EDITORIAL

Familial Alzheimer Disease in Canada

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Alzheimer disease (AD) is the most common adult-onset dementia. It is associated with pathological changes including cerebral cortical atrophy, beta-amyloid plaque formation, and intraneuronal neurofibrillary tangles. Common clinical findings include confusion, memory loss, withdrawal, poor judgment, language and visuospatial disturbances, seizures, increased muscle tone, myoclonus, incontinence, and eventually mutism. Familial AD is suspected when there is more than one family member affected and it usually implies several cases over multiple generations. By contrast, early-onset familial AD (EOFAD) is diagnosed in families with multiple affected cases with a mean age of onset before 65 years. These families will usually harbor mutations in APP (10-15%), PS1 (30-70%), or PS2 (<5%)[1]. Genetic discoveries in EOFAD have had a very significant contribution to our current understanding of the pathophysiology of AD. Since clinical genetic testing is now available for all these genes, the diagnosis of EOFAD has also been much simplified, and now allows a more complete and accurate genetic counselling.

In this issue of the Journal, Butler et al[2] report a novel mutation in the PS1 gene causing EOFAD in a large Aboriginal kindred from British Columbia. Their discovery enhances the current understanding of EOFAD since they report a mutation (L250S) that causes an amino acid substitution at codon 250 in the PS1 gene, which had been reported previously in only three other families (United Kingdom, Japan, Bulgaria) comprised of 16 affected individuals. One notable phenotypic difference with previously described families is that none of the cases with the L250S mutation were found to have myoclonus or seizures. This difference in phenotype, however, may simply reflect phenotypic heterogeneity[3], without necessarily implying differences in pathophysiology. In order to achieve a better understanding of the biological impact of individual mutations, we will need to have autopsy material available to determine if given mutations or categories of mutations can produce specific patterns on pathology. Additionally, it will be important to perform *in vitro* studies to discover the functional impact of given mutations at the protein level.

Neuropsychological deficits are consistent with those observed in sporadic AD and include impairments in memory, language and visuoconstruction skills as well as the behavioural manifestations of anxiety, depression and hallucinations later in the disease. Contrary to typical sporadic AD, however, the current study results are interpreted in the context of confounders including a past history of head injury and alcohol abuse in almost all patients, and the absence of appropriate normative data for cognitive testing in an Aboriginal cohort with variable levels of education. All six individuals with a confirmed PS1 mutation have reportedly complained of memory problems before diagnosis, which is not typical of sporadic AD and may suggest a long prodromal phase with subtle cognitive deficits in this group. Disease progression was also quite variable three years after diagnosis, ranging from remaining independent with personal activities of daily living and stable memory, to being placed in a care facility. Whether this reflects phenotypic heterogeneity is unknown yet and further long-term detailed neurobehavioural observations will be needed to better characterize the pattern of changes in PS1 mutations as well as their use in the differential diagnosis of other dementing conditions.

The epidemiology of AD in Canada has been well studied[4], but the contribution of genetic risk to AD at the populational level is still not well established. We know of the universal effect of the E4 allele of apolipoprotein E relating to the age of onset of AD, since all populational studies of AD have replicated this finding[1]. However, we lack a database of the known mutations contributing to EOFAD in Canada, and thus rely on case reports to document their presence. Canada is a large country with many historical populations as well as more recent urban migration, which results in both populational isolates and admixture. For example, the French-Canadian population has been extensively studied for many neurodegenerative disorders. It has been established, at least for some categories as the hereditary ataxias, spastic parapareses, and neuropathies, that specific populational effects have to be accounted for to explain the disease spectrum[5]. In terms of the Aboriginal populations, a lot remains to be studied. These populations are widespread geographically, often have been isolated for centuries until recently, stem from a non-Caucasian ethnic background, and may have more difficulties gaining access to medical care and expertise. For this reason, special attention has to be given to these populations, since the impact of inherited disorders on these communities may be substantial.

At the present time, there are no specific treatments for EOFAD, but promising research will certainly lead over the next decade to clinical trials or therapeutic options for different subtypes based on known pathophysiology. The identification of the subtypes present in Canada will allow these patient populations to benefit from these advances. Genetic counselling remains the main benefit of molecular testing, and it should be available even in remote communities, since it may have a large impact on decisions patients will make relative to reproduction and life planning.

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