Recent Advances in Frontotemporal Dementia

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There have been major advances in the characterisation of frontotemporal dementia (FTD) over the past two decades culminating in the development of internationally accepted diagnostic criteria for each of the clinical subtypes. The behavioural variant of FTD (bvFTD) is characterised by changes in personality and behaviour which have now been clearly defined with levels of diagnostic certainty: possible, probable and definite (Table 1). For cases presenting with progressive aphasia, three variants are now recognised: the semantic variant (semantic dementia) characterised by fluent speech with anomia and impaired single word knowledge in association with anterior temporal lobe atrophy; the non-fluent variant with apraxia of speech and/or agrammatism associated with inferior frontal atrophy; and the logopenic variant in which word finding difficulties and impaired verbal span predominate, and atrophy is centred around the angular gyrus (Table 2). The distinction is not purely academic since underlying neuropathology is highly predictable. Those with semantic variant have TDP-43 type C and are rarely genetic. Those with the nonfluent form mostly have tau based FTD pathology, which may be genetic, and the logopenic form is associated predominantly with Alzheimer's pathology,[1,2] the pathology remains heterogeneous with an approximate 50-50 split between FTD-tau and FTD-TDP43 (Figure 1).

Table 1: Diagnostic criteria for bvFTD

1. Possible bvFTD – at least three of the following features must be present
a. Disinhibition
b. Apathy
c. Lack of sympathy/empathy
d. Stereotypic/ritualistic behaviours
e. Change in dietary preferences
f. Frontal dysexecutive cognitive profile
2. Probable bvFTD – all of the following features must be present
a. Meet criteria for possible (as above)
b. Show functional disability/decline
c. Frontal and or temporal abnormalities on neuroimaging (MRI or PET)
3. Definite bvFTD - either a or b must be present
a. FTLD pathology at autopsy
b. Known pathogenic genetic mutation

Developments in neuroimaging, notably functional MRI (fMRI), have heralded the concept of dysfunction within neural networks as the anatomical basis for abnormal behaviours and cognitive dysfunction in FTD. The salience network,

Figure 1 below represents the clinical and pathological subtypes of Frontotemporal Dementia. Weighted lines represent the approximate frequency of pathology for each variant.

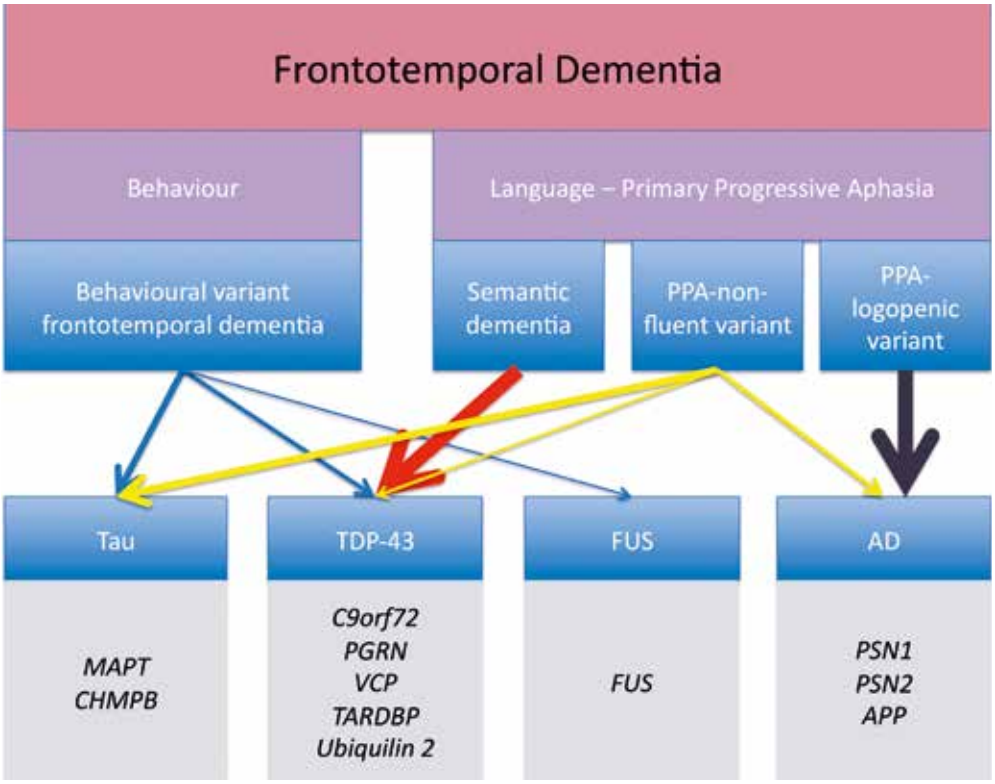

Table 2: Diagnostic criteria for PPA
1. PPA – all of the following must be met (a-d)
a. Language disturbance is the most prominent clinical feature
b. Language impairment is the cause of impairment in activities of daily living
c. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease
d. No other condition should better account for the presentation
2. PPA–sv (semantic variant) – Both of the following must be met
a. Poor confrontation naming (pictures/objects) particularly for low familiarity items
b. Impaired single word comprehension
Plus at least three of the following must be met
a. Poor object and/or person knowledge, particularly for low frequency or low familiarity objects
b. Surface dyslexia
c. Spared single word repetition
d. Spared motor speech, melody and phrase length
Plus neuroimaging abnormality – Predominant anterior temporal lobe
3. PPA-nfv (agrammatic/non-fluent variant) – At least one of the following must be met
a. Grammatical errors and simplification in language production
b. Effortful, halting speech with speech sound errors consistent with apraxia of speech
Plus at least three of the following must be met
a. Impaired naming, particularly of action verbs
b. Impaired comprehension of syntactically complex sentences
c. Spared content word comprehension
d. Spared object knowledge
Plus neuroimaging abnormality – Predominant left posterior fronto-insular
4. PPA-lv (logopenic variant) – Both of the following must be met
a. Impaired single word retrieval in spontaneous speech & confrontational naming
b. Impaired repetition of sentences and phrases
At least three of the following must be met
a. Phonological errors in spontaneous speech and naming
b. Spared motor speech
c. Spared single word comprehension
d. Spared object knowledge
Plus neuroimaging abnormality – Predominant left posterior perisylvian or parietal

comprising the insula, anterior cingulate cortex, amygdala, and a network of thalamic and subcortical structures, is involved early in the course of bvFTD and is implicated in the generation of social and emotional dysfunction.[3] The link between FTD, deranged metabolism and abnormal eating behaviour is becoming clearer and seems likely to be linked to a complex neural network centred on the hypothalamus.[4] Together these findings have encouraged FTD researchers to consider the contribution made by brain regions outside of the frontal and temporal cortices. The cerebellum, previously considered to be concerned primarily with motor function, has been implicated in a range of cognitive dysfunctions, and the thalamus, a key relay station for the signaling of sensory information and integration throughout the cortex, may also be involved.

Until recently MRI and Fluorine-18-Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) have been the imaging modalities of choice for the diagnostic work-up of patients with FTD. In more recent years, amyloid Pittsburgh compound B (PIB)-PET imaging has been useful to tease apart atypical cases when distinction from AD is clinically difficult. Following the success of amyloid PET imaging, researchers turned towards finding suitable tracers for tau protein and a number have been developed.[5] Tau imaging has the potential to improve diagnostic accuracy in FTD through the identification of tauopathies during life, whereas currently the underlying pathology can be identified post-mortem only. This may allow more accurate case selection for clinical trials and subsequent pharmacological therapies. Tau PET imaging could also improve disease staging, as tau burden is closely linked with cognitive impairment, and determine the role of tau deposition in the preclinical stages of neurodegeneration. Although the potential benefits of tau imaging for clinicians, researchers and patients are clear there are issues to be resolved before the ideal ligand is identified and introduced to clinical practice.

It seems likely that future research will focus on *in-vivo* identification of other pathological proteins notably trans-activating responsive (Tar) sequence DNA binding protein (TDP-43). The discovery of TDP-43 consolidated the overlap between FTD and MND given that this protein is found in a proportion of those with FTD and the vast majority of familial and sporadic MND cases.[6] Clinical overlap between these conditions has long been recognised but only fairly recently has the concept of an FTD-MND disease continuum become widely accepted.[7] Cognitive/behavioural deficits may develop in parallel with motor deficits although either can occur initially. Cognitive and behavioural abnormalities are reported to occur in 50-75% of MND cases while approximately 15-25% of patients meet criteria for FTD.[7] Of all the cognitive functions, executive function has received the most attention in MND that may have consequences for financial, medical and end of life decisions. Language deficits may be as common as executive dysfunction and adds another level of complexity to communication issues for MND patients. Similarly, social and emotional cognition domains are affected and behaviour is impaired, specifically a degree of apathy is found in up to 80% of patients, and disinhibition, lack of empathy and rigidity are also present.[8] Conversely around 10% of FTD cases develop frank MND but subclinical motor features can be found in a much higher proportion of cases. Patients with the FTD-MND overlap syndrome tend to have the shortest survival of all FTD syndromes with death occurring within two to three years.

In 2011 the concept of the FTD-MND continuum was cemented, with identification of the *C9orf72* genetic expansion on chromosome 9p21.1.[9] This genetic expansion, a hexanucleotide GGGGCC repeat found on the non-coding region of chromosome 9, is pathogenic at greater than 30 repeats with most patients having repeat lengths in the thousands. Studies of affected carriers, asymptomatic carriers and their family members will provide further insight into this gene defect which, may have features in common with other repeat disorders. The exact penetrance is still unknown but it is believed that it is not fully penetrant, as unaffected elderly carriers have been identified. Three pathological mechanisms have been proposed to cause disease in *C9orf72* carriers: loss of function of the protein encoded by the gene, toxic effects of RNA products which aggregate in the cell and toxicity caused by dipeptide repeat proteins. The *C9orf72* expansion has been identified with mutations in other well-known causative genes in FTD including *GRN* and *MAPT*,[10,11] which has led researchers to hypothesise that these genes and others may play a modifying role in *C9orf72* expression. This expansion accounts for approximately one-third of familial FTD and up to 75% of familial FTD-MND cases. Notably, a significant minority (5-20%) of patients with apparently sporadic bvFTD also have the expansion.[12] Collectively the three major genes, *C9orf72*, *GRN* and *MAPT* account for over 50% of familial FTD cases indicating there are clearly gene mutations yet to be discovered.

There is marked geographical variation in prevalence of the *C9orf72* expansion with high rates of the expansion found in northern European countries, while remaining rare in Asian populations. Across the clinical spectrum of FTD, the predominant phenotype associated with the *C9orf72* expansion is bvFTD, often occurring with features of MND, although non-fluent variant PPA cases have been reported. *C9orf72* positive patients can be distinguished from negative cases based on a family history of MND, Parkinsonism and prominent psychosis at presentation.[12] Delusions and hallucinations are generally rare in FTD but are a frequent presenting feature of the *C9orf72* expansion some of

who have a long history of psychiatric illness. A distinctive neuroanatomical signature has also emerged, with generally mild atrophy involving the thalamus and cerebellum in addition to the typical orbitomedial frontal and anterior temporal atrophy seen in bvFTD.[13] A proportion of patients labelled as 'slow-progressors' or 'phenocopy' cases habour the *C9orf72* expansion and in a study from our centre the proportion of possible bvFTD cases with the mutation was higher than found in cases with probable bvFTD.[14]

With regard to therapies for FTD, disease-modifying treatments have so far focused on tau pathology. Recent attempts to inhibit tau phosphorylation using lithium and tideglusib have failed, however a methylene blue derivative, leucomethylthioninium, shows promise as an inhibitor of tau aggregation and phase III clinical trials are currently underway. The discovery of the *C9orf72* expansion has led to the theory that antisense oligonucleotide therapy, which show activity against toxic RNA effects as seen in the *C9orf72* expansion, may be effective in the treatment of MND-FTD.[15]

In summary, the last few decades have seen rapid advances in our understanding of FTD encompassing clinical, neuroimaging, genetic and pathological fields with hopefully even more exciting discoveries on the horizon. Better awareness of FTD, together with the development of diagnostic criteria, has facilitated earlier diagnosis to ensure that these patients have timely access to necessary care and support although FTD is still poorly recognised in non-specialist settings. The identification of the *C9orf72* expansion has challenged the concept of MND and FTD as single disease entities by explaining the genetic link between the conditions, and provides a platform to study the complex underlying molecular pathogenesis of these diseases.

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Pooled Phase III data presented at the American Epilepsy Society Annual Meeting on the use of Fycompa® (Perampanel) in the treatment of primary and secondary generalised tonic clonic seizures

Abstracts provide a wealth of data to support the use of perampanel in patients with primary and secondary generalised tonic clonic seizures

Data presented at the American Epilepsy Society (AES) 69th Annual Meeting Philadelphia, show that Fycompa® (perampanel) treatment reduces primary and secondary generalised tonic clonic seizures and is well tolerated versus placebo. Results from a post-hoc analysis demonstrate treatment with perampanel was associated with a greater 50% responder rate versus placebo (61.8% vs 37.8%; p<0.0001) and conferred a median 65.5% reduction in primary and secondary generalised seizure frequency over 28 days versus placebo (-24.6; p<0.0001).

The analysis evaluated the efficacy and tolerability of 8mg/day perampanel on 492 people with primary or secondary generalised tonic clonic seizures, across four phase III studies. 26.9% of participants achieved seizure-free status with perampanel compared to 12.6% of people with placebo. Treatment with perampanel was well tolerated.

"Findings from this pooled analysis of Phase III data provide an important look into the efficacy and tolerability of perampanel in people with primary and secondary generalised tonic clonic seizures. It is encouraging that this examination of perampanel has shown it to offer a median 65.5% reduction in primary and secondary generalised seizures against placebo," comments Professor Eugen Trinka, Professor and Chair of the Department of Neurology, Paracelsus Medical University, Salzburg, Austria.

Perampanel is indicated for the adjunctive treatment for partial onset seizures, with or without secondarily generalised seizures, in patients with epilepsy aged 12 years and older and for adjunctive treatment of primary generalised tonic-clonic seizures, in patients with idiopathic generalised epilepsy.

Analysis of real world data on use of Zebinix to manage partial onset seizures

Real-world data at The American Epilepsy Society report that when Zebinix® (eslicarbazepine acetate) was used as add-on to antiepileptic monotherapy in 45 people with partial-onset seizures, who had a documented non-response to carbamazepine, after 6 months, the retention rate was 88.9% (95%CI 75.9 – 96.3%, n=45).

The AES represented a significant milestone for eslicarbazepine acetate, with 19 abstracts presented over four days with two important sub analyses from a European real-world study. This was the largest number of abstracts for eslicarbazepine acetate at a single congress which demonstrates its strong scientific presence in epilepsy.

The post hoc subgroup analysis examined data from the EPOS (Eslicarbazepine acetate in Partial-Onset Seizure) study programme, a multicentre evaluation of 247 people with partial-onset seizures across eight European countries over six months. Responder rates and seizure freedom rates in the eslicarbazepine acetate arm were 95.1% (95% CI 83.5–99.4%; n=41) and 33.3% (95% CI 19.6-49.5%, n=42) respectively. Mean QOLIE-10 score decreased from 2.8 (n=21) at baseline to 2.2 (-13.0%; n=18) after 6 months. A decreasing QOLIE-10 score is a measure of improvement in quality of life.

"People with partial-onset seizures may try several therapies before they find one they respond to. This data shows that a good proportion of people with partial-onset seizures, who have not responded when treated with carbamazepine, may respond to eslicarbazepine acetate. The results of the study further highlight the importance of trying different treatment options, "commented Professor Martin Holtkamp from the University Hospital Charité, Germany.