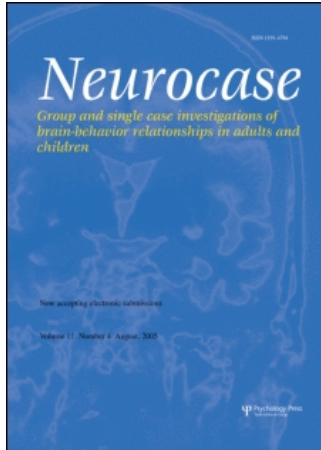


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Knight's move thinking? Mild cognitive impairment in a chess player

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We report the case of a chess player with superior premorbid cognitive function who presented to the Cognitive Disorders clinic at the National Hospital for Neurology and Neurosurgery with a 2-year history of symptoms of possible memory loss. Initially the MRI scan appearance was within normal limits and his cognitive scores inside the normal range; subsequently his cognitive function deteriorated and he fulfilled criteria for Mild Cognitive Impairment (MCI) two years later. Unexpectedly he died of an unrelated illness seven months later and post mortem examination of the brain was carried out, revealing advanced Alzheimer's disease (CERAD definite and NIA-Regan Institute high likelihood).

This case highlights the difficulties encountered in assessing patients with superior premorbid function in the early stages of Alzheimer's disease, and reveals the value of serial MRI and neuropsychological assessment in detecting and monitoring early neurodegenerative disease.

Introduction

Mild Cognitive Impairment (MCI) is a term used to describe a transitional stage between normal ageing and dementia. To fulfil criteria for this classification a patient must have significant memory impairment defined by reports from the patient, relatives or carer and evidence from neuropsychological testing (performance at 1.5 SD below age and education-matched controls on indices of memory function). This classification also requires the absence of established dementia or impairments in activities of daily living (Jack, Jr. *et al.*, 1999). Patients with MCI are an important diagnostic group, as it is known that such individuals progress to Alzheimer's disease (AD) at a rate of approximately 12% per year (Petersen *et al.*, 1999). Nevertheless some patients with MCI will not develop dementia, and others may develop a neurodegenerative process other than AD. Identifying those patients with MCI who will develop AD is a priority, as it is these patients with early

or incipient disease who may be most likely to benefit from disease-modifying agents, when they become available.

Longitudinal studies of both presymptomatic subjects at risk of familial Alzheimer's disease (FAD) and subjects with normal baseline cognition who developed sporadic AD, have demonstrated that excess cerebral atrophy occurs years prior to the onset of cognitive deficit sufficient to diagnose MCI or AD (Fox *et al.*, 1996; Jack *et al.*, 2000; Schott *et al.*, 2003; Rusinek *et al.*, 2003). This excess atrophy is particularly prominent in medial temporal lobe structures, including the hippocampus. Several studies have used medial temporal lobe atrophy to predict which patients will progress from MCI to AD (Petersen *et al.*, 2001). Similarly neuropsychological assessments in these groups of patients have indicated that subtle deficits in verbal and visual recall can be predictive of future cognitive impairment (Fox *et al.*, 1998; Elias *et al.*, 2000).

It is often difficult for clinicians to identify which patients with memory complaints will go on to develop measurable memory deficits and progress to AD. This may be particularly relevant to high functioning individuals, where due to greater cognitive reserve absolute clinical deficit may not accurately reflect the underlying disease process. Generally it is only when a subject presents with memory deficits sufficient to impinge upon their daily functioning that a diagnosis of dementia can be made (American Psychiatric Association, 1994) and therapy considered.

In this article we describe a patient who presented with early symptoms of memory impairment, and subsequently declined to fulfil criteria for MCI. During the clinical transition from MCI to early AD, the subject died of other causes,

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permitting a definitive histological diagnosis of sporadic Alzheimer's disease to be made.

The subject was investigated and monitored throughout the disease process with sequential neuroimaging and neuropsychological evaluation, allowing assessment of the potential of these investigative tools to detect the onset of cognitive decline and monitor its progression.

Methods and materials

Neuropsychology

Neuropsychology was performed at four time points (see Table 1). A standardized battery was performed, including the National Adult Reading Test (NART) (Nelson and Willison, 1991), the verbal and performance sub-scales of the Wechsler Adult Intelligence Score-Revised (WAIS) (Wechsler, 1981), the Recognition Memory Test for words and faces (RMTw and RMTf) (Warrington, 1984), Paired Associates Learning Test (PALT) (Warrington, 1996), the Graded Naming Test (GNT) (McKenna and Warrington, 1983), the Oldfield picture naming test (Oldfield and Wingfield, 1965), two subsets from the VOSP battery (Warrington and James, 1991), word fluency and cognitive estimates (Shallice and Evans, 1978).

Magnetic Resonance Imaging

T1-weighted volumetric MR scans were acquired at five points, over a 36-month interval on the same 1.5-T GE Signa Unit (General Electric, Milwaukee, WI) using a spoiled gradient-echo technique (256 × 192 matrix, FOV 20 × 20 cm, TE 4.2-14/INVISIO/NEXI/FLIP 20°) giving 124 contiguous 1.5-mm thick slices. T2-weighted and proton-density scans were acquired at each time point. An experienced neuroradiologist reported all MR scans. Image processing was carried out

using the MIDAS software tool (Freeborough *et al.*, 1997). A previously described nine-degrees-of freedom rigid body registration (Freeborough *et al.*, 1996) was used to match serial scans accurately to each other. The brain boundary shift integral (BBSI) (Freeborough and Fox, 1997) was used to quantify whole brain loss. Semiautomated techniques, using intensity threshold, were applied to delineate regions of interest on registered scans and allow calculation of hippocampal and ventricular volumes at each timepoint.

Case history

A 73-year-old right-handed retired academic presented to the Cognitive Disorders clinic at the National Hospital for Neurology and Neurosurgery in December 1998, reporting a two-year history of decline in his ability to play chess. He complained that whilst previously he could plan his game seven moves in advance, he could now only plan three or four. He had only noticed this change gradually with no suggestion of a stepwise decline in his abilities. His wife felt that he might be slower at picking up the subject of conversations and was becoming slightly more repetitive in his remarks; however, it was generally felt by the family that there were no significant cognitive impairments and that he alone was convinced that he was suffering from progressive memory loss. He continued to do the finances at home, and there was no change in personality, language, writing or praxis.

Medical history was unremarkable apart from a prostatectomy for bladder outflow obstruction (with benign histology). He was a nonsmoker and there was no history of diabetes mellitus, hypertension or ischaemic heart disease. Information on cognitive impairment in other family members was not available.

General examination was unremarkable. He scored 27 out of 30 on the mini-mental state examination (MMSE) (Folstein

Table 1. Cognitive assessments scores

Date	7.12.98	26.7.99	4.5.01	23.4.02
VIQ	117	128	118	127
PIQ	126	122	128	123
RMTw	47/50 (75-90%)	40/50 (25%)	40/50 (25%)	34/50 (<5%)
RMTf	43/50 (50-75%)	39/50 (25%)	35/50 (5%)	34/50 (<5%)
PALT T1	17/24 (75%)	14/24 (50-75%)	4/24 (5%)	8/24 (10-25%)
PALT T2	21/24 (50-75%)	18/24 (50%)	12/24 (10-25%)	12/24 (10-25%)
GNT	20/30 (25-50%)	18/30 (25%)	15/30 (10%)	13/30 (5%)
Oldfield	28/30	28/30	26/30	25/30
Object Decision	18/20	15/20	15/20	15/20
Incomplete letters	19/20		19/20	19/20
Word fluency	31 (S)	22 (S)	23 (S)	26 (S)
Cognitive estimates	reasonable	reasonable	reasonable	Reasonable
Digit span	5	5	4	4

VIQ = Verbal Intelligence Quotient, PIQ = Performance Intelligence Quotient, RMTw = Recognition Memory Test for Words, RMTf = Recognition Memory Test for Faces, PAL T1 and PAL T2 = Paired Associate Learning Test trial 1 and trial 2, GNT = The Graded Naming Test. Percentiles in parentheses next to the scores.

et al., 1975). Investigations at that time revealed a normal chest x-ray and ECG; routine blood tests including thyroid function tests, autoimmune profile and vitamin B12 levels were normal apart from a raised cholesterol level at 6.9 mmol/L. The EEG showed a mild non-specific disturbance of cerebral activity in the left temporal region, with preserved alpha rhythm and no epileptiform activity. At the first assessment, the neuropsychological investigation was essentially within normal limits with only two exceptions, naming and verbal short term memory. This average score coupled with a few circumlocution errors was taken to indicate mild nominal difficulties in the context of his superior expressive and reading vocabulary, even making allowance for German being his first language. His forward digit span was only five, which was also noticeable in the context of his otherwise high average/superior cognitive performance (Table 1). Initial MRI scanning revealed generalized cerebral atrophy thought to be in keeping with normal ageing, although the hippocampal volumes were at the lower end of normal. White matter change compatible with mild vascular disease was noted as well as a small peripheral haemorrhage in the right parietal region. Whilst not reaching criteria for MCI (Jack Jr. *et al.*, 1999), the assessing clinician felt that the patient's history was suggestive of very early Alzheimer's disease.

The patient was reviewed three times over the following year. During this period, neither he nor his wife reported significant progression of symptoms, although when playing chess he now reported a tendency to lose the pattern of play in addition to difficulty planning moves. The second MMSE 6 months after presentation was 28 out of 30. However, repeat neuropsychology at the same time revealed mild decline in both verbal and visual memory, as well as tests of perception and word retrieval (Table 1). A few semantic errors were noted (e.g., trampoline for trapeze). Repeat MRI in November of 1999 was again reported as showing mild generalized atrophy within normal limits for his age. However, registration of this scan to the initial MRI carried out 9 months earlier demonstrated ventricular enlargement and hippocampal and whole brain atrophy, in excess of that seen in normal ageing.

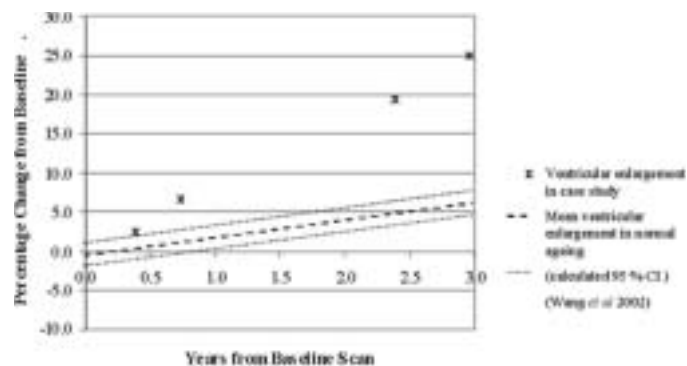


Fig. 1a. Graph to show percentage change of brain volume from baseline scan over a three-year period. The 95% confidence intervals are based on standard errors.

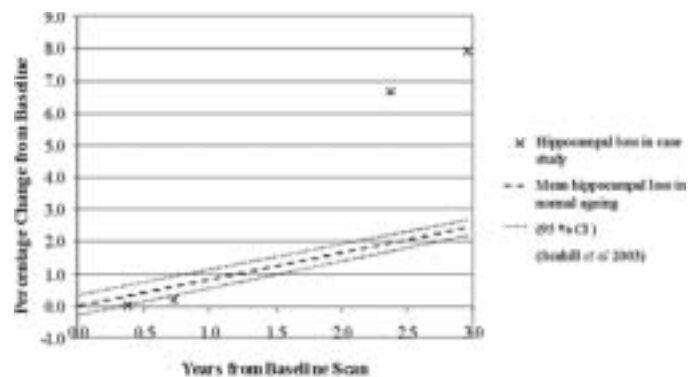


Fig. 1b. Graph to show percentage change of total hippocampal (left plus right) volume from baseline scan over a three-year period. The 95% confidence intervals are based on standard errors.

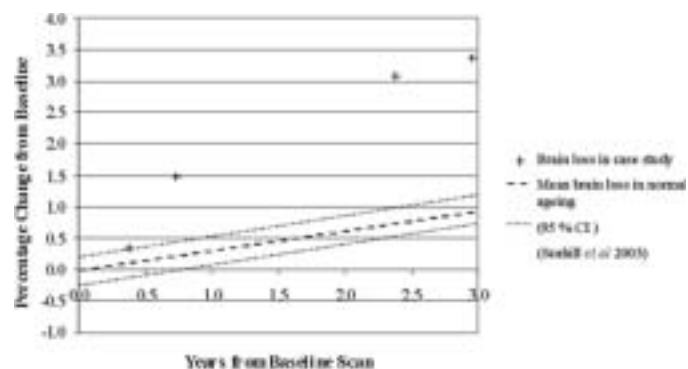


Fig. 1c. Graph to show percentage change in ventricular volume from baseline scan over a three-year period. The 95% confidence intervals are based on standard errors.

He was next seen in February 2001, at which time he reported continued difficulty remembering day-to-day events and names. Although still reading historical books, he complained that this took longer than before and he had essentially stopped playing chess. Whilst still managing the home finances, he found this more difficult mainly due to problems with calculation. He continued to drive competently and was never disorientated in familiar surroundings. The MMSE was now 25 out of 30. His third neuropsychological assessment revealed a further decline in his verbal and visual memory function. For the first time he obtained scores at 5th percentile on the visual recognition memory test and on the first trial of the paired associates learning test. With impaired scores, more than 1.5 standard deviations from the mean (Jack, Jr. *et al.*, 1999), he now fulfilled diagnostic criteria for MCI. A further decline was also observed in his nominal functions. An EEG carried out at this time demonstrated occasional paroxysmal theta activity over the left fronto-temporal region but well preserved alpha rhythm.

In October 2001, his wife reported a slow but definite deterioration in his memory. She had taken over running of the home finances and the family had noticed that he had become increasingly repetitive in questioning. In July 2002 the patient

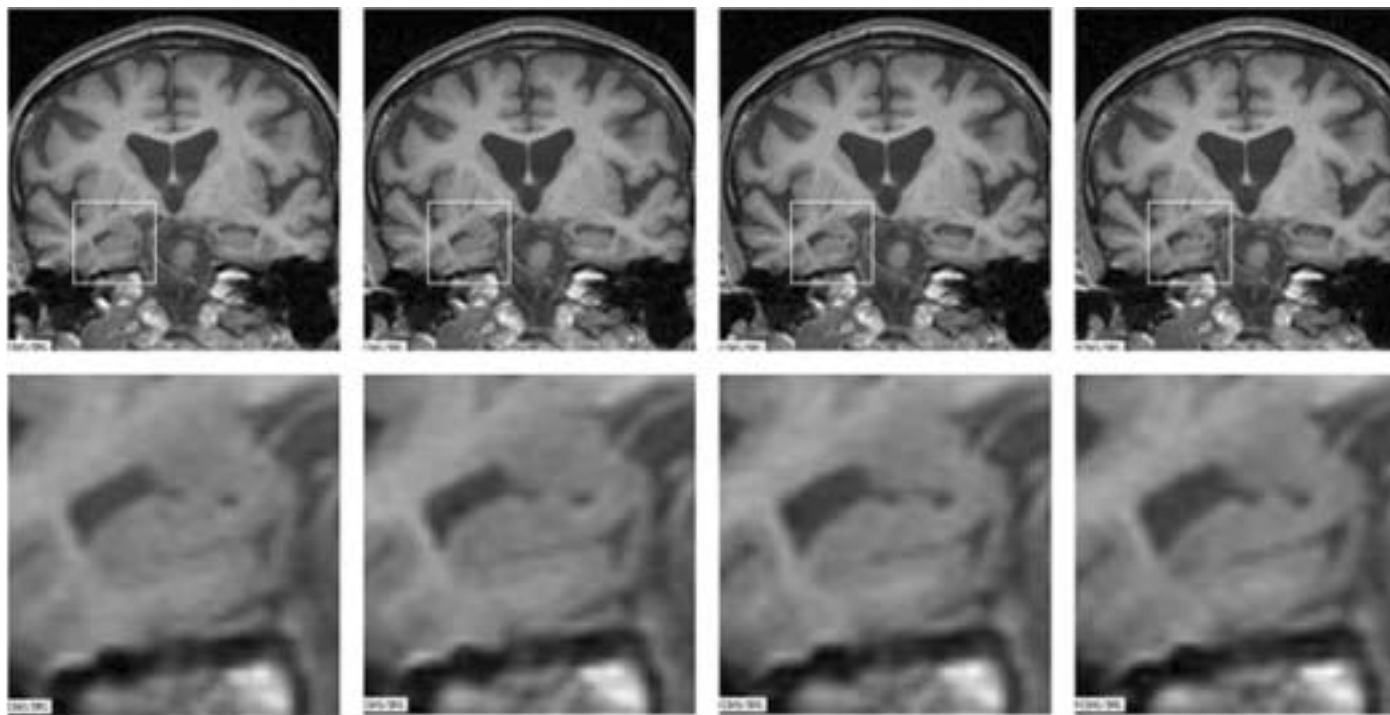


Fig. 2. Magnetic Resonance Images showing coronal sections of the brain at baseline, 9 months, 2 years and 3 years (from left to right).

reported that as well as his memory slowly worsening, he was less comfortable in social situations, forgetting his colleagues' names and details of what he had recently read. He now reported getting lost in unfamiliar environments. However he was still enjoying his daily activities of shopping, cooking and chess, and had learnt how to use a computer.

The neuropsychological assessment at that time showed global severe memory and nominal impairment, the majority of his errors on the naming task were semantic and circumlocution. Interestingly, his performance remained in the superior range on tests of general intelligence throughout the four assessments. MRI scans carried out in 1999, 2001, and 2002 were compared using image registration, and showed pathological increase in ventricular size. A pathological decrease in hippocampal volume was seen comparing the baseline scan to those acquired in both 2001 and 2002 (Figure 2 and Figure 3). The neuroimaging features were thought to be compatible with a diagnosis of Alzheimer's disease. However, in the light of reports of his high level of daily functioning (through correspondence and at consultations, from both the patient and his family), clinically the diagnosis was felt to fall between MCI and AD. The patient was offered treatment with a cholinesterase inhibitor, which he declined. Shortly after the fourth assessment the patient died of an unrelated cause and a post-mortem examination was performed.

Pathological examination

At post mortem the brain weighed 1318 grams. The right half of the brain was fixed in 10% formalin and examined neuropatho-

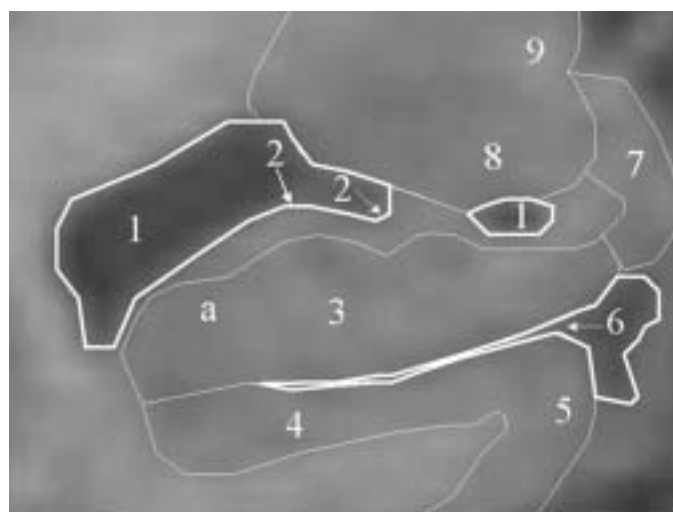


Fig. 3. Schematic coronal overlay showing the hippocampus and surrounding structures: (1) temporal horn of lateral ventricle; (2) internal digitations; (3) cornu ammonis CA1; (4) subiculum; (5) parahippocampal gyrus; (6) uncal sulcus; (7) subiculum in uncinate gyrus; (8) accessory basal nucleus of amygdala; (9) cortical nucleus of amygdala.

logically while the left half was frozen and stored at -80°C . Neuropathological examination showed that there was minimal enlargement of the sulci of the right frontal lobe, but no other evidence of cortical atrophy. The temporal horn of the right lateral ventricle was moderately enlarged due to reduction in

size of the posterior hippocampus. The main basal arteries showed mild atheroma. There was mild pallor of the locus coeruleus. Histological examination revealed frequent A β -positive neuritic plaques in the temporal neocortex, which were moderate in number in the frontal and parietal cortices. The severity and extent of the neurofibrillary tangle pathology was such that it corresponded to Braak and Braak stage VI. In addition there was evidence of severe cerebral amyloid angiopathy and Lewy body pathology in brainstem and limbic structures.

The diagnosis was of Alzheimer's disease (CERAD definite and NIA-Regan Institute high likelihood) with severe cerebral amyloid angiopathy and evidence of transitional Lewy body disease.

Discussion

This case demonstrates the limitations of currently available clinical investigation in the diagnosis of individuals with very early Alzheimer's disease. This is particularly relevant in high functioning individuals where, due to high cognitive reserve, the absolute clinical deficit may not be proportional to the cerebral changes found on histopathology.

When first assessed, this gentleman who presented with a 2-year history of memory impairment had a neuropsychological assessment within normal limits for age and education, the only exception being a weak performance on nominal and verbal short term memory tasks. MCI was diagnosed 2 years later after he had developed sufficient impairment on the visual version of the Recognition Memory Test and on one of the trials of the Paired Associate Learning Test to fulfil diagnostic criteria (Jack Jr. *et al.*, 1999). At his final assessment, it was unclear whether he met the criteria for probable Alzheimer's disease. Although there were documented impairments in recognition memory and nominal functions, these were at odds with reports of his daily functioning from his wife who maintained that at that time he had "excellent mental awareness."

These results highlight the potential difficulty in detecting and following subtle memory deficits in high functioning individuals at the onset of a dementing process. Where MR images were individually reported as demonstrating changes within normal limits for ageing, registration of serial MR images suggested that increased cerebral atrophy characteristic of AD was occurring as early as 1999. Similarly the change seen on serial neuropsychological assessments better demonstrated and was more representative of the disease process than single assessments.

One of the difficulties in assessing cognitive complaints may be the qualitative rather than quantitative nature of the reported symptoms, such as misplacing objects or forgetting dates. Without an accurate knowledge of the premorbid state it is difficult to gauge whether the severity of symptoms has changed. In this case, the symptoms were quantifiable, as the subject described a change in his ability to plan from 7 moves ahead to only 4 in a game of chess.

Memory complaints are usually the first symptoms of Alzheimer's disease and occur before cognitive deficits can be demonstrated on tests (Fox *et al.*, 1998). In this case the subject had subjective memory impairment two years prior to presentation. In longitudinal studies of subjects at risk of familial AD the most common symptoms declared by individuals who subsequently developed AD, were very mild episodic memory problems (Fox *et al.*, 1998). In this series the subject, spouse or close family member typically noticed these problems 6 months prior to the first measurable cognitive deficits.

Population studies have also indicated that memory complaints are of importance particularly in highly educated elderly individuals, and should be taken seriously due to the ceiling effect of short cognitive screening tests (Jonker *et al.*, 2000).

Many population studies have emphasized the importance of an informant history (i.e., from a spouse or relative) in the evaluation of memory complaints, particularly when investigating symptoms of memory loss as predictors of cognitive impairment (McGlone *et al.*, 1990; Jorm, 2003). The informant's impression of their relative's memory is important as it is likely to be more objective and less influenced by a patient's anxiety or depression. However, the drawback of relying too heavily upon this information is illustrated in this case, as well into the course of the disease his family felt that he had no perceivable memory deficits (letter written by the subject's wife prior to his third consultation in 1999).

Although initial MRI scans showed atrophy within the range for normal ageing, registration of the MR images from 1999 showed definite increased atrophy (Figure 2). These findings are in keeping with previous reports, demonstrating that both global and medial temporal lobe atrophy occurs years prior to diagnostic criteria being met (Jack *et al.*, 2000; Schott *et al.*, 2003; Rusinek *et al.*, 2003). Repeat neuropsychological assessment revealed mild further decline in nominal and memory functions but certainly the advanced Alzheimer's pathology seen at post-mortem would not have been predicted in an individual with a clinical history of only mild decline in functioning, whose verbal and performance IQs were both still above 120. By contrast, the MR images compared over the same period revealed clear ventricular enlargement and medial temporal lobe atrophy (Figure 1 and Figure 2) more typical of moderate to severely advanced Alzheimer's disease.

Whilst MCI is a useful concept, alerting both physicians and patients alike to the fact that there is a transitional stage between normal aging and development of dementia, this case illustrates some of the problems still associated with the current diagnostic criteria for MCI. Criteria requiring memory to be impaired 1.5 standard deviations below the mean (Jack, Jr. *et al.*, 1999) clearly require a greater decline of cognitive function in high-functioning individuals than in those performing at an average, or sub-average premorbid level.

When disease-modifying treatments become available, it will become increasingly important to develop strategies for the early detection and diagnosis of AD (and its pathological

correlates) to allow treatment to be introduced at a time when the patient can still benefit, and pathology is not as advanced as it was in this case.

It is interesting to note that a percentage of cognitively normal elderly patients coming to post mortem are found to have a degree of AD pathology; this is in general to a lesser extent than that found in the current case (Knopman *et al.*, 2003). These authors suggest that AD pathology appears to exert no dramatic influence on cognition until a certain threshold is reached. In this case report it seems likely that the severe AD pathology was responsible for the progressive cognitive deficits and imaging changes demonstrated. A consistent feature of Alzheimer's disease (even at its very early stages) is progression, and in the absence of an identifiable mutation, as found in familial Alzheimer's disease, cognitive impairment is better demonstrated on serial assessments than on single measurement. Such an approach might incorporate atrophy derived from serial volumetric MR imaging, alongside clinical and neuropsychological testing, to detect subtle progressive cognitive impairment in high functioning individuals even if the cut-off of 1.5 SD below the mean required by MCI criteria has not been reached.

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