Slowly progressive behavioural presentation in two UK cases with the R406W MAPT mutation

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Mutations in the gene encoding microtubule-associated protein tau (MAPT) are associated with neurodegeneration characterized by the accumulation of tau-positive intracellular inclusion bodies and manifest clinically as frontotemporal dementia (FTD), with variations in clinical phenotype arising due to differences in the location of the mutation (eg intronic versus exonic) and the topographical distribution of the associated neuronal loss. The R406W MAPT mutation is typically associated with an early onset tauopathy presenting clinically with progressive memory decline [1-8] but associated with symmetrical frontotemporal atrophy on MRI [9]. Here we report the first UK cases of the R406W mutation in two unrelated patients with familial FTD, who present with a hitherto-undescribed clinico-radiological phenotype in the form of a slowly progressive behavioural disorder associated with predominantly right-sided temporal lobe atrophy.

The pathogenicity of the R406W mutation has been linked to a partial loss of function whereby microtubule assembly is impaired as a result of alteration in the ability of tau to bind the axonal membrane cortex [10]. It has previously been identified in families from Sweden, Denmark, Belgium, the Netherlands, the US and Japan and in all but one case the phenotype is of slowly progressive memory impairment (mean disease duration: 14.6 +/- 7.0 years) similar to the presentation of typical Alzheimer's disease [1-8], with the one exception to date presented instead with a rapidly progressive neuropsychiatric syndrome [11]. The characteristic neuroimaging change is that of symmetrical frontotemporal atrophy [9]. Post-mortem examination in four R406W kindreds has revealed gross frontotemporal atrophy with abundant neurofibrillary tangles in the medial temporal lobes [7, 8, 11].

Case One was a 66 year old woman with a 12 year history of slowly progressive change in personality, the development of ritualistic behaviours and a preference for sweet foods. Subsequently she developed impairment of episodic memory, prosopagnosia and loss of insight. There was a family history of young onset dementia; her mother developed "similar changes in character" in her fifties and died aged 62 years, and a maternal uncle had dementia. On examination there was no Parkinsonism. Speech was fluent but devoid of content and associated with surface dyslexia. Neuropsychological testing revealed a frontal dysexecutive syndrome accompanied by profound anomia and impairment of verbal and nonverbal memory (see supplementary materials); clinical assessments were not available from other affected family members. Brain MRI revealed temporal lobe atrophy predominantly affecting the right side.

She died shortly after presentation. Post-mortem examination of the brain revealed moderate generalised atrophy with severe temporal lobe involvement and striking atrophy of the hippocampal formation (Figure 1a). Microscopic examination revealed severe neuronal loss in the medial temporal lobe, involving all hippocampal subfields, the entorhinal cortex and adjacent temporal neocortex. Tau immunohistochemistry showed extensive accumulation of pathological tau in the form of intraneuronal cytoplasmic inclusions. These were numerous throughout the brain, particularly in the hippocampi, but also in subcortical nuclei, the cerebellar dentate nucleus, cingulate cortex and other frontal cortical regions. Tau inclusions were hetereogeneous with some resembling Pick bodies and others in the form of coarse tangles and astrocytic plaques (Figure 1b,c).

Case Two, a 64 year old woman, presented with a 13 year history of behavioural change associated with confabulation and altered food preference in favour of sweet foods. Ten years after symptom onset, she developed impairment of episodic and spatial memory and perseverative speech. There was a strong family history of young onset dementia; her paternal grandmother, father, two paternal siblings and brother were diagnosed with dementia before the age of 65 years. Her father had a 21-year history of memory impairment notable for the report of prosopagnosia. General neurological examination was normal with no parkinsonian features. Formal neuropsychological testing revealed a frontal dysexecutive syndrome accompanied by impairment of naming, verbal and non-verbal memory (see supplementary materials); clinical data was not available for other affected family members. Interval MRI brain scans revealed progressive, asymmetrical anteromedial and inferior temporal lobe atrophy, more prominent on the right (see supplementary materials). Subsequent simultaneous FDG-PET/MRI studies revealed primarily right-sided temporal lobe hypometabolism that was more extensive that the corresponding atrophy (Figure 2; Cohen's kappa 0.3).

FTD associated with right temporal lobe atrophy, also termed "right temporal lobe variant" FTD (rtvFTD), is a clinically heterogenous disorder with core clinical features that include behavioural change, prosopagnosia, impairment of episodic memory and 'getting lost'; it is only with neuroimaging support that the diagnosis is usually considered [12]. Emotional detachment, the loss of empathy and irritability are particularly common early features of rtvFTD and are often misattributed to primary psychiatric disease [12]. Disease progression is usually marked by worsening social disinhibition or by progressive aphasia that reflects neuropathological involvement of the right orbitofrontal cortex and contralateral temporal neocortex respectively. The largest clinicopathological series to date of this FTD variant observed either FTLD-Tau or FTLD-TDP-43 in all cases; 7/8 FTLD-Tau cases were associated with MAPT mutations while Pick bodies were observed in the remaining case. In contrast to the majority of MAPT mutations, the morphology and immunocytochemistry of the paired helical filaments usually observed in R604W mutations are identical to those observed in Alzheimer's disease and comprise all six brain tau isoforms [13].

In conclusion both patients, the first cases with the R406W MAPT mutation to be identified in the UK, presented with a slowly progressive behavioural disturbance associated with predominant right temporal lobe atrophy. This represents a novel phenotype in association with the R406W mutation.

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