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LETTER TO THE EDITOR

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 *Eco*N1 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 *Eco*N1 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 100 kb 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

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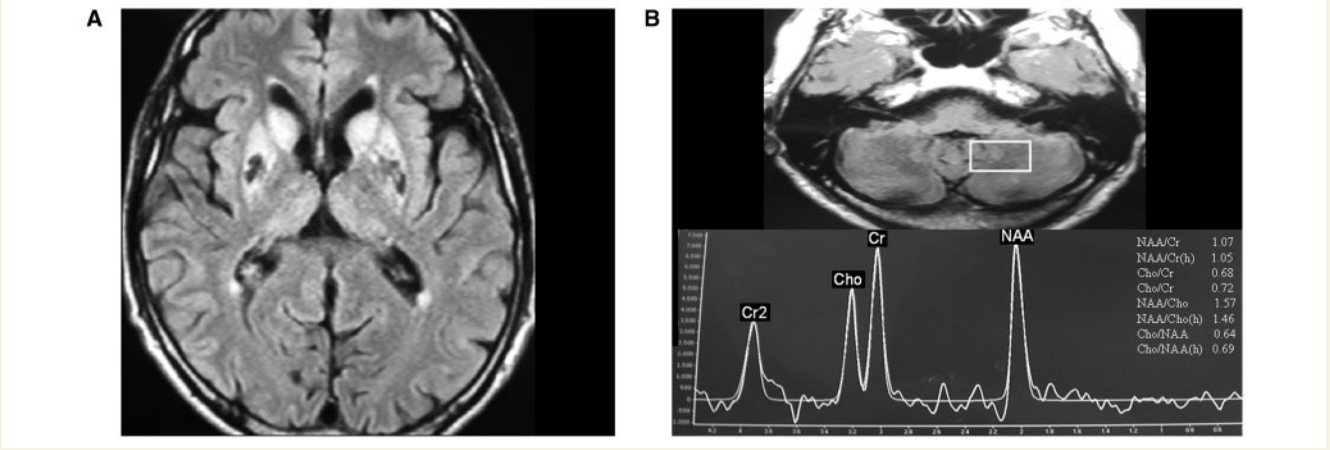

Figure 1 (**A**) Axial-T_2-weighted image showing high signal within caudate and lenticular nuclei associated with cystic cavitation. (**B**) The spectrum acquired with a single voxel technique at long echo time (144 ms) in the deep left cerebellum including the dentate nucleus shows a decrease of NAA/Cr (1.07) and Cho/Cr (0.68) ratios related to neuronal dysfunction and a disturbance of neuronal membrane turnover.

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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