Clinicopathological concordance and discordance in three monozygotic twin pairs with familial Alzheimer's disease

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In monozygotic twin pairs with Alzheimer's disease, a high concordance of neuritic plaque and tangle pathology was found but differences in age of onset, duration of disease, apo E status and development of symptoms in the course of the disease

Alzheimer's disease (AD) is on its way to becoming the most frequent neurological disorder globally, with a staggering 81 million affected individuals expected in 2050.¹ The cause of AD is still largely unknown although the role of amyloid beta in the form of soluble oligomers or aggregated in the form of neuritic plaques seems to be key.² The "nature versus nurture" debate is also relevant for AD because genetic factors have been found and are known to cause AD, usually at a younger age of onset. Environmental factors are also important and may explain variance in age of onset, duration and course of disease.

Studies of monozygotic twins with AD offer a unique opportunity to study this issue, but are very rare.

In this issue of *J Neurol Neurosurg Psychiatry*, Brickell and colleagues³ offer us the case histories of three monozygotic twins with full neuropathology and genetic information (see page 1050). The most striking findings included a high

concordance of neuritic plaque and tangle pathology among all twins, but differences in age of onset, duration of disease, apo E status and development of symptoms in the course of the disease.

What does the story of these six individuals tell us? Clearly, despite only one twin pair having an established PS1 mutation, the genetic information on the two other pairs suggest a strong genetic influence. The concordance of pathology suggests that this is highly genetically determined, while clinical expression may vary under the influence of environmental factors. What these environmental factors are remains obscure, because in fact the presented twin pairs did not differ that much in this respect. This observation seems to be in contrast with the suggestion that genetic factors influence clinical symptomatology, albeit referring to apoE status only.^{4,5}

What do these findings imply for AD in general? The trend in AD research is more and more towards determination of the

underlying (AD) pathology by CSF markers, amyloid imaging with PET and (serial) structural MRI rather than clinical features alone.⁶ This approach is supported by the findings of Brickell and colleagues,³ as typical AD pathology was uniformly present among all, while clinical features differed.

Another interesting observation relates to the occurrence of Lewy body pathology in these twins. This was discordant and seemed to be more related to age at onset and disease duration than genetic factors, indicating that the longer the disease duration the higher the Lewy body burden. Also, there may be differential genetic and/or environmental factors between AD and Lewy body pathologies.

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