

Editorial

The amnestic prodrome of Alzheimer's disease

The launch of two new drugs (Aricept® and Exelon®) for the treatment of Alzheimer's disease heralds the end of an era of therapeutic nihilism in the dementias and emphasizes the need for accurate early diagnosis. It is generally accepted that if disease-modifying treatments of this type are to be effective then it is imperative that we have more sensitive and discriminating methods of establishing a diagnosis before the onset of global cognitive impairment. Numerous papers have been published which address the neuropsychological or imaging findings in early Alzheimer's disease, but the paper by Fox *et al.* (1998) is an important step in the quest to determine the earliest cognitive changes in Alzheimer's disease. In addition to this work its relevance to the question of early diagnosis has important theoretical implications for understanding the pathological changes which occur in Alzheimer's disease.

In order to understand the relevance of Fox *et al.*'s findings it is necessary to cover some recent history. The concept of dementia, and hence Alzheimer's disease—the commonest cause of dementia—has undergone revolutionary changes over the past two decades. Sadly, medical students are still taught old definitions of dementia along the lines of 'progressive global cognitive decline in clear consciousness', whereas it is increasingly clear that each neurodegenerative disorder has a distinct cognitive signature, at least in the early stages of the disease, which mirrors the distribution of the neuropathological changes. In the case of Alzheimer's disease, the earliest neuropathological changes (neurofibrillary tangles and amyloid plaques) are typically seen in the medial temporal lobe including the hippocampal complex (Braak and Braak, 1991), although it will be argued below that this view is probably an oversimplification. To reflect this evolving concept, more modern definitions of dementia, such as the widely used NINCDS-ADRDA criteria require 'deterioration in two or more areas of cognition, including memory, sufficient to interfere with work or social function'. This is obviously an improvement, but still requires the presence of substantial cognitive impairment which arguably delays diagnosis beyond the stage at which disease modification is likely to have a substantial impact. If the pathological changes of Alzheimer's disease actually begin in a consistent and circumscribed brain area, then it is reasonable to predict that the earliest changes may occur in a single aspect of cognition. A central focus of neuropsychological research in Alzheimer's disease is, therefore, aimed at addressing the question: 'what goes first?' The paper by Fox *et al.* adds further weight to the argument that the first deficit, at

least in familial Alzheimer's disease, is in the domain of anterograde episodic memory (i.e. new memory for distinct events or episodes), but it also draws attention to the fact that memory loss may not be the only impairment in the initial stage.

Demonstrating that memory impairment is the earliest deficit in sporadic Alzheimer's disease has been methodologically difficult, but evidence has slowly accrued in support of this hypothesis. It is certainly well established that tests of anterograde episodic memory (such as story recall and word list learning) discriminate best between patients with mild Alzheimer's disease and normal elderly controls (e.g. Welsh *et al.*, 1991). The devastation of episodic memory in Alzheimer's disease is illustrated by the fact that delayed recall of verbal material is so poor that we have been unable to find any significant difference on this measure between patients with very mild and moderate dementia (Hodges and Patterson, 1995; Greene *et al.*, 1996a). It should be noted, however, that few patients present with pure memory loss and according to current criteria such patients would not qualify for a diagnosis of Alzheimer's disease. To address this question, a number of investigators have followed up elderly patients with isolated memory impairment (sometimes termed questionable or minimal Alzheimer's disease) and shown an extremely high rate of subsequent dementia (Tierney *et al.*, 1996; Bowen *et al.*, 1997). Group and single-case studies suggest that this 'predementia stage' of isolated amnesia may persist for many years prior to the development of overt dementia (Linn *et al.*, 1995; Caffarra and Venneri, 1996). In our own clinic-based studies we have followed patients with severe, but isolated, amnesia for 5 or more years before other cognitive deficits develop, typically in the domains of semantic memory or attentional function.

The problem with all of the studies outlined above remains the lack of pathological verification of diagnosis, plus the fact that patients with non-amnestic presentations may be excluded, hence biasing studies in favour of showing that memory problems predominate in early Alzheimer's disease. Over the last 5 years we (like other groups) have documented patients with pathologically proven Alzheimer's disease who present with progressive biparietal atrophy, causing Balint's syndrome (Mackenzie-Ross *et al.*, 1996), progressive visual failure or progressive non-fluent aphasia (Greene *et al.*, 1996b). Indeed, one of our best studied patients with the latter syndrome (case P.G., Croot *et al.*, 1998), who performed normally on tests of memory and lived independently for over 5 years, recently came to post-mortem examination and

had classic Alzheimer's pathology (amyloid plaques and tau positive intraneuronal neurofibrillary tangles), albeit with an atypical distribution.

Against this background it can be seen why patients at risk of developing familial Alzheimer's disease present a unique opportunity: they tend to develop the disease at a predictable age, there is no doubt about the diagnosis, bias in case selection according to initial symptoms is avoided and unaffected family members are ideal controls. Fox *et al.* have shown that presymptomatic cognitive deficits may be present up to 5 years before individuals fulfil criteria for probable Alzheimer's disease and that episodic memory impairment is the clearest indicator of subsequent disease, confirming, indirectly, the hypothesis that the brunt of pathology falls on the medial temporal lobe. As the hippocampal complex appears to be particularly vital for recall memory rather than recognition memory (Aggleton and Saunders, 1997), it is possible that recall-based tests of memory may be even more sensitive. It should also be noted that the early cognitive deficits were not *confined* to the domain of memory: the impairment in performance IQ suggests that more widespread changes may be present, perhaps more subtle alterations in synaptic function in posterior cortical areas.

In their discussion, the authors raise the very important issue of which method of investigation is the most sensitive for early diagnosis. In other words, do neuropsychological deficits precede, parallel or follow changes which have been shown by functional (reduced glucose metabolism on PET) and structural (hippocampal atrophy on MRI) brain imaging? Other unresolved issues are the applicability of the findings in familial to sporadic Alzheimer's disease, and the question of cognitive heterogeneity. The consideration of group data may well mask individual patient profiles presenting with other isolated cognitive impairments.

This study emphasizes the central role of neuropsychological assessment in the evaluation of patients with failing memory. It also edges us closer to a diagnosis of suspected Alzheimer's disease before the onset of dementia proper, on the basis of isolated memory impairment (or other cognitive syndromes yet to be fully elucidated), supported by appropriate functional and/or volumetric brain imaging. Gone are the days when a brief mental state examination and a CT scan were adequate for the investigation of suspected Alzheimer's disease.

John Hodges

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