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ELIZABETH SAKAMOTO VALENTE

FENOCÓPIAS DA DEMÊNCIA FRONTOTEMPORAL: REVISÃO SISTEMÁTICA

BELO HORIZONTE

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Monografia apresentada à UFMG – Universidade Federal de Minas Gerais, como requisito parcial para obtenção do título de especialista em Neurociências.

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RESUMO

Introdução: A síndrome da fenocópia da demência frontotemporal (fDFT) refere-se a pacientes os quais mimetizam a variante comportamental da demência frontotemporal, mas não apresentam atrofia frontotemporal na neuroimagem e não progridem para demência franca durante o acompanhamento. É importante reconhecer a “síndrome da fenocópia” para fins clínicos e de pesquisa.

Objetivo: O objetivo deste estudo foi realizar uma revisão sistemática na literatura disponível sobre a fenocópia da demência frontotemporal (fDFT), considerando seus aspectos clínicos, cognitivos, de imagem, genéticos e patológicos.

Métodos: Os seguintes termos foram pesquisados em duas bases de dados eletrônicas (PubMed e Scopus): “frontotemporal dementia and slowly progressive”, “frontotemporal dementia and phenocopy”, “frontotemporal dementia and non-progressive”, “frontotemporal dementia and benign progression” e “frontotemporal dementia and benign”. Não incluímos artigos de revisão; não foram adotados limites cronológicos.

Resultados: Um total de 235 estudos foram encontrados na pesquisa inicial. Um total de 31 artigos compuseram a seleção final. Pacientes com fDFT são, geralmente, do sexo masculino e não apresentam déficits cognitivos significativos, com preservação de funções executivas e memória episódica Alguns casos de DFT lentamente progressiva foram associados à expansão genética de *C9orf72.* Existem apenas quatro estudos que relatam dados patológicos na fDFT, com dois casos sem achados neurodegenerativos e dois com degeneração lobar frontotemporal.

Conclusão: As bases neurobiológicas da fDFT permanecem desconhecidas. É controverso se a fDFT pertence ao espectro da DFT. Mais estudos com biomarcadores e dados patológicos podem ajudar a desvendar a questão.

Palavras-chave: Demência frontotemporal não-progressiva. Síndrome da fenocópia. Fenocópia da DFT. Demência frontotemporal de progressão lenta.

ABSTRACT

Background: The phenocopy syndrome frontotemporal dementia (phFTD) refers to patients who mimic behavioral variant of frontotemporal dementia (bvFTD), but lack frontotemporal atrophy on neuroimaging and do not progress to frank dementia during the follow-up. It is important to recognize phFTD for clinical and research purposes.

Objective: The aim of this study was to perform a systematic review of available literature about phFTD, considering its clinical, cognitive, imaging, genetic and pathological aspects.

Methods: We searched for the following terms on two electronic databases (PubMed and Scopus): “frontotemporal dementia and slowly progressive”, “frontotemporal dementia and phenocopy”, “frontotemporal dementia and non-progressive”, “frontotemporal dementia and benign progression” and “frontotemporal dementia and benign”. We did not include review articles; no chronological limits were adopted.

Results: A total of 235 studies were retrieved on the initial search. A total of 31 studies composed the final selection. Patients with phFTD are generally male and have no major cognitive deficits, with globally preserved executive functions and episodic memory. Some cases of slowly progressive FTD have been associated to *C9orf72* genetic expansion. There are only four studies reporting pathological data on phFTD, with two cases with no neurodegenerative findings and two with frontotemporal lobar degeneration.

Conclusion: The neurobiological underpinnings of phFTD remain unknown. It is controversial whether phFTD belong to the FTD spectrum. More studies with biomarkers and pathological data may help to disentangle the question.

Keywords: nonprogressive frontotemporal dementia; phenocopy syndrome; FTD phenocopy; slowly progressive frontotemporal dementia.

LISTA DE ABREVIATURAS E SIGLAS

ACE-R	Addenbrooke's Cognitive Examination – Revised
AMPS	Assessment of Motor and Process Skills
APNF	Afasia progressive não fluente
CBI	Cambridge Behavioural Inventory
C9ORF72	*Chromosome 9 Open Reading Frame 72*
CHMP2B	Charged multivesicular body protein 2 B
DFT	Demência frontotemporal
DFTvc	Demência frontotemporal variante comportamental
fDFT	Fenocópia da demência frontotemporal
DLFT	Degeneração lobar frontotemporal
DMN	Default mode network
DS	Demência semântica
DTI	Difusion tensor imaging
FDG–PET	Fluorodeoxyglucose (18 F) - Positron emission tomography
FTLD tau	Frontotemporal lobar degeneration with tau immunoreactive inclusions
FTLD-TDP	Frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions
FTLD-FUS	Frontotemporal lobar degeneration with FUS immunoreactive inclusions
FUS	Fused-in-sarcoma
GRN	Progranulin
MAPT	Microtubule associated protein tau
MMSE	Mini-Mental State Examination
PET	*Positron emission tomography*
RNM	Ressonância nuclear magnética
SELDI-TOF	*Surface-enhanced laser desorption/ionization time-of-flight*
SPECT	*Single photon emission computed tomography*
TARDP	*Transactive response DNA-binding protein*
TASIT	*The Awareness of Social Inference*
VBM	*Voxel based morphometry*
VCP	*Valosin-containing protein*
WM	*White matter*

SUMÁRIO

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1. INTRODUÇÃO

A demência frontotemporal (DFT) é um grupo de transtornos neurodegenerativos caracterizados por distúrbios do comportamento ou da linguagem, além de progressiva disfunção executiva associados à atrofia dos lobos frontais e/ou temporais (FINGER, 2016). A DFT é a segunda causa mais comum de demência antes dos 65 anos de idade, embora também ocorra em idade avançada (PRESSMAN, 2014). A doença incide igualmente entre homens e mulheres (FINGER, 2016). Subdivide-se em duas categorias, de acordo com os sintomas prevalentes; ou seja, o subtipo comportamental (DFTvc) que representa metade dos casos de DFT e o subtipo de linguagem, que abrange as variantes não fluente e semântica de afasia progressiva primária (FINGER,2016).

A DFT foi primeiramente descrita por Arnold Pick em 1892, em um paciente com afasia, atrofia lobar e demência pré-senil. Em 1911, Alois Alzheimer descreveu as inclusões intraneuronais argentofílicas e das células vacuolizadas conhecidas como corpúsculos e células de Pick, respectivamente (BANG, 2015). A expressão “doença de Pick” foi substituída pelo termo “demência frontotemporal” após observação de que apenas uma fração dos pacientes com afasia, distúrbios comportamentais e atrofia frontal tinham corpúsculos de Pick ao exame anatomopatológico.

O início da DFT é insidioso e progressivo. O diagnóstico é clínico, já que, até o momento, inexistem biomarcadores definitivos da doença. Os critérios adotados em último consenso internacional para o diagnóstico de DFTvc foram publicados pelo Corsórcio Internacional de DFTvc em 2011, a fim de aumentar a sensibilidade do diagnóstico e o manejo precoce da DFT (Rascovsky, 2011). Para o diagnóstico de DFTvc, é necessário que o paciente apresente deterioração progressiva do comportamento e/ou da cognição observadas pelo cuidador. DFTvc possível é diagnosticada quando três ou mais dos sintomas estão presentes: 1 – desinibição comportamental; 2 - apatia ou inércia; 3 – perda da empatia ou simpatia, inclusive diminuição da resposta às necessidades e simpatia das outras pessoas e diminuição

do interesse social; 4 – comportamento perseverativo, estereotipado ou ritualístico/compulsivo; 5 – hiperoralidade e alterações dietéticas; 6 – perfil neuropsicológico com déficit executivo e relativa preservação da memória episódica e de habilidades visuo-espaciais. O diagnóstico de DFTvc provável requer, além dos critérios de DFT possível, um declínio funcional significativo e atrofia frontal e/ou temporal na ressonância nuclear magnética (RNM) ou tomografia computadorizada (TC) ou hipometabolismo/hipoperfusão na tomografia por emissão de pósitrons (PET) ou tomografia por emissão de fóton único (SPECT). O diagnóstico de DFTvc definitiva requer evidência de uma mutação genética patogênica ou exame histopatológico característico. Para o diagnóstico de DFT, devem ser excluídas outras condições médicas, neurológicas ou psiquiátricas que possam causar os sintomas cognitivos e comportamentais.

A Demência semântica (DS) caracteriza-se pela perda de conhecimento do significado das palavras, com dificuldade em encontrar palavras e diminuição do vocabulário. A Afasia progressiva não fluente (APNF) está relacionada com disfunções associadas à linguagem expressiva, com discurso laborioso, não fluente, erros fonêmicos, agramatismo e desestruturação sintáxica.

Há sobreposição da DFT a outras síndromes com características de parkinsonismo (degeneração corticobasal ou paralisia supranuclear progressiva) ou de doença do neurônio motor (esclerose lateral amiotrófica).

Cerca de 33% dos pacientes com DFT têm história familial positiva (HODGES, 2003). Muitos casos familiais da doença não têm causa conhecida enquanto que cerca de 10-20% são atribuídos a uma mutação genética (PIGUET, 2013; PARMERA, 2015). As mutações em genes codificantes de diferentes proteínas associadas à DFT genética mais comuns são: *progranulina (GRN), microtubule associated protein tau (MAPT) e expansões de repetições do gene Chromosome 9 Open Reading Frame 72 (C9ORF72)* (FINGER, 2016; TAKADA, 2015). Outras mutações genéticas associadas à etiologia da DFT foram também identificadas como a *transactive response DNA-binding protein (TARDP), valosin-containing protein (VCP), fused-in-sarcoma (FUS) e charged multivesicular body protein 2B (CHMP2B)* (FINGER,2016; TAKADA, 2015).

O substrato patológico da DFT é a degeneração lobar frontotemporal (DLFT). A DLFT é classificada de acordo com o componente protéico patológico das inclusões neuronais e gliais (BANG, 2015). Os subtipos principais da DLFT são associados à proteína TDP-43 (DLFT-TDP), seguido pela DLFT-Tau e, mais rara, a DLFT-FUS (*fused in sarcoma*).

A DFT tem curso progressivo e média de sobrevida de 3 anos a partir do diagnóstico (HODGES, 2003) e 6-8 anos a partir do início dos sintomas (GARCIN, 2009). Porém, estudos mostraram um curso não progressivo da doença em alguns pacientes com quadro clínico de DFT. Estes pacientes foram nomeados com o termo “síndrome da fenocópia” (DAVIES, 2006). Davies et al.(2006) observaram que, dentre os pacientes com DFTvc, um subgrupo apresentava imagem borderline ou normal na RNM convencional e um prognóstico mais benigno da doença, pois não evoluía para franca demência no período de 3 anos (DAVIES, 2006). Nos quadros típicos de DFTvc, os pacientes apresentavam uma evolução progressiva para demência e eram institucionalizados ou evoluíram para o óbito no período de até 3 anos (DAVIES, 2006).

A partir de tais achados, alguns questionamentos foram feitos. Como explicar as alterações comportamentais similares na DFT típica e na fenocópia da DFT (fDFT) sem sinais de atrofia dos lobos frontais ou temporais na neuroimagem neste último grupo? Como explicar o mecanismo fisiopatológico na “síndrome da fenocópia”? Muitos autores levantaram a hipótese de que a “síndrome da fenocópia” seria um transtorno psiquiátrico ou, numa segunda hipótese, de que seria uma forma indolente da DFT. A fenocópia da DFT não satisfaz critérios para DFT provável, já que a neuroimagem, nestes casos, apresenta-se normal. Na DFT possível, existe a probabilidade de se tratar de “síndrome da fenocópia” ou de evoluir para a categoria provável ou definitiva. Como a neuroimagem apresenta-se normal ou borderline nos pacientes com fDFT, surgiu mais um questionamento se a RNM seria insensível à degeneração frontotemporal em alguns pacientes (KIPPS, 2007).

O cenário da fenocópia ficou ainda mais complicado após a identificação de casos de DFT com progressão lenta, classificados inicialmente como DFT possível,

porém, após estudo genético, mostraram ser portadores de mutação *C9ORF72* e, dessa forma, foram diagnosticados como DFT definitiva (DEVENNEY, 2015)

A definição da DFT através de exame histopatológico nos casos da fenocópia esbarra nas dificuldades de seguimento nestes pacientes que possuem uma evolução da doença de até 30 anos. Os dados histopatológicos na DFTf são escassos.

A fDFT foi relacionada mais frequentemente à variante comportamental da DFT. Uma possível explicação para esta associação seria o achado de neuroimagem normal em cerca de 50% dos casos da DFTvc, enquanto que nas variantes da linguagem, a neuroimagem frequentemente apresenta sinais de atrofia fronto-temporal (KIPPS, 2007).

A identificação de marcadores que possam diferenciar os pacientes com DFT típica e fDFT pode facilitar a orientação de familiares em relação ao prognóstico e a separação de ambos os grupos pode ter impacto significativo nos resultados de pesquisas de tratamento medicamentoso e outras intervenções não medicamentosas.

2. OBJETIVO

Realizar revisão sistemática na literatura acerca da “síndrome da fenocópia” da DFT, abordando seus aspectos clínicos, cognitivos, comportamentais, de neuroimagem, genéticos e patológicos.

3. ARTIGO

PHENOCOPY SYNDROME OF FRONTOTEMPORAL DEMENTIA: A SYSTEMATIC REVIEW

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Keywords: frontotemporal dementia, phenocopy

Abstract

Background: The phenocopy syndrome frontotemporal dementia (phFTD) refers to patients who mimic behavioral variant of frontotemporal dementia (bvFTD), but lack frontotemporal atrophy on neuroimaging and do not progress to frank dementia during the follow-up. It is important to recognize phFTD for clinical and research purposes.

Objective: The aim of this study was to perform a systematic review of the available literature about phFTD, considering its clinical, cognitive, imaging, genetic and pathological aspects.

Methods: We searched for the following terms on two electronic databases (PubMed and Scopus): “frontotemporal dementia and slowly progressive”, “frontotemporal dementia and phenocopy”, “frontotemporal dementia and non-progressive”, “frontotemporal dementia and benign progression” and “frontotemporal dementia and benign”. We did not include review articles; no chronological limits were adopted.

Results: A total of 235 studies were retrieved on the initial search. A total of 31 studies composed the final selection. Patients with phFTD are generally male and have no major cognitive deficits, with globally preserved executive functions and episodic memory. Some cases of slowly progressive FTD have been associated to *C9orf72* genetic expansion. There are only four studies reporting pathological data on phFTD, with two cases with no neurodegenerative findings and two with frontotemporal lobar degeneration with ubiquitine-positive inclusions.

Conclusion: The neurobiological underpinnings of phFTD remain unknown. It is controversial whether phFTD belongs to the FTD spectrum. More studies with biomarkers and pathological data may help to disentangle this issue.

Introduction

Frontotemporal dementia (FTD) is a neurodegenerative dementia featuring progressive deterioration of behavior or language associated with marked atrophy of frontal and/or temporal lobes (Bang et al 2015). The disease is the second most common cause of early-onset dementia, also affecting older patients (Bang et al 2015). FTD comprises three clinical phenotypes: behavioral variant, semantic aphasia and non-fluent primary progressive aphasia. The behavioral variant of FTD (bvFTD) is the most frequent subtype (Bang et al 2015).

Patients with bvFTD present with progressive deterioration of behavior and/or cognition. According to consensual diagnostic criteria for bvFTD (Rascovsky et al 2011), a possible bvFTD requires at least three of six characteristics: disinhibition, apathy/inertia, loss of empathy and/or sympathy, perseveration/compulsive behaviors, hiperorality, and neuropsychological profile of executive dysfunction with relative sparing of episodic memory and visuospatial skills. Probable bvFTD additionally requires significant functional decline and prominent signs of focal frontotemporal involvement either on structural or functional neuroimaging exams (Rascovsky et al 2011). Definite bvFTD is reserved for patients with known pathogenic genetic mutation or with histopathological evidence of frontotemporal lobar degeneration (FTLD) (Rascovsky et al 2011).

The mean survival of bvFTD was estimated on 6-8 years from the symptom onset (Garcin et al 2009). However, over the past few years, some studies have identified a group of patients clinically indistinguishable from typical FTD, but who do not progress to frank dementia during the follow-up. These patients fulfill criteria for

possible bvFTD, and have limited or no imaging features of bvFTD, such as focal prefrontal atrophy on MRI (Davies et al 2006). Since their condition remains stable over many years, such group was called “phenocopy” of FTD (phFTD), or FTD “phenocopy syndrome”, or “nonprogressive” FTD, or “benign” FTD, or slowly progressive FTD (Davies et al 2006, Hornberger et al 2008, Khan et al 2012, Kipps et al 2010). It is worth emphasizing that phFTD patients do not satisfy criteria for probable bvFTD since neuroimaging is normal or borderline.

Despite efforts to characterize phFTD in terms of clinical, behavioral, cognitive and pathological aspects, the results have been controversial. For instance, while some studies reported preserved global cognitive efficiency in phFTD (Devenney et al 2018, Meijboom et al 2017, Pennington et al 2011), others described that phFTD performed worse than controls on general measures of cognition (Hornberger et al 2008, Steketee et al 2016). From a neuropathological point of view, the question remains open as there are only a few histopathological studies from these patients. Some authors argue that phFTD may represent ‘an indolent variant’ of FTD (Brodtmann et al 2013). Indeed, there are patients with slowly progressive bvFTD associated to *C9orf72* mutation (Gomez-Tortosa et al 2014, Khan et al 2012), suggesting that phFTD could be due to FTLD. The hypothesis of an indolent FTD places the phenocopy group in the FTD spectrum and raises the issue whether phFTD represents a slow neurodegenerative process. Conversely, phFTD has been conceptualized as late-onset forms of psychiatric disorders including late-onset schizophrenia, late onset bipolar disorder, Asperger-Autism spectrum disorder and personality disorders (Devenney et al 2018, Dols et al 2016).

In practical terms, phFTD has been considered as a clinical entity similar to bvFTD, but with relatively normal cognitive performance, intact activities of daily living, no neuroimaging features of bvFTD and without clinical progression over three or more

years of follow-up (Kipps et al 2010). However, several questions remain unanswered. How is it possible to explain the behavioral overlap between phFTD and typical bvFTD in the absence of cerebral atrophy on the former? Are there other clinical and cognitive features distinguishing phFTD from bvFTD? The identification of phFTD is highly relevant for clinical purposes, such as optimal medical and familial support, and establishing outcomes for these patients. The aim of this study was to perform a systematic review of the available literature about phFTD, considering its clinical, cognitive, imaging, biological, genetic and pathological aspects.

Methods

We conducted a systematic review according to the guidelines proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al 2009). This search was independently performed by two investigators (ESV and LCS) on July 2018. We searched for the following terms on two electronic databases (PubMed and Scopus): “frontotemporal dementia and slowly progressive”, “frontotemporal dementia and phenocopy”, “frontotemporal dementia and non-progressive”, “frontotemporal dementia and benign progression” and “frontotemporal dementia and benign”. We adopted the following filters: clinical articles, comparative studies, historical articles, journal articles, letter, classical articles, case report, comments and clinical trials. We did not include review articles or abstracts of scientific meetings. They had to be written in English, Spanish, Portuguese or French. No chronological limits were adopted. Disagreements of eligibility were resolved through discussion among the authors.

We carried out the following procedure: 1) Titles and Abstracts were screened and non-pertinent studies were excluded; 2) after this initial screen, the selected articles were subsequently read in full-text and non-pertinent articles were excluded.

This systematic review was registered on PROSPERO international platform under the number CRD42018107060

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Results

A total of 235 studies were retrieved on the initial search. A total of 31 studies composed the final selection (see Figure 1). Table 1 presents the main findings from the selected studies. Table 2 shows comparative data between phFTD and bvFTD.

Results are presented in three parts: Part I, composed of epidemiological aspects; Part II, which describes cognitive and functional results; Part III, which presents behavioral and psychiatric profiles; Part IV, presenting neuroimaging results, and Part V, describing biomarkers, genetic and pathological findings in phFTD.

Part I: Epidemiological aspects

The prevalence of phFTD patients among bvFTD series is variable. In a cohort of 124 patients with bvFTD, semantic dementia or progressive non-fluent aphasia, no case of phFTD was observed (Nunnemann et al 2011). However, non-progressive FTD cases (n=30) were 33.7% in a series of bvFTD patients (Hornberger et al 2008). Twenty-four (26.4%) phenocopy cases were identified among 91 bvFTD patients (Garcin et al 2009). Thirty-three (18%) phFTD cases were identified among 181 suspected bvFTD (Gossink et al 2016). It should be noted, however, that this study included phFTD with less than 3 years of follow-up (Gossink et al 2016). Another study assessed and followed 89 patients with possible bvFTD; after at least three years of follow up, the diagnosis of phFTD was established for 26 patients (29%) (Devenney et al 2018).

Most papers report a higher percentage of men among phFTD patients (Bertoux et al 2014, Davies et al 2006, Devenney et al 2015, Garcin et al 2009, Gossink et al 2016, Hornberger et al 2008, Hornberger et al 2009, Irish et al 2012, Kerklaan et al 2014, Mattsson et al 2008, Mioshi & Hodges 2009, Mioshi et al 2009, Steketee et al 2016). Some studies reported that patients with phFTD are younger (45-65 years) than bvFTD (50-75 years) at symptom onset (Garcin et al 2009, Gossink et al 2016), but this was not observed in other series (Davies et al 2006, Hornberger et al 2008, Hornberger et al 2009, Irish et al 2012). Non-progressive FTD usually do not present with neurological signs (e.g. primitive reflexes) on physical examination (Devenney et al 2015) and family history for dementia is typically absent (Devenney et al 2015, Garcin et al 2009).

Part II: Cognitive and Functional profile

Most studies did not find differences between phFTD patients and healthy controls on measures of global cognitive efficiency, such as the Mini-Mental Status Examination (MMSE) and Addenbrooke's cognitive Examination-Revised (ACE-R) (Bertoux et al 2014, Hornberger et al 2010, Irish et al 2012, Pennington et al 2011). However, Steketee et al reported that phFTD patients had significantly lower MMSE scores than controls (Steketee et al 2016). Similarly, patients with non-progressive FTD performed worse than controls on the ACE-R in another study (Hornberger et al 2008).

Most studies also report that phFTD patients have better cognitive performance than bvFTD, as measured by the MMSE and the ACE-R (Bertoux et al 2014, Garcin et al 2009, Hornberger et al 2008, Hornberger et al 2009). A study assessed structural (MRI) and functional neuroimaging (fluorodeoxyglucose-positron emission tomography [FDG-PET]) in a group of 24 patients with bvFTD (Kipps et al 2009). bvFTD patients were classified according to brain MRI: a subgroup with atrophy

pattern suggestive of bvFTD (n=15) and a subgroup without abnormalities (n=9). bvFTD patients with abnormal MRI performed worse than bvFTD group with normal MRI on the ACE-R, but almost a third of bvFTD with abnormal MRI had ACE-R scores overlapping with the normal MRI subgroup (Kipps et al 2009). This finding suggests that global cognitive efficiency may not be an optimal measure to distinguish progressive from non-progressive FTD (phFTD).

There is evidence indicating that episodic memory performance may distinguish progressive from non-progressive patients presenting with FTD-related behavioral disorders. Patients with phFTD syndrome have normal performance on episodic memory tests, performing better than typical bvFTD patients (Bertoux et al 2014, Hornberger et al 2010, Pennington et al 2011). Moreover, memory scores seem very sensitive to detecting progressive bvFTD cases at initial presentation. Immediate recall score from the Rey Auditory Verbal Learning Test correctly predicted progression of bvFTD with 85% accuracy (Hornberger et al 2010). Data from the Australian cohort also corroborate episodic memory deficits as marker of bvFTD progression (Devenney et al 2015). Source memory tasks may also distinguish bvFTD from phFTD at initial presentation. Tests of source memory usually require subjects to encode and retrieve information about the context in which items were studied. Patients with progressing bvFTD had impairment on temporal and spatial source retrieval, while phFTD patients displayed only temporal source deficits (Irish et al 2012).

Executive tasks do not seem to provide distinction between bvFTD and phFTD, as some bvFTD patients may have normal executive performance (Hornberger et al 2008, Hornberger et al 2009). Even if there is evidence that phFTD patients perform better than bvFTD in executive tests such as Digit Span, Letter Fluency, Trails, and Hayling (Hornberger et al 2008), up to 20% of bvFTD patients have normal

performance on these tests (Hornberger et al 2008). Of note, the frequency of disexecutive syndrome at presentation did not differ between bvFTD and phFTD groups in a cohort of 91 patients (Garcin et al 2009). In the same cohort, executive dysfunction was not associated with a shorter survival (Garcin et al 2009).

Language disorders seem more common in bvFTD than phFTD patients (Garcin et al 2009). Word-finding difficulty and semantic deficits were associated with shorter disease duration in progressive patients (Garcin et al 2009).

The assessment of social cognition can help differentiating bvFTD and phFTD. A longitudinal study investigated social cognition (emotion recognition and sarcasm detection) in bvFTD (Kumfor et al 2014). Patients with bvFTD were classified according to their neuroimaging profile: those with marked atrophy at baseline (typical bvFTD) and those with limited brain atrophy at baseline (bvFTD-la). At baseline, all patients (typical bvFTD and bvFTD-la) performed worse than healthy controls on emotion recognition (Kumfor et al 2014). Patients with typical bvFTD performed worse than controls on the sarcasm detection task, while bvFTD-la had normal performance (Kumfor et al 2014). Patients with marked atrophy (typical bvFTD) declined at a faster rate than the bvFTD-la group, which remained stable over time. These results suggest that social cognition tasks may be a useful tool to distinguish progressive from non-progressive bvFTD (Kumfor et al 2014). However, it must be point out that bvFTD-la patients had functional decline at baseline and the follow-up was inferior to 3 years, preventing their classification as phFTD (Kumfor et al 2014).

The functional profile of phFTD has been investigated. One study compared the performance on activities of daily living (ADL) in phFTD and bvFTD (Mioshi et al 2009). Importantly, the minimal follow-up period for the phFTD group in this study was of two years. The ADL ability was assessed with two ADL measures: a

caregiver-based scale, the Disability Assessment of Dementia (DAD) and a patient-based scale, the Assessment of Motor and Process Skills (AMPS). There was no difference between phFTD and bvFTD in DAD scale, but there was a clear distinction on the performance-based measure (AMPS), with bvFTD patients presenting worse performance than phFTD (Mioshi et al 2009). Another study from the same group (Mioshi & Hodges 2009) evaluated the rate of change in ADLs between phFTD and bvFTD. Although both groups had similar levels of functional skills at baseline, bvFTD patients deteriorated in ADLs over 12 months, while phFTD patients did not. Taken together, these data support that there is no evidence of functional impairment in phFTD, suggesting that the assessment of daily activities may be used to differentiate phFTD from bvFTD at initial presentation.

Part III: Behavioral and Psychiatric profiles

Some studies compared behavioral features between bvFTD and phFTD. One study (Hornberger et al 2009) compared progressors and nonprogressors patients regarding the behavioral profile on the Cambridge Behavioral Inventory (CBI) at initial presentation. There was no difference on bvFTD core diagnostic features between progressors and non-progressors (Hornberger et al 2009). However, distractibility and stereotypic speech were more common in progressors (Hornberger et al 2009), while current depression was more frequent in non-progressors (Hornberger et al 2009). Stereotypical and compulsive behaviors have also been associated with clinical and functional decline in a large series of patients with 5-year follow-up (Devenney et al 2015). Confabulation was reported in one phFTD patient (Poletti et al 2011). On the contrary, other studies showed that the two groups were indistinguishable on behavioral features at presentation (Davies et al 2006, Hornberger et al 2008, Mioshi et al 2009).

One retrospective study (Gossink et al 2016) investigated psychiatric and psychological conditions in phFTD and found a higher frequency of recent life events, relationship problems and cluster C personality traits in this group when compared with bvFTD patients. Bipolar disorder seemed to be more frequent in phFTD patients than in bvFTD group (Gossink et al 2016). One phFTD patient had autism spectrum disorder (Gossink et al 2016).

Dols et al reported four patients with bipolar disorder gradually developing a clinical syndrome marked by apathy, disinhibition, loss of empathy, stereotypical behavior, and compulsiveness, similar to bvFTD (Dols et al 2016). Patients had modest cognitive impairment and did not progress over three to seven years of follow-up. Neuroimaging was normal and *C9orf72* screening was negative in all cases. These authors hypothesized that end-stage bipolar disorder would be the underlying cause of the phenocopy syndrome (Dols et al 2016).

In sum, only one study systematically assessed psychiatric antecedents among phFTD patients (Gossink et al 2016). There is some evidence of clinical overlapping between phFTD and bipolar disorder.

Part IV: Neuroimaging

Patients with phFTD do not exhibit evident frontotemporal atrophy on brain MRI or focal hypometabolism/hypoperfusion on functional methods. It has been demonstrated that focal frontotemporal atrophy is a marker of clinical and functional decline during the follow-up, as patients with normal or almost normal MRI had significantly longer time to institutionalization or death than those with frontotemporal atrophy on MRI (Davies et al 2006, Kerklaan et al 2014).

Steketee et al compared bvFTD, phFTD and controls with quantitative methods in functional and structural MRI (Steketee et al 2016). The phFTD group (n = 7) showed

cortical atrophy, most prominently in the right temporal lobe, whereas bvFTD group (n = 11) had an extensive frontotemporal atrophy (Steketee et al 2016). Compared to bvFTD and controls (n = 20), cerebral perfusion measured with arterial spin labeling was increased in phFTD patients, with higher perfusion in the left prefrontal cortex (Steketee et al 2016).

Functional connectivity and white matter (WM) microstructure were investigated in bvFTD and phFTD (Meijboom et al 2017). Compared to controls (n = 17), phFTD patients (n = 7) showed higher connectivity on the default mode network (DMN) than bvFTD patients (n = 12). There were frontotemporal WM abnormalities in both bvFTD and phFTD groups, but they more pronounced in bvFTD patients (Meijboom et al 2017). Enhanced DMN connectivity was also reported in slowly progressive patients with *C9orf72* expansion and no characteristic atrophy on structural MRI (Lee et al 2014).

Hypometabolism on the fluorodeoxyglucose (FDG)-positron emission tomography (PET) may be abnormal in cases of normal brain MRI (Kerklaan et al 2014, Kipps et al 2009). A typical pattern of frontotemporal metabolism is usually associated to functional decline over the years, but patients with clinical behavioral features of bvFTD and abnormal metabolism on FDG-PET may remain stable over the years (Kerklaan et al 2014, Kipps et al 2009, Kipps et al 2007). Normal MRI has a high negative predictive value of normal PET-FDG (Kipps et al 2009), but FDG-PET increases the specificity of the diagnosis of bvFTD by excluding other neuropsychiatric diagnosis, such as depression, bipolar disorder or partner relational disorder (Kerklaan et al 2014). As PET-FDG is a sensitive marker of neurodegeneration, the results showing absence of typical frontotemporal metabolism in most phFTD patients reinforce the absence of an underlying neurodegenerative process in this condition.

Taken together, while some data suggest that phFTD patients share some structural and functional abnormalities with bvFTD (Lee et al 2014, Meijboom et al 2017), other findings are not indicative of neurodegenerative process (Kipps et al 2009).

Part V: Biomarkers, Genetics and Neuropathological data

C9orf72 expansion has been identified in patients with slowly progressive FTD (Gomez-Tortosa et al 2014, Khan et al 2012, Llamas-Velasco et al 2018, Suhonen et al 2015). For instance, three cases of slowly progressive FTD associated with *C9orf72* expansion were reported in the same family (Gomez-Tortosa et al 2014). Two siblings had mild cognitive impairment for more than a decade and their mother had slow cognitive deterioration over more than 30 years (Gomez-Tortosa et al 2014). Conversely, a longitudinal study with 58 bvFTD patients found that *C9orf72* expansion was associated to clinical and neuroimaging decline during follow-up (five years) (Devenney et al 2015).

The *R406W MAPT* mutation is typically associated with a slowly progressive memory decline with symmetrical frontotemporal atrophy on MRI. A novel phenotype associated with the *R406W* mutation has been identified, presenting with a slowly progressive behavioral disorder associated with predominant right temporal lobe atrophy (Wood et al 2016).

Only few patients with phFTD underwent autopsy (Brodtmann et al 2013, Devenney et al 2016). Two phFTD cases with behavioral disorders, mild dysexecutive function and unchanged neuropsychological testing during follow-up (5 years and 10 years)

did not have FTLD pathology on *post-mortem* pathological exam (Devenney et al 2016).

On the other hand, spongiosis and gliosis associated with ubiquitin-positive inclusions was reported in one patient featuring typical FTD behavioral symptoms but no abnormalities on both structural and functional neuroimaging after 3 years of follow-up (Mattsson et al 2008). On the same study, the peptides profiles in the cerebrospinal fluid (CSF) measured with mass spectroscopy technique differed between patients with rapidly progressive FTD (n = 13) and slowly progressive FTD (n = 11), indicating that these may be valuable markers of establishing FTD prognosis (Mattsson et al 2008).

FTLD with ubiquitin pathology was also found in a patient with a 20-year history of behavioral disorders with slow functional decline (Brodtmann et al 2013). Staining for *fused-in-sarcoma* (FUS) and *TAR DNA-binding protein 43* **(**TDP-43) proteins was negative and no amyloid plaques were observed in this patient (Brodtmann et al 2013). Tau pathology (neurofibrillary tangle) was scarce. Interestingly, his son presented a similar history without significant changes over 15 years and stable MRI and PET (Brodtmann et al 2013).

Discussion

For many years, bvFTD was considered as a clinically homogeneous condition marked by stereotypical behaviors, typical neuropsychological profile (severe executive dysfunction and preserved episodic memory) and shorter survival than Alzheimer's disease. Recent data from longitudinal studies of bvFTD patients with cognitive, molecular and neuroimaging tools have challenged this classic clinical profile of bvFTD and highlighted the pronounced phenotypical heterogeneity of FTD,

expanding its possible clinical and behavioral presentations. More specifically, a subgroup of slowly progressive patients with no frank neuroimaging features of FTD has been recognized. FTD patients with no or slow decline over years have been generally referred as phenocopies of bvFTD (phFTD). In other terms, phFTD is characterized by marked changes in behavior but with normal neuroimaging, fulfilling criteria for possible bvFTD. Moreover, phFTD patients have no or very slow decline on follow-up.

The phenocopy syndrome of FTD is a clinical and scientific challenge. From a clinical perspective, distinguishing bvFTD from phFTD is crucial for prognosis purposes, clinical care and familial support. From a scientific perspective, the inclusion of phFTD patients in cohorts of bvFTD patients may hamper the development of disease-modifying strategies against FTD. Researchers on the field of FTD should be aware of phFTD for optimal cognitive and behavioral characterization of patients.

The nomenclature “phenocopy syndrome of bvFTD” deserves critical considerations. The term “Phenocopy” is usually employed to refer to *“a non-genetically produced phenotype that mimics or resembles the genetically produced one”* (Brodtmann et al 2013). For instance, it has been used to refer to patients with Huntington’s disease phenotype, but who lack the typical genetic mutation (Hensman Moss et al 2014). It should be pointed out that most bvFTD cases are not monogenic as Huntington’s disease (Takada 2015) and most studies on phFTD did not test for known pathogenic mutations related to FTD. Thus, the term “phenocopy” may not be appropriate. Similarly, considering that phFTD lacks functional decline, it may also be inadequate to label them “phenocopy of FTD”, as dementia is a criterion for establishing the diagnosis of FTD (Kerklaan et al 2014).

Studies reported variable frequency of phFTD patients among FTD series (Devenney et al 2018, Nunnemann et al 2011). Methodological issues, such as different

diagnostic definitions of phFTD and distinct periods of follow-up, hamper establishing a precise prevalence of phFTD.

There is some evidence that cognitive measures may help to distinguish bvFTD from phFTD. Some studies found that bvFTD and phFTD differs in terms of performance in episodic memory tests (Bertoux et al 2014, Hornberger et al 2010, Pennington et al 2011). Consensual diagnostic criteria for bvFTD state that episodic memory is relatively spared in bvFTD (Rascovsky et al 2011). However, there is increasing evidence that episodic memory impairment is present in bvFTD (Hornberger & Piguet 2012, Poos et al 2018) in similar degree as observed in Alzheimer's disease (Bertoux et al 2014, Bertoux et al 2018, Fernandez-Matarrubia et al 2017, Hornberger et al 2010, Hornberger et al 2012). It has been demonstrated that amnesia in bvFTD is associated to involvement of medial temporal structures, such as hippocampal and perihippocampal regions (Bertoux et al 2018, Fernandez-Matarrubia et al 2017, Hornberger & Piguet 2012, Hornberger et al 2012). phFTD patients seem to have normal performance on episodic memory tests, suggesting preservation of Papez's circuit. These findings suggest the frank episodic memory impairment may be a marker of progressive FTD, distinguishing bvFTD from phFTD.

Executive functions seem to be more impaired in bvFTD than in phFTD (Hornberger et al 2008, Hornberger et al 2009), but dysexecutive syndrome at presentation does not seem a prognostic factor for shorter survival among bvFTD patients (Garcin et al 2009). Moreover, a subset of bvFTD patients does not manifest prominent executive dysfunction at presentation and may perform normally in executive tests (Castiglioni et al 2006, Hornberger et al 2008, Torralva et al 2009). Therefore, the absence of executive dysfunction in a patient with behavioral features of bvFTD should not be considered as a marker of non-progression.

Tests addressing social cognition skills, such as theory of mind, may provide distinction between groups (Kumfor et al 2014). However, more studies are warranted to define the predictive value of social cognition deficits in patients presenting with behavioral disorders mimicking bvFTD.

The overall preservation of cognitive functions such as episodic memory, executive functions and social cognition in phFTD is supported by the lack of frank neuroimaging abnormalities in these patients. By definition, phFTD patients do no exhibit clear frontotemporal involvement in brain imaging. However, a recent study reported functional connectivity changes and microstructural WM abnormalities in phFTD (Meijboom et al 2017). Compared to phFTD, patients with bvFTD had a similar topographical pattern of alterations, but abnormalities were more intense (Meijboom et al 2017). Patients with phFTD had mild increase in DMN connectivity, while bvFTD had lower increase in the same measure (Meijboom et al 2017). Microstructural WM changes in bvFTD were extensive, while limited to frontal tracts in phFTD (Meijboom et al 2017). The authors proposed that the increase of DMN connectivity would be a compensatory mechanism to early diminished neuronal functioning (Meijboom et al 2017). The authors suggest that these findings support the hypothesis that phFTD may belong to the same disease spectrum as bvFTD or even might speculate whether phFTD is a prodromal phase of bvFTD (Meijboom et al 2017). More studies are warranted to test this hypothesis.

One fundamental question is whether there is an underlying neurodegenerative process in phFTD. There are only four phFTD reports with *post mortem* neuropathological study. No FTLD pathology was found in two cases (Devenney et al 2016), while FTLD pathology was documented in two patients (Brodtmann et al 2013, Mattsson et al 2008).

The study of biological markers of neurodegeneration can shed some light into question whether phFTD belongs to FTD spectrum. However, to the best of our knowledge, there is no study phFTD patients with molecular neuroimaging markers such as flortaucipir, which has been used in FTD patients (Makaretz et al 2017, Spina et al 2017). There is only one study investigating CSF markers in phFTD patients (Mattsson et al 2008). In the next future, CSF biomarkers or molecular neuroimaging with pathophysiological markers may improve *in vivo* distinction between phFTD and bvFTD.

To further complicate the scenario, recent studies have reported slowly progressive bvFTD in carriers of *C9ORF72* expansion (Devenney et al 2015, Gomez-Tortosa et al 2014, Khan et al 2012, Llamas-Velasco et al 2018, Suhonen et al 2015). The *C9ORF72* mutation adds important implications to the diagnosis of phFTD. The presence of pathogenic mutation in bvFTD patients, regardless of neuroimaging findings, establishes the diagnosis of “definite” bvFTD (Rascovsky et al 2011). In the absence of genetic testing, phFTD patients with *C9orf72* expansion are classified as “possible” bvFTD. Indeed, one-half of *C9orf72* carriers initially met criteria for possible bvFTD in a large longitudinal series of patients (Devenney et al 2015). Thus, some patients with phenocopy syndrome may have a neurodegenerative pathology and a definite FTD diagnostic when a screening for the *C9orf72* is extended to them. We consider that genetic investigation for *C9orf72* should be considered in cases of suspected phFTD.

This issue becomes more complex with the finding of the *C9orf72* expansion in psychiatric disorders like late-onset psychosis, bipolar disorder, and depression (Meijboom et al 2017). Some authors argue that phFTD actually represent late-onset psychiatric disorders, including late onset schizophrenia and bipolar disorder, and/or autism spectrum disorders and personality traits decompensated in old age (Davies

et al 2006, Hornberger et al 2008, Hornberger et al 2009, Kipps et al 2007). Indeed, there is evidence of higher frequency of psychiatric or psychological syndromes in phFTD than in bvFTD (Gossink et al 2016). Interestingly, some authors hypothesized that there is higher frequency of depression among phFTD than in bvFTD because phFTD patients have greater insight and some emotional responding (Khan et al 2012). This hypothesis warrants confirmation. The predominance of men among phFTD patients led some authors (Devenney et al 2015, Devenney et al 2018, Hornberger et al 2010, Hornberger et al 2008, Hornberger et al 2009, Pennington et al 2011) to hypothesize the possibility of Asperger's disorder which is more frequent in male than in women. However, the clinical characteristics of autism spectrum disorder are evident from early childhood. Cluster C personality traits seem more frequent among phFTD patients compared to bvFTD group (Gossink et al 2016). It is controversial whether personality traits change in old age. Late-onset schizophrenia is more common in women and its course is characterized by psychotic symptoms with relative preservation of affect. The question whether phenocopy syndrome represents a primary psychiatric disorder or a slowly neurodegenerative process remains open, as it does not present classical features of bvFTD, neither does it fit a typical primary psychiatric disorder.

The caveats of the literature on phFTD must be pointed out. First, the studies are limited by the small number of patients. One critical point is that most studies came from few research centers, and it is possible that there is an overlap of patients across different studies from the same research group.

Another limitation is that the length of follow-up across studies was variable, with some studies including phFTD patients with a clinical follow-up as short as one year. It is therefore possible that a longer follow-up would detect patients with clinical progression or imaging changes. Most studies did not perform genetic investigation

for *C9orf72* expansion. The dearth of neuropathological data and studies addressing the neurobiological basis of phFTD must be noticed as well.

In conclusion, phFTD represents a clinical condition with the same behavioral features of typical bvFTD, but without brain atrophy on MRI and no functional decline. Whether these cases belong to the FTD spectrum is still controversial. The next advances on biomarkers and molecular neuroimaging may provide valuable markers for the diagnosis and follow-up of these patients, and may also clarify the pathophysiological pathways between phFTD and bvFTD, with possible clinical outcomes.

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References

Bang J, Spina S, Miller BL. 2015. Frontotemporal dementia. *Lancet* 386: 1672-82

Bertoux M, de Souza LC, Corlier F, Lamari F, Bottlaender M, et al. 2014. Two distinct amnesic profiles in behavioral variant frontotemporal dementia. *Biol Psychiatry* 75: 582-8

Bertoux M, Flanagan EC, Hobbs M, Ruiz-Tagle A, Delgado C, et al. 2018. Structural Anatomical Investigation of Long-Term Memory Deficit in Behavioral Frontotemporal Dementia. *J Alzheimers Dis* 62: 1887-900

Brodtmann A, Cowie T, McLean C, Darby D. 2013. Phenocopy or variant: a longitudinal study of very slowly progressive frontotemporal dementia. *BMJ case reports* 2013

Castiglioni S, Pelati O, Zuffi M, Somalvico F, Marino L, et al. 2006. The frontal assessment battery does not differentiate frontotemporal dementia from Alzheimer's disease. *Dement Geriatr Cogn Disord* 22: 125-31

Davies RR, Kipps CM, Mitchell J, Kril JJ, Halliday GM, Hodges JR. 2006. Progression in frontotemporal dementia: identifying a benign behavioral variant by magnetic resonance imaging. *Arch Neurol* 63: 1627-31

Devenney E, Bartley L, Hoon C, O'Callaghan C, Kumfor F, et al. 2015. Progression in Behavioral Variant Frontotemporal Dementia: A Longitudinal Study. *JAMA neurology* 72: 1501-9

Devenney E, Forrest SL, Xuereb J, Kril JJ, Hodges JR. 2016. The bvFTD phenocopy syndrome: a clinicopathological report. *J Neurol Neurosurg Psychiatry* 87: 1155-6

Devenney E, Swinn T, Mioshi E, Hornberger M, Dawson KE, et al. 2018. The behavioural variant frontotemporal dementia phenocopy syndrome is a distinct entity - evidence from a longitudinal study. *BMC Neurol*18: 56

Dols A, Krudop W, Moller C, Shulman K, Sajatovic M, Pijnenburg YA. 2016. Late life bipolar disorder evolving into frontotemporal dementia mimic. *Neuropsychiatr Dis Treat* 12: 2207-12

Fernandez-Matarrubia M, Matias-Guiu JA, Cabrera-Martin MN, Moreno-Ramos T, Valles-Salgado M, et al. 2017. Episodic Memory Dysfunction in Behavioral Variant Frontotemporal Dementia: A Clinical And FDG-PET Study. *J Alzheimers Dis* 57: 1251-64

Garcin B, Lillo P, Hornberger M, Piguet O, Dawson K, et al. 2009. Determinants of survival in behavioral variant frontotemporal dementia. *Neurology* 73: 1656-61

Gomez-Tortosa E, Serrano S, de Toledo M, Perez-Perez J, Sainz MJ. 2014. Familial benign frontotemporal deterioration with C9ORF72 hexanucleotide expansion. *Alzheimers Dement* 10: S284-9

Gossink FT, Dols A, Kerssens CJ, Krudop WA, Kerklaan BJ, et al. 2016. Psychiatric diagnoses underlying the phenocopy syndrome of behavioural variant frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 87: 64-8

Hensman Moss DJ, Poulter M, Beck J, Hehir J, Polke JM, et al. 2014. C9orf72 expansions are the most common genetic cause of Huntington disease phenocopies. *Neurology* 82: 292-9

Hornberger M, Piguet O. 2012. Episodic memory in frontotemporal dementia: a critical review. *Brain* 135: 678-92

Hornberger M, Piguet O, Graham AJ, Nestor PJ, Hodges JR. 2010. How preserved is episodic memory in behavioral variant frontotemporal dementia? *Neurology* 74: 472-9

Hornberger M, Piguet O, Kipps C, Hodges JR. 2008. Executive function in progressive and nonprogressive behavioral variant frontotemporal dementia. *Neurology* 71: 1481-8

Hornberger M, Shelley BP, Kipps CM, Piguet O, Hodges JR. 2009. Can progressive and non-progressive behavioural variant frontotemporal dementia be distinguished at presentation? *J Neurol Neurosurg Psychiatry*80: 591-3

Hornberger M, Wong S, Tan R, Irish M, Piguet O, et al. 2012. In vivo and post-mortem memory circuit integrity in frontotemporal dementia and Alzheimer's disease. *Brain* 135: 3015-25

Irish M, Graham A, Graham KS, Hodges JR, Hornberger M. 2012. Differential impairment of source memory in progressive versus non-progressive behavioral variant frontotemporal dementia. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists* 27: 338-47

Kerklaan BJ, van Berckel BN, Herholz K, Dols A, van der Flier WM, et al. 2014. The added value of 18-fluorodeoxyglucose-positron emission tomography in the diagnosis of the behavioral variant of frontotemporal dementia. *Am J Alzheimers Dis Other Demen* 29: 607-13

Khan BK, Yokoyama JS, Takada LT, Sha SJ, Rutherford NJ, et al. 2012. Atypical, slowly progressive behavioural variant frontotemporal dementia associated with C9ORF72 hexanucleotide expansion. *J Neurol Neurosurg Psychiatry* 83: 358-64

Kipps CM, Hodges JR, Fryer TD, Nestor PJ. 2009. Combined magnetic resonance imaging and positron emission tomography brain imaging in behavioural variant frontotemporal degeneration: refining the clinical phenotype. *Brain* 132: 2566-78

Kipps CM, Hodges JR, Hornberger M. 2010. Nonprogressive behavioural frontotemporal dementia: recent developments and clinical implications of the 'bvFTD phenocopy syndrome'. *Curr Opin Neurol* 23: 628-32

Kipps CM, Nestor PJ, Fryer TD, Hodges JR. 2007. Behavioural variant frontotemporal dementia: not all it seems? *Neurocase* 13: 237-47

Kumfor F, Irish M, Leyton C, Miller L, Lah S, et al. 2014. Tracking the progression of social cognition in neurodegenerative disorders. *J Neurol Neurosurg Psychiatry* 85: 1076-83

Lee SE, Khazenzon AM, Trujillo AJ, Guo CC, Yokoyama JS, et al. 2014. Altered network connectivity in frontotemporal dementia with C9orf72 hexanucleotide repeat expansion. *Brain* 137: 3047-60

Llamas-Velasco S, Garcia-Redondo A, Herrero-San Martin A, Puertas Martin V, Gonzalez-Sanchez M, et al. 2018. Slowly progressive behavioral frontotemporal dementia with C9orf72 mutation. Case report and review of the literature. *Neurocase* 24: 68-71

Makaretz SJ, Quimby M, Collins J, Makris N, McGinnis S, et al. 2017. Flortaucipir tau PET imaging in semantic variant primary progressive aphasia. *J Neurol Neurosurg Psychiatry*

Mattsson N, Ruetschi U, Pijnenburg YA, Blankenstein MA, Podust VN, et al. 2008. Novel cerebrospinal fluid biomarkers of axonal degeneration in frontotemporal dementia. *Molecular medicine reports* 1: 757-61

Meijboom R, Steketee RM, de Koning I, Osse RJ, Jiskoot LC, et al. 2017. Functional connectivity and microstructural white matter changes in phenocopy frontotemporal dementia. *Eur Radiol* 27: 1352-60

Mioshi E, Hodges JR. 2009. Rate of change of functional abilities in frontotemporal dementia. *Dement Geriatr Cogn Disord* 28: 419-26

Mioshi E, Kipps CM, Hodges JR. 2009. Activities of daily living in behavioral variant frontotemporal dementia: differences in caregiver and performance-based assessments. *Alzheimer Dis Assoc Disord* 23: 70-6

Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine* 6: e1000097

Nunnemann S, Last D, Schuster T, Forstl H, Kurz A, Diehl-Schmid J. 2011. Survival in a German population with frontotemporal lobar degeneration. *Neuroepidemiology* 37: 160-5

Pennington C, Hodges JR, Hornberger M. 2011. Neural correlates of episodic memory in behavioral variant frontotemporal dementia. *J Alzheimers Dis* 24: 261-8

Poletti M, Borelli P, Bonuccelli U. 2011. The neuropsychological correlates of pathological lying: evidence from behavioral variant frontotemporal dementia. *J Neurol* 258: 2009-13

Poos JM, Jiskoot LC, Papma JM, van Swieten JC, van den Berg E. 2018. Meta-analytic Review of Memory Impairment in Behavioral Variant Frontotemporal Dementia. *Journal of the International Neuropsychological Society : JINS* 24: 593-605

Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, et al. 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 134: 2456-77

Spina S, Schonhaut DR, Boeve BF, Seeley WW, Ossenkoppele R, et al. 2017. Frontotemporal dementia with the V337M MAPT mutation: Tau-PET and pathology correlations. *Neurology* 88: 758-66

Steketee RM, Meijboom R, Bron EE, Osse RJ, de Koning I, et al. 2016. Structural and functional brain abnormalities place phenocopy frontotemporal dementia (FTD) in the FTD spectrum. *NeuroImage. Clinical* 11: 595-605

Suhonen NM, Kaivorinne AL, Moilanen V, Bode M, Takalo R, et al. 2015. Slowly progressive frontotemporal lobar degeneration caused by the C9ORF72 repeat expansion: a 20-year follow-up study. *Neurocase* 21: 85-9

Takada LT. 2015. The Genetics of Monogenic Frontotemporal Dementia. *Dement Neuropsychol* September 9: 219-29

Torralva T, Roca M, Gleichgerrcht E, Bekinschtein T, Manes F. 2009. A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia. *Brain* 132: 1299-309

Wood R, Moodley K, Hodges JR, Allinson K, Spillantini MG, Chan D. 2016. Slowly progressive behavioural presentation in two UK cases with the R406W MAPT mutation. *Neuropathol Appl Neurobiol* 42: 291-5

Table 1. Synthesis of articles included in the present review

Table 1. Synthesis of articles included in the systematic review

Title	Authors	Journal	Year	Population	Methods	Results
Progression in Frontotemporal Dementia: identifying a benign behavioral variant by magnetic resonance imaging	Davies et al.	Arch Neurol	2006	n= 31 patients with bvFTD	Brain MRI Clinical, cognitive (ACE) and behavioral measures	Patients with normal or borderline MRI (n=15) showed significantly longer survival to institutionalization or death than those (n=16) with definite frontotemporal atrophy.
Behavioural variant Frontotemporal Dementia: Not all it seems?	Kipps et al.	Neurocase	2007	n= 2 patients with bvFTD;	Case report with clinical, neuropsychological and neuroimaging (MRI and PET-FDG) follow-up (5 years)	Case 1 had clinical decline over 10 years from symptom onset, progressive atrophy and frontotemporal hypometabolism. Case 2 did not develop atrophy or hypometabolism and remained clinically stable, a decade from symptom onset.
Novel cerebrospinal fluid biomarkers of axonal degeneration in frontotemporal dementia	Mattsson et al.	Molecular Medicine Reports	2008	n=24 FTD patients (13 with rapidly progressive FTD and 11 patients with slowly progressive FTD and normal brain MRI.	Mass spectrometry for analysis of peptide profiles in the CSF	Peptides profiles in the (CSF) differed between patients with rapidly progressive FTD and slowly progressive FTD
Executive function in progressive and nonprogressive behavioral variant frontotemporal dementia	Hornberger et al.	Neurology	2008	n=90 (27 bvFTD progressors, 23 bvFTD nonprogressors, 40 controls).	Neuropsychological and behavioral tests.	The nonprogressors performed in the normal range on executive tasks, Progressors were impaired on Digit Span Backward, Hayling Test, Letter Fluency, and Trails B. A subgroup of progressors had normal executive functioning.
Can progressive and non-progressive behavioural variant frontotemporal dementia be distinguished at presentation?	Hornberger et al.	J Neurol Neurosurg Psychiatry	2009	n= 71 patients with bvFTD: 45 progressive and 26 non-progressive cases	Neurological, behavioural (CBI) and neuropsychological evaluation	Progressors had worse performance on the ACE-R, worse functional profile and higher frequency of distractibility, and stereotypic speech.
Combined magnetic resonance imaging and positron emission tomography brain imaging in behavioural variant frontotemporal degeneration: refining the clinical phenotype	Kipps et al.	Brain	2009	24 bvFTD patients (abnormal MRI = 15; normal MRI = 9);12controls.	Cognitive and behavioral measures (MMSE, ACE, CDR, CBI); MRI and FDG-PET;	bvFTD with abnormal MRI showed definite frontotemporal hypometabolism on FDG-PET. Most bvFTD patients with normal MRI had no hypometabolism. Almost a third of bvFTD with abnormal MRI had ACE-R scores overlapping with the normal MRI subgroup.
Determinants of survival in behavioral variant frontotemporal dementia	Garcin et al.	Neurology	2009	n= 91 patients diagnosed with bvFTD: “pathologic” bvFTD (n=67) and phenocopy cases (n=24). Nonprogression was defined as a lack of progression on the ACE and ADLs over a period of 3 years follow-up and normal MRI at presentation.	Retrospective review of medical records, including neurological and psychiatric assessments, cognitive and behavioral measures (CBI, MMSE and ACE) and neuroimaging (MRI) data.	Phenocopy cases were younger and had longer survival than “pathologic” FTD

Continue

Activities of daily living in behavioral variant frontotemporal dementia: differences in caregiver and performance-based assessments	Mioshi et al.	Alzheimer Dis AssocDisord	2009	n= 18bvFTD patients: phenocopy (n =10); pathologic bvFTD(n =8). Phenocopy was considered as a subgroup without evidence of atrophy on MRI at presentation and with no progression over at least 2 years of follow-up. .	Behavioral and neuropsychological tests; functional scales of daily living (DAD and AMPS)	PhFTD and pathologic bvFTD did not differ on the DAD, but differed at AMPS (qualitive rating).
Rate of Change of Functional Abilities in Frontotemporal Dementia	Mioshi et al.	Dement Geriatr Cogn Disord	2009	n= 26 (bvFTD = 5; phFTD=10; SemDem = 8; PNFA = 3).	Behavioral and neuropsychological tests (initiation, planning and execution scores); functional scales of daily living (DAD)	Only phFTD did not show significant functional decline after 12 months. On average, the phFTD group lost 5 points on their DAD score and the bvFTD pathological lost 27 points annually. The decline in ADL and cognitive scores were significantly correlated.
How preserved is episodic memory in behavioral variant frontotemporal dementia?	Hornberg et al.	Neurology	2010	n= 62 bvFTD patients: progressors (n =39); phenocopies (n =23); AD (n =64);healthy controls (n =64).	Multidisciplinary assessment with behavioral (CBI) and neuropsychological tests (RAVLT)	The degree of episodic memory impairment in true bvFTD was similar to AD. PhFTD patients performed significantly better than progressors and AD patients.
Survival in a German Population with Frontotemporal Lobar Degeneration	Nunnemann et al.	Neuroepidemiology	2011	n=124 FTLD patients	Clinical data	Phenocopy cases were not identified in this sample.
Neural Correlates of Episodic Memory in Behavioral Variant Frontotemporal Dementia	Pennington et al.	Journal of Alzheimer's Disease	2011	n= 59 subjects in total (14 bvFTD, 6 phFTD, 14 AD and 15 healthy controls.	Cognitive assessment and MRI scanning with ratings of regional brain atrophy;	BvFTD and AD patients were similarly impaired on memory scores. PhFTD group did not differ to controls on memory scores and atrophy ratings.
The neuropsychological correlates of pathological lying: evidence from behavioral variant frontotemporal dementia	Poletti et al.	J Neurol	2011	n = 1	Case report. Neurological, neuropsychiatric, neuropsychological and neuroimaging exam.	Pathological lying was observed in a patient 57-year-old, with suggestive bvFTD and lack of prefrontal hypometabolism.
Atypical, slowly progressive behavioural variant frontotemporal dementia associated with C9ORF72 hexanucleotide expansion	Khan et al	J Neurol Neurosurg Psychiatry	2012	n= 384 patients with FTD and AD. Of the 384 patients, 87 had bvFTD (23 of them with *C9orf72* mutation). Four patients (2 C9+, 2 C9-) were identified as slowly progressive course (bvFTD-SP) and were selected.	Neuropsychological and functional tests; *C9ORF72* screening; Structural MRI/ voxel based-morphometry (VBM) analysis. The 2 C9+bvFTD-SP were compared between 44 C9-bvFTD and 85 controls.	Both C9+ bvFTD-SP patients initially met the criteria for possible bvFTD with imaging uncharacteristic of bvFTD and remained stable on neuropsychological and functional performance during the follow-up. VBM revealed thalamic and posterior insular atrophy in patient 1 and cortical atrophy with subtle frontal and insular volume loss in patient 2

Differential Impairment of Source Memory in progressive Versus Non-progressive behavioral Variant Frontotemporal Dementia	Irish et al.	Archives of Clinical Neuropsychology	2012	7 patients with progressive bvFTD; 12 non-progressive bvFTD; 16 controls.	Cognitive tests including a source monitoring Task.	Progressive patients had more severe impairment of temporal source memory than non-progressive patients.
Phenocopy or variant: a longitudinal study of very slowly progressive frontotemporal dementia	Brodtman et al	BMJ Case Rep	2013	n=2	Case report of a patient and his father with very slowly progressive cognitive decline and personality change. Neuropsychological tests, MRI and PET were performed on patient. Genetic testing in both. Histopathological examination of the patient's father.	PET and MRI scans were unchanged over 15 years in the patient. Neuropsychological assessments revealed no cognitive deterioration. Histopathology of his father demonstrated early stage frontotemporal lobar degeneration with ubiquitin.
Tracking the progression of social cognition in neurodegenerative disorders	Kumfor et al.	J. Neurol Neurosurg Psychiatry	2014	n=37. 20 bvFTD (8 with limited brain atrophy-la and 12 with marked atrophy-ma), 17 AD patients and 24 healthy controls	Behavioral and neuropsychological tests, including social cognition tests (Ekman 60 and TASIT).	BvFTD with and without brain atrophy were impaired on the general cognition and emotion recognition tasks. On the sarcasm detection task only the bvFTD-ma group was impaired. On the emotion recognition and sarcasm tasks, the bvFTD-ma group declined more rapidly than bvFTD-la and AD patients. BvFTD-la group remained stable over time on the emotion recognition and sarcasm measures.
Two Distinct Amnesic Profiles in Behavioral variant Frontotemporal Dementia	Bertoux et al.	Biol Psychiatry	2014	n=134 (56 AD, 44 bvFTD, 12 phFTD and 22 healthy controls).	Neuropsychological assessment with the Free and Cued Selective Reminding Test (FCSRT).	A subgroup of bvFTD had low memory performance, similar to AD. Phenocopies and non-amnestic FTD performed similar to controls on the FCSRT.
The Added Value of 18-Fluorodeoxyglucose-Positron Emission Tomography in the Diagnosis of the Behavioral variant of Frontotemporal Dementia	Kerklaan et al.	American Journal of Alzheimer's Disease & other Dementias	2014	n= 52 patients with suspected bvFTD but lacking characteristic structural neuroimaging results.	Neuropsychological and behavioral assessment, MRI or CT, 18-FDG-PET The diagnosis of bvFTD was based on clinical diagnostic criteria in the presence of functional decline after at least 2 years of follow-up. Patients with funcional decline (bvFTD/fd+) were compared with patients without functional decline (bvFTD/fd-).	15 cases fulfilled diagnosis of bvFTD/fd+ and eight cases fulfilled criteria for bvFTD/fd-. The sensitivity of FDG-PET for bvFTD/fd+ was 47% at a specificity of 92%. The 18F-FDG-PET was abnormal in only 1 of the 8 cases of phenocopy group (bvFTD/fd-).

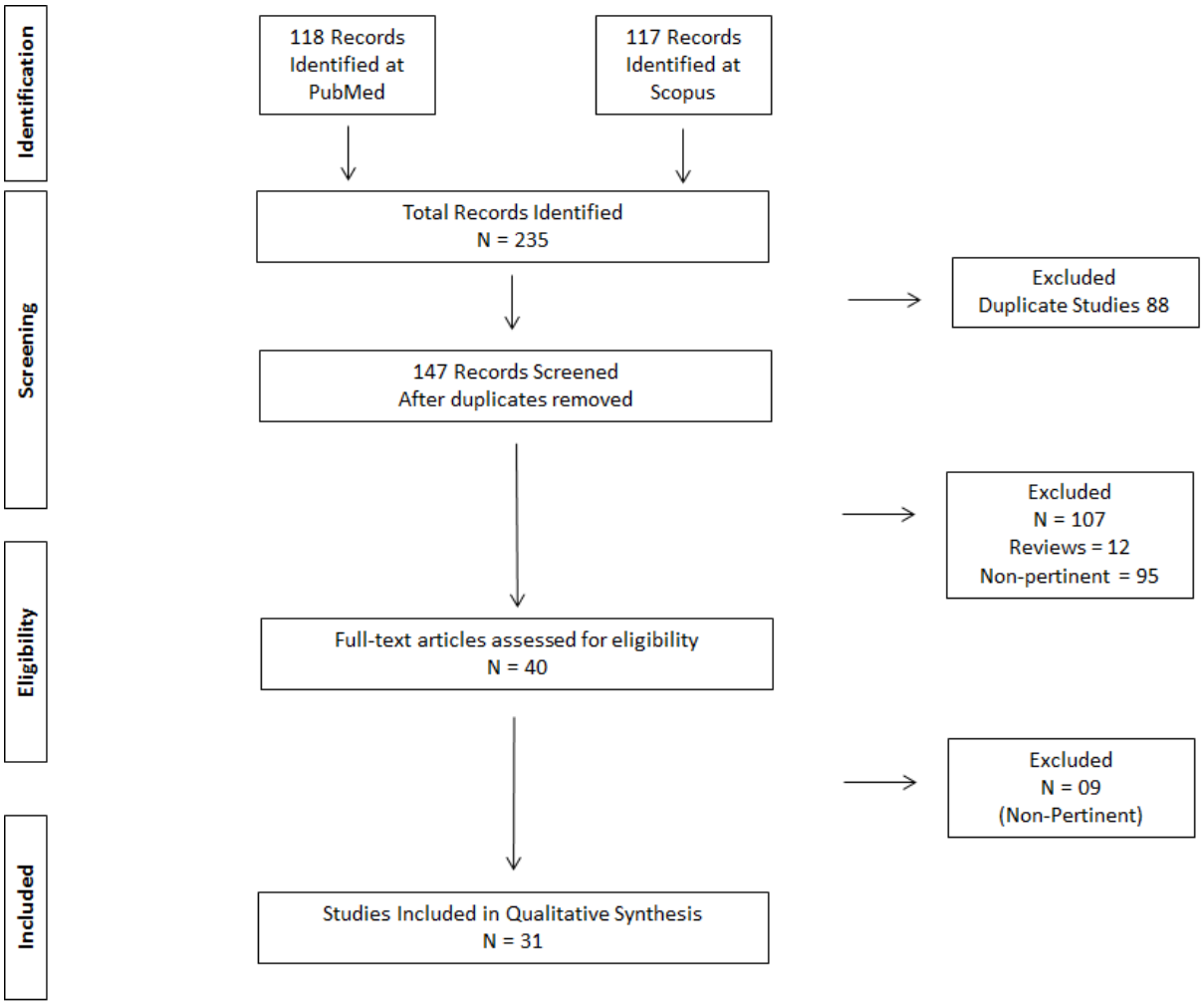
Familial benign frontotemporal deterioration with C9ORF72 hexanucleotide expansion	Gomés-Tortoza et al.	Alzheimer's & Dementia	2014	n=3 patients of the same family with benign FTLD associated with *C9ORF72* gene hexanucleotide expansion	Case report of three patients from the affected family	Two siblings had cognitive complaints, preserved ADLs, mild-moderate atrophy on MRI and evolved to slow progression of deficits over more than ten years. Their mother had mild cognitive impairment and slowly progressive dementia over a time frame of>30 years.
Altered network connectivity in frontotemporal dementia with C9ORF72 hexanucleotide repeat expansion	Lee et al.	Brain	2014	n=28 patients with bvFTD (14 *C9ORF72* mutation carriers and 14 non carriers) and 14 healthy controls.	Neuropsychological exam and task-free functional MRI	*C9ORF72* (-) bvFTD patients had increased default mode network connectivity compared to controls and mutation carriers. *C9ORF72* (+)bvFTD patients with early stage or slowly progressive symptoms (n=4) had salience network disruption and default mode network enhancement.
Slowly progressive frontotemporal lobar degeneration caused by the *C9ORF72* repeat expansion: a 20-year follow-up study	Suhonen et al.	Neurocase	2015	n=1 patient with slowly progressive FTD.	Neuropsychological examination; MRI, FDG-PET.	52 year-old man with semantic variant PPA associated with *C9ORF72* repeat expansion. Structural MRI revealed mild frontal atrophy whereas FDG-PET showed significantly reduced glucose metabolism in the temporal and frontal lobes. The disease did not progress to dementia during over 20 years from the onset.
Progression in Behavioral Variant Frontotemporal Dementia: A Longitudinal Study	Devenney et al.	JAMA Neurology	2015	n= 58 patients with bvFTD.	The prognostic value of clinical, genetic, neuropsychological, and neuroimaging parameters was analyzed.	A family history of dementia, episodic memory deficits, and clinical findings (e.g., parkinsonism, frontal release signs) were key features of progression. Most of progressors (n=8 out 11) were *C9orf72* carriers.
Structural and functional brain abnormalities place phenocopy frontotemporal dementia (FTD) in the FTD spectrum	Steketee et al.	NeuroImage: Clinical	2016	n= 7 FTD phenocopy patients n= 11 bvFTD patients n= 20 controls The criteria for phFTD was no imaging findings consistent with bvFTD, and no progression for at least one year after initial diagnostic.	Neuropsychological and functional examination; genetic screening for *C9ORF72,* brain MRI (volumetric and perfusion analyses).	None of the phFTD patients had a *C9ORF72* mutation. Gray matter volume did not differ between phFTD and controls, whereas bvFTD showed extensive frontotemporal atrophy. Compared to FTD, phFTD had increased perfusion in the left prefrontal cortex.
Psychiatric diagnoses underlying the phenocopy syndrome of behavioural variant frontotemporal dementia	Gossink et al.	J NeurolNeurosurg Psychiatry	2016	n= 52; phenocopy syndrome (n=33); probable bvFTD (n=19). Phenocopy cases were considered as possible bvFTD, with normal MRI and PET scans, without functional decline the course of their disease of at least one year.	Retrospective chart review; Neurological and psychiatric evaluation.	In the phenocopy group, 85.2% of patients had psychiatric or psychological conditions (cluster C personality traits) were more frequent in the phenocopy group (85.2%) than in the bvFTD group 47.4%.

Slowly progressive behavioural presentation in two UK cases with the R406W MAPT mutation	Wood et al.	Neuropathology and Applied Neurobiology	2016	n=2	Clinical follow-up; Neuropsychological testing; brain MRI;	Both patients presented a slowly progressive bvFTD associated with predominantly right temporal lobe atrophy, with the *R406W MAPT* mutation.
The bvFTD phenocopy syndrome: a clinicopathological report	Devenney et al.	J NeurolNeurosurPsychhiatry	2016	n= 2	Report of clinical and pathological findings in two phenocopy cases.	The 2 cases showed behavioral changes consistent with bvFTD. They did not show brain atrophy or hypometabolism on neuroimaging. Both patients did not have FTLD at *post-mortem* pathological exam.
Late life bipolar disorder evolving into frontotemporal dementia mimic	Dols et al.	Neuropsychiatric Disease and Treatment	2016	n= 4	Psychiatric, neurological, and neuropsychological examination; MRI.	All cases had early and late-onset bipolar disorder who subsequently developed gradually progressive behavioral and social-emotional changes. All cases fulfilled criteria for possible bvFTD. After 3 to 7 years of follow-up,there was no progression to “probable” bvFTD.
Functional connectivity and microstructural white matter changes in phenocopy frontotemporal dementia	Meijboom et al.	Eur Radiol	2016	n= 36 patients: 7 phenocopies, 12 bvFTD and 17 controls.	Neuropsychological assessment; functional MRI; and DTI. DMN connectivity and WM measures were compared between groups.	PhFTD showed subtly increased DMN connectivity and subtle microstructural changes in frontal WM tracts. BvFTD showed abnormalities in similar regions as phFTD, but had lower increased DMN connectivity and more extensive microstructural WM changes.
Slowly progressive behavioral frontotemporal dementia with *C9orf72* mutation. Case report and review of the literature	Llamas-Velasco et al.	Neurocase	2018	n=1 patient	Case report of one patient with personality changes and functional decline over more of 30 years.	The patient met diagnostic criteria for possible bvFTD and had slow progression. He carried *C9orf72* hexanucleotide expansion.
The behavioural variant frontotemporal dementia phenocopy syndrome is a distinct entity – evidence from a longitudinal study	Devenney et al.	BMC Neurology	2018	Phenocopy bvFTD (n =16) Probable bvFTD (n = 27)	Behavioral (CBI) and neuropsychological tests. Genetic screening for the *C9orf72.* Long-term follow-up were available in six phFTD cases.	Only one of 16 phFTD cases (6.25%) had the *C9orf72* expansion. There was no functional decline over 13 to 21 years of follow-up.

Table 2: Comparison of behavioral variant frontotemporal dementia (bvFTD) and phenocopy syndrome of FTD (phFTD)

	bvFTD	phFTD
Sex	No sex predominance	Male predominance
Family history for dementia	Generally present	Rare
Behavioral symptoms	Frontal behavior	Frontal behavior
Global cognitive efficiency	Mild to severe impairment	Generally preserved
Executive function	Moderate to severe impairment	Normal to mild impairment
Episodic memory	Moderate to severe impairment	Normal
Activities of daily living	Moderate to severe impairment	No impairment
MRI	Frontotemporal atrophy	Normal to borderline
FDG-PET	Frontotemporal hypoperfusion	Usually normal

Figure 1: PRISMA flow diagram for studies of phenocopy syndrome of frontotemporal dementia.



4. CONCLUSÃO

Há evidências de que os pacientes denominados “fenocópias” apresentam quadro clínico similar àqueles diagnosticados com demência frontotemporal variante comportamental, porém com uma evolução mais benigna que o usual, com uma média de sobrevida maior e ausência de declínio funcional, além de ausência de atrofia frontotemporal na RNM.

O substrato etiopatológico da fDFT é desconhecido. Ainda permanece controverso na literatura se o grupo fenocópia pertenceria ao espectro da DFT ou se integraria os transtornos psiquiátricos. A ausência de alterações anátomo-patológicas compatíveis com DLFT em dois dos somente quatro pacientes com diagnóstico de fDFT, com exame *post-mortem*, reforça a hipótese da fenocópia ser uma entidade distinta das doenças não degenerativas. Por outro lado, relato de seis casos portadores da mutação em *C9orf72*, cuja média de evolução da doença foi até 20 anos, reforça o quão heterogênea pode ser a apresentação da DFT. Outros estudos utilizando técnicas de neuroimagem funcional, que mostraram alterações microestruturais em substância branca em tratos frontais que se sobrepõem à DFT, sugerem que o grupo com fenocópia faça parte do espectro da DFT.

Deve-se ter cuidado quanto às orientações de prognóstico em pacientes com DFT. Casos com RNM normal, história familiar de doença degenerativa ou de mutação genética, sugere-se, se possível estudo genético. Maiores avanços em biomarcadores e em técnicas de imagem molecular talvez possam fornecer marcadores para o diagnóstico e acompanhamento dos pacientes com DFT ou mesmo esclarecer os mecanismos fisiopatológicos da fDFT.

REFERÊNCIAS

1. GARCIN, B. et al. Determinants of survival in behavioral variant frontotemporal dementia. Neurology, v.73, p. 1656-1661, 2009.

2. FINGER, E. C. Frontotemporal Dementias. CONTINUUM: Lifelong Learning in Neurology, v. 22, n. 2, p.454-489, apr, 2016.

3. HODGES, J.R.; DAVIES R..; XUEREB J.; KRIL J.; HALLIDAY G Survival in frontotemporal dementia. Neurology, v. 61, p. 349-354, 2003.

4. KIPPS, C. M.; NESTOR, P. J.; FRYER, T. D.; HODGES, J. R. Behavioural variant Frontotemporal Dementia: Not all it seems? Neurocase, v. 13, p. 237-247, 2007.

5. PARMERA, J. C.; NITRINI, R. Demências: da investigação ao diagnóstico. Rev. Med, São Paulo, v. 94, n.3, p. 179-84, jul-set, 2015.

6. PIGUET, O..; HODGES, J. R. Behavioural variant frontotemporal dementia: An update. Dement Neuropsychol, v.7, p. 9-11, march, 2013.

7. PRESSMAN, P. S.; MILLER, B. L. Diagnosis and Management of Behavioral Variant Frontotemporal Dementia. Biol Psychiatry, v. 75, p. 574-581, 2014.

8. RASCOVSKY, K.; HODGES, J. R.; KNOPMAN, D.;MENDEZ, M.F.; KRAMER, J. H. et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain, 134 (pt 9), p 2456-77, sep 2011.

9. TAKADA, L. T. The Genetics of Monogenic Frontotemporal Dementia. Dement Neuropsychol, v. 9, n. 3, p.219-229, jul-sep, 2015.