CLINICAL DIAGNOSIS AND MANAGEMENT OF ALZHEIMER’S DISEASE
Other Titles by Serge Gauthier

## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>List of contributors</td>
<td></td>
<td>viii</td>
</tr>
<tr>
<td></td>
<td>Foreword</td>
<td></td>
<td>xii</td>
</tr>
<tr>
<td></td>
<td>Preface to the Third Edition</td>
<td></td>
<td>xiv</td>
</tr>
<tr>
<td>I</td>
<td>Introduction to the Disease Process</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Definitions and diagnostic criteria</td>
<td>Jeffrey L Cummings</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Pathophysiology: a neurochemical perspective</td>
<td>Stéphanie Bélanger, Vanessa Pearson and Judes Poirier</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Pathophysiology: an epidemiological perspective</td>
<td>Lenore J Launer</td>
<td>27</td>
</tr>
<tr>
<td>II</td>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Typical clinical features</td>
<td>Rémi W Bouchard and Martin N Rossor</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
<td>Differentiation from non-Alzheimer dementia</td>
<td>Richard Camicioli</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>Neuropsychological assessment</td>
<td>Constant Rainville, Nicole Caza, Sylvie Belleville and Brigitte Gilbert</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>Structural brain imaging</td>
<td>António J Bastos Leite, Frederik Barkhof and Philip Scheltens</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>Functional brain imaging</td>
<td>Agneta Nordberg</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>Electrophysiological tests</td>
<td>Cornelis J Stam</td>
<td>111</td>
</tr>
<tr>
<td>10</td>
<td>Biological markers</td>
<td>Douglas Galasko</td>
<td>125</td>
</tr>
</tbody>
</table>
### NATURAL EVOLUTION

11. Natural decline and prognostic factors  
   **Marie Sarazin, Nikki Horne and Bruno Dubois**  .......................................................... 137

12. Global assessment measures  
   **Kenneth Rockwood and John C Morris**  ................................................................... 149

13. Depressive syndrome in Alzheimer’s disease  
   **Lilian Thorpe**  ............................................................................................................ 159

14. Cognition  
   **Sven Joubert, Steve Joncas, Emmanuel Barbeau, Yves Joanette and Bernadette Ska**  .... 165

15. Functional autonomy  
   **Isabelle Gélinas**  ........................................................................................................ 177

16. Behaviour  
   **Edmond Teng and Jeffrey L Cummings**  ................................................................... 189

### MEDICAL MANAGEMENT

17. Mild cognitive impairment and very early stage Alzheimer’s disease  
   **Howard Chertkow**  ........................................................................................................ 205

18. Mild to moderate stages  
   **Michael Woodward and Howard Feldman**  ................................................................ 221

19. Care of patients in the severe stage of dementia  
   **Per-Olof Sandman, David Edvardsson and Bengt Winblad**  ...................................... 233

20. Terminal stage  
   **Ladislav Volicer**  ........................................................................................................ 247

21. Co-existent medical problems and concomitant diseases  
   **Roy Jones**  ..................................................................................................................... 257

22. Management of neuropsychiatric symptoms  
   **Nathan Herrmann**  ........................................................................................................ 265

### COMMUNITY AND INSTITUTIONAL MANAGEMENT

23. Caregiver support: support of families  
   **Henry Brodaty and Karen Berman**  ................................................................................ 279

24. Community-based formal support services  
   **Lilly Katofsky**  ............................................................................................................. 299

### ETHICAL AND QUALITY OF LIFE ISSUES

25. Ethical issues  
   **Jason Karlawish**  ........................................................................................................ 315

26. Competency  
   **Daniel C Marson and Laura E Dreer**  ......................................................................... 325

27. Genetic counselling  
   **Simon Lovestone and A Dessa Sadovnick**  .................................................................. 341
28. Health-related quality of life measurement techniques in the management of dementia
   Sam Salek and Mel Walker ........................................................................................................ 351

VII CONCLUSION

29. Future diagnosis and management of Alzheimer’s disease
   Serge Gauthier, Leon L Thal and Martin N Rossor ........................................................................ 379

Index ............................................................................................................................................. 383
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Foreword

Although Alzheimer’s disease was described as a clinical neuropathologic entity one hundred years ago by Alois Alzheimer, the preponderance of knowledge on the disease has accumulated since the 1970s, propelling the disease from near obscurity to the forefront of modern biomedical science. The remarkable transformation of this field of study is reflected by the exponential increase in the numbers of investigators, publications, and funded projects. The current preeminence of dementia research is largely due to the increasing numbers and quality of significant breakthroughs in understanding the molecular neurobiology of the disease. Multiple promising leads now have created an atmosphere of optimism about the prospects of discovering effective interventions to delay the progression of the disease. Some of the key factors that influenced the pace of progress and helped to change the ‘status’ of dementia research were: (a) recruitment of new scientific talent and perspectives from different disciplines; (b) convergence of know-how and technologies from both basic and clinical research; (c) several crucial discoveries in molecular neurobiology of dementia; and (d) establishment of several nationwide networks of collaborating interdisciplinary research teams, programs and shared resources, e.g. Alzheimer’s Disease Centers [ADCs], Alzheimer Disease Clinical Studies [ADCS], European Alzheimer’s Disease Consortium [EADC], Alzheimer’s Disease Neuroimaging Initiative [ADNI], Clinical and Genetic National Databases, etc.

This volume on Clinical Diagnosis and Management of Alzheimer’s Disease by Serge Gauthier through its third and current edition reflects the advances in evidence-based clinical knowledge and the remarkable improvements in the accuracy of the clinical diagnosis. During the last two decades, the procedures for clinical assessment have steadily advanced toward well-validated algorithms for identification of positive clinical phenotypes of the disease. Twenty years ago what would have been considered ‘mild’ dementia, now more likely would be staged as ‘moderate’ dementia. Capabilities for early diagnosis and the prospects for even earlier detection of the disease has been one of the most important clinical accomplishments, with profound implications for: more accurate assessment of the true prevalence of AD, initiating treatments with optimal benefit, and better understanding the biology of the disease. The efforts to improve algorithms for distinguishing early stages from non-demented people, including attempts to define or characterize border-zone conditions and the introduction of mild cognitive impairment (MCI) concept as a potential precursor of the disease were significant accomplishment.

This work sets the stage for the next important step: exploration of biomarkers.

Advances in molecular neurobiology and emerging imaging technologies promise to provide early markers of the asymptomatic stages of AD. The individual chapters in Clinical Diagnosis and Management of Alzheimer’s Disease reflect how rapidly the classification of degenerative dementias is moving, not just toward diagnostic and prognostic biomarkers, but toward antecedent biomarkers; a system of categorization based on combined behavioral and biological abnormalities.

Recent advances in neuroimaging technologies offer the potential to detect and follow longitudinally the clinical course of the disease. The potential value of structural and functional neuroimaging for early diagnosis is that, in the future, it may be possible to monitor more direct monitoring of some biological phenotypes of the disease (e.g. brain metabolic changes, Aβ, Tau, synapse loss or cell death). The
prospects are promising that validated molecular and bio
chemical markers may soon complement clinical
approaches in making early and valid diagnoses. In the
future the combination of neuropsychological mea-
surements with well-validated imaging measurements
could allow clinicians to follow the more proximal
brain changes associated with disease progression.
However, prior to use as a routine clinical tool, any
potential biomarker must detect a fundamental bio-
logical feature of the disease and must be validated in
neuropathologically confirmed cases. At present, none
of the putative biomarkers have been validated in ade-
quately powered investigations; the Alzheimer’s
Disease Neuroimaging Initiative (ADNI) study is a
first attempt to address this need.

The current edition of Clinical Diagnosis and
Management of Alzheimer’s Disease documents how
much has been learned about the pathogenesis, diag-
nosis, treatment and management of dementia-neu-
rodegeneration. At the publication of the first edition
the idea of a ‘cure’ was inconceivable and the concept
of ‘prevention’ was a remote possibility. People at risk
for the disease were not easy to identify and clinical
trials to delay the symptoms were not well developed.
In contrast, this edition describes novel intervention
strategies that are being developed on multiple fronts,
from basic science to genetics to drug therapy to care
giving.

In summary, the third edition of Clinical Diagnosis
and Management of Alzheimer’s Disease edited by
Serge Gauthier provide an excellent overview of the
remarkable advances in understanding the cause, diag-
nosing, treating, and caring for patients with Alzheimer and shows how dramatically the prospect
of discovering disease modifying therapies have
improved in the course a few short years.

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There has been steady progress in our understanding of the natural history, prognostic factors and treatments for Alzheimer’s disease since the first edition of this textbook was published in 1996. The authors are happy to share their knowledge with all interested readers who care for someone afflicted by this condition. The chapters deal with the full spectrum of populations at risk, persons in prodromal stages, and patients from mild to severe and even terminal stages. Quality of life for patients and families is paramount in our thoughts and hopes for the future.

SG
I Introduction to the disease process
Definitions and diagnostic criteria

Jeffrey L Cummings

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder with characteristic clinical and pathological features. Alzheimer’s disease is aetiologically heterogeneous and can be produced by mutations of chromosomes 21, 14 and 1 as well as by as yet unrecognized causative factors. Clinical variations are common including differences in age at onset, rate of progression, pattern of neuropsychological deficits, and occurrence of non-cognitive neuropsychiatric symptoms.1 Except in rare cases of identifiable mutations in presymptomatic individuals, there are currently no biological markers available for AD that allow preclinical detection or definitive premorbid diagnosis. Pathologically, characteristic findings include neuronal loss, neurofibrillary tangles, neuritic plaques and amyloid angiopathy; the severity of each of these changes differs considerably among individual patients. Thus, AD exhibits aetiological, clinical and pathological heterogeneity. This diversity makes accurate diagnosis more difficult. Correct diagnosis is critical to advancing research in AD, implementing treatment of AD and identifying non-AD causes of dementia. This introductory chapter reviews current clinical definitions of AD, discusses strengths and weaknesses of the three major definitional approaches, describes disorders with features that overlap with those of AD and makes recommendations for improving diagnostic precision.

Detection of AD early in its clinical course has proven to be an elusive goal despite the fact that the disease was described almost 100 years ago. Although there have been substantial research advances in the past 20 years, there is still no generally accepted biological marker for the disease that allows early diagnosis or facilitates differential diagnosis. Mild cognitive impairment (MCI) is increasingly recognized as a transitional state denoting the earliest stages of a dementia, but not all patients with MCI progress to AD or dementia. AD must be distinguished from other dementing illnesses such as vascular dementia, frontotemporal dementias, movement disorders with dementia and many others. Clinical criteria must allow for clinical variability in symptoms based on the patient’s intelligence, language and memory skills, social and cultural background, presence of non-cognitive emotional disorders and differences in how the disease affects the brain (e.g. differences in symmetry and rate of brain involvement).

Diagnostic accuracy has been improved through the development of specific criteria for dementia, AD and other causes of dementia, but the sensitivity and specificity of these criteria are imperfect and errors continue to occur. Definitive diagnoses can be achieved through a combination of clinical and pathological studies but the relationship between clinical and pathological changes is also incompletely defined: patients with advanced dementia and limited cellular changes as well as patients with little or no dementia and marked AD-type pathology at autopsy are observed. It is increasingly recognized that AD is heterogeneous and the different etiologic contributions may lead to different clinicopathological relationships. Many aspects of AD including clinical manifestations, risk factors and response to therapeutic agents, are influenced by this heterogeneity. Despite the causative diversity of AD, the evidence suggests that there is activation of a similar cascade of events by different processes, eventually leading to cell dysfunction, loss of synapses and neuronal death. An ideal biological marker would allow detection of the occurrence of the earliest steps in this cascade, would be inexpensive and would be non-invasive.2 Until such a marker is available, the clinician must rely on the careful application of clinical diagnostic criteria; this chapter reviews these criteria and provides a perspective on their utility.
DEFINITIONS OF ALZHEIMER’S DISEASE

There are three widely used criteria-based approaches to the diagnosis of AD: the International Classification of Diseases, 10th revision (ICD-10), the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) Work Group criteria. Not surprisingly, the three definitions share many common features. Table 1.1 compares the principal features of the three approaches.

Three common misconceptions regarding AD – that it is a global disorder, that it is a diagnosis of exclusion and that it can be diagnosed only at autopsy – are all eschewed by the three diagnostic frameworks. All require that attention be sufficiently intact to exclude delirium as the cause of the mental status changes, whereas a global disorder would include attentional abnormalities. All the definitions specify expected findings (memory impairment, absence of focal findings), thus utilizing inclusionary criteria in the diagnosis rather than approaching the disorder as a diagnosis of exclusion. All are predicated on the feasibility of clinical diagnosis and most series find autopsy-confirmed, accuracy rates of 85–90 per cent based on these criteria.

ICD-10 criteria

The ICD-10 defines dementia as a disorder with deterioration in both memory and thinking which is sufficient to impair personal activities of daily living. The impair-
ment of memory is noted to typically affect the registration, storage and retrieval of new information. The definition requires that the patient have deficits in thinking and reasoning in addition to the memory disturbance.

The diagnostic guidelines for AD include the presence of dementia, insidious onset and slow deterioration of cognition, absence of clinical or laboratory evidence of a systemic illness or brain disease that can induce a dementia and absence of a history of sudden onset of neurological signs indicative of focal brain injury. Early-onset (before age 65) and late-onset subtypes are recognized as well as atypical and mixed types (i.e. mixed AD–vascular dementia).

**DSM-IV criteria**

The DSM-IV\(^4\) and DSM-IV Text Revision\(^5\) define dementia as a syndrome characterized by the development of multiple cognitive deficits including memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia or a disturbance in executive functioning. The deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previously higher level of functioning.

AD is defined as a dementia syndrome that has a gradual onset and continuing cognitive decline. Other neurological disorders, systemic conditions or substance abuse sufficient to induce dementia must be excluded. The deficits must not occur exclusively during a delirium and must not be attributable to a major psychiatric disorder such as depression or schizophrenia. Subtypes of AD recognized in DSM-IV include early-onset (at age 65 or below) and late-onset types as well as AD with delirium, with delusions or with depressed mood. Behavioural subtypes are noted.

**NINCDS-ADRDA criteria**

The NINCDS-ADRDA criteria\(^6\) take a somewhat different approach; definite, probable and possible AD are defined. Differences between definite, probable and possible reflect the available information (clinical and pathological versus clinical only) and how closely the patient’s syndrome resembles classic AD. Criteria for definite AD require that the patient has met clinical criteria for probable AD while living and has histopathological evidence of AD obtained by biopsy or autopsy. This is a radical departure from earlier formulations in requiring that both clinical and pathological criteria be present to establish a diagnosis of AD. Abandoning the earlier approach that gave diagnostic pre-eminence to the pathologist, these criteria prohibited the identification of AD on the basis of pathological examination alone; both clinical observations and pathological information were required.

Probable AD is characterized by the presence of dementia established by a questionnaire and confirmed by neuropsychological testing, deficits in two or more areas of cognition, progressive worsening of memory and other cognitive functions, no disturbance of consciousness, onset between ages 40 and 90 and absence of systemic disorders or brain diseases that could account for the memory and cognitive deficits. Dementia is defined in these criteria by decline in memory and other cognitive functions in comparison with one’s previous level of function. Features that support the diagnosis of AD but are not required for diagnosis include: progressive deterioration of specific functions such as language (aphasia), motor skills (apraxia) and perception (agnosia); impaired activities of daily living and altered patterns of behaviour; family history of similar disorders, particularly if confirmed neuropathologically; normal routine cerebrospinal fluid studies; normal or non-specific changes on EEG and evidence of cerebral atrophy on computerized tomography (CT) with progression documented by serial observation. Clinical features that are consistent with the diagnosis of AD (but not required for diagnosis) include: plateaus in the course of the illness; associated symptoms such as depression, insomnia, incontinence, delusions, hallucinations, catastrophic outbursts, sexual disorders and weight loss; motor signs such as increased muscle tone, myoclonus or gait disturbances, especially late in the course of the illness; seizures in advanced stages of disease and CT that is normal for age.

Features that make the diagnosis of probable AD uncertain or unlikely include sudden onset, focal neurological findings or seizures or gait disturbances early in the course of the illness.

Possible AD is diagnosed when: (a) the patient has a dementia syndrome with no apparent cause but there are variations in the onset, presentation or clinical course compared with typical AD; (b) the patient has a second brain disorder or systemic illness that is sufficient to produce dementia but is not considered to be the cause of the dementia and (c) the patient has a single gradually progressive deficit in the absence of any other identifiable cause. The latter could indicate MCI.

**Comment on current definitions**

These three commonly used definitions of AD – ICD-10, DSM-IV, NINCDS-ADRDA – have similar features. They all require that the patient exhibit a dementia syndrome and that memory loss be a major