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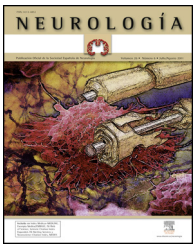

REVIEW ARTICLE

Biomarkers: a new approach to behavioural variant frontotemporal dementia☆

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KEYWORDS
Behavioural variant frontotemporal dementia;
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Abstract
Introduction: Lobar frontotemporal degeneration (FTLD) encompasses a group of molecular disease defined by the deposition of an abnormal protein in the central nervous system. Behavioural variant frontotemporal dementia (bvFTD) is the most frequent clinical presentation of FTLD. The past two decades of research have contributed to a better understanding of this entity, which may be the first manifestation in many different neurodegenerative disorders.
Development: We reviewed correlations between clinical, pathological, and genetic findings and the main disease biomarkers of FTLD, with particular interest in bvFTD. Anatomical pathology findings in FTLD are heterogeneous and the syndrome is not associated with any one specific histopathological type. Promising available biomarkers include structural and functional neuroimaging techniques and biochemical and genetic biomarkers. Disease-modifying drugs designed for specific molecular targets that are implicated in FTLD pathogenesis are being developed.
Conclusions: BvFTD is a frequent cause of dementia. Of all the clinical variants of FTLD, behavioural variant is the one in which establishing a correlation between clinical and pathological signs is the most problematic. A biomarker evaluation may help predict the underlying pathology; this approach, in conjunction with the development of disease-modifying drugs, offers new therapeutic possibilities.

PALABRAS CLAVE
Demencia frontotemporal variante conductual;
Degeneración lobar frontotemporal;

Demencia frontotemporal variante conductual: biomarcadores, una aproximación a la enfermedad

Resumen
Introducción: Las degeneraciones lobares frontotemporales (DLFT) son un grupo de patologías moleculares que se definen en función de la proteína acumulada en el sistema nervioso central. La demencia frontotemporal variante conductual (DFT vc) es el síndrome clínico de

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Biomarcador;
TDP-43;
Tau;
Genética

presentación más frecuente. Los avances realizados en los últimos años han contribuido a un mayor conocimiento de esta entidad, que puede ser el modo de presentación de diferentes enfermedades neurodegenerativas.
Desarrollo: Se revisa la correlación entre clínica, patología y genética de las DLFT, en especial de la DFT vc, así como los principales biomarcadores de la enfermedad. La anatomía patológica de la DFT vc es muy variada, sin mostrar asociación significativa con ningún subtipo histopatológico concreto. Entre los biomarcadores disponibles, destacan la neuroimagen anatómica y funcional, los biomarcadores analíticos y la genética. Se están diseñando fármacos dirigidos contra dianas moleculares concretas implicadas en la patogenia de las DLFT.
Conclusiones: La DFT vc es una causa frecuente de demencia. De entre todas las variantes clínicas de las DLFT, es en la que resulta más difícil establecer una relación clínico-patológica. El uso de biomarcadores puede ayudar a predecir la anatomía patológica subyacente, lo que junto al desarrollo de fármacos ligando-específicos ofrece nuevas posibilidades terapéuticas.

Introduction

The term frontotemporal lobar degeneration (FTLD) designates a pathological concept that includes a group of molecular diseases that are classified according to the protein that accumulates in the central nervous system. In 2007, Cairns et al.[1] established 4 main subtypes according to the protein deposits: tauopathies (FTLD-tau), ubiquitinopathies (FTLD-U), dementia without specific histopathological changes, and neuronal intermediate filament inclusion disease. Since then, following new breakthroughs in pathology and molecular biology, this classification system has been modified. FTLD cases are now classified into 3 main subtypes according to pathology: FTLD associated with tau protein (FTLD-tau), FTLD associated with the TAR DNA-binding protein 43 (FTLD-TDP), and FTLD associated with the fused-in sarcoma protein (FTLD-FUS). Only a very small percentage of cases will not fit any of these subtypes (FTLD-other).[2] Each of these main pathological groups can be subdivided into different entities or variants according to the distribution and morphology of protein inclusions and the histological characteristics specific to the case (Table 1). These groups give rise to 6 well-defined syndromes: the 3 clinical variants of frontotemporal dementia or FTD (behavioural variant frontotemporal dementia [bv-FTD], progressive nonfluent aphasia [PNFA], semantic dementia [SD]); frontotemporal dementia associated with motor neuron disease (FTD-MND); progressive supranuclear palsy syndrome (PSPS); and corticobasal syndrome (CBS).

A small percentage of cases with clinical features suggesting FTD actually have Alzheimer disease (AD).[3] This finding is more frequent in cases of logopenic primary progressive aphasia (PPA),[4] but it has also been described in some cases of SD (10%)[5] and bv-FTD (5%-7%).[5–7] Cases of AD with an antemortem diagnosis of bv-FTD are referred to as frontal-variant AD.[8]

The purpose of this study is to revise the clinical-pathological and biomolecular correlations in FTD subtypes, especially bv-FTD, as well as the diagnostic accuracy of biomarkers used to hypothesise which disease was responsible for clinical symptoms.

Clinical-pathological and biomolecular correlations in frontotemporal lobar degeneration

FTLDs have classically been regarded as a heterogeneous group of neurodegenerative diseases and researchers have found it extraordinarily difficult to establish links between clinical presentation and the underlying pathological process. Doctors also believed it was not possible to deduce the type of clinical manifestation based on the pathological diagnosis. Advances in neuropathology, biochemistry, molecular biology, and genetics now let us establish clinical, histological, biomolecular, and genetic correlations, in addition to links between clinical and pathological findings.

In 2011, Josephs et al.[9] published a review of several clinical-pathological studies[10–17] performed in the preceding decade in 6 hospitals in the United States, Canada, the UK, and Australia, including a total of 544 cases of FTLD. They observed that bv-FTD showed similar percentages of underlying FTLD-tau and FTLD-TDP. Almost all cases of PSPS and CBS presented FTLD-tau, whereas 100% of the cases of FTD-MND displayed FTLD-TDP. FTLD-TDP was present in 83% of the patients with SD, whereas PNFA was fundamentally associated with FTLD-tau (70%). Examining by specific groups (FTLD-TDP and FTLD-tau), these researchers found significant associations between clinical phenotype and histopathological subtype, except for PNFA and the FTLD-tau subtype, for which associations were not statistically significant. Patients with bv-FTD and tauopathy were associated with Pick disease (PiD) in 70% of all cases. Those with TDP histopathology demonstrated an association with subtype 1 in the Mackenzie et al. classification.[18] Nevertheless, the association between bv-FTD and the histopathological subtype was not robust (Fig. 1).

In some cases of bv-FTD, doctors may find clinical features that point towards a specific histopathological subtype.[19] One clinical subtype is characterised by changes in behaviour and personality, especially hypersexuality, hyperphagia, and stereotyped or obsessive behaviour. This subtype is strongly associated with atypical FTLD with immunoreactivity to ubiquitin only (aFTLD-U).[20,21] These