

Frontotemporal dementia

Frontotemporal dementia: Clinical diagnosis, pathological hallmarks and genetics

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Frontotemporal dementia (FTD) is a devastating dementia affecting primarily the frontal and temporal part of the brain. It is the second most common form of dementia in people under the age of 65, generally presenting between 45 – 65 years of age. Despite the high incidence of frontotemporal dementia (FTD) in persons under the age of 65, relatively little is known about how pathogenic events lead to cognitive decline.

FTD is clinically characterised as the dementia arising by the specific degeneration of the frontal and anterior temporal lobes – this degeneration is termed frontotemporal lobar degeneration (FTLD). This degeneration clinically results in progressive changes in behaviour, executive dysfunction and language impairment (reviewed in Rabinovic and Miller 2010). Patients may also exhibit movement dysfunction associated with diseases such as parkinsonisms and motor neuron disease (Roeber et al., 2008). There are three main subtypes of FTD defined by predominate behaviour and personality changes or language disturbances presented (Sieben et al., 2012; Seltman 2012):

Behavioural variant FTD

Behavioural variant FTD (BvFTD) is caused by specific degeneration predominately affecting the frontal lobe. This type of FTD is characterised by progressive decline in behaviour and executive function resulting from disruption of local circuits in this region. Symptoms can include lethargy, apathy and most prominently disinhibition, whereby a range of socially inappropriate responses reflect the decline of faculties specific to the frontal lobe, such as personality, judgment and planning.

Progressive nonfluent aphasia

Progressive nonfluent aphasia (PNFA) is caused by a predominant left peri-sylvian atrophy. This type of FTD is characterised by expressive or motor speech deficits. Symptoms include loss of speech fluency due to difficulties with word articulation, phonology and syntax. Word comprehension is preserved.

Semantic dementia

Semantic dementia (SD) is caused by increased left anterior temporal lobe degeneration. This type of FTD is characterised by loss of knowledge in relation to objects, facts and word meaning (semantic). Semantic memory gives meaning to our sensory experience, and when it is lost, in the case of this disease, individuals can lose the ability to recall or associate words, objects and even faces with their previously accepted meanings. The initial symptom of semantic decline in SD is usually a regression in language abilities, whereby individuals can complain of a loss of memory for words.

Pathologically, the FTLN that results in FTD is defined by the presence of neuronal inclusion bodies, and can be divided into two subclasses depending upon the specific inclusion. These subclasses were originally defined as tau-positive inclusions (FTLN-tau) and tau-negative, ubiquitin-positive inclusions (FTLN-U) (reviewed in Sieben et al., 2012). Of these FTLN-U cases, which account for more than 50% of all FTLN cases, it has now been identified that 80-95% were positive for the RNA binding protein TDP-43 (FTLN-TDP) (Roeber et al., 2008). Genetic mutations have now been linked to the misprocessing of these proteins into inclusion bodies. Specifically, mutations in the microtubule-associated gene has been linked with the tau inclusion cases and mutations in the progranulin gene was identified to be present in the majority of the tau-negative TDP-43 positive cases and most recently, mutations in C9orf72 gene (DeJesus-Hernandez et al., 2011; Renton et al., 2011). Whilst it is clear that the inclusion bodies play an important role in neuronal death, it remains unclear if they are the cause or consequence, or potentially both, of neuronal dysfunction and ultimately death. Furthermore, involvement of other non-neuronal supporting cell types must also be considered, with pathology indicating dysfunction of oligodendrocyte and astrocyte populations (Arai et al., 2003). This raises further questions about the role of these inclusions in the selective vulnerability of neuronal subtypes. Nonetheless, the advancement in the underlying genetic mutations, coupled with the identification of the biological inclusion markers discussed, has created the opportunity for the development of biologically driven, disease specific therapies for FTD (Rabinovici and Miller 2010).

References

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