

# Dementia: Not Only Alzheimer's Disease, an Eye on Frontotemporal Dementia



## Demência: Mais do que uma Doença de Alzheimer, um Olhar sobre a Demência Frontotemporal

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The term Frontotemporal Lobar Degeneration (FTLD) encompasses three main clinical syndromes: behavioural variant Frontotemporal Dementia (bvFTD), Progressive Non Fluent Aphasia (PNFA) and Semantic Dementia (SD). It represents a common cause of dementia in subjects under 65 years. The age at onset is typically 45-65 years, with a mean average in the 50s, and the prevalence, equal among men and women, is 10-15 individuals out of 100 000. bvFTD is the most frequent FTLD phenotype. It is primarily characterised by behavioural changes and progressive deterioration of personality. Throughout the disease, patients show a wide spectrum of symptoms, including behavioural alterations, such as disinhibition, overeating and impulsiveness, and impairment of cognitive functions, with relative sparing of memory. Changes in social behaviour, loss of empathy and impairment of social insight are early and consistent symptoms of bvFTD. In the last few years, it has become clearer and clearer that FTLD represents a challenging diagnosis: quite often it can present also with memory impairment, thus resembling Alzheimer's disease, or with a psychiatric illness, when characterized by psychosis.<sup>1</sup> In this context, the availability of biomarkers, i.e. objective measures of an ongoing pathogenic process, represents a crucial point for early diagnosis and treatment of FTLD. In an elegant update and guide for clinicians, Pelicano Paulos and Massano<sup>2</sup> carefully described the current knowledge about FTLD, including clinical presentation, diagnosis, genetics, and pathology.

Regarding the diagnosis, new criteria have been published for bvFTD,<sup>3</sup> and language presentations.<sup>4</sup> Regarding the former, the main feature is the progressive deterioration of behaviour and/or cognition by observation or history (provided by a knowledgeable informant). If this criterion is satisfied, there are three further levels of certainty for bvFTD: possible, probable, or definite. 'Possible' bvFTD requires three out of six clinically discriminating features (disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviours, hyperorality and dysexecutive neuropsychological profile). 'Probable' bvFTD meets the criteria of 'possible' bvFTD plus 1) a significant

functional decline (by caregiver report or evidenced by Clinical Dementia Rating Scale of Functional Activities Questionnaire score) 2) imaging results consistent with bvFTD (frontal and/or anterior temporal atrophy on MRI or CT, or frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT). 'Definite' bvFTD imply the histopathological evidence of FTLD on biopsy or post mortem or the presence of a known pathogenic mutation. These new criteria have a flexible structure to account for the high heterogeneity at initial presentation.

The inclusion of genetics in new criteria derives from the recent demonstration that about 10% of cases have actually a genetic cause, dominantly inherited. Mutations in different genes, including Microtubule Associated Protein Tau (*MAPT*), Progranulin (*GRN*) and chromosome 9 Open Reading Frame 72 (*C9ORF72*), are associated with a variety of phenotypes and age at presentation. Notably, the presence of the hexanucleotide repeat expansion in *C9ORF72* is often associated with FTLD with motor neuron disease (MND), that is usually observed in about 20% of cases.

The pathology associated with FTLD is intriguing. The first histopathological findings were described in 1911 by Alois Alzheimer, who observed ballooned neurons containing tau protein and argyrophilic intracytoplasmic inclusions. He named them 'Pick cells' and 'Pick bodies', respectively, after Arnold Pick, who reported the first case in 1892. Decades later, it was observed that these characteristics were absent in some Pick disease brains, resulting in the term 'FTLD lacking distinctive histopathology'. A positive staining for ubiquitin was shown in these cases and, in 2006, truncated and hyperphosphorylated isoforms of the TAR-DNA binding protein (TDP)-43 were recognized as main components of the ubiquitin-positive inclusions.<sup>5</sup>

Despite these advances in the definition of mechanisms at the basis of FTLD, the disease is often unfamiliar to citizens and physicians. To fill this gap, in their review, Pelicano Paulos and Massano<sup>2</sup> give information on the clinical management of the disease, including genetic counselling for subjects with a positive family history for

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dementia.

The ultimate aim of a better management of FTLD and a better understanding of mechanisms at its basis is the identification of targets to develop treatments. Considering the wide heterogeneity of the pathology, the big future challenge will be to identify biomarkers for recognizing in life specific changes occurring in the brain, in order to develop tailored disease-modifying treatments for different

pathologies (i.e. inhibitors of tau protein deposition or drugs able to restore TDP-43 functioning).

#### CONFLICT OF INTERESTS

None stated.

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#### REFERENCES

- Galimberti D, Fenoglio C, Serpente M, Villa C, Bonsi R, Arighi A, et al. Autosomal dominant frontotemporal lobar degeneration due to the C9ORF72 hexanucleotide repeat expansion: late-onset psychotic clinical presentation. *Biol Psychiatry*. 2013; S0006-3223(13)00130-3.
- Pelicano Paulos J, Massano J. Clinical, genetic and neuropathological features of frontotemporal dementia: an update and guide. *Acta Med Port*. 2013;26:392-401.
- Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134:2456-77.
- Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76:1006-14.
- Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science*. 2006;314:130-3.