Frontotemporal dementia (FTD) is a devastating neurodegenerative disease that describes a group of early onset, non-Alzheimer’s disease dementias. FTD affects 15 per 100,000 people between the age of 45-64 years and is as common as Alzheimer’s disease in this age group [1]. In 2011, it was estimated that 23,900 Australian’s under the age of 65 were living with young onset dementia [2]. FTD has an average age of onset of 58 years with a disease duration of 3-8 years [3]. Unsurprisingly, FTD places a significant emotional and financial burden on families and caregivers, which sadly goes mostly unrecognised by the patient.

Two broad clinical presentations of FTD are recognised: behavioural variant-FTD and the primary progressive aphasias (PPA). Patients with behavioural variant-FTD typically present with deterioration in social function, behaviour and personality, loss of empathy or altered eating patterns. Patients with PPA present with a progressive breakdown in language skills, which can be further sub-divided into three clinical groups according to the type of language dysfunction [4,5]. In the semantic variant-PPA, patients show impaired word comprehension and naming, whereas fluency, grammar and sentence construction are preserved e.g. “what is toast? I don’t know what this is”. The non-fluent variant-PPA is characterised by word finding difficulty and effortful, non-fluent speech. Patients will often speak in shorter sentences and eventually become monosyllabic or mute e.g. “She comed yesterday” instead of “she came yesterday”, or “aminal” instead of “animal”. A third subtype of PPA, the logopenic variant is characterised by deficits in word retrieval, comprehension and sentence repetition e.g. “scinners…sivvers…scissors” [5].

There is also substantial overlap between FTD and motor disorders with approximately 10% of FTD patients developing motor neuron disease [6]. Other motor conditions are also associated with FTD e.g. corticobasal syndrome where in late stages of the disease, patients often develop cognitive impairments and frontal executive dysfunction, similar to FTD [7]. Overall, there is substantial overlap between the clinical FTD syndromes and as the disease progresses, distinguishing them clinically can be challenging, especially in advanced disease stage.

A positive family history is present in up to 40% of patients, suggesting a strong genetic component in the cause of FTD [8,9]. The remaining cases are sporadic with no family history or known genetic cause of disease. In 1998, mutations in the gene that encodes a protein known as microtubule-associated protein tau (MAPT) were identified in a number of FTD families. This was the first genetic mutation known to cause FTD and is found in up to 20% of familial FTD cases. Since then, five other genes have been identified that when mutated, cause FTD. These genes are called progranulin (GRN), valosin-containing protein (VCP), charged multivesicular body
protein (CHMP2B), transactive response DNA binding protein (TARDBP) and fused in sarcoma (FUS) [10]. More recently in 2011, an abnormality in a gene called C9orf72 was discovered and is the most common genetic cause of familial FTD with and without motor neuron disease [11,12]. The discovery of these genes has generated a huge amount of research into the genetics of FTD and potential screening of family members, which hope to improve diagnosis and the development of target-specific therapies in the future. However, genetic mutations underlying many familial FTD cases are yet to be discovered.

At post-mortem, FTD patients show shrinkage of the brain, which is caused by cell loss. The pathology underlying FTD is classified based on the type of abnormal protein that accumulates in remaining brain cells. Three major pathologies have been identified: FTLD-Tau (deposition of the microtubule-associated binding protein tau), FTLD-TDP (deposition of TAR DNA binding protein 43, TDP-43) and FTLD-Fus (deposition of the fused in sarcoma protein, Fus) [13]. In a recent study of clinical FTD cohorts in Sydney and Cambridge, approximately one third of all cases have Tau pathology, 35% have TDP pathology and 26% show Alzheimer’s pathology. FTD cases with underlying Fus pathology comprise only a small percentage of cases [14]. Further classification within these main pathological subgroups is recognised, which is based on the type and distribution of cellular changes. However, many subgroups have overlapping features making accurate diagnosis more challenging. In addition, a small percentage of cases show no abnormal protein aggregates in neurons whereas others have abnormal protein aggregates in neurons that do not contain Tau, TDP or Fus. These studies indicate that other proteins causing neuronal degeneration underlying FTLD await discovery.

Unlike other neurodegenerative conditions such as Alzheimer’s and Parkinson’s disease, the neuropathology underlying FTD is highly variable and can even differ between relatives with the same genetic mutation. For these reasons, it is very difficult to predict, let alone treat, the pathological cause of the disease. A number of studies have found that the underlying pathology can influence patient survival, with Tau deposition associated with a longer disease duration and later disease onset [3]. Studies like this are essential for directing future research and informing about the cause of neurodegeneration. However, although significant progress has been made in FTD, further research is crucial to understand disease mechanism/s, improve diagnosis and develop effective therapeutic strategies.

References:


