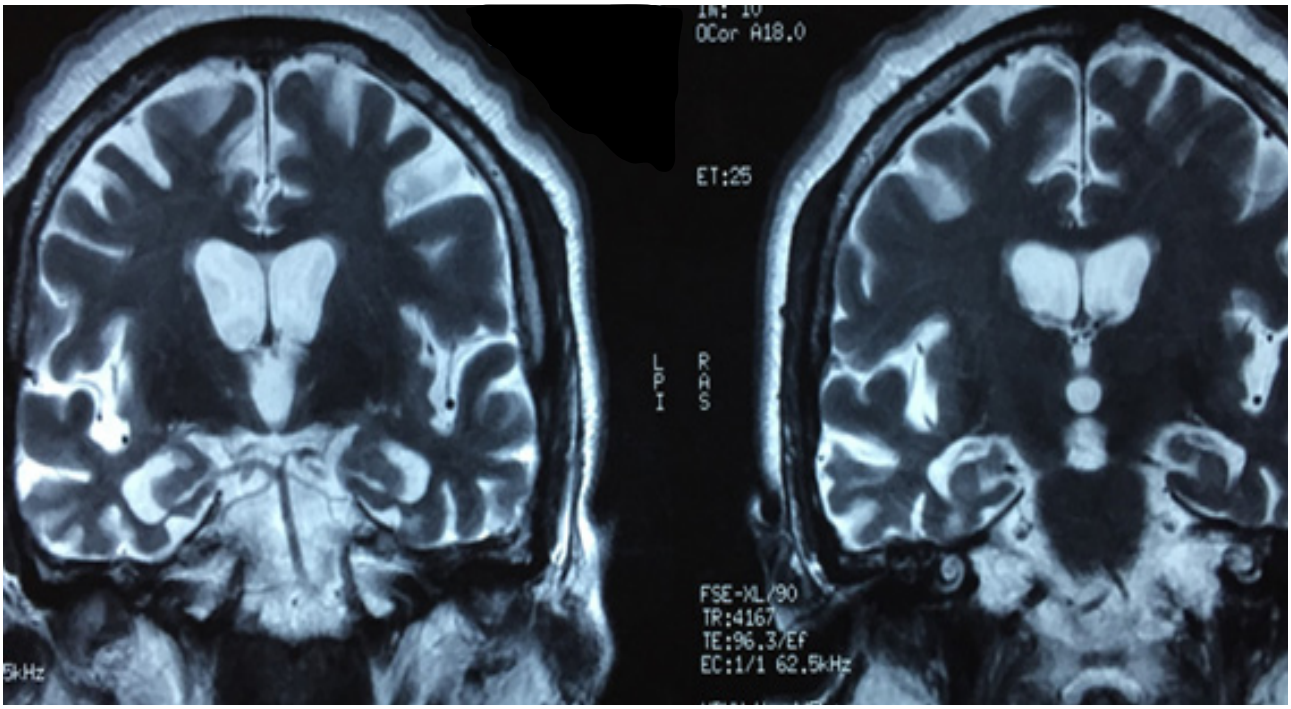


Figure 3. Nuclear magnetic resonance imaging, coronal-T2 brain section: Insular and frontal cortical bilateral atrophy, predominantly right-sided, with lateral and third ventricles dilatation. Pronounced hippocampal atrophy



fferent complex patterns of tissue impairment and protein accumulations have been described according to the genetic findings described.

As it has been pointed out, an intact episodic memory is still a criterion to differentiate bvFTD from AD. However, 10-15% of confirmed FTD pathological cases show episodic memory disturbances in the initial stages of the disease; this had already been noted in historical cases of FTD[14]. The different results in different series can be explained by the heterogeneity of FTD cases, genotype variants, and the varying ways of exploring mnemonic functions[6]. In our case, the neuropsychological evaluation confirmed the prominent memory impairment. This amnesic phenotype seems to be associated with C9orf72 gene expansions and TDP-43 protein accumulations, especially in the hippocampus.[15]

Recent findings regarding the "phenocopies" suggest that they are variants of the same bvFTD, because they include frontotemporal cortical structural abnormalities as well as neuropathological abnormalities[16,17]. There is a spectrum of continuity between "phenocopies" and bvFTD. Furthermore, there are interesting contributions from research on Alzheimer's with behavioral variants (dissociative and behavioral), that is, Alzheimer's disease but with symptoms that are typical of bvFTD[18]: as if there were a vast spectrum whose extremes are typical AD and FTD, but which encompasses intermediate clinical pictures in which our case could be located, with its typical FTD symptoms but with memory impairment similar to AD. For our case, it would be ideal to complete the study with the respective genetic markers to characterize it appropriately. Currently, it has been proposed that the adequate identification of dementia manifestations would be based on biological markers, and not solely on pathological manifestations: this allows for multiple possibilities of diagnosis and requires not only a robust clinical examination but also the respective technological advancements[19].

In our setting, there is no adequate knowledge among medical professionals in charge of diagnosing dementia, especially FTD[20]. bvFTD can be considered as a neurological disorder with a psychiatric presentation. For its proper diagnosis and treatment, it is essential to disseminate proper knowledge of FTD. It is a complex matter, and as such, it requires early detection to avoid inadequate diagnoses and treatments. Ad-

ditionally, as a promising scientific perspective, given the overlap of symptoms between bvFTD and various psychiatric pathologies, the heuristic perspective of a hypothetical genetic base at least partially shared arises[10].

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