Correlation Between Neurological Findings and Neuropsychiatric Symptoms in Behavioral Variant Frontotemporal Dementia: A Systematic Review.

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Introduction: *Within Frontotemporal Dementia (FTD), Behavioral variant (BvFTD) is the most prevalent, is associated with a marked alteration in behavior and emotional regulation.* ***Objective:*** *Describes the neuroanatomical correlate in subjects with BvFTD and the neuropsychiatric clinical characteristics described in them.* ***Methodology:*** *A systematic review of articles published between 2013 and 2018 has been carried out in relation to the BvFTD in English and Spanish databases that meet the inclusion criteria.* ***Results:*** *The BvFTD is associated with a hypofunction in the areas of the prefrontal cortex, cingulate cortex, and others. Apathy and disinhibition are the primary symptomatology of study. Conclusions. There is a lack of updated articles that describe neuropsychiatric characteristics and their imaging description in this population that favors the development of medical and non-medical approaches.*

Keywords: *frontotemporal dementia, frontotemporal lobar degeneration, neuropsychiatry*

Introduction

The world is experiencing a demographic change characterized by an increase in the aging of the population. The WHO[(1)] estimates that people aged 60 and over will go from 900 million in 2015 to 2100 million in 2050, representing 25% of the Latin American population. With this, chronic non-communicable psychiatric pathologies are on the increase, with major neurocognitive disorders[(2)], also known as dementias, one of the highest prevalence[(3) (4)].

Dementias are a clinical syndrome caused by neuronal degeneration, characterized by a deterioration of cognitive abilities and self-valence in daily life activities. The one with the highest incidence is due to Alzheimer's disease (AD) [(5) (6)], while among Frontotemporal Dementias (FTD), the most frequent is behavioral variant frontotemporal dementia (BvFTD)[(7)].

BvFTD is a type of early-onset dementia, commonly defined before the age of 65, part of the group of frontotemporal lobar degeneration disorders (FLDD), where Pick's disease[(8)] and other variants of FTD are also found, such as Primary Progressive Aphasia (PPA)[(9)] and its semantic (vsPPA), non-fluent (nfvPPA) and logopenic (lvPPA)[(10)] subtypes are.

People with BvFTD[(11)] are characterized by presenting severe, insidious changes in personality and behavior[(12)] in the absence of other causes that could cause it, due to a dysfunction in circuits that connect the orbitofrontal, dorsolate-

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ral, and medial zones of the prefrontal cortex and subcortical structures such as the nuclei of the base and thalamus[13], which in turn maintain the connection with the temporal and parietal lobes.

The behavioral profiles point to disinhibition, the presence of apathy, depression, hallucinations, among other symptoms, which were defined by the International Consortium of Diagnostic Criteria for BvFTD[11], based on the possible, probable or definitive classification, depending on the number of criteria that it meets.

Relevant to establish a precise diagnostic is the evaluation process, which is based on cognitive assessment through screening instruments that have proven that the Mini-mental State Examination (MMSE)[14] —despite being the most widely diffused in its category— is not sensitive for the detection of BvFTD[15] [16], unlike Addenbrooke's Cognitive Examination (ACE) [17], which, in its different versions, has shown sensitivity for discrimination between EA and BvFTD[17] [18] [19] [20]. In addition to the above, the use of more precise neuropsychological evaluation batteries is essential to delimit difficulties at the level of executive functioning and other cognitive domains that allow differential diagnoses to be established. The use of the Frontal Assessment Battery (FAB)[21], Tower of London[22], or Wisconsin Classification Cards[23], to name but a few, may be helpful. On the other hand, for neuropsychiatric characteristics, the Neuropsychiatric Inventory (NPI)[24], which, precisely, allows us to verify the presence of neuropsychiatric symptoms through the report of a family member or caregiver, is often used for this purpose.

The objective of the present review is to determine the correlates between the neuroanatomical findings and the neuropsychiatric symptoms present in BvFTD.

Methodology

In October 2018, a systematic search of the bibliography was conducted according to the PRISMA guidelines[25], in the Web of Science, PubMed and Scopus databases in English and Spanish, of reports published between 2013 and 2018, using the following operators: search with the Boolean operators AND and OR: Behavioral Variant Frontotemporal Dementia, neural correlates, clinical correlates, and neuropsychiatric symptoms.

Through their title and abstract, the articles were identified and included where (a) the neuroanatomical findings of the BvFTD were evaluated by neuroimaging, and (b) the neuropsychiatric symptoms of the subjects evaluated by neuroimaging were described.

Single case studies, other systematic reviews, or papers that did not present an experimental design were excluded (Figure).

The information of the chosen works was transferred to a document in Microsoft Word, where the following information was compiled: title, authors, year of publication, objectives, sample size, neuroimaging evaluation used, neuroanatomical findings, and neuropsychiatric symptoms studied.

Results

After the electronic search engine review, a total of twenty-four references were obtained: Four in Web of Science, seven in PubMed, and thirteen in Scopus, all in English. Eight articles were excluded as they were duplicates. The sixteen resulting works were reviewed considering the inclusion and exclusion criteria, from which one was discarded for being a review, two for being non-experimental works, three for not analyzing neuropsychiatric symptoms, and five for not using imaging evaluation. Finally, five articles were considered eligible and were included in this systematic review (Table 1).

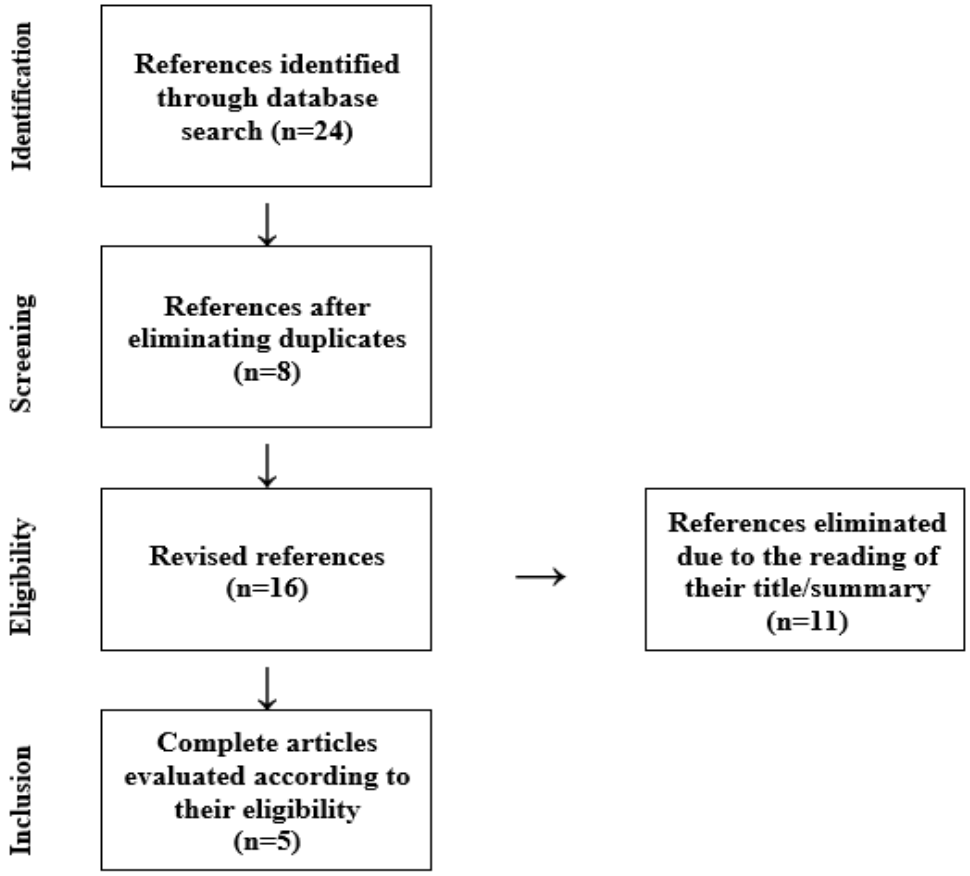
Neuropsychiatric symptomatology study frequency

Of the articles selected between 2013 and 2018, one was carried out in 2014, three in 2016, and one in 2018. Of these, one took place in the United States, one in Spain, one in Latin American countries (Argentina, Chile, and Colombia), one in Belgium and one in Korea.

Neuroimaging tests used

Of the selected articles, one used Positron Emission Tomography (PET), one Voxel-Based Morphometry (VBM), one various me-

Figure. Phases of the systematic review



thods such as Structural Magnetic Resonance Imaging (MRI), Computed Tomography (CT), positron emission computed tomography (SPECT) or Positron emission tomography with F-fluorodeoxyglucose (FDG-PET) and in two only MRI.

Neuropsychiatric symptoms and neurological findings

Out of the five reports, three of them analyzed the presence of apathy and disinhibition as a study objective, as they are prevalent and early-onset symptoms in BvFTD. Apathy was observed as one of the most severe symptoms[26]. In this regard, studies agree on the lower activation of areas of the prefrontal cortex and the cingulate cortex[27] [28] (Table 2).

The levels of apathy found in the BvFTD were higher compared to those with AD[27]. Temporal portion of the left uncinate bundle.

On the other hand, when analyzing the symptom of disinhibition[28], reduced values of MBV were obtained in the right dorsolateral prefrontal cortex, right orbitofrontal cortex, bilateral anterior cingulate cortex, bilateral superior temporal gyrus, bilateral frontal medial regions, and insula bilateral. On the other hand, a regression analysis was related to the frequency of severity of disinhibition, observing a reduction in the values of fractional anisotropy in the right radiated crown[29].

When evaluating areas that were involved in the generation of both symptoms, an overlap in the right caudate nucleus, left cingulate cortex, and bilateral insula was observed[28].

Neurochemical findings

One of the studies performed neurochemical analyzes of neurotransmitters[30] in post-mortem brains, finding that for all the brain regions analyzed, FTD patients had the lowest proportions of MHPG/NA (methoxy-4-hydroxyphenylglycol; metabolite of noradrenaline), indicative of catabolic noradrenergic rotation, compared to AD, observing the most pronounced differences in the Brodmann Areas AB6, AB9, AB10, AB11, AB24, amygdala, and hippocampus.

Table 1. Characteristics of the study and sociodemographic sample

	Objective of the study	Participants	Average age (years)	Years of schooling	Neuropsychiatric evaluation	Cognitive evaluation
Fernández-Matarrubia, M. et al.	To compare the clinical apathy profile of patients with BvFTD and AD and to analyze the relationship between apathy and brain metabolism measured by PET with F-18 fluorodeoxyglucose (FDG-PET).	*n= 114*			NPI-apathy	MMSE:
		Control group: 30	67.1 ±11.3	9.3 ±3.9		27.54 +2.06
		BvFTD: 42	71.6 ± 8.3	8.0 ± 4.9	9.43 +4.42	22.86 +5.89
		Alzheimer: 42	76.3 ±6.9	8.1 ±5.1	5.39 +5.27	21.24 +5.33
Santamaría-García, H. et al.	To analyze neurocognitive correlates of patients with BvFTD who started with apathy or disinhibition as the first symptom of the disease.	*n= 64*			FrSBe total:	MMSE:
		Control group: 30	60.1 ±6.55	13.22 ±4.8	NE	27.4 +2.1
		BvFTDA: 34	58.0 ±7.43	13.68 ±4.3	48.4 ±31.4	22.7 +6.5
		BvFTDB:	57.0 ±8.64	14.67 ±3.7	47.8 ±27.7	23.7 +4.5
Jung, N-Y. et al.	To determine if the neuropsychiatric manifestations of PiB (-) Subcortical vascular dementia and BvFTD differ.	*n=79*			CGA-NPI	MMSE:
		BvFTD: 31	63.7 ±7.7	12.7 ±42	Without results:	21.0 ±6.0
		D. Vascular: 48	71.8 ±7.2	8.5 ±4.8		21.6 ±4.4
Vermeiren, Y. et al.	To determine the damage in serotonergic and dopaminergic neurotransmission in FTD compared to AD	*n=30*			NPI	No data
		Control group: 10	No data	No data	Without results	
		FTD: 10				
		Alzheimer: 10				
Powers, J. et al.	Relate changes in fractional anisotropy associated with BvFTD with measures of apathy and disinhibition.	*n=45*			NPI	MMSE
		Control group: 34	62.8 ±1.4		Without results	
		BvFTD: 11	60.5 ±2.0			25.0 ±1.4

Table 2. Correlation between apathy and neuroanatomical findings

	Neuroanatomical findings
Fernández-Matarrubia, M. et al.	Lower metabolism in left lateral prefrontal (AB 6, 8, 45), left medial prefrontal / anterior cingulate (AB 10, 32), left lateral orbitofrontal (AB 10, 11) and left anterior insular cortex (AB 13)
Santamaría-García, H. et al.	Reduced values of MBV in the right dorsolateral prefrontal cortex, bilateral orbitofrontal cortex, bilateral anterior cingulate cortex, and bilateral caudate nucleus
Powers, J. et al.	Reduction in values of fractional ansiotropy in the temporal portion of the left uncinate bundle.

Discussion

BvFTD is a type of dementia with high prevalence within the spectrum of FTDs[7], which is characterized by the presence of behavioral disturbances, determined by neuropsychiatric symptoms, as detailed by current diagnostic criteria[11]. The low number of studies found regarding the establishment of correlates between neuroanatomical findings and the main symptoms of a neuropsychiatric nature accounts for a reality that is visible in the clinic, where there are ignorance and consequent underdiagnosis of this pathology[31], in contrast to other dementia pictures. Studies on neuropsychiatric disorders are concentrated in Alzheimer's type dementia [32] [33], as it is the most prevalent and incidental in the world population. This fact would prevent the study in relation to the medical and pharmacological approach from finding a greater response to the intervention of this type of early dementia.

The findings of the presented studies concur with previous evidence described in the literature, where different subdivisions of the prefrontal cortex, cingulate cortex, and related neural circuits, present atrophy that would justify clinical symptoms observed at the level of behavioral regulation[34] [35].

Apathy seems to be a symptom studied in the description of the BvFTD[36], the NPI being a valid instrument[37], and, therefore, of high frequency of use for the evaluation of neuropsychiatric symptoms of people with dementia.

The present work that aims to provide systematized information on the neuroanatomic correlates of BvFTD and its neuropsychiatric symptoms is not without limitations. The methodological quality of the reviewed articles was not rated. Despite performing an exhaustive electronic search in reliable databases, it is possible that some articles have not been identified because they were not published in the digital media consulted.

In conclusion, up-to-date information has been presented regarding the neuropsychiatric symptoms present in the BvFTD, highlighting the scarce number of recent data in this regard. This fact could have implications in the theoretical description of the table, consequently, of the diagnostic process and the medical approach to pathology, since this updated information is required to improve therapeutic guidelines, for example, pharmacological ones that have been developed to date for its management, as well as non-medical management of behavior and emotion. This demonstrates the need to focus studies on dementias other than Alzheimer's.

Bibliography

(1) OMS (2016). Acción multisectorial para un envejecimiento saludable basado en el ciclo de vida: proyecto de estrategia y plan de acción mundiales sobre el envejecimiento y la salud. 69ª Asamblea Mundial de la Salud.

(2) American Psychiatric Association (2013). Manual diagnóstico y estadístico de los trastornos mentales (5ta ed.). Washington, DC, USA.

(3) Prince, M., Bryce, R., Albanese, E., Wimo. A., Ribeiro, W. & Ferri, C.P. The global prevalence of dementia: A systematic review and meta-analysis. Alzheimers Dement. 2013; 9: 63-75.

(4) Prince, M., Ali, G-C., Guerchet, M., Prina, A.M. & Albanese, E. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. Alzheimers Res Ther. 2016; 8:23.

(5) Brookmeyer, R., Evans, D.A., Hebert, L., Langa, K., Heeringa, S.G., Plassman, B. & Kukull, W. National estimates of the prevalence of Alzheimer's disease in the United States. Alzheimers Dement. 2011; 7: 61-73.

(6) Fiest, K.M., Roberts, J.I., Maxwell, C.J., Hogan, D.B., Smith, E.E., Frolkis, A. et al. The prevalence and incidence of dementia due to Alzheimer's Disease: a Systematic Review and Meta-Analysis. Can J Neurol Sci. 2016; 43: 51-82.

(7) Hoggan, DB., Jetté, N., Fiest, K.M., Roberts, J.I., Pearson, D., Smith, E.E., et al. The prevalence and Incidence of Frontotemporal Dementia: a Systematic Review. Can J Neurol Sci. 2016; 43: 96-109.

(8) Takeda, N., Kishimoto, Y. & Yokota, O. (2012). Pick's Disease. In Ahmad, Sh. (Ed.) Neurodegenerative Diseases. New York, USA: Springer.

(9) Rabinovici, G.D. & Miller, B.L. Frontotemporal Lobar Degeneration. Epidemiology, Pathophysiology, Diagnosis, and Management. CNS Drugs. 2010; 24: 375-398.

(10) Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., Kertesz, A., Mmendez, M., Cappa, S.F. et al. Classification of primary progressive aphasia and its variants. Neurology. 2011; 76: 1006-1011.

(11) Rascovsky, K., Hodges, J.R., Knopman, D., Mendez, M.F., Kramer, J.H., Neuhaus, J. et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011; 134: 2456-77.

(12) Liu, W., Miller, B.L., Kramer, J.H., Rankin, K., Wyss-Coray, C., Gearhart, R. et al. Behavioral disorders in the frontal and temporal variants of frontotemporal dementia. Neurology. 2004; 62: 742-748.

(13) Lanata, S.C. & Miller, B.L. The behavioural variant frontotemporal dementia (bvFTD) syndrome in psychiatry. J Neurol Neurosurg Psychiatry. 2016; 87: 501-511.

(14) Folstein, M.F., Folstein, S.E. & McHugh, P.R. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12: 189-198.

(15) Freitas, S., Simoes, M., Alves, L., Duro, D. & Santana, I. Montreal Cognitive Assessment (MoCA): Validation study for Frontotemporal Dementia. J Geriatr Psychiatry Neurol. 2012; 25: 146-154.

(16) Coleman, K.K., Coleman, B.L., MacKinley, J.D., Pasternack, S.H. & Finger, E.C. Detection and Differentiation of Frontotemporal Dementia and Related Disorders From Alzheimer Disease Using the Montreal Cognitive Assessment. Alzheimer Dis Assoc Disord. 2016; 30: 258-263.

(17) Mathuranath, P.S., Nestor, P.J., Berrios, G.E., Rakowicz, W. & Hodges, J.R. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. Neurology. 2000; 55: 1613-1620.

(18) Mioshi, E., Dawson, K., Mitchell, J., Arnold, R. & Hodges, J.R. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. Int J Geriatr Psychiatry. 2006; 21: 1078-1085.

(19) Hsieh, S., Schubert, S., Hoon, C., Mioshi, E. & Hodges, J.R. Validation of the Addenbrooke's Cognitive Examination III in Frontotemporal Dementia and Alzheimer's Disease. Dement Geriatr Cogn Disord. 2013; 36: 242-250.

(20) Sarasola, D., Calcagno, M., Sabe, L., Caballero, A. y Manes, F. Utilidad del Addenbrooke's Cognitive Examination en Español para el Diagnóstico de Demencia y para la diferenciación entre la Enfermedad de Alzheimer y la Demencia Frontotempora. Revista Argentina de Neuropsicología. 2004; 4: 1-11.

(21) Dubois, B., Slachevsky, A., Litvan, I. & Pillon, B. The FAB: a Frontal Assessment Battery at bedside. Neurology. 2000; 55: 1621-1626.

(22) Shallice, T. Specific impairments of planning. Philos Trans R Soc Lond B Biol Sci. 1982; 298: 199-209.

(23) Grant, D.A. & Berg, E.A. A behavioral analysis of the degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. J Exp Psychol. 1948; 38: 404-411.

(24) Cummings, J.L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D.A. & Gornbein, J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994; 44: 2308-2314.

(25) Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P.A., et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanations and elaboration. Journal of clinical epidemiology. 2009; 62: e1-34.

(26) Jung, N.Y., Kim, H.J., Kim, S., Seo, S.W, Kim, E.J. & Na, D.L. Neuropsychiatric characteristics of PiB-negative subcortical vascular dementia versus behavioral variant frontotemporal dementia. Arch Gerontol Geriatr. 2016; 67: 86-91.

(27) Fernández-Matarrubia, M., Matías-Guiu, J.A., Cabrera-Martín, M.N., Moreno-Ramos, T., Valles-Salgado, M., Carreras, J.L. & Matías-Guiu, J. Different apathy clinical profile and neural correlates in behavioral variant frontotemporal dementia and Alzheimer's disease. Int J Geriatr Psychiatry. 2018; 33: 141-150.

(28) Santamaría-García, H., Reyes, P., García, A., Baéz, S., Martínez, A., Santacruz, J.M. et al. First Symptoms and Neurocognitive Correlates of Behavioral Variant Frontotemporal Dementia. J Alzheimers Dis. 2016; 54: 957-970.

(29) Powers, J.P., Massimo, L., McMillan, C.T., Yushkevich, P.A., Zhang, H., Gee, J.C. & Grossman, M. White Matter Disease Contributes to Apathy and Disinhibition in Behavioral Variant Frontotemporal Dementia. Cogn Behav Neurol. 2015; 27: 206-214.

(30) Vermeiren, Y., Janssens, J., Aerts, T., Martin, J.J., Sieben, A., Van Dam, D. & De Deyn, P.P. Brain Serotoninergic and Noradrenergic Deficiencies in Behavioral Variant Frontotemporal Dementia Compared to Early-Onset Alzheimer's Disease. J Alzheimers Dis. 2016; 53: 1079-1096.

(31) Shinagawa, Sh., Catindig, J., Block, N.R., Miller, B. & Rankin, K. When a Little Knowledge Can Be Dangerous: False-Positive Diagnosis of Behavioral Variant Frontotemporal Dementia among Community Clinicians. Dement Geriatr Cogn Disord. 2016; 41: 99-108.

(32) Hu, X., Meiberth, D., Newport, B. & Jessen, F. Anatomical correlates of the neuropsychiatric symptoms in Alzheimer's disease. Curr Alzheimer Res. 2015; 12: 266-277.

(33) Bruen, P.D., McGeown, W.J., Shanks, M.F. & Venneri, A. Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer's disease. Brain. 2008; 131: 2455-2463.

(34) Rosen, H.J., Gorno-Tempini, M.L., Goldman, W.P., Perry, R.J., Schuff, N., Weiner, M. et al. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. Neurology. 2002; 58: 198-208.

(35) Tekin, S. & Cummings, J.L. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: An update. J Psychosom Res. 2002; 53: 647-654.

(36) Liu, W., Miller, B.L., Kramer, J.H., Rankin, K., Wyss-Coray, C., Gearhart, R. et al. Behavioral disorders in the frontal and temporal variants of frontotemporal dementia. Neurology. 2004; 62: 742-748.

(37) Lai, C. The merits and problems of the Neuropsychiatric Inventory as an assessment tool in people with dementia and other neurological disorders. Clin Interv Aging. 2014; 9: 1051-1061

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