Scientific Commentary

Commentary on: Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson’s syndrome and PSP–parkinsonism, by D. Williams, R. de Silva, D. Paviour, et al. (Brain-2004-01045.R1)

When J. Clifford Richardson presented the first clinical report of eight cases of progressive supranuclear palsy (PSP) at the American Neurological Association meeting in June 1963, a number of eminent discussants felt that the condition must be rare, and wondered whether a toxic aetiology might be responsible, as the cases were clustered in Ontario, Canada. With impressive foresight, Richardson remarked: ‘I doubt very much that there is any local geographic incidence. I expect that a good many cases of the same disease will be identified in other areas’ (Steele, 1992).

Fast-forward 40 years, and the prevalence of PSP has been established by two community-based UK studies to be at least 5 per 100 000 (Schrag et al., 1999; Nath et al., 2001). The clinical picture of PSP, at least in its full-blown form, is now readily recognized by neurologists the world over (Burn and Lees, 2002). The patient has a fixed Mona Lisa stare, with a very low blink frequency, the head is retracted and speech is reduced to a distinctive slurred growl. The patient walks clumsily and unsteadily, with a marked tendency to fall backwards. Clothes are soiled with spilled food because the patient is unable to look at the plate when eating and also has dysphagia. Motor recklessness is an early feature of the condition, as are personality change and behavioural disturbance. Pathologically, PSP is characterized by the destruction of several subcortical structures, including the substantia nigra, globus pallidus, subthalamic nucleus, and midbrain and pontine reticular formation. Large numbers of neurofibrillary tangles, neuropil threads and tufted astrocytes are found within these brain regions. These distinctive inclusions are made up of insoluble aggregates of tau phosphoprotein.

In common with many aspects of medicine, the diagnosis of PSP is based upon pattern recognition. Neurologists feel comfortable when they elicit the physical signs outlined above, safe in the knowledge that their clinical diagnosis is likely to be confirmed should the patient come to post-mortem. The paper by Williams and colleagues in this issue of Brain calls into question this neat clinicopathological packaging of PSP and suggests a broader clinical phenotype, particularly in the early disease stages, that is diagnostically challenging. Using 103 pathologically confirmed consecutive cases of PSP as their starting point, the authors extracted clinical information into a standardized proforma from all available medical records. Twenty-nine complete sets of clinical variables were then entered into a principal components analysis, using data from the first 2 years of disease, and two groups were thus identified. Extrapolation of the clinical characteristics to those patients not included in the original analysis confirmed that phenotypic separation into two groups appeared to be robust, with only a low percentage of cases unclassified according to this division. In the first group, called ‘Richardson’s syndrome’ by the authors, mean age at disease onset was 66.1 years, and there was a male over-representation (64% of the cases). The disease duration of this group was entirely in keeping with published literature for survivorship of PSP, at around 6 years (Nath and Burn, 2000). Patients were characterized by early onset of postural instability and falls, supranuclear vertical gaze paresis and cognitive dysfunction, and therefore resembled classic PSP, as described above. In the second group, termed ‘PSP-P’, mean age at disease onset did not differ from that for Richardson’s syndrome, but the sex distribution was approximately even and the disease duration rather more benign, at over 9 years. Moreover, PSP-P patients presented with asymmetrical onset, tremor, and a moderate initial therapeutic response to levodopa. Their condition was, unsurprisingly, frequently confused with Parkinson’s disease.

Williams and colleagues also found that the isoform composition of insoluble tangle-tau isolated from the basis pontis differed significantly between the two groups. Although there was no difference in relative amounts of
pooled guanidine-solubilized four-repeat tau (4R-tau) between the two clinical groups, there was 57% more three-repeat tau (3R-tau) in the PSP-P group compared with Richardson’s syndrome. Thus, the mean 4R-tau/3R-tau ratio was higher in Richardson’s syndrome (2.84) than in the PSP-P group (1.63).

Should these findings surprise us? Recent work suggests that 4.0–5.0% of parkinsonian patients presenting to specialist clinics in Western Europe cannot be categorized using currently available clinical diagnostic criteria for parkinsonian syndromes (Katzenschlager et al., 2003). Might some PSP-P patients be amongst this group? Phenotypic variability has been previously described for PSP, albeit in a non-systematic way. Thus, pathologically confirmed cases of PSP have been reported in which there was pure akinesia, whilst others have documented early and severe dementia (Davis et al., 1985; Matsuo et al., 1991). Additional reports have described features that would conventionally be considered to be unusual for PSP, including unilateral limb dystonia or apraxia, prominent tremor, palatal myoclonus and cricopharyngeal dysfunction (Barclay and Lang, 1997; Masucci and Kurtzke, 1989; Pharr et al., 1999; Schleider and Nagurney, 1977). Furthermore, false-positive misdiagnosis of PSP is not uncommon. Of 180 cases with a clinical diagnosis of PSP in one recent series, 24% did not meet pathological criteria for PSP (Josephs and Dickson, 2003). A history of tremor, psychosis, dementia and asymmetrical findings were more common in the misdiagnosed cases. Several of these findings are common to the PSP-P clinical phenotype described by Williams and colleagues, potentially adding to the diagnostic confusion. Finally, the broadening clinical spectrum of another tauopathy, corticobasal degeneration (CBD) might serve as an example. Originally believed to be a highly asymmetrical akinetic–rigid syndrome with associated dystonia and an alien limb, it is now recognized that CBD is just as likely to present with dementia or aphasia (Bergeron et al., 1998).

Further studies are clearly needed to confirm (or refute) the findings of Williams and colleagues. Principal components analysis can identify groupings within a given data set, and can generate hypotheses, but is not necessarily predictive of differences in independent populations. Furthermore, as the authors themselves acknowledge, there is ascertainment bias inherent in a brain-bank cohort, potentially skewing the proportion of cases in each clinical group (Maraganore et al., 1999). Nevertheless, the low percentage of cases unclassified by the analysis and the additional neurobiological plausibility reflected by tau isoform differences between Richardson’s syndrome and PSP-P reinforce the notion that these two clinical groupings are likely to be real and not spurious.

Future challenges include elucidating why certain brain areas, notably the striatum, pallidum or subthalamic nucleus, are differentially vulnerable to the pathological process, what determines tau isoform composition, and the factors underpinning both temporal and spatial disease evolution. In the meantime, Williams and colleagues have yet again reminded us that there is no such thing as a discrete clinicopathological entity in the movement disorders clinic, and that we need to keep our eyes (and minds) open to the possibility of phenotypic variability. Also, that there is no substitute for repeated and careful clinical assessment of our patients. It is probably better to accept uncertainty, particularly in the early stages of the disease process, than to have the tricky task later of trying to remove a square peg from a round hole.

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References