European Journal of Pharmacology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Full length article

Clinical and biological phenotypes of frontotemporal dementia: Perspectives for disease modifying therapies

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ARTICLE INFO

Keywords:
FTD
Therapy
Frontotemporal

ABSTRACT

Frontotemporal Dementia (FTD) is a progressive neurodegenerative condition which encompasses a group of clinically, neuropathologically and genetically heterogeneous disorders characterized by selective involvement of the frontal and temporal lobes. FTD is characterized by changes in behaviour and personality, frontal executive deficits and language dysfunction. Different phenotypes have been defined on the basis of presenting clinical symptoms, behavioural variants of FTD (bvFTD) and primary progressive aphasia (PPA), which includes nonfluent/agrammatic variant PPA (avPPA) and semantic variant PPA (svPPA). These presentations can overlap with atypical parkinsonian disorders (i.e., corticobasal syndrome, progressive supranuclear palsy) and amyotrophic lateral sclerosis. Each syndrome can be associated with one or more neuropathological hallmark, and in some cases it may be due to autosomal inherited disorder caused by mutations in a number of genes.

Currently, there is no specific treatment available to prevent disease progression. FTD treatment is based on symptomatic management, and most therapies lack quality evidence from randomized, placebo-controlled clinical trials. Recent advances in the understanding of FTD pathophysiology and genetics have led to the development of potentially disease-modifying therapies.

In this review, we discussed current knowledge and recommendations with regards to symptomatic and disease-modifying therapies.

1. Introduction

Since the first description of circumscribed cerebral cortical atrophy, published by Arnold Pick in 1892, our knowledge of Frontotemporal Dementia (FTD) has received a great boost.

From 1911, with the identification of argyrophilic globular neuronal cytoplasmic inclusions named Pick's bodies, this group of heterogeneous conditions was labelled “Pick's Disease” (PiD).

However, the clinical and neuropathological heterogeneity of cases with frontotemporal lobar atrophy led Constantinidis and colleagues to remark on the presence of cases with Pick's bodies and swollen, achromatic cells (group A), cases with only swollen, achromatic cells (group B), and cases with neither Pick's Bodies nor swollen neurons (group C) (Constantinidis et al., 1974).

The subsequent works by Brun in the late eighties (Brun, 1987) and Mann in the early nineties (Mann et al., 1993), which underlined the high frequency of non-specific neuropathological changes in these cases, led to the coining of the term “dementia lacking distinctive histological features” (DLDH) (Knopman et al., 1990).

It was in the nineties that researchers made the most important discoveries in this field. In 1990, Okamoto described the presence of ubiquitin-positive intraneuronal inclusions in the cortex of patients with amyotrophic lateral sclerosis (ALS) (Okamoto et al., 1991). This evidence was rapidly followed by similar findings in the cortex of patients with ALS plus dementia (Wightman et al., 1992) and FTD (Tolnay and Probst, 1995). These cases, neuropathologically defined FTLD-U, accounted for a large part of the previously defined DLDH.

The nineties also led to the identification of Tau aggregates in Pick's Disease, Corticobasal Degeneration (CBD) and Progressive Supranuclear Palsy (PSP) (Delacourte et al., 1996; Sergeant et al., 1999). Only in the last ten years has the neurobiology of FTD been characterized appropriately. In 2006, Neumann and colleagues discovered that ubiquitin-positive inclusions (both in ALS and FTD cases) consisted of TDP-43 aggregates (Neumann et al., 2006).

This historical introduction shows how complex FTD is. So far, neuropathological criteria recognise two main pictures, namely FTD-Tau, FTD-TDP43, covering most cases (Cairns et al., 2007). At autopsy, some cases lack both Tau and TDP43 inclusions, being rarer forms of the disease.

Until now, FTD has been overshadowed by disease-modifying trials

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http://dx.doi.org/10.1016/j.ejphar.2017.05.056
Received 18 October 2016; Received in revised form 28 March 2017; Accepted 30 May 2017
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Please cite this article as: Gazzina, S., European Journal of Pharmacology (2017), http://dx.doi.org/10.1016/j.ejphar.2017.05.056

for Alzheimer's Disease (AD), but expanding knowledge and the strong genetic influence in this condition could lead to better patients' selection and to pharmacological trials in prodromal or presymptomatic phases.

After giving a clinical and pathogenic background, this review will address current recommendations and advances in symptomatic and disease-modifying therapy.

2. Clinical phenotypes

The term FTD encompasses a group of clinically and pathologically heterogeneous disorders (Armstrong et al., 2013; Gorno-Tempini et al., 2011; Litvan et al., 1996; Neary et al., 1998; Strong et al., 2009) (Rascovsky et al., 2011) characterized by relatively selective atrophy of the frontal and temporal lobes (Cairns et al., 2007).

It represents the second most common dementing disorder in individuals younger than 65 years, and accounts for 5–15% of all cases of dementia. The estimated prevalence is 15–22 per 100,000 and population studies indicate an equal gender distribution (Hogan et al., 2016; Onyike and Diehl-Schmid, 2013). FTD is a highly heritable disorder with approximately 30–50% of cases reporting a positive family history (Rohrer et al., 2009a) and about 10–20% showing a clear autosomal-dominant inheritance (Rohrer et al., 2015).

Current clinical criteria identify different phenotypes on the basis of presenting clinical symptoms: a behavioural-dysexecutive disorder, i.e. behavioural variant of FTD (bvFTD) (Rascovsky et al., 2011) and the language variants, i.e. the nonfluent/agrammatic variant of primary progressive aphasia (avPPA) and the semantic variant of PPA (svPPA) (Gorno-Tempini et al., 2011; Mesulam, 1982).

Finally, FTD can overlap with atypical parkinsonian disorders, such as progressive supranuclear palsy (PSP) (Litvan et al., 1996), corticobasal syndrome (CBS) (Armstrong et al., 2013) and with motor neuron disease/amyotrophic lateral sclerosis (FTD–MND/ALS) (Strong et al., 2009). BvFTD manifests itself in progressive decline in social skills, difficulties with planning and higher level thinking due to executive dysfunction and progressive changes in personality, lack of insight, disinhibition, apathy, binge eating, obsessive-compulsive behaviours, yet with relative preservation of other cognitive areas such as episodic memory and visuospatial function in the early stages (Rascovsky et al., 2011). These cognitive and behavioural changes are due to the atrophy of the frontal and anterior temporal regions as well as the anterior cingulate, anterior insula, and anterior temporal and parietal regions (Rohrer et al., 2009b). The most recent diagnostic criteria for bvFTD (Rascovsky et al., 2011) have 85–95% sensitivity and 82% specificity for a diagnosis of possible bvFTD, and 75–85% sensitivity and 95% specificity for probable bvFTD (Harris et al., 2013; Rascovsky et al., 2011).

The PPAs are characterized by isolated language deficits during the initial stage, with an insidious onset (Gorno-Tempini et al., 2011). Patients with avPPA have non-fluent speech, with the two core features being agrammatism and speech apraxia (Gorno-Tempini et al., 2011). Agrammatism presents with short, simple sentences, with changes in the morphology of nouns and verbs, word order, and phrase structure (Mesulam, 2003; Rohrer et al., 2008). Speech apraxia impairs the patient's ability to program and plan the motor aspects of speech production properly, leading to slow speaking rate, abnormal prosody and distorted sound substitutions, additions, repetitions and prolongations, sometimes accompanied by groping and trial and error articulatory movements (Josephs et al., 2006). The classical neuroimaging feature is atrophy of the left posterior (and inferior) frontal lobe and left superior temporal lobe with associated insular atrophy (Rohrer et al., 2009b). Conversely, in svPPA, spontaneous speech is fluent whilst anomia and impaired single word comprehension are the core features (Gorno-Tempini et al., 2011). Poor understanding of single words is frequently one of the early symptoms. Initially naming errors occur, mainly for unfamiliar or atypical items, and consist of semantic paraphasias, generalizations, omissions, and circumlocutions (Kertesz and Harciarek, 2014). Patients often have difficulties with reading and writing, particularly with irregular or ambiguous words, leading to the phenomenon of surface dyslexia or surface dysgraphia (Baxter and Warrington, 1987; Warrington, 1975). Other cognitive domains are usually spared, including episodic and topographical memory, visuoperceptual function, praxis, calculation and non-verbal executive function (Cipolotti and Maguire, 2003; Warrington, 1975). svPPA shows markedly asymmetrical anterior left temporal lobe atrophy, particularly affecting the temporal pole, the fusiform and middle temporal gyri, but also the anterior hippocampus and amygdala (Hodges et al., 1992; Mummery et al., 2000; Mummery et al., 1999; Rohrer et al., 2009b). Less frequently, patients present with predominant right temporal lobe atrophy at onset, often called right semantic dementia (Chan et al., 2009; Evans et al., 1995; Thompson et al., 2003).

When extrapyramidal features are the main complaint at onset, they can configure an atypical parkinsonism, namely PSP or CBS. PSP is characterized by oculomotor disturbances and severe postural instability with frequent falls. CBS, instead, presents with an asymmetrical parkinsonian syndrome with additional motor and non-motor manifestations such as myoclonus and dystonia, followed by focal cortical deficits (Siuda et al., 2014).

Coexistence of FTD and motor neuron disease (MND) occurs in about 15–20% of subjects receiving diagnosis of amyotrophic lateral sclerosis (ALS) (Burrell et al., 2011; Lomen-Hoerth et al., 2002).

3. Genetics

Many cases of FTD have a family history for dementia or psychiatric illnesses, typically with a dominant inheritance pattern (Rohrer et al., 2009a). Genetic studies have identified several genes associated with FTD. A core clinical and pathological phenotype is recognized for each gene, although clinical distinction is still poorly defined; thus, no clear-cut genotype–phenotype correlations have been identified yet.

The first gene found to be associated with hereditary FTD was the *microtubule-associated protein tau (MAPT)* gene on chromosome 17, discovered in 1998 (Hutton et al., 1998; Spillantini et al., 1998). *MAPT* codes for the protein tau and individuals with *MAPT* mutations have abnormal accumulation of this protein in affected neurons. Mutations in *MAPT* account for 5–10% of all FTD cases, with over 50 different causal mutations known (Spillantini and Goedert, 2013). *MAPT* mutations are rare in sporadic patients, whereas in familial patients frequency range from 5% to 20% (Pottier et al., 2016).

Intronic and some exonic mutations may affect the alternative splicing of exon 10, leading to tau dysfunction and consequently to accumulation. Missense mutations impair the ability of tau to bind microtubules and to promote microtubule assembly (Irwin et al., 2015). Mutations in the *MAPT* gene are associated with the clinical diagnosis of FTDP-17, which stands for FTD with parkinsonism on chromosome 17. MAPT mutations are associated with Tau inclusions (FTD-Tau) and present clinically with an extremely heterogeneous picture: they have been associated largely with bvFTD and PPA, but PSP and CBS clinical phenotypes have also been described (Charlesworth et al., 2012; Forman et al., 2006; Forman et al., 2002).

In 2006, mutations of the *Granulin* gene were identified as causative of autosomal dominant FTD (Baker et al., 2006; Cruts et al., 2006). The protein product, progranulin, is a secreted glycoprotein, cleaved into granulin peptides and found in the brain and serum with roles in inflammatory diseases, diabetes and obesity. Pathogenic mutations in *GRN* are mainly nonsense and splice site mutations resulting in the loss of one *GRN* allele with functional haploinsufficiency; some mutations, however, are missense mutations causing mistrafficking within the cell (Irwin et al., 2015). Serum levels of progranulin are reduced by about 50% in mutation carriers (Finch et al., 2009; Ghidoni et al., 2008; Lashley et al., 2015; Sleegers et al.,

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