

SOFT BOUNDARIES BETWEEN FRONTOTEMPORAL DEMENTIAS AND ATYPICAL PARKINSONISMS

Elka Stefanova

Clinic of Neurology, CCS, University of Belgrade, Serbia

Frontotemporal dementia (FTD) encompasses a group of neurodegenerative diseases characterized by focal atrophy of frontal and anterior temporal lobes and non-Alzheimer pathology. In people under 65 years of age, FTD is as common as Alzheimer's disease (AD) and its prevalence has been estimated in 15 per 100,000 patients between 45 to 64 years of age. Patients with FTD display a heterogeneous clinical picture, which may include behavioral, cognitive, and motor manifestations. However, based on the predominant initial symptoms, FTD can be readily separated into two groups: the behavioral variant (bv-FTD), which is characterized by loss of insight, personality changes, and disturbances in social cognition and the language variant, also referred as primary progressive aphasia (PPA). The latter can be further divided into a well-defined clinical-pathological entity, semantic dementia (SD) and progressive nonfluent aphasia (PNFA). However, logopenic/phonological (LPA) variant has been recently described, showing a distinctive pattern of brain atrophy and often associated to Alzheimer's disease pathology.

The diagnosis of FTD is challenging, since there is clinical, pathological, and genetic overlap between the variants and other neurodegenerative diseases, such as motoneuron disease (MND) and corticobasal degeneration (CBD). Despite this classification, there is a clinical, pathological, and genetic overlap. For instance, SD cases may develop features of bv-FTD, and patients with the clinical variant often have common areas of brain atrophy and family history of another variant. Moreover, there is increasing evidence of overlap between FTD and other neurodegenerative disease, notably Motor Neuron disease (MND), Progressive Supranuclear Palsy (PSP), and Corticobasal

degeneration (CBD). For example, cases initially diagnosed as PNFA may end up showing a clinical picture and pathology of CBD. Indeed, some argue that those entities should all be included under the rubric of Pick's complex.

Differentiating one variant of FTD from another, as well as from other neurodegenerative and nondegenerative diseases (particularly psychiatric conditions) remains challenging. Fortunately, recent advances in molecular pathology and genetics, improved imaging techniques, and better clinical descriptions have contributed enormously to our understanding of these conditions and are offering new insights, which we hope will be helpful for improved diagnosis and management of patients with these devastating disorders. In addition, patients with gene mutations (tau and progranulin) display an inconsistent clinical phenotype and the correspondence between the clinical variant and its pathology is unpredictable. New cognitive tests based on social cognition and emotional recognition together with advances in molecular pathology and genetics have contributed to an improved understanding. There is now a real possibility of accurate biomarkers for early diagnosis. In the last twenty years, a great deal of progress on molecular genetic and imaging has led to new insights about FTD syndromes. New imaging methods, for instance voxel based morphometry (VBM), has given a detailed account of pattern of brain atrophy, allowing an unbiased comparison of patients groups, while the development of radiotracers, such as PiB has enabled to identify the accumulation of extracellular beta-amyloid, and therefore, rule out cases of AD. Patients with bv-FTD show atrophy of the orbitobasal and medialfrontal lobes, together with anterior temporal

and insular involvement. SD is associated with atrophy of the anterior temporal lobe involving particularly polar, anterior parahippocampal, and fusiform regions including the perirhinal cortex. The atrophy is bilateral, but typically asymmetric and often more severe on the left. In PNFA, the changes are subtler and involve the left inferior frontal lobe and anterior insula cortex. In logopenic/phonological variant the atrophy involves the left hemisphere, particularly the posterior temporal lobe (superior and middle temporal gyri) and inferior parietal lobe and lesser involvement of the precuneus. These changes can also be detected using simpler MRI-based visual rating scales, which simply use standard coronal cuts. These scales aid diagnosis and monitoring of progression. Ligands specific to tau and TDP-43 are eagerly awaited.

Around 40% of patients report a family history of dementia, although in many instances this is almost certainly unrelated, but 10–20% have a clear pattern

of autosomal dominant inheritance, with at least two relatives having young onset dementia or MND. The heritability, however, varies according to the variant FTD: SD showing the least, whereas bv-FTD and FTD with MND the most inheritable. The commonest identified mutations are MAPT and progranulin (PGRN), both in chromosome 17q21. Although the prevalence of mutations varies among studies, the two mutations have a similar frequency, being found in around 5–10% of patients. Other mutations involve the Valosin-containing protein (VCP) and CHMP2B genes, but are very rare. Advances in neuropsychological assessment have also led a better understanding of the language and social cognitive difficulties seen in FTD. Many issues remain unresolved. The relationship between genetic, pathologic, and clinical phenotype is of key importance as is the ability to identify pathological subtypes in vivo by the use of biomarkers.