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Behavioral changes to frontotemporal dementia diagnosis

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Abstract

Introduction: Frontotemporal dementia (FTD) was first described in 1892 and consists of a frontotemporal atrophy that preserves the posterior lobes. Genetically, several changes have been associated with the disease. Its clinical manifestation occurs through three presentations, such as: behavioral variant, non-fluent variants and semantics. The diagnosis relies on magnetic resonance imaging to rule out other diseases. Treatment is through the use of Serotonin Reuptake Inhibitors (SSRIs) to improve behavioral symptoms, including

aggression, disinhibition and agitation. **Methods**: This is a systematic review of behavioral changes for the diagnosis of FTD. The PUBMED database was used for the research using the following keywords: "FTD", "behavioral variant of FTD" and "diagnosis of frontotemporal dementia". **Results**: Clinical manifestations correlate with the affected brain region. FTD patients may have apathy, which is one of the most common and disabling. It can also cause changes in sexual behavior. It is associated with a family history of neurodegeneration. Its most common form has a prognosis of survival of about 6 years. Discussion: There is a significant heterogeneity in psychiatric and neurological diseases, including neurodegenerative diseases, of which the most prevalent diagnosis was vcDFT, but there is a great shortage of studies on the subject. Tests such as the Mini Mental State Examination (MMSE) and the Frontal Assessment Battery (FAB) are among the most commonly used short screening instruments to assess these changes and differentiate syndromes. The diagnostic criteria aim to categorize patients regarding vcDFT as 'possible', '' likely '' and '' defined ''. Effective, careful and appropriate medical evaluation is necessary to understand aspects of family history of neurodegenerative disorders. In addition, physical examination and cognitive assessment have the ability to identify most cases with likelihood of progression and can guide healthcare professionals to properly identify specific cases of FTD and refer patients to specific services if important. **Conclusion**: Therefore, due to their similarity with other dementia syndromes, it is necessary to create more specific instruments for their differentiation. It is also important to note that when the ability to perform executive activities is assessed, it is observed that there is impairment, whether in patients with progressing or controlled disease, which may be important in identifying and differentiating other dementia syndromes.

1.Introduction

Frontotemporal dementia (FTD) was first described by a Czech neurologist named Pick in

1892. Since then, it has undergone several changes in its nomenclature and categorization (Pick, 1892). FTD corresponds to a frontotemporal atrophy with preservation of the posterior lobes. In histology, there is the presence of balloon cells and cortical and subcortical gliosis. Pick's disease presents as clinical syndrome the increase of behavioral alterations, the lack of perception and the relative presence of apraxia and agnosia (Thibodeau & Miller, 2013). Genetically, several mutations have been associated with FTD and its related disorders. Mutations associated with tau protein (MAPT), granulin precursor (GRN) and hexanucleotide expansion (C9ORF72) genes are the main disease-related changes. Other changes are less common, but may occur, such as the presence of protein valosine (PCV), body-loaded multivesicular protein 2B (CHMP2B) and TANK 1 (TBK1) binding kinase (Sieben et al., 2012). Per year, the incidence of FTD is estimated at 1.61 per 100,000 people, with prevalence in the age group of 65 and 69 years (Coyle-Gilchrist et al., 2016). Frontotemporal disease manifests itself through three clinical presentations: the behavioral variant DFT (vcDFT) and two types of primary progressive aphasia (PPA): non-fluent variants and semantics. Behavioral variant FTD (vcDFT) is the most common clinical subtype and early changes include: Disinhibition (such as kissing and urinating in public); apathy and loss of empathy, associated with disinterest and demotivation for social activities; dietary changes with altered dietary preferences, such as carbohydrate cravings, particularly sweet foods; compulsive behaviors such as collecting objects, checking or cleaning places constantly, and expressing intense religious habits; routine stiffness; etc. (Teixeira et al., 2006). Diagnosis is aided by imaging (magnetic resonance imaging) to rule out other structural pathologies. Drug treatment is primarily by Serotonin Reuptake Inhibitors (SSRIs), which improves symptoms of agitation, aggression and disinhibition. Other studies have attempted to show efficacy in the use of acetylcholinesterase inhibitors, but so far no proven benefits. Because they are

individuals with major behavioral changes, they end up generating a great burden for their families and caregivers (Mulkey, 2019).

2. **Methods**

This is a systematic review of behavioral changes for the diagnosis of DFT. To identify the primary studies, the PUBMED database was consulted, and the search was performed by combining the keywords "frontotemporal dementia", "behavioral variant of frontotemporal dementia" and "diagnosis of frontotemporal dementia". The inclusion criterion of the study for review consisted of the presence of the three cited descriptors and articles from the last 5 years. By inserting the descriptors in the database, 311 articles were obtained. Thus, for the search results, the initial selection occurred by reading the abstracts found, discarding those not related to the theme. Articles that met the inclusion criteria were fully analyzed, including those that contemplated the proposal of this systematic review. Thus, 8 articles remained, which underwent a careful evaluation in the data analysis phase.

3. **Results**

Patients with FTD may have apathy, which is one of the most common and disabling dementia syndromes (Fernández-Matarrubia et al., 2018). These patients now require greater intensity of emotional stimuli to provoke suffering and emotional expression when compared to healthy people (Carr et al., 2018). However, in the early phase of the disease, other manifestations may be present, such as disinhibition, which will determine the course of the disease and the anatomical changes developed (Santamaria-Garcia et al., 2016).

Disorders related to sexual behavior are also present in these patients, with sexual hyperfunction present in the minority of patients and sexual hypofunction in most of them (Ahmed et al., 2018).

Clinical manifestations correlate with dysfunctions in different brain regions. Apathy is related to atrophy of the frontal and striated lobes, disinhibition

correlates with atrophy of the orbitofrontal and ventromedial cortex (Santamaria-Garcia et al., 2016). While sexual hypofunction is related to atrophy of the right supramarginal gyrus, middle frontal gyrus, and thalamus, sexual hyperfunction is associated with cerebellar atrophy (Ahmed et al., 2018). One of the differences between the apathy of AD with FTD is that in the former there are no anatomical changes, while in the latter there is atrophy of the anterior cingulate cortex, ventromedial prefrontal cortex and anterior temporal lobes (Carr et al., 2018).
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Moreover, an important point to be sought during the construction of the clinical trajectory is the family history of neurodegeneration, since the presence of clinical abnormalities such as stereotyped and compulsive behaviors in first-degree relatives can be considered progression markers (Devenney et al., 2015).

Regarding prognosis, vcDFT has a survival time of about 6 years. Some factors may negatively influence, such as language impairment, including here the difficulty of finding words and semantic deficits (Ghosh & Lippa, 2013).

4. Discussion

There is significant heterogeneity in diseases of psychiatric and neurological causes, including neurodegenerative diseases, of which the most prevalent diagnosis was vcDFT (Krudop et al., 2015). Added to this is the scarcity of studies in the literature analyzing the progression of vcDFT, which makes it difficult to identify markers that allow the discrimination of DFT, as well as the recognition of the factors that determine the progression and prognosis of the disease (Devenney et al., 2015).

As for clinical symptoms, vcDFT syndrome has great heterogeneity and can be classified based on the severity of apathy and disinhibition symptoms, which are explained by different patterns of brain atrophy (Connor et al., 2017). Among the most frequent symptoms seen in vcDFT is personality change, manifested by apathy with social withdrawal, loss of

empathy, loss of spontaneity, abulia, uninhibited outbursts, emotional dullness and change in eating patterns, inability to adhere to routines, inflexibility and loss of attention (Ghosh & Lippa, 2013).

Although FTD may vary, there are two more prevalent clinical presentations called apathetic and uninhibited. Both may be present concomitantly during the course of the disease, but the predominant clinical form is that with which the disease manifested. Thus, it can be stated that the first symptom developed determines the clinical and neuroanatomical profile of the disease, and may be useful in tracking predominant behavioral manifestations (Santamaria-Garcia et al., 2016).

Thus, apathy is more common than disinhibition in vcDFT and has a greater negative functional effect. Patients with severely apathetic phenotypes are functionally impaired and have more extensive brain atrophy than those with mild apathy or severe disinhibition alone. In turn, disinhibition, when present, is usually accompanied by apathy and when isolated does not appear to negatively influence functional disability, but is more associated with higher levels of caregiver distress. Also, related to this, it is valid to mention that the right middle temporal region is critical for the development of disinhibition (Connor et al., 2017).

Furthermore, confirmation that severe apathy results in greater functional impairment has substantial clinical relevance for two main reasons: first, that apathy is widespread in vcDFT and should be a primary focus of intervention, and secondly that disinhibition behaviors such as theft in socially inappropriate shops or behavior tend to prevail in the clinical setting so that apathy is often overlooked (Krudop et al., 2015).

In this context, it is also important to mention that at an early stage patients with vcDFT may express remarkably small abnormalities in neuropsychological tests. The Mini Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) are among the most commonly used short screening instruments to assess these changes (Krudop et al., 2015).

The diagnostic criteria aim

to categorize patients regarding vcDFT as 'possible', '' likely '' and '' defined ''. To characterize possible degeneration, it requires 3 of 6 clinically discriminating characteristics: disinhibition, apathy / inertia, loss of sympathy / empathy, persevering / compulsive behaviors, hyperorality, and non-executive neuropsychological profile. In relation to the "probable" category, it also requires functional disability and characteristic neuroimaging, in addition to these symptoms. Finally, the "definitive" needs a histopathological confirmation or a pathogenic mutation (Ghosh & Lippa, 2013).

Thus, effective, careful and appropriate medical evaluation is necessary to understand aspects of family history of neurodegenerative disorders. In addition, physical examination and cognitive assessment have the ability to identify most cases with likelihood of progression and can guide healthcare professionals to properly identify specific cases of FTD and refer patients to specific services if it is important (Devenney et al., 2015).

Although FAB, an assessment specifically developed for frontal dysfunction, has been shown to differentiate vcDFT from Alzheimer's Disease (AD), it is worth emphasizing the importance of finding other tools when necessary to differentiate vcDFT from other causes of frontal lobe syndrome (Krudop et al. ., 2015). In this sense, the assessment of memory by means of specific tests can differentiate cases with potential for progression from those whose condition will remain stable. Nevertheless, when the ability to perform executive activities is evaluated, it is observed that there is an impairment, whether in patients with disease progression or controlled, which may be important in identifying.

5. Conclusion

Therefore, due to their similarity with other dementia syndromes, it is necessary to create more specific instruments for their differentiation. It is also important to note that when the ability to perform executive activities is assessed, it is observed that there is impairment, whether in patients with progressing or controlled

disease, which may be important in identifying and differentiating other dementia syndromes.

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