Unpicking frontotemporal lobar degeneration

Not so long ago, frontotemporal lobar degeneration (FTLD) seemed quite simple. Apart from rare variants of Alzheimer’s disease and the occasional obscure neurodegenerative disease that could not be classified, FTLD was synonymous with Pick’s disease, first described by Arnold Pick (1892) in a series of patients with ‘circumscribed atrophy’ and aphasia. The neuropathological findings in two such patients were later reported by Alois Alzheimer (1911) to include distinct argyrophilic ‘globes’ (subsequently called Pick bodies) within some neurons, and other neurons that were swollen by homogeneously argyrophilic material (Pick cells). Patients whose brains were found to contain the argyrophilic inclusions and swollen neurons were said to have typical Pick’s disease. Those who had frontotemporal atrophy in the absence of these features or any alternative diagnosis such as Alzheimer’s disease were said to have ‘atypical’ Pick’s disease (sometimes subdivided into two or more subgroups, depending largely on the precise distribution of pathology), on the assumption that the underlying pathological process was similar even if the neurons lacked argyrophilic inclusions. In 1986, Pollock et al. (1986) showed that Pick bodies contain the microtubule-associated protein tau and in 1988 they were reported to contain ubiquitin (Love et al., 1988). Later, the Pick body-like inclusions in several other forms of FTLD were shown also to contain ubiquitin but not tau (Cooper et al., 1995; Bergmann et al., 1996). We have come a long way in a relatively short period. Current classifications recognize at least 16 pathological subtypes of FTLD (Mackenzie et al., 2010).

The most recently described category of FTLD is characterized pathologically by aberrant accumulation of fused-in-sarcoma protein (FUS) in distinct inclusion bodies in the neuronal cytoplasm and sometimes in the nucleus. The gene encoding FUS was first identified as part of a fusion gene in patients with liposarcomas (Crozet et al., 1993; Rabbitts et al., 1993). Recognition of the involvement of FUS in neurodegenerative disease came only in 2009, with the identification of mutations in FUS in several families with amyotrophic lateral sclerosis/motor neuron disease (Kwiatkowski et al., 2009; Vance et al., 2009). A flurry of papers followed in which FUS mutations were reported in further families with amyotrophic lateral sclerosis, FTLD or a combination of the two (e.g. Corrado et al., 2010; Hewitt et al., 2010; Millecamps et al., 2010; Waibel et al., 2010; Yan et al., 2010). In brain and spinal cord tissue from those patients who underwent post-mortem examination, immunohistochemistry revealed neuronal inclusion bodies that contained FUS. The protein was also detected in neuronal inclusion bodies in brain and spinal tissue from some patients with sporadic FTLD, with or without amyotrophic lateral sclerosis; and three fairly distinct subgroups were rapidly identified. The first comprises patients designated as having atypical FTLD with ubiquitinated inclusions (FTLD-U)—atypical in that, unlike most patients with FTLD (Neumann et al., 2006, 2007; Cairns et al., 2007; Seelaar et al., 2007), the inclusions do not contain tau or transactive response DNA-binding protein-43 (TDP-43). The second subgroup consists of patients who usually develop a movement disorder with dementia; in many, the neuronal inclusions can be labelled with antibodies to the type IV intermediate filaments, α-internexin and neurofilaments—hence the designation neuronal intermediate filament inclusion disease (NIFID; Neumann et al., 2009). The last subgroup is of patients usually presenting with early-onset amyotrophic lateral sclerosis, sometimes accompanied by dementia, in whom neurons contain basophilic inclusions, staining strongly with haematoxylin (Munoz et al., 2009).

In the current issue of Brain, Lashley et al. (2011) describe their clinicopathological analysis of 14 patients in two of these subgroups: seven with atypical FTLD-U and seven with NIFID. The findings confirm much but not all the work recently reported by Mackenzie et al. (2011) and add more detailed clinical and neuroradiological information that helps to define these two forms of FUSopathy. NIFID is clinically a more variable form of FTLD, with prominent early motor involvement and relatively rapid progression. The disease usually starts in the 40’s or 50’s but occasionally affects people in their 20’s. Patients with atypical FTLD-U present with a more typical frontotemporal dementia and are likely to experience a slower decline but to show earlier and more pronounced orbitofrontal, anterior temporal and caudate atrophy, often asymmetrical, on neuroimaging.

In keeping with the neuroradiological findings, on pathological examination patients with atypical FTLD-U tend to have more
severe frontotemporal and caudate nucleus neuronal loss and gliosis than those with NIFID. Most have severe hippocampal sclerosis. FUS-positive inclusions are quite numerous in both types of FUSopathy but particularly so in NIFID. Of the grey matter structures that are routinely examined, only the cerebellar cortex is usually free of FUS-positive inclusions (Lashley and colleagues describe an occasional FUS-positive intranuclear inclusion in Purkinje cells in one patient with NIFID). The morphology of the FUS-positive inclusions is more variable in NIFID than in atypical FTLD-U but the two subgroups show considerable overlap in appearance of the inclusions. One of the main differences between the present series (Lashley et al., 2011) and that of Mackenzie et al. (2011) relates to the detection of neuronal intranuclear inclusions. Lashley and colleagues found these to be present in only occasional neocortical neurons and only in NIFID. In contrast, Mackenzie et al. (2011) found neuronal intranuclear inclusions to be much more numerous in atypical FTLD-U. The explanation for this apparent discrepancy is not clear. It may reflect methodological differences, e.g. in the panels of antibodies used in the two studies. Lashley and colleagues found that FUS-positive neurites in the subcortical white matter point strongly to the diagnosis of atypical FTLD-U.

There is a rough correspondence between the distribution of inclusions and that of neurodegeneration but the precise relationship between these two pathological processes is still unclear. Although patients with atypical FTLD-U tend to have fewer FUS-positive inclusions in subcortical nuclei, Lashley et al. (2011) report that these patients usually have more severe neuronal loss and astrogliosis in the hippocampus, caudate nucleus, putamen, claustrum, substantia nigra and affected regions of neocortex. The authors suggest that the paucity of inclusions in the cerebral neocortex in atypical FTLD-U may, in part, reflect the loss of neurons but their semi-quantitative data indicate poor correlation between the number of inclusions and the extent of neuronal loss in other parts of the brain.

Lashley et al. (2011) have made an initial attempt to characterize the FUS in atypical FTLD-U and NIFID in terms of solubility in high-salt buffer, detergent (sodium dodecyl sulphate) and 8 M urea. The findings suggest that FUS from patients with atypical FTLD-U is less soluble in high-salt buffer, possibly reflecting post-translational modifications that might contribute to the particular phenotype of this form of FUSopathy. However, the small number of samples analysed biochemically, the variability between samples in the same subgroup and methodological limitations relating to quantification of protein by western blot (such as the non-linear relationship between band density and concentration) make it difficult to draw firm conclusions from these assays.

Two further messages emerge from this and other recent clinico-pathological studies of atypical FTLD-U and NIFID. The first is that we surely need, yet again, to revise the terminology used to describe these diseases and to find better ways of defining them neuropathologically: a diagnosis of atypical FTLD-U no longer depends on the use of immunohistochemistry for ubiquitin. Similarly, in NIFID the immunopositivity of inclusions for α-internexin and neurofilament is very variable, with many inclusions not marking for either of these antigens. The second is an affirmation of the value of careful post-mortem assessment, with systematic, detailed recording of clinical and neuropathological information in a manner that facilitates the subsequent retrieval and analysis of cases on the basis of particular constellations of findings. It is only through this type of careful clinical and pathological phenotypic analysis and molecular correlation that we continue to make progress in understanding the pathogenesis of these neurodegenerative diseases and in identifying possible points of therapeutic intervention.

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doi:10.1093/brain/awr176

References


