Sense and sensitivity of novel criteria for frontotemporal dementia

The story goes that when Marco Polo first saw a rhinoceros on Java, he called it a unicorn. As a meticulous observer, he hastened to tell us that these unicorns appeared rather strange (Eco, 2000). Diagnostic categories in medicine guide our attention to discriminating nosological features and prevent us from misidentifying rare disease entities as more familiar diseases they may resemble. Interest in frontotemporal dementia (FTD) was rekindled in the late 1980s when patterns of hypoperfusion and hypometabolism distinct from those seen in functional images of Alzheimer’s disease were noted (Neary et al., 1987, 1988). Clinicopathological series collected in Lund and Manchester and international conferences on FTD in Lund led to the Lund–Manchester criteria for frontotemporal lobar degeneration (FTLD: Brun et al., 1994; Neary et al., 1998) suggesting a common denominator for three different phenotypical presentations: FTD, in which behavioural and personality changes predominate; progressive non-fluent aphasia; and semantic dementia. Other authors have since proposed restricting the term FTLD to neuropathologically confirmed disease (Josephs et al., 2011). The clinical neurological examination in FTD can remain essentially normal until well into the disease course. The history provided, however, often abounds with concrete examples of changes in personal and social conduct that together may be expressed as a qualitative difference in the patient’s personality. The Lund–Manchester papers (Neary et al., 1987, 1988, 1998; Brun et al., 1994) provided clinicians with a vocabulary that allowed these complex patterns to be encapsulated in discrete components: five core features, and an 11-item list of supportive features and nine exclusionary clinical features. According to the literal interpretation, each of the five core criteria listed of supportive features and nine exclusionary clinical features. According to the literal interpretation, each of the five core criteria...
strict requirement may have increased the specificity of the criteria, it had a cost in sensitivity: some of the core features, such as emotional blunting or lack of insight, are missing in a substantial proportion of cases with a behavioural phenotype due to neuropathologically confirmed FTLD (Piguet et al., 2009). Conversely, pronounced amnestic deficits of the hippocampal type, an exclusionary feature, may occur even in the early stages of neuropathological FTLD (Hodges et al., 2004; Knopman et al., 2005). Class I evidence for accuracy of the in vivo diagnosis of FTD at expert centres comes from unselected prospective clinicopathological series (Knopman et al., 2005; Snowden et al., 2011a). The ante-mortem diagnosis of FTD was based on clinical, neuropsychological and imaging findings, incorporating the Lund–Manchester criteria as they became available. In one series based on 433 cases from an academic memory clinic between 1991 and 2003, specificity was 99% and sensitivity 85% (Knopman et al., 2005). Values in the same range are reported in the current issue of Brain (Snowden et al., 2011a) based on a prospective single-centre clinicopathological series from the Manchester group of 228 unselected cases of dementia with relatively early onset who came to autopsy between 1987 and 2009. During life, at expert centres, the clinical diagnosis of FTD can be made with high specificity and sensitivity (Snowden et al., 2011a). Also in this issue of Brain, the International FTD Criteria Consortium (iFTDC) proposes a revision of the Lund–Manchester criteria (Rascovsky et al., 2011). Although there is no single clinical symptom not already listed in one of the original Lund–Manchester papers (Neary et al., 1987, 1988; Brun et al., 1994; Neary et al., 1998), the novelty of these revised criteria lies in the way symptoms are grouped under a limited set of headings and in the flexible approach to the number of symptoms/criteria needed to support the diagnosis. The iFTDC criteria distinguish possible, probable and definite behavioural variant FTD. Three out of six clusters of symptoms have to be positive in order to reach a diagnosis of possible behavioural variant FTD. The clusters are rather intuitive and easy to memorize; and easily applicable to use in the clinician’s office. They refer to global domains of social cognition, behaviour and cognitive functioning and are organized according to some of the more recent insights from social neuroscience. Whereas in the Lund–Manchester criteria, imaging findings were a supportive feature, positive imaging findings have become obligatory for a diagnosis of probable behavioural variant FTD, i.e. hypometabolism, hypoperfusion or volume loss in prefrontal or anterior temporal neocortex. A new element in the criteria is also the exclusion of cases from a diagnosis of probable behavioural variant FTD in whom positive biomarker evidence is found for Alzheimer’s disease based on cerebrospinal fluid analysis or PET amyloid imaging. The iFTDC criteria only relate to the behavioural variant FTD subtype, whereas semantic dementia and progressive non-fluent aphasia have now been defined in a new and separate set of criteria and renamed the semantic and the agrammatic/non-fluent variant of primary progressive aphasia (Gorno-Tempini et al., 2011). For the clinician, it may be useful to realize that the behavioural and language subtypes can overlap to varying degrees despite the fact that the diagnostic guidelines have now been separated. Rascovsky et al. (2011) also provide preliminary empirical evidence for the validity of these criteria. Charts were reviewed of 137 cases of neuropathological FTLD assembled from 16 different centres, excluding cases with primary progressive aphasia or prominent extrapyramidal signs. Among cases with disease onset before 65 years of age, only 60% met the Lund–Manchester FTD criteria compared with 90 and 85% of cases using the novel iFTDC criteria for possible and probable behavioural variant FTD, respectively. Sensitivity decreased by ~20% in the population over 65 years of age at disease onset. The lower sensitivity of the Lund–Manchester diagnostic criteria reported by Rascovsky et al. (2011) compared with earlier series (Knopman et al., 2005; Snowden et al., 2011a) may relate to various factors. For instance, the chart reviewers rigorously adhered item-by-item to the strict requirements of the Lund–Manchester criteria, interpreted literally. In clinical practice (Knopman et al., 2005; Snowden et al., 2011a), criteria will be weighted in a more liberal and experience-based fashion. Diagnostic criteria are essential as means of assessing eligibility for academic and industry-sponsored research studies and for health authorities. To define study populations in clinical trials, a rigorous and literal adherence to criteria is part of Good Clinical Practice, rendering the development of novel criteria an essential step for trial design in behavioural variant FTD (Rascovsky et al., 2011). Prospective validation, however, of the revised criteria will be needed to determine the trade-off between sensitivity and specificity (Chui and Lee, 2003) by comparison with the Lund–Manchester criteria. In Alzheimer’s disease, several novel techniques using spinal fluid or PET studies have opened a window on the underlying pathogenetic processes rather than the anatomical distribution of changes. No in vivo biomarkers that closely reflect the underlying pathophysiological process in terms of neuropathological hallmark lesions exist for FTD, at present. Recent progress in neuropathological characterization of intraneuronal inclusions in FTLD has led to a nosological classification distinguishing three neuropathological subtypes (Neumann et al., 2009; Josephs et al., 2011; Snowden et al., 2011b): FTLD with tau inclusions (FTLD-tau); FTLD with TAR DNA binding Protein (TDP)-43 inclusions (FTLD-TDP; Neumann et al., 2006); and FTLD with fused in sarcoma inclusions (FTLD-FUS; Neumann et al., 2009; Mackenzie et al., 2010)—the most recent piece of the puzzle grouping atypical FTLD with tau-and TDP-43-negative, ubiquitin-positive inclusions (atypical FTLD-U), neuronal intermediate filament inclusion disease and basophilic inclusion-body disease (Neumann et al., 2009). Cases with a neuropathological diagnosis of atypical FTLD-U often had a young disease onset ranging between 22 and 45 years, in the absence of a family history, and a behavioural variant FTD phenotype; but this association will need to be confirmed prospectively (Neumann et al., 2009; Snowden et al., 2011b). The neuropathological subtypes have revolutionized our views on FTLD and may guide further developments in the diagnostic approach to behavioural variant FTD. The future development of in vivo markers for tau, TDP-43 or FUS could be a critical factor determining the pace of progress towards more efficacious therapy. Can careful clinical phenotyping provide indirect measures of the underlying pathophysiological subtype (FTLD-tau, FTLD-TDP or FTLD-FUS)? One of the basic tenets in cognitive neurology is the probabilistic relationship between the neuroanatomical topography of lesions that determines the clinical
symptoms and the underlying neuropathological lesion type (Mesulam, 2000). Comparisons between groups of patients may provide some guidance. In the current issue of Brain, Rohrer et al. (2011) report that interhemispheric symmetry on structural scans and the preponderance of temporal lobar involvement differ between neuropathological FTLD subtypes (Rohrer et al., 2011). For clinical care, it is the predictive value at the individual level that will be most relevant. In the case of the behavioural variant FTD phenotype, approximately half of the cases had FTLD-tau and half FTLD-TDP (Hodges et al., 2004; Snowden et al., 2007; Josephs et al., 2011; Rohrer et al., 2011; Snowden et al., 2011a), with only 10–15% having FTLD-FUS (Josephs et al., 2011; Rohrer et al., 2011; Snowden et al., 2011a). Neuropathological Alzheimer’s disease may still, although rarely, be diagnosed as possible or probable behavioural variant FTD (Alladi et al., 2007; Snowden et al., 2011a). At the individual level, in behavioral variant FTD there are only a few elements which allow one to predict the underlying neuropathological FTLD subtype with high certainty. A patient with behavioural variant FTD who develops signs of motor neuron disease is nearly 100% certain to have FTLD-TDP (the rare exceptions being examples of neuronal intermediate filament inclusion disease; Josephs et al., 2011). The identification of a genetic mutation also allows accurate prediction of the underlying neuropathology (Josephs et al., 2011). For the remainder, intensive research is under way to determine which in vivo parameters in behavioural variant FTD best distinguish different neuropathological subtypes (Rohrer et al., 2011), ultimately leading to algorithms that allow reliable predictions of the underlying pathological FTLD subtype in behavioural variant FTD to be made at the individual level.

Over the past 3 years, revisions of diagnostic criteria have sprung up in the field of Alzheimer’s disease and mild cognitive impairment (Dubois et al., 2010; Jack et al., 2011), primary progressive aphasia (Gorno-Tempini et al., 2011) and, now, also behavioural variant FTD (Rascovsky et al., 2011). Except for preclinical Alzheimer’s disease, each of the revisions retains a striking emphasis on detailed phenotyping at the clinical level. In clinical practice, adherence to the novel criteria will probably not necessitate extra technical investigations beyond those currently requested. Fortunately, none of the criteria even gives a hint that in the future, technical investigations may render redundant the time spent in our offices with patients and informants and the clinical diagnostic acumen. The revision of the FTD criteria provides clinicians with a map to navigate through the world of estrangement caused by FTD and will hopefully also lead us one step closer to successful treatment trials.

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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 frontaltemporal 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 (Crozat et al., 1993; Rabbits 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-interfilaments 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...