Alzheimer's Disease

Clinical characteristics of late-onset Alzheimer's disease (LOAD)

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The burden of late-onset Alzheimer's disease

Late-onset Alzheimer's disease (LOAD) is the commonest cause of dementia in the world. At present, 0.9% of 65-year-olds, 4.2% of 75-year-olds, and 14.7% of 85-year-olds, worldwide, are estimated to have been diagnosed with LOAD [1]. Approximately 26.6 million people worldwide [2], and 296,000 people in Australia [3], are currently suffering from a dementia. By 2050, these numbers are expected to rise to 106.8 million [4] and 1.13 million [3], respectively. The total annual, direct and indirect costs, associated with the diagnosis, treatment, and ongoing care, of dementia sufferers are estimated to be 350.45 billion (AUS) worldwide, and 6.6 billion (AUS), in Australia [3]. The emotional and psychological costs to sufferers, and their families and carers, is incalculable. Caring for a person with dementia is associated with increased stress, anxiety, and sometimes depression [5, 6].

Clinical characteristics

Diagnostic criteria for LOAD have been proposed by the National Institute of Neurological Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders (NINCDS-ADRDA)[7], the American Psychiatric Association [8] in the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition - Text Revised (DSM-IV-TR), and the World Health Organisation in the International

Statistical Classification of Diseases and Health Related Problems - 10th Edition (ICD-10).

The criteria proposed by the NINCDS-ADRDA [7], are perhaps the most widely used in research settings. According to these criteria, a definitive diagnosis of LOAD can only be made postmortem, upon verification of its neuropathological hallmarks [9,10]. Thus, any individual who displays its *typical* cognitive and psychological characteristics antemortem is diagnosed with probable dementia of the Alzheimer type (DAT)[7]. The term "probable" is used to reflect the certainty of the diagnosis. To meet criteria for this diagnosis, a person must demonstrate (i) a slowly progressive, greater-than-six-month history of subjective memory complaints (SMCs), as reported by the individual in question, or a reliable informant, and (ii) an objective episodic memory impairment (OEMI) on standard neuropsychological testing. Episodic memory refers to the ability to remember events with specific spatiotemporal contexts. On neuropsychological testing, impairments in episodic memory manifest as an inability to learn new information. The OEMI can be isolated, or accompanied by impairment in another cognitive domain, including executive and visuospatial function, language, and semantic knowledge. In addition, there must be impairment of social and/or vocational functioning.

These features must also be supported by a structural neuroimaging marker (e.g., atrophic changes in the hippocampus, entorhinal cortex, amygdala, on magnetic resonance imaging [MRI]), a biochemical marker (i.e., low beta-amyloid [Aβ] concentrations, increased tau protein concentrations in cerebrospinal fluid), or a functional neuroimaging marker (i.e., reduced glucose metabolism in the bilateral temporoparietal lobes on positron emission tomography [PET]).

The DSM-IV-TR and ICD-10 criteria differ slightly to those proposed by the NINCDS-ADRDA, in that they require impairments in at least two cognitive domains before a diagnosis of dementia can be made. For example, the DSM-IV-TR criteria require impairments in memory, *and* aphasia, apraxia, agnosia, *or* executive functioning. Furthermore, the ICD-10 criteria require impairment in memory *and* "a decline in other cognitive abilities characterised by deterioration in judgment and thinking, such as planning and organisation, and in the general processing of information" (WHO, 1992, p.45). The DSM-IV-TR and ICD-10 criteria also require that these cognitive impairments interfere significantly with social and occupational functioning, and basic activities of daily living (ADLs). However, this has not been explicitly stated in the NINCDS-ADRDA criteria.

Despite their differences, all three criteria acknowledge that the most important cognitive feature of the clinical phenotype of LOAD is progressive episodic memory impairment, which eventually leads to an amnestic state.

The amnestic phenotype of late-onset Alzheimer's disease

There has been increasing acknowledgment in the literature that while the clinical phenotype of LOAD is dominated by EMI and impairment in other cognitive domains, in the middle-to-late stages of the dementia phase, the order in which impairments in certain cognitive domains emerge can vary markedly. The most common clinical phenotype of LOAD, herein referred to as amnestic LOAD, is characterised by an early and slowly progressive anterograde amnesia, which manifests in reported memory decline, and an impairment in new learning on neuropsychological testing (i.e., an objective episodic memory impairment [OEMI] characterised by rapid forgetting). In the years leading up to a dementia diagnosis,

amnestic LOAD patients have problems remembering recent events, where their possessions are kept, the names and faces of people they have recently met, and details of important conversations [11]. They will also consistently miss important dates and appointments, and get lost in familiar surroundings. As the disease progresses, the patient's anterograde amnesia is so profound that he or she is unable to function independently on a daily basis.

On neuropsychological testing, amnestic LOAD patients display a moderate-to-severe OEMI, which is characterized by an inability to recall and recognize arbitrary word pairs (e.g., Verbal Paired Associates [VPA] subtest of Weschler Memory Scale [WMS]), lists of words (e.g., Rey Auditory Verbal Learning Task [RAVLT]), stories (e.g., Logical Memory [LM] subtest of the WMS), and abstract shapes (e.g., Visual Reproduction [VR] subtest of the WMS, or the Rey-Osterrieth Complex Figure Test [RCFT][12], particularly after a long delay filled with other activities [13]. Moreover, because these performances stem from a problem encoding and consolidating new information [14], they are typically not aided by cues.

Amnestic LOAD patients also display impairments in other cognitive domains, including language, semantic knowledge, visuospatial and executive function, but these are mild by comparison [11, 15; 16; 17], reinforcing the notion that episodic memory dysfunction is the earliest cognitive feature of this phenotype [18; 19; 20; 21]. This critical feature distinguishes amnestic LOAD from other cognitive phenotypes of the condition in which episodic memory dysfunction emerges only *after* impairments in other cognitive domains have reached an advanced stage; e.g., a longitudinal clinic-pathological study of LOAD [22] examined the neuropsychological profiles of 20 patients with definite AD (i.e., confirmed by autopsy), and found that although all patients displayed an OEMI on

neuropsychological testing, for some patients, these impairments were overshadowed by more significant impairments in language or visuospatial function, suggesting that the latter problems were evident in the earliest stages of the disease.

Conclusions

LOAD represents a significant burden to sufferers, carers and the health care system. The amnestic clinical phenotype of LOAD, characterized by early and marked impairments in subjective or informant reported episodic memory function, is the most commonly encountered in a clinical setting. There is, however, increasing awareness that other phenotypes exists, in which memory impairment is secondary to impairments in other cognitive domains. This differentiation between amnestic and non-amnestic phenotypes of AD might have implications for genetic studies, particularly if each phenotype is governed by different genetic factors.

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