SCIENTIFIC COMMENTARY

With or without FUS, it is the anatomy that dictates the dementia phenotype

Not so long ago, Alois Alzheimer’s dominance over Arnold Pick appeared total and irreversible. Alzheimer’s disease was placed at the helm of a global pandemic whilst Pick’s disease was declared a rare curiosity and other non-Alzheimer dementias faced the embarrassment of lacking distinctive histopathology. How rapidly things change! We now know that the family of frontotemporal lobar degenerations (FTLDs), which includes Pick’s disease, is arguably the most important cause of pre-senescence dementia; that its hereditary forms can be transmitted through mutations in the tau or progranulin (PGRN) genes; and that the abnormal protein accumulations include hyperphosphorylated tau and the TAR DNA binding protein TDP-43 (Arai et al., 2006; Bigio, 2008; Boeve and Hutton, 2008; Josephs, 2008; Neumann et al., 2006).

Despite this relatively rapid progress over the past 15 years, there still remain FTLD cases either having non-specific ubiquitin deposits or lacking distinctive inclusions. One of these lingering pockets of resistance now appears to have yielded to the work of Mackenzie and colleagues (Mackenzie et al., 2009). In this issue of *Brain*, these investigators report that 100% of their FTLD cases with heretofore uncharacterized ubiquitin inclusions harbour abnormal accumulations of the ‘fused in sarcoma’ (FUS) product, a protein also recently linked to amyotrophic lateral sclerosis (Kwiatkowski et al., 2009; Vance et al., 2009).

The addition of FUS to the FTLD landscape gives neuropathologists and geneticists additional cause for celebration. But what about clinicians who see patients rather than stained brain slices? Can they use this new knowledge to infer the nature of the pathology at the bedside? Conversely, is there a straight path from molecular pathology to cognition, so that a disease-specific blood or cerebrospinal fluid biomarker may in time prove as informative for clinical deficits as a neuropsychological assessment? The answers are intricate because there is no one-to-one correspondence between cellular pathology and dementia phenotype (Weintraub and Mesulam, 1993). Each neuropathological entity has a preferred, but by no means unique, regional distribution of the damage it causes. The same cellular pathology, therefore, can cause multiple phenotypes, albeit with varying frequencies. A most vivid illustration comes from cases of hereditary FTLD where one member of the family may develop a behavioural dementia whereas another, bearing the same mutation, displays primary progressive aphasia (PPA) or the corticobasal degeneration syndrome (Bugiani et al., 1999; Rademakers et al., 2007).

This complex relationship between pathotype and phenotype has led to a paradoxical state whereby the neuropathologist is confused rather than enlightened by the multiplicity of clinical syndromes, while the clinician may feel equally bewildered by the growing number of molecular pathologies lacking a simple relationship to dementia phenotypes. This confusion is further compounded by the predicament of having to use clinical acronyms for neuropathological diagnoses. For example, the post-mortem diagnosis of progressive supranuclear palsy can apply to patients who had no eye movement abnormality in life; patients with classic manifestations of the corticobasal degeneration syndrome may not necessarily display the pattern of corticobasal degeneration pathology at autopsy; and motor neuron disease-type neuropathology can be seen in many patients with no motor neuron symptoms. As experts in the field have realized for many years, this confusion arises because the ultimate determinant of the clinical phenotype is the anatomical distribution rather than the molecular nature of neurosynaptic dysfunction; and because the relationship between these two components is not fixed.

This principle can be illustrated with multiple examples derived from the two leading causes of dementia, Alzheimer’s disease and FTLD (Fig. 1). In Alzheimer’s disease, cellular death is closely related to the presence of neurofibrillary tangles. The hippocampo–entorhinal complex, a critical node of the episodic memory network, is the initial and principal target of neurofibrillary tangles, giving rise to the progressive atrophy of this region within the continuum that leads from physiological ageing to mild cognitive impairment and dementia (Braak and Braak, 1991). In keeping with this anatomical distribution, an impairment of episodic memory is commonly the initial and most salient clinical manifestation of Alzheimer’s disease. This relationship is so robust and Alzheimer’s disease so common that the predominantly amnestic dementia phenotype has come to be known as ‘dementia of the Alzheimer type’.

However, Alzheimer’s disease pathology may also be expressed as other clinical phenotypes. In some patients, the neurofibrillary tangles are unusually numerous in parieto-occipital areas and the
superior colliculus, leading to the syndrome of posterior cortical atrophy where visuo-spatial disorientation is the most salient deficit (Feher et al., 1989; Hof et al., 1993). In others, the neurofibrillary tangles show their greatest concentrations in prefrontal cortex, leading to predominantly comportmental-executive dysfunction, clinically similar to what is currently designated the behavioural variant of frontotemporal dementia (bvFTD) (Johnson et al., 1999). In still another group of affected individuals, the logopenic subtype of PPA (PPA-L) is associated with left perisylvian atrophy and the neuropathological findings of Alzheimer's disease (Mesulam et al., 2008). The relationship of Alzheimer's disease to these additional syndromes is not exclusive. Infrequent cases of posterior cortical atrophy, slightly less than half of the patients with the logopenic subtype of PPA, and the majority of those with progressive behavioural syndromes have FTLD rather than Alzheimer's disease pathology (Caine, 2004; Kertesz et al., 2005; Mesulam et al., 2008).

The FTLD phenotypes are equally diverse. Occasionally an amnestic dementia of the Alzheimer type will arise in patients with FTLD pathology, especially when onset is pre-senescent (Hodges et al., 2004). More commonly, FTLD leads to various forms of PPA and the behavioural variant of frontotemporal dementia. At least three different clinical aphasia syndromes can be associated with FTLD (Gorno-Tempini et al., 2004; Mesulam et al., in press). In keeping with the asymmetric representation of language, the one common denominator in all three PPA variants is the greater atrophy of the left hemisphere. The agrammatic subtype (PPA-G), characterized by impaired use of grammar and effortful speech, is the one PPA subtype with the greatest atrophy in the inferior frontal gyrus (Broca's area); whereas the semantic subtype (PPA-S), characterized by word comprehension deficits but preserved grammar, is associated with anterior perisylvian and temporal atrophy. The third subtype, manifesting word-finding hesitations and tempo-parietal atrophy (PPA-L), is most commonly linked to Alzheimer's disease pathology but can also be seen, somewhat less frequently, with FTLD. Within the aphasic phenotypes, the agrammatic subtype (PPA-G) is most frequently linked to tau-positive FTLD (FTLD-T) whereas the semantic variant (PPA-S) is most frequently associated with FTLD and TDP-43 positive inclusions (FTLD-TDP; Knibb et al., 2006; Mesulam et al., 2008). However, these are preferential rather than exclusive relationships. There are no known clinical features that reliably differentiate agrammatic patients (PPA-G) with the various forms of FTLD; or logopenic patients (PPA-L) with Alzheimer's disease pathology from those with the pathological features of FTLD.

The second common FTLD phenotype encompasses impairments in the realms of behaviour and executive function (bvFTD). In this issue of Brain, Whitwell and colleagues report a sophisticated analysis that identifies several patterns of clinicano-anatomical concordances in the behavioural subtype (bvFTD), including one with atrophy that is predominantly prefrontal and another where it is predominantly anterior temporal (Whitwell et al., 2009). Major behavioural abnormalities are common to both. However, the former [designated behavioural variant of frontotemporal dementia with predominantly frontal atrophy, bv(F)TD] is also associated with major impairment of executive function whereas the latter [behavioural variant frontotemporal dementia with predominantly temporal atrophy, bv(T)D] displays additional language and memory impairments, reflecting the continuity of its anatomical distribution with that of semantic PPA (PPA-S) and dementia of the Alzheimer type. These more detailed dissections of the syndrome are in keeping with previously reported clinicano-anatomical correlations in groups of patients with the behavioural phenotype (bvFTD) (Liu et al., 2004; Seeley et al., 2008; Chan et al., 2009). Within the small subset of patients who came to autopsy, Whitwell et al. found that the prefrontal-dominant subtype [bv(F)TD] was associated with FTLD-T in three cases, FTLD-TDP in five cases, and with FTLD with non-specific ubiquitin inclusions and Alzheimer’s disease in single cases. In the anterior temporal group [bv(T)D] only patients with MAPT mutations yielded neuropathological information, so that the spectrum of neuropathology in the sporadic forms of this variant remains unknown.

All of the cases with FTLD and FUS inclusions, reported by Mackenzie et al., manifested the behavioural phenotype and had prominent frontotemporal atrophy, further supporting the obligatory concordance between the anatomy of brain damage and clinical phenotype. It is not yet known whether the behavioural syndrome of FTLD with FUS inclusions will subdivide into predominantly temporal or frontal variants described by Whitwell...
et al. and whether FUS pathology will also lead to PPA syndromes. The chances are that there will be considerable heterogeneity in the anatomical distribution and clinical prototypes of FTLD with FUS inclusions since abnormal FUS deposits have also been described in amyotrophic lateral sclerosis (Kwiatkowski et al., 2009; Vance et al., 2009).

The reports by Mackenzie et al. and Whitwell et al. break new ground, one in the cellular biology of FTLD, the other in its clinico-anatomical characterization. We need the former to develop rational treatments and the latter to navigate the maze of phenotypes in a more enlightened way. A major challenge for the future is to clarify the mechanisms that determine the preferential affinities of cellular pathways for distinct neurocognitive networks (Mesulam, 2009; Seeley et al., 2009). Progress in quantifying these differential affinities will increase the precision with which the clinician can predict the disease process. However, until specific biomarkers are developed, it is prudent to remember that such predictions are bound to have considerable margins of error since clinical phenotypes do not have fixed relationships to the molecular nature of the underlying cellular pathology.

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