Clinical features and natural history of neuroferritinopathy caused by the 458dupA FTL mutation

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Sir, In 2007, we described the clinical features and natural history of neuroferritinopathy in 41 patients defined at the molecular genetic level by the presence of EcoN1 restriction digestion site in exon 4 of FTL (also referred to as FTL1), the gene coding for the ferritin light polypeptide (Chinnery et al., 2007). Three French patients in our paper (Cases 13, 36 and 39 in Table 1) had an identical restriction enzyme banding pattern to the original Cumbrian neuroferritinopathy family (Curtis et al., 2001). Their early clinical course (Caparros-Lefebvre et al., 1997) and molecular genetic analysis (Chinnery et al., 2003) had been previously described. We recently received a DNA sample to confirm the diagnosis in a new member of the same French family. Given the recent description of three new FTL mutations (Vidal et al., 2004; Maciel et al., 2005; Mancuso et al., 2005; Ohta et al., 2008), we now sequence exon 4 of FTL to provide a more comprehensive molecular diagnostic approach. This showed that the new French patient had a different mutation, 458dupA, which segregated with the phenotype in the French family and was not found in 300 European controls. This mutation creates the same EcoN1 restriction site as 460dupA described in the original neuroferritinopathy family (Curtis et al., 2001), and given that both the French and English pedigrees shared a microsatellite marker 100kb telomeric to the FTL mutation (Chinnery et al., 2003), we originally concluded that the disease in both families was caused by the same FTL mutation. We now know that this is not the case.

Here, we provide a more comprehensive description of the clinical course of the three previously published males (Caparros-Lefebvre et al., 1997) and the new female case from the next generation harbouring 458dupA. Although the overall phenotype was broadly similar to the 38 cases with 460dupA, there were a number of obvious differences, especially relating to the disease progression since the original publication (Caparros-Lefebvre et al., 1997). The patients with 458dupA developed symptoms between 24 year and 44 years of age, which is well within the 95% confidence intervals for the 38 cases with 460dupA. They displayed the typical presenting clinical feature of ‘fixed’ or ‘mobile’ dystonia in one limb, causing writing difficulties or a gait disorder. Within 2 years, orofacial, pharyngeal and laryngeal dystonia appeared in all four 458dupA cases leading to anarthria and severe dysphagia after a mean time of 10 years. The dystonia remained asymmetrical and did not respond to L-DOPA in any of the four patients. As with the 460dupA patients (Chinnery et al., 2007), none of the 458dupA cases developed spasticity, abnormal tendon reflexes, Babinski signs, abnormal ocular fundi or marked tremor.

On the other hand, three deceased members of the oldest generation of the French family with 458dupA eventually developed cerebellar ataxia. In addition, the new female case in the youngest generation developed a severe static and locomotor cerebellar syndrome rendering her wheelchair bound within 10 years. Although not previously described in the 38 patients with 460dupA (Chinnery et al., 2007), cerebellar ataxia has been described in other neuroferritinopathy families caused by different mutations in FTL (Maciel et al., 2005; Mancuso et al., 2005). A further difference was the rate of clinical progression. 458dupA
was associated with the rapid progression of akineto-rigid syndrome in the three males, cerebellar ataxia with hypotonia in the female and cognitive and behavioral symptoms in all four. This led to a moderate subcortico-frontal dementia (Mattis score ranged from 120 to 128/144; mean Mini Mental State Examination = 24/30, mean Frontal Assessment Battery = 13/18) with apathy (mean Lille Apathy Rating Scale = –8/36, cutoff –17). Two had a diagnosis of depression. The parkinsonian syndrome was characterized by no or slight rest tremor, a mild L-DOPA sensitivity of 30%, an off-UPDRS part III ranging from 30 to 44 and axial involvement responsible for postural instability and falls. Other atypical features included a limitation of vertical eye movements and mild dysautonomia (orthostatic hypotension, constipation, urinary incontinence) developing between 5 years and 10 years. Two patients had a central apnoea syndrome with restrictive respiratory insufficiency (Vital Capacity of 64%) causing excessive daytime sleepiness. In one case this was effectively treated with non-invasive positive pressure ventilation. All developed severe weight loss requiring tube feeding after 10 years in three cases, contributing to death aged 70 years in one. One patient died from a cardiomyopathy at the age of 60 years. Thus, the clinical course in the family with 458dupA, with parkinsonism and dementia, differs from the remaining 38 patients with 460dupA where there was only slight or no parkinsonian features and a mild decrease in verbal fluency (Chinnery et al., 2007).

Structural MR imaging in the family with 458dupA (Fig. 1A) revealed iron deposition and cystic cavitation of the basal ganglia in all patients in a pattern characteristic of neuroferritinopathy (McNeill et al., 2008). This included the dentate nuclei, where functional MR showed abnormalities consistent with neuronal disruption and altered membrane turnover (Fig. 1B). Other clinical investigations revealed similar results to those published previously (Chinnery et al., 2007). Serum ferritin levels were below the normal range in all four cases, despite normal haemoglobin and serum iron levels. Electromyography, electroretinography and peripheral nerve conduction studies were normal. Visual evoked potentials were slightly altered in the two patients tested.

These clinical differences are intriguing, given that both 458dupA and 460dupA disrupt the same restriction site and lead to a shift in the reading frame which lengthens the ferritin light polypeptide by four residues. However, the 458dupA allele is predicted to alter residue 153 from histidine to glutamine, disrupting the subsequent amino sequence. In contrast, residue 153 is wild-type in patients with the 460dupA allele, which is predicted to change residue 154 from an arginine to lysine. Residue 154 is a glutamine in patients with 458dupA, but the subsequent amino acid sequence is predicted to be identical for both mutated alleles. Different neurological and psychiatric features have been described in one family with a mis-sense mutation in FTL (c.474G>A/p.A96T) (Maciel et al., 2005) including cerebellar ataxia. Although it is difficult to reach a firm conclusion at this stage, our observations in the French family with 458dupA support the view that subtle differences in a critical region of the ferritin protein sequence modulate the phenotype of neuroferritinopathy.

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