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Genetic determinants of white matter hyperintensities and amyloid angiopathy in familial Alzheimer's disease

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ABSTRACT

Familial Alzheimer's disease (FAD) treatment trials raise interest in the variable occurrence of cerebral amyloid angiopathy (CAA); an emerging important factor in amyloid-modifying therapy. Previous pathological studies reported particularly severe CAA with postcodon 200 *PSEN1* mutations and amyloid beta coding domain *APP* mutations. As CAA may manifest as white matter hyperintensities (WMH) on magnetic resonance imaging, particularly posteriorly, we investigated WMH in 52 symptomatic FAD patients for associations with mutation position. WMH were visually rated in 39 *PSEN1* (18 precodon 200); 13 *APP* mutation carriers and 25 healthy controls. Ten *PSEN1* mutation carriers (5 precodon 200) had postmortem examination. Increased WMH were observed in the *PSEN1* postcodon 200 group and in the single *APP* patient with an amyloid beta coding domain (p.Ala692Gly, Flemish) mutation. WMH burden on MRI correlated with severity of CAA and cotton wool plaques in several areas. The precodon 200 group had younger ages at onset, decreased axonal density and/or integrity, and a greater T-lymphocytic response in occipital deep white matter. Mutation site contributes to the phenotypic and pathological heterogeneity witnessed in FAD.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia, which affects around 36 million people worldwide with numbers predicted to double every 20 years unless effective disease-modifying therapies are found (Fox and Petersen, 2013; Prince et al., 2013). Familial Alzheimer's disease (FAD), caused by autosomal dominantly inherited mutations in *APP*, *PSEN1*, *PSEN2*, and *APP* duplications, accounts for a small minority of AD cases. However, insights revealed through studying FAD have contributed to our understanding of AD pathophysiology, and therapies with the potential for disease modification have been developed in animal models harboring FAD gene mutations. An emerging view is that therapeutic success may only be possible with intervention very early in the disease course. This has motivated the development of treatment trials specifically for FAD, which offers the possibility of treating individuals at a preclinical disease stage (Bateman et al., 2011; Reiman et al., 2010). Furthermore, the young age of patients with FAD, which typically manifests in the 30s–50s, means that comorbidities such as atherosclerotic cerebrovascular

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disease that can complicate clinical trials in sporadic AD are rare. However, the launch of FAD treatment trials necessitates a deeper understanding of the heterogeneity that exists within FAD, particularly with regards to cerebral amyloid angiopathy (CAA), which appears to be an important factor in amyloid-modifying therapeutic trials (Boche et al., 2008; Sakai et al., 2014; Sperling et al., 2011).

Heterogeneity within FAD is apparent in the clinical phenotype and is also present at a molecular and histopathological level. Clinically, although most patients present with progressive amnesia, behavioral and language presentations can occur, and there may be additional neurological features such as seizures, myoclonus, spastic paraparesis, cerebellar and extrapyramidal syndromes (Ryan and Rossor, 2010). Furthermore, different mutations influence amyloid production and deposition in a variety of ways. Some increase amyloid beta 42 (Aβ42) concentrations, others increase the ratio of Aβ42/40 but some do neither, increasing instead the propensity to form protofibrils, which may accelerate Aβ deposition (Nilsberth et al., 2001). Increasingly, it appears to be the qualitative shifts in Aβ profile production caused by FAD mutations that underlies their pathogenicity (Chavez-Gutierrez et al., 2012). Pathological findings in *PSEN1* mutation carriers have revealed considerable heterogeneity in terms of neuronal loss; the type, number, and distribution of amyloid plaques; and the amount and distribution of neurofibrillary tangles (Gomez-Isla et al., 1999; Maarouf et al., 2008; Shepherd et al., 2009). Of particular importance, marked variability in the amount of CAA has been observed that may be driven by the location of the mutation within *PSEN1*. Mutations before codon 200 have been reported to be associated with many diffuse and cored plaques, few white matter plaques, and only mild to moderate CAA, mainly confined to leptomeningeal blood vessels. By contrast, mutations beyond codon 200 have been described as demonstrating larger diffuse and cored plaques surrounding amyloid-laden arteries, with severe CAA that involves both leptomeningeal and intraparenchymal arteries (Mann et al., 2001). Certain *APP* mutations are also associated with very severe CAA, particularly those that lie within the Aβ coding sequence (Revesz et al., 2003, 2009; Shepherd et al., 2009) including the Dutch (p.Glu693Gln), Flemish (p.Ala692Gly), Arctic (p.Glu693Gly), and Iowa (p.Asp694Asn) mutations. Although all these mutations cause prominent CAA, the occurrence of plaques and tangles varies, as does the clinical phenotype (Ryan and Rossor, 2010). The Dutch mutation typically presents with recurrent cerebral hemorrhage, usually followed by dementia; the Flemish mutation presents with hemorrhages or dementia, and the Arctic and Iowa mutations present with dementia only.

Postmortem studies of AD patients who participated in the initial, active, Aβ42 AN1792 immunotherapy (vaccination) trial have revealed that parenchymal amyloid removal may be accompanied by an increase in CAA, thought to be secondary to Aβ42 accumulation via perivascular drainage pathways (Boche et al., 2008). The era of disease-modifying treatment trials for FAD therefore necessitates better characterization and understanding of the variable occurrence of CAA in individuals with *APP* and *PSEN1* mutations. Radiological features of CAA include WMH on T2-weighted magnetic resonance imaging (MRI); corticosubcortical intracerebral hemorrhages including microbleeds on gradient echo imaging; and atrophy best seen on T1-weighted imaging (Chao et al., 2006). Although WMH on MRI are common in the elderly, in whom they may represent multiple pathologies, the young age of patients with FAD makes them less likely to have significant conventional vascular risk factors and MRI manifestations of atherosclerotic small vessel disease (Hopkins et al., 2006). Prominent WMH in this population are, therefore, much more likely to be indicative of an aspect of FAD pathology. The aim of this study was to investigate the degree and location of WMH in symptomatic *APP* and *PSEN1* mutation carriers, together with the age-matched controls and to explore whether the reports of increased CAA in intradomain *APP* mutations and *PSEN*1 mutations located beyond codon 200 are reflected in greater WMH burden on MRI. Pathological investigations were also carried out in 10 cases who had postmortem examination.

2. Materials and methods

2.1. Study subjects

The study was conducted at the Dementia Research Centre, University College London Institute of Neurology at the National Hospital for Neurology and Neurosurgery. Individuals with FAD have been participating in research with our group for over two decades and all symptomatic subjects with a confirmed *APP* or *PSEN1* mutation and appropriate imaging were included in this retrospective study. Fifty-two patients were studied: 13 with *APP* mutations and 39 with *PSEN1* mutations. In the *PSEN1* cohort, 18 subjects had precodon 200 mutations; 21 had postcodon 200 mutations. All FAD subjects were clinically affected and met criteria for probable AD at the time of MRI acquisition. Twenty-five healthy control subjects, mainly spouses and mutation-negative siblings, were also recruited. All subjects gave informed consent, and approval was received from the local ethics committee. Mutation analysis was conducted on genomic DNA, and *APOE* genotype was established for all patients (excluding controls). All subjects with FAD underwent clinical assessment. In most cases, a comprehensive medical history was recorded and from this, the presence or absence of hypertension, diabetes, hyperlipidemia, stroke, transient ischemic attack, and coronary artery disease was assessed to create a composite score for vascular risk that was the sum of the factors present, ranging from 0 to 6 (DeCarli et al., 2004). This information was not available for some of the historical cases and controls but could be analyzed for a large subset (Table 1).

2.2. Imaging

All subjects underwent T2-weighted (T2 or fluid-attenuated inversion recovery) and volumetric T1-weighted MRI. As this study was a retrospective analysis of individuals scanned over almost 20 years, images acquired on 1.5 Tesla and 3 Tesla scanners were included, and there was also some variability in the parameters of the sequences used. However, an equivalent proportion of individuals were scanned at each magnetic field strength in each group. An experienced neurologist (Geert-Jan Biessels), blinded to clinical diagnosis, visually assessed all scans. The scans were rated using the age-related white matter change (ARWMC) scale (Wahlund et al., 2001). The ARWMC scale (range 0–30) rates the degree of WMH on a 4-point scale for 5 different brain regions (frontal, parieto-occipital, temporal, infratentorial, and basal ganglia including thalamus) for the right and left cerebral hemispheres separately. The ARWMC scale was chosen as it has been shown to provide robust results when applied to both computed tomography and MRI, and therefore would be applicable to the T2-weighted MR images available in this study, which were acquired on a variety of different scanners and field strengths. T2*-weighted imaging sensitive to microbleeds was only available in the 12 most recently scanned patients (1 *APP* and 11 *PSEN1* mutation carriers) and has been reported elsewhere (Ryan et al., 2011), so was not included in the present study.

2.3. Pathology

Brains were donated to the Queen Square Brain Bank for Neurological Disorders, University College London Institute of