Recognising Early Symptoms of Alzheimer's Disease in Routine Clinical Practice

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Abstract

The prevalence of Alzheimer's disease is expected to significantly increase over the next few decades. Recognising symptoms in the routine clinical setting can be challenging, particularly in the early stages. Memory loss that causes disruption to everyday life may be the first presenting complaint; however, more subtle changes may occur much earlier. These may include difficulty in performing complex activities of daily living, decline in objective neuropsychological testing and apathy, which may be present for a decade before a diagnosis is made. In the non-specialist setting, the Mini Mental State Examination and the clock-drawing test still predominate and there is limited scope for applying tests such as magnetic resonance imaging (MRI) scanning or plasma markers. At present we remain poor at diagnosing Alzheimer's dementia, particularly in the early stages; therefore, improved awareness of early symptoms as well as a belief in the value of early diagnosis may lead to more effective management of patients.

Keywords

Alzheimer's disease, dementia, recognising early symptoms, routine clinical practice, function, apathy, diagnosis

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In the EU, more than seven million people are estimated to have dementia.[1] An ageing population will lead to an increase in dementia cases,[1] with prevalence rates in both western and eastern Europe expected to at least double by 2040.[2] Worldwide, it is forecast that one in 85 people will be living with Alzheimer's disease (AD) by 2050.[3] In Europe, AD is the most common form of dementia, accounting for approximately two-thirds of cases.[4] It is suggested that about half of dementia cases remain undiagnosed;[2,5] however, rates of missed diagnosis or under-recognition vary, and a large proportion (up to 90%) of patients with mild disease remain undiagnosed.[6,7] Several reasons have been cited for this lack of recognition, including a lack of awareness among care-givers of the symptoms of Alzheimer's dementia, a lack of recognition of Alzheimer's dementia by physicians and late referral of patients to a specialist.[8] As primary care physicians play a crucial role in the identification, diagnosis and overall management of patients with dementia, their interface with secondary care is of great significance.

Alzheimer's dementia is the consequence of a degenerative disorder and has an insidious onset. In both sporadic and familial AD, genetic mutations and genetic risk factors will be present at birth. However, multiple environmental factors interact with the ageing process and genetic vulnerability to determine the age at onset of disease and, thereafter, dementia. At the time of the diagnosis of dementia (usually in individuals over 60 years of age), pathological changes and cell death have already occurred. As there are currently no validated diagnostic biomarkers available, a definitive diagnosis can only be made at autopsy.[9] Clinical diagnosis may be made by using a combination of neuropsychological testing, neuroimaging and plasma, urinary and cerebrospinal fluid markers, but the diagnosis of AD is never 100% accurate until *post mortem*. In the absence of definitive, widely available and accurate diagnostic tests for AD before the development of dementia, definition of the early stages of cognitive impairment thought to presage Alzheimer's dementia or represent its earliest manifestations are very much reliant on specific changes in cognition and function, often observed by the patient's care-givers and family.

The Alzheimer's Association lists 10 warning signs for Alzheimer's dementia on its website. These may prompt someone who is concerned about their own or a loved one's memory to visit their doctor. Memory loss that disrupts everyday life is not considered a normal part of ageing. People with Alzheimer's dementia may forget entire experiences, with later recall of those experiences being rare. They are gradually unable to follow written/spoken directions and eventually become unable to use notes as reminders.[10] Their memory loss interferes with activities of daily living[11–13] and they gradually become unable to care for themselves.[10] An important sign of Alzheimer's dementia is a change over time in levels of function. This is of particular importance to the care-giver and significantly affects the quantity and quality of care required.[12] People will often have reduced levels of functioning for a long time before a clinical diagnosis of Alzheimer's dementia is made, with one population-based study showing that people who later developed dementia

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performed worse in complex activities of daily living up to 10 years before a clinical diagnosis was made.[14] In this study, participants who were restricted in at least two out of the four instrumental activities of daily living (telephone, transportation, medication and finances) at baseline had a higher risk of dementia 10 years later. Difficulty with finances at baseline was a particularly strong predictor of dementia during the course of the study.[14] In one large prospective cohort study in France, elderly people living in the community were followed up every two years for 20 years. Decline in objective neuropsychological tests (semantic memory and conceptual formation) was manifest as many as 12 years before a diagnosis of dementia was made. These symptoms progressed through a stage of increased memory complaints and depressive symptoms consistent with the genesis of more generalised global deficits. Later still, an increase in dependence on others in undertaking activities of daily living was seen as a consequence of the initial and developing cognitive dysfunction. The last three years prior to diagnosis showed ongoing worsening in all of these impairments.[15] In essence, biological markers of AD that are known to pre-date dementia diagnosis[9,12] have associated changes in cognition and function before the dementia diagnosis is fulfilled.

Once Alzheimer's dementia is diagnosed (based principally on clinical observations), the ability to carry out normal activities worsens as time passes and the underlying AD progresses. Functional impairment is particularly relevant when planning support and services for the patient and care-giver. Functional impairment in early Alzheimer's dementia (associated with a Mini Mental State Examination [MMSE] score between 21 and 30) includes forgetting details of conversations or what has been read, undertaking complex hobbies, work, driving, using money and shopping or remembering to take medication. Getting lost, misplacing things and beginning to need more constant supervision are associated with moderate Alzheimer's dementia (MMSE score 10–20).[13]

Beyond the cognitive symptoms and functional consequences of these symptoms, patients often develop distressing neuropsychiatric symptoms. The study of apathy and passiveness in Alzheimer's dementia and other neuropsychiatric symptoms has been a topic of growing interest among clinicians and researchers.[16,17] Apathy is the most frequent behavioural change occurring in Alzheimer's dementia and mild cognitive impairment.[19] It has now been established that apathy is typically the earliest neuropsychiatric symptom to manifest in AD, pre-dating the onset of dementia, and that it worsens steadily throughout the course of the illness.[19,20] The relationship between apathy and level of cognitive impairment appears to move in concert.[20] Apathy is thus an early consequence of AD and may be more observable than subtle cognitive decline. Therefore, individuals who display both apathy and cognitive impairment may be demonstrating early clinical features of AD and hence are at high risk of developing dementia.[21]

Given the prominence of this neuropsychiatric symptom, a task force was convened in 2008 to reach agreement on criteria for apathy given that it is a symptom of many medical and other psychiatric diagnoses. The task force defined apathy as diminished motivation that persists over time (present for at least four weeks) and a reduction in goal-directed behaviour, goal-directed cognitive activity and/or emotions.[16] Furthermore, apathy is now recognised as a primary contributing factor mediating functional decline.[21]

The *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) states that in order to make a diagnosis of Alzheimer's dementia, there has to be an impaired ability to learn new information or recall previously learned information, accompanied by other cognitive impairments such as aphasia. These cognitive deficits must also cause significant impairments in social or occupational functioning and represent a significant decline from a previous level of functioning. The course of the disease is a progressive decline.[22] Other classifications are similarly biased towards the clinical phenotype. While these criteria and other guidelines may be important for facilitating a timely diagnosis of dementia, they have been shown to be infrequently used and not always available – a particularly prominent problem in primary care or non-specialist settings. The under-recognition of Alzheimer's dementia in these situations may well be mediated by a lack of knowledge of or reference to diagnostic criteria.

In terms of care pathways that arise on the basis of a diagnosis being made, one study exploring the primary care diagnosis of dementia in Europe showed that referral pathways often depended on the individual healthcare systems and that diagnostic strategies differed on the basis of varied cultural influences. The study identified that there needs to be a focus on timely diagnosis and that guidelines for this need to be developed and implemented. Following this, referral pathways from primary to secondary care, as well as diagnostic strategies in both of these settings, which will include collaboration among medical professionals, need to be identified. In this regard 'timely diagnosis' is defined as 'the time when the patient or care-giver and the primary care physician recognise that a dementia syndrome may be developing'. Timely diagnosis implies that methodologies should concentrate not on population screening, but on a speedy response to the first reported signs of changed behaviour and functioning in the patient.[23] The implications of screening a well population mean that we are not yet ready for this approach. However, patients seeking help for a cognitive problem expect accurate initial assessment. It may be that initial case ascertainment in primary care has high sensitivity for there being a possible neurodegenerative illness and that the specificity of diagnosis need only be achieved in secondary care, where more targeted assessments and investigations can be undertaken where appropriate.

Although much work still needs to be carried out researching the most accurate and effective mechanism to effect a good referral from primary to secondary care, primary care physicians should still be encouraged to take the simple steps of excluding a medical co-morbidity – for example an occult infection or thyroid disorder – as the aetiology for the cognitive impairment. It is also worthwhile for general practitioners to undertake some basic cognitive testing.

There have been numerous brief cognitive screens developed for use in non-specialist settings. Undoubtedly, the two tests that predominate and can be applied in primary care are the MMSE and clock-drawing test (CDT).

The MMSE was one of the first cognitive tests to be developed and has subsequently found common usage in assessing patients with dementia.[24] While it may not have the psychometric properties of more elaborate tests, it is simple to apply and has good face validity. However, it is affected by patient education level, has an over-reliance on verbal assessment of memory and has very low specificity for the underlying neurological disorders.[24,25] Moreover, sensitivity for detecting early-stage Alzheimer's dementia can be as low as 31%.[25]

The CDT taps into a wide range of cognitive abilities, including executive functions. It has high sensitivity for detecting Alzheimer's dementia and specificity for differentiating this from other dementias, and shows high levels of inter-rater and test–re-test reliability as well as good positive predictive value, despite significant variability in the scoring systems.[26] The CDT has been shown to be a very efficient screening test for mild to moderate Alzheimer's dementia and may be useful for the early detection of this. It has low false-negative and false-positive rates, especially if scored according to the Shulman scale and combined with the MMSE and informant reports.[26,27]

In primary care there is limited scope for applying what remain expensive tests, such as magnetic resonance imaging (MRI) scanning or plasma markers. These tests remain for the most part at the near horizon of application, awaiting the results of conclusive definition of their accuracy – a process being assisted by the recent establishment of a Cochrane Collaboration group dedicated to this task. However, a good referral will be made when the primary care physician recognises the risk that AD may be mediating the cognitive complaints and performs some bedside cognitive tests.

In summary, the near future will see us expecting to be able to diagnosis AD earlier and earlier in its course, certainly well before dementia develops. However, we remain poor at diagnosing Alzheimer's dementia even when behavioural, cognitive and functional symptoms and features are clearly manifest. Awareness of the diagnosis, what features should constitute concern and a belief that there is good reason from a biopsychosocial perspective to make the diagnosis will mediate better, earlier and more effective management of patients with AD. ■

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