LETTER TO THE EDITOR

Very early-onset frontotemporal dementia with no family history predicts underlying fused in sarcoma pathology

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Sir, Neumann et al. (2009) recently described a new subtype of frontotemporal lobar degeneration (FTLD). They examined 15 cases of FTLD with inclusions that stained positive for ubiquitin (FTLD-U) but not transactive response DNA-binding protein (TDP-43), and found positive staining for the fused in sarcoma (FUS) protein in all cases.

Interestingly, this case series was also characterized by an early age of onset and absence of family history. The mean age of onset was 38 years, and 12 out of the 15 cases had an age of onset of ≤40 years (Mackenzie et al., 2008; Roeber et al., 2008). Since this early age of onset is highly unusual for frontotemporal dementia (Neary et al., 2005), we hypothesized that an age of onset at ≤40 years, in the absence of a family history, could also predict underlying FUS pathology.

We tested this hypothesis by reviewing the Sydney Brain Bank. From 1993 to 2009, there were 64 cases of pathologically proven FTLD. Within this group, only two brain bank participants had an age of onset ≤40 years and one of these two had familial frontotemporal dementia. Thus, we identified one person satisfying our clinical criteria.

This man had no family history of frontotemporal dementia, although his father does have a late-onset, dopa-responsive Parkinsonian syndrome. He was previously in good health except for some recreational drug use. He was working as a project manager in a large company at the age of 32 years, when he began to lose interest in his appearance, became increasingly disorganized and made uncharacteristically vulgar comments to his family and friends. He had limited insight into his illness. Over the following 3 years, he became increasingly inappropriate and aggressive in his behaviour and was neglecting self-care to the extent that residential care was required. When assessed at the age of 37 years, he was jovial, disinhibited, distractable and echolalic. He paced incessantly and stuffed his mouth with food and non-food. He scored 16/30 on the Mini-Mental State Examination, losing 5 points with orientation, 4 points with serial sevens, 3 points with verbal recall and 1 point each with written and verbal commands. He was perseverative and had a verbal fluency of 5 per min and animal fluency of 7 per min. Bedside neuropsychological examination found impaired frontal executive function (set-shifting) and memory recall, with relative preservation of visuospatial function. Neurological examination found frontal release signs and a mild resting tremor with cogwheel rigidity in the context of anti-psychotic use. There were no fasciculations or alien limb phenomenon. Shortly before his death at the age of 39 years, he was no longer able to vocalize or obey simple commands and had utilization behaviour. Brain MRI found gross frontal and temporal lobar atrophy. Sequencing of the tau, progranulin and charged multivesicular body protein 2B genes did not reveal any mutations.

Brain-only autopsy found knife-edged atrophy of the frontal and temporal lobes bilaterally, with relative sparing of the primary
sensorimotor regions. There was also severe atrophy of the caudate nucleus and putamen. Microscopically, there were rare intracytoplasmic ubiquitin-positive, TDP-43-negative inclusions in the dentate gyrus and frontal regions (Fig. 1). These regions also stained positive with the antibody for FUS (diluted 1:1200; HPA008784 Sigma, St Louis, USA).

Thus, our patient presented clinically with behavioural variant frontotemporal dementia and satisfied the consensus criteria for frontotemporal dementia (Neary et al., 1998). In terms of our hypothesis, although we were only able to identify one case with very early-onset and no family history, this clinical picture did appear to predict underlying FUS pathology. While this appears specific, it is currently unknown as to how sensitive it is. Indeed, a number of cases with FUS-positive inclusion pathology in the original series did have an age of onset >40 years (Neumann et al., 2009).

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Figure 1 Identification of pathological inclusions in the dentate gyrus using routine immunohistochemistry with cresyl violet counterstain. (A) Ubiquitin immunoperoxidase (using Z0458 antibody, DAKO, Denmark; 1:200) showing intracytoplasmic inclusions (see inset for higher magnification). (B) phospho-tau immunoperoxidase (using AT8 antibody, Thermo Scientific, Rockford, IL, USA; 1:1000) showing an absence of pathological inclusions. (C) TDP-43 immunoperoxidase (using 10782-2-AP antibody, Proteintech Group, Chicago, IL, USA; 1:500) showing normal nuclear staining and an absence of pathological inclusions. (D) FUS immunoperoxidase (using HPA008784 antibody, Sigma, St Louis, IL, USA; 1:1200) showing intracytoplasmic inclusions (see inset for higher magnification).

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References