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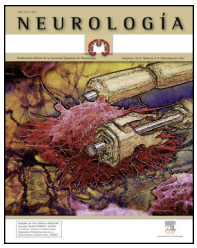

REVIEW ARTICLE

Behavioural variant frontotemporal dementia: Clinical and therapeutic approaches☆

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Abstract
Introduction: Behavioural variant frontotemporal dementia (bvFTD) is the most frequent presentation in the clinical spectrum of frontotemporal dementia (FTD) and it is characterised by progressive changes in personality and conduct. Major breakthroughs in molecular biology and genetics made during the last two decades have lent us a better understanding of this syndrome, which may be the first manifestation in many different neurodegenerative diseases.
Development: We reviewed the main epidemiological, clinical, diagnostic and therapeutic aspects of bvFTD. Most cases manifest sporadically and the average age of onset is 58 years. Current criteria for bvFTD propose three levels of diagnostic certainty: possible, probable, and definite. Clinical diagnosis is based on a detailed medical history provided by family members and caregivers, in conjunction with neuropsychological testing. Treatments which have been used in bvFDT to date are all symptomatic and their effectiveness is debatable. New drugs designed for specific molecular targets that are implicated in frontotemporal lobar degeneration are being developed.
Conclusions: BvFDT is a frequent cause of dementia. It is a non-specific syndrome associated with heterogeneous histopathological and biomolecular findings. The definition of clinical subtypes complemented by biomarker identification may help predict the underlying pathology. This knowledge, along with the development of drugs designed for molecular targets, will offer new treatment possibilities.

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PALABRAS CLAVE
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Tratamiento

Demencia frontotemporal variante conductual: aproximación clínica y terapéutica

Resumen
Introducción: La variante conductual de la demencia frontotemporal (DFT vc) es el síndrome clínico más frecuente de las demencias frontotemporales (DFT) y se caracteriza por una alteración progresiva de la personalidad y la conducta. En las últimas 2 décadas, los avances en biología molecular y genética han contribuido a un mayor conocimiento de esta entidad, que puede ser el modo de presentación de diferentes enfermedades neurodegenerativas.
Desarrollo: Se revisan los principales aspectos epidemiológicos, clínicos, diagnósticos y terapéuticos de la DFT vc. La mayoría de los casos son esporádicos, iniciándose en torno a los 58 años de media. Los criterios diagnósticos vigentes establecen 3 niveles de certeza diagnóstica: posible, probable y definitivo. El diagnóstico clínico se basa en la anamnesis detallada de familiares, complementada con la realización de test neuropsicológicos dirigidos. Hasta la fecha, los tratamientos empleados son solo sintomáticos y de eficacia controvertida. Se están diseñando fármacos dirigidos contra dianas moleculares específicas implicadas en la patogenia de las degeneraciones lobares frontotemporales.
Conclusiones: La DFT vc es una causa frecuente de demencia. Se trata de un síndrome amplio, heterogéneo desde el punto de vista histopatológico y biomolecular. La definición de subtipos clínicos y la identificación de biomarcadores podrían ayudar a predecir la afección subyacente, lo que junto con el desarrollo de fármacos dirigidos contra dianas moleculares ofrece nuevas posibilidades terapéuticas.

Introduction and concepts

Since Pick described the first case in 1892, it has taken nearly a century for neurology to renew its interest in frontotemporal dementia (FTD).[1] In the past 20 years, developments in molecular biology and genetics have produced an undeniable revolution in our knowledge of different types of FTDs. This has enabled researchers to make significant progress in understanding their causal mechanisms. As a result, new diagnostic criteria and classifications that give shape to the current FTD classification scheme have been drafted.

FTDs are listed as the third most common cause of degenerative dementia after Alzheimer disease (AD) and dementia with Lewy bodies. In patients younger than 65, they represent the second most common cause.[2,3] Population studies have shown that FTD prevalence rates range between 2.7/100 000 (with a peak of 9.4/100 000 in subjects aged 60-69) in the Netherlands[3] and 15.1/100 000 in adults younger than 65 in Cambridge (UK). In this last age group, AD prevalence was the same.[2] Although it has traditionally been considered a rare cause of dementia in subjects over 65, it is probably more frequent than previously believed. Some authors identify FTD in 20-25% cases of dementia in patients older than 65 years.[2,4,5] Onset normally takes place in the sixth decade of life although this may vary greatly and cases have been reported in patients aged between 30 and 90.[2,4,5]

Lack of homogeneity in terminology has added to the confusion for years. Frontotemporal dementia is a clinical term that refers to the group of syndromes characterised by progressive decline in behaviour or language and associated with focal atrophy of the frontal and temporal lobes. Predominant symptoms and their time of onset during the course of the disease define 3 main clinical syndromes: behavioural variant of FTD (bvFTD), semantic dementia (SD), and non-fluent primary progressive aphasia (nfPPA).[6] Patients in whom FTD is associated with signs of motor neuron disease are diagnosed with FTD/MND.[7,8] Furthermore, another 2 syndromes are closely related to FTD: corticobasal syndrome and progressive supranuclear palsy. All 6 clinical syndromes are linked to a heterogeneous group of molecular disorders characterised by cortical neurodegeneration, neuronal loss, and microspongiosis of frontal and temporal lobes. These syndromes are classified as frontotemporal lobar degeneration (FTLD). The term FTD is therefore a clinical concept, while FTLD refers to a pathological concept. In this article, we will review clinical, diagnostic, and therapeutic aspects of bvFTD.

Clinical considerations of behavioural variant frontotemporal dementia

The most frequent clinical syndrome of FTD is bvFTD. It is characterised by the early onset (within the first 3 years) of insidious changes in personality and behaviour. There are 3 clinical subtypes corresponding to the affected prefrontal areas: dorsolateral (dysexecutive syndrome, pseudodepression, or frontal convexity syndromes), orbitomedial (disinhibition syndrome, pseudomania, or pseudopsychopathy), or medial frontal/cingulate gyrus (apathetic syndrome, akinetic syndrome).[9,10] Onset of the disease usually occurs before the age of 65 and typical age of onset is about 58 years.[4] Nevertheless, time of onset is frequently hard to determine since these patients present poor insight; detection of early symptoms will therefore depend on the powers of observation of their relatives and caregivers.