Dementia is a devastating diagnosis for patients. Dementia comes in many forms that can be hard to differentiate. Arriving at an accurate diagnosis without subjecting an already wary patient to unnecessary tests requires clinical acumen. Identifying the correct dementia and determining a probable prognosis allow agreement on appropriate management and care with patients and their caregivers. But how much testing is needed? What do the tests tell you? What management options are available?

Dementia provides a progressive approach to help you identify and manage the many forms of this complex and devastating disease. Dr Quinn has assembled a team of expert neurologists and gerontologists to provide the foundation knowledge you need to develop the clinical wisdom for effective dementia care. Dementia clearly explains the diagnosis, investigations, and management for:

- Normal pressure hydrocephalus
- Vascular dementia
- Mild cognitive impairment
- Dementia with Lewy bodies
- Alzheimer’s disease
- Frontotemporal dementia.

Clinical in approach, practical in execution, Dementia will help you diagnose and treat your patients more effectively.
Dementia
Dementia

EDITED BY

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Series Foreword

The genesis for this book series started with the proposition that, increasingly, physicians want direct, useful information to help them in clinical care. Textbooks, while comprehensive, are useful primarily as detailed reference works but pose challenges for uses at the point of care. By contrast, more outline-type references often leave out the “hows and whys” – pathophysiology, pharmacology – that form the basis of management decisions. Our goal for this series is to present books, covering most areas of neurology, that provide enough background information to allow the reader to feel comfortable, but not so much as to be overwhelming; and to associate that with practical advice from experts about care, combining the growing evidence base with best practices.

Our series will encompass various aspects of neurology, with topics and the specific content chosen to be accessible and useful.

Chapters cover critical information that will inform the reader of the disease processes and mechanisms as a prelude to treatment planning. Algorithms and guidelines are presented, when appropriate. “Tips and Tricks” boxes provide expert suggestions, while other boxes present cautions and warnings to avoid pitfalls. Finally, we provide “Science Revisited” sections that review the most important and relevant science background material, and references and further reading sections that guide the reader to additional material.

We welcome feedback. As additional volumes are added to the series, we hope to refine the content and format so that our readers will be best served.

Our thanks, appreciation, and respect go out to our editors and their contributors, who conceived and refined the content for each volume, assuring a high-quality, practical approach to neurological conditions and their treatment.

Our thanks also go to our mentors and students (past, present, and future), who have challenged and delighted us; to our book editors and their contributors, who were willing to take on additional work for an educational goal; and to our publisher, Martin Sugden, for his ideas and support, for wonderful discussions and commiseration over baseball and soccer teams that might not quite have lived up to expectations. We would like to dedicate the series to Marsha, Jake and Dan; and to Janet, Laura and David. And also to Steven R. Schwid, MD, our friend and colleague, whose ideas helped to shape this project and whose humor brightened our lives, but he could not complete this goal with us.

Robert A. Gross
Jonathan W. Mink

Rochester, NY, USA
Preface

This book is the culmination of an effort to meet the request for a brief, practical clinician's guide to dementia. As in clinical practice, we start with “Diagnosis,” the traditional responsibility of the neurologist. Chapter 1 is an overview reiterating practice parameters and standard guidelines, but we recognize that the cases that cause practicing neurologists to reach for a textbook are the atypical ones. After considering the categories of atypical cases most often referred to memory disorder clinics, we devoted the next several chapters to the special problems of dementias with rapid progression, young onset, features suggestive of normal pressure hydrocephalus, the pseudodementia of depression, and prodromal dementia or MCI. Throughout these first six chapters there is an emphasis on the treatable possibilities, with the goal of helping clinicians to recognize these important (if rare) cases.

While the neurologist’s role in dementia is often confined to the diagnosis, Chapter 7 explicitly describes the potential role of the neurologist in the continuing care of dementia patients. This overview is followed by more detailed discussions of the use of psychotropic drugs and palliative care, relying on our colleagues from psychiatry and palliative care to cover two practical topics which are not addressed in most neurology textbooks. These chapters are intended to provide tips for medical management of dementia patients, but as practicing clinicians appreciate, the management of dementia goes beyond medicine, with legal and ethical considerations presenting a number of non-“medical” challenges for clinicians to navigate, so Chapter 10 is devoted to this important topic.

The last two chapters look to the future of dementia care and in some ways are “works in progress.” Chapter 11 reviews options for monitoring outcomes in dementia, a likely necessity for clinical practice as health care systems move toward an emphasis on patient outcomes for reimbursement. The final chapter addresses the issue of dementia prevention, providing something of a roadmap for clinicians to provide to the worried children of adult patients who either serve as caregivers or who show up in clinic asking for early assessment and intervention.

We selected these chapter topics based on the questions most often referred to us in a memory disorders clinic from practicing neurologists. The goal was not to be comprehensive but to be helpful to clinicians. During the initial planning phases of the book, some reviewers voiced concerns that it would be outdated before it was printed, as disease-modifying therapy would be approved by now and completely change the landscape of dementia care. We sincerely hope that this text does become obsolete as clinical research advances, but in the meantime trust that these efforts will assist practicing clinicians with the challenge of caring for patients with dementia.
Introduction

The burden of dementia, a substantial public health concern, is felt in all societies. After defining dementia, in the following chapter we discuss the diagnosis and differential diagnosis. We outline an approach to the general diagnostic work-up in this chapter, with detailed recommendations for specific situations (e.g. rapid progression, young onset, prominent depression, question of normal pressure hydrocephalus) in the chapters to follow.

Definitions

Dementia is a syndrome in which multiple-domain cognitive impairment, generally including memory impairment, is sufficiently severe to significantly affect everyday function. Memory and one additional area of cognitive impairment, including aphasia, apraxia, agnosia, and executive dysfunction, are required to be affected according to common criteria (DSM-IV). There are other generic dementia criteria, including the ICD-10 criteria, which require that several domains are affected, and newer dementia criteria are being developed (i.e. DSM-V) (Table 1.1). Some criteria have not required memory impairment as a necessary condition for dementia, since it might not be prominently impaired in non-Alzheimer’s dementias, and even occasional patients with Alzheimer’s disease can exceptionally have relatively preserved memory.

There are specific criteria for patients with cerebrovascular disease (vascular cognitive impairment/vascular dementia) and Parkinson’s disease (Parkinson’s disease dementia - PDD), both of which have a high risk of dementia. Recently, new criteria for Alzheimer’s disease (AD) have been proposed to take into account developments in biomarkers and recognition of a prodromal state, termed mild cognitive impairment, which often leads to dementia. Dementia with Lewy bodies (DLB) shares pathologies of Parkinson’s disease and Alzheimer’s disease. Frontotemporal dementia also has distinct features and varied pathology, and typically presents with prominent behavioral features (behavioral variant frontotemporal dementia) or language impairment (non-fluent/agrammatic/logopenic primary progressive aphasia or semantic dementia). Some patients, particularly those with logopenic progressive aphasia, actually have Alzheimer’s disease pathology. Some frontotemporal dementia patients develop co-existent motor neuron disease. Progressive supranuclear palsy (PSP), corticobasal ganglionic degeneration (CBGD), and Huntington’s disease are other neurodegenerative disorders that usually have obvious and prominent motor features; patients with these conditions often have cognitive and behavioral problems and develop dementia. Thus, while diagnostic criteria for the dementias are in evolution, making a diagnosis and identifying the specific etiology remain critical in the clinical setting.

Distinct pathologies can be successfully identified by current clinical criteria, albeit with a rate of misdiagnosis. The recognition of unusual presentations, atypical onset, and the prodromal phase of dementias may be assisted by biomarkers (which may differ in these settings). Clinicians must
Table 1.1 Comparison of key guidelines for the assessment of dementia

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Mental status</th>
<th>Activities of daily living</th>
<th>Behavioral symptoms</th>
<th>Blood tests</th>
<th>Brain imaging</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAN, 2001</td>
<td>Yes</td>
<td>No specific recommendation</td>
<td>Depression screen</td>
<td>CBC, TSH, B12, glucose, electrolytes, BUN/Cr, liver function tests</td>
<td>Structural imaging</td>
<td>Selective</td>
</tr>
<tr>
<td>Canadian Consensus, 2004</td>
<td>Yes</td>
<td>No specific recommendation</td>
<td>No specific</td>
<td>B12, TSH, electrolytes, calcium, glucose</td>
<td>CT or MRI: &lt;60, rapid onset (&lt;2 mo), short duration (&lt;2 yrs), head trauma, neurological signs or symptoms, urinary incontinence, gait disorder, cancer, anticoagulants, atypical cognitive features</td>
<td>Selective</td>
</tr>
<tr>
<td>European Federation of Neurology, 2010</td>
<td>Yes, and assess specific domains</td>
<td>Yes</td>
<td>Yes</td>
<td>B12, folate, TSH, calcium, glucose, CBC, renal and liver tests</td>
<td>CT or MRI may be used</td>
<td>Dopamine SPECT scan to differentiate AD and LBD</td>
</tr>
</tbody>
</table>

AD, Alzheimer’s disease; BUN, blood urea nitrogen; CBC, complete blood count; CR, creatine; CT, computed tomography; LBD, Lewy body dementia; MRI, magnetic resonance imaging; SPECT, single photon emission computed tomography; TSH, thyroid-stimulating hormone.
nevertheless recognize these possibilities. Also, it is important to keep in mind that overlapping pathology often occurs in older patients with cognitive impairment or dementia, which might influence the clinical picture.

Other chapters consider young-onset and rapidly progressive dementia. Here we consider dementia in people 65 years of age and older.

**Epidemiology**

In 2010, dementia was estimated to affect 35.7 million people worldwide. Alzheimer’s disease is the most common dementia in people older than age 65 years, yet Alzheimer’s disease pathology is often accompanied by vascular disease or Lewy bodies. The latter two types of dementia can also occur in “pure” form. The diagnosis of dementia increases mortality risk, regardless of age or etiology of dementia. It is important to recognize that dementia may lead to a debilitated state and death in order to direct interventions appropriately, including palliative approaches. Prediction of death can be challenging in patients with dementia, which may make initiation of formal palliative care services difficult. (Chapter 9 provides a detailed discussion of the role of palliative care in dementia.)

The clinical diagnosis of Alzheimer’s disease is confirmed at brain autopsy in 90% of patients. The clinical diagnosis of vascular dementia, Lewy body dementia, and frontotemporal dementia predicts the brain autopsy diagnosis, but not as well as a clinical diagnosis of Alzheimer’s.

**Assessment**

**History**

Obtaining an accurate medical history is central to the diagnosis of dementia. This should identify and qualify the nature of the symptoms as well as their onset and progression. A critical challenge to obtaining an accurate history is that patients themselves may not be able to self-monitor because of their cognitive problems, so obtaining a collateral history is necessary. Memory impairment is a central feature of many dementias and can be expected to interfere with recall of key historical events. In addition, lack of insight can occur in dementia and interfere with the acknowledgment of symptoms. It is important to interview the informant and patient separately at some point in the diagnostic process. While some standardized questionnaires are useful in identifying complaints, these do not replace a thorough history, which remains the gold standard. Instruments that can complement the clinical history include the AD8 dementia screening questionnaire, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), the Deterioration Cognitive Observation Scale (DECO), and the Alzheimer Questionnaire (AQ). The General Practitioner Assessment of Cognition (GPCog) includes both a cognitive screen and questions regarding cognitive changes and activities of daily living based on caregiver report, which improves sensitivity and specificity for the diagnosis of dementia.

While the initial focus of the history should be on cognitive complaints and their functional implications, which allow for meeting dementia criteria, psychiatric and behavioral changes need to be identified as they are often present in early dementia, and can be prominent in some patients. In many patients referred for cognitive decline, psychiatric issues may predominate and may be the cause of the so-called cognitive decline. Depression should routinely be assessed in patients with cognitive complaints. It is key to screen for depressive symptoms, and scales such as the Geriatric Depression Scale, which has 15- and 30-item versions (www.stanford.edu/~yesavage/GDS.html), and the Montgomery-Asberg Depression Scale, can be helpful in this regard, though the gold standard is a psychiatric evaluation using a standardized interview schedule. The Cornell Scale for Depression in Dementia is validated for the dementia population. Depression can be a risk factor for or coincident with the diagnosis of dementia. Moreover, it can occur de novo in the course of dementia. Although they are distinct symptoms, depression and anxiety often co-exist. Other mood symptoms, such as elation or euphoria, also can occur in dementia, but primary psychiatric disorders should be kept in the differential diagnosis if these are prominent.

While not absolute, the nature of cognitive deficits can help in differentiating depression from dementia. Patients with depression have long response latencies.
Diagnosis and Differential Diagnosis of Dementia

whereas typical patients with Alzheimer’s disease respond with normal latencies. Memory impairment in depression is related to retrieval problems, rather than problems with encoding, where cueing does not improve recall. Alzheimer’s patients also have additional cognitive deficits, particularly in visuospatial and language domains, that would not be seen in depression. As noted, depression can co-exist with dementia and it is common in Alzheimer’s disease as well as vascular dementia and dementia with Lewy bodies.

Other neuropsychiatric problems that should be considered include positive symptoms such as disinhibition, irritability, agitation, aggression, or abnormal motor behavior as well as negative symptoms such as apathy. Delusions and hallucinations are also highly relevant. These symptoms can be assessed using standardized instruments such as the Neuropsychiatric Inventory (NPI). They can occur early in the course of dementia and can evolve over time. The Frontal Behavior Inventory can help with the differentiation of Alzheimer’s disease from frontotemporal dementia. Patients with frontotemporal dementia often lack emotional responsiveness and can develop apathy, which can be mistaken for depression but is characterized by lack of motivation. Psychotic features, particularly visual hallucinations, are characteristic of PDD and DLB. Delusions are not as specific but can be equally disturbing to family members.

It is critical to identify functional impairment. By definition, patients with mild cognitive impairment (MCI) do not have substantial functional impairment, while patients with dementia do. Practically speaking, at the time of diagnostic evaluation, assessment of basic and instrumental activities of daily living is performed by asking the patient and their caregiver how the patient performs everyday tasks. Basic activities of daily living such as getting in and out of bed, dressing, walking, toileting, bathing, and eating are not affected early in the course of dementia. Instrumental activities of daily living (IADL) such as answering the phone, taking pills, handling money, shopping, cooking, and driving are affected early in the course.

Typically a standardized questionnaire is used to address activities of daily living. Examples include the Functional Activities Questionnaire (FAQ) which addresses IADLs, the Lawton and Brody IADL and Physical Self-Maintenance Scale and the OARS Functional Assessment Questionnaire. Assessment is not as straightforward as it seems, as there is often a mild degree of functional impairment in MCI, where such impairments may predict future cognitive decline. Moreover, a given patient’s living situation might not tax their functional capacity. Conversely, a patient who is working might have some workplace impairment despite relatively well-preserved cognitive assessment. In the setting of a disorder that affects motor function, such as Parkinson’s disease or after a stroke, it can be challenging to determine if a change in a patient’s function is related to cognitive or motor function.

Prescribed and over-the-counter medications, as well as substances of abuse (notably alcohol), are important to identify as they might contribute to cognitive impairment. If the patient is not able to list these accurately, this suggests an important area of functional impairment that requires intervention. All co-morbid medical conditions need to be identified. Vascular risk factors such as smoking, diabetes, obesity, hyperlipidemia, hypertension, atrial fibrillation, and non-central nervous system (CNS) vascular disease (cardiac, renal, peripheral) increase the risk for cerebrovascular events, which can contribute to dementia, and can be covert. These are risk factors for dementia in the absence of identifiable stroke as well. Symptoms suggestive of cancer, especially in patients with a rapid course, raise the concern of direct or indirect central nervous system involvement.

A detailed family history is critical. While familial dementia commonly has a young onset, risk of dementia in older people is also increased in the setting of a family history. A third to half of people with frontotemporal dementia have a family history compared to roughly one in 10 patients with Alzheimer’s disease. At a minimum, all first-degree relatives should be identified and the presence of neurological disorders determined. This history should not be restricted to examining dementia risk, since disorders such as Parkinson’s disease and motor neuron disease may be associated with an increased risk of dementia in family members. If the family history is consistent with a hereditary dementia, testing can be offered but this should be done after appropriated counseling. At-risk family members should only be tested after genetic counseling. Huntington’s disease is a relatively common cause of dementia in younger individuals,
but can occasionally be identified for the first time in older patients without an obvious family history.

**Physical examination**

**General examination**
The general examination might identify specific co-morbid conditions, such as atrial fibrillation, congestive heart failure or chronic obstructive pulmonary disease (COPD). An abdominal or rectal mass, suggesting a neoplasm, might be uncovered. These might directly or indirectly contribute to cognitive dysfunction. Some findings on general examinations, such as postural hypotension, may suggest a specific diagnosis such as dementia with Lewy bodies.

**Cognitive evaluation**

Cognitive assessment at the bedside is important for both differential diagnosis and rating the severity of cognitive impairment. Cognitive domains to be assessed correspond to those involved in the diagnosis, including attention, orientation, memory, executive function, language, praxis, and visuospatial abilities.

Several standardized assessment instruments have improved clinicians’ abilities to assess cognition. While these are helpful, the clinician needs to be able to go beyond such instruments at times, given their limitations in scope and sensitivity. The Mini-Mental Status Examination (MMSE) is the most commonly used instrument and its advantages include its widespread use and extensive validation. Disadvantages include its relative insensitivity to the diagnosis of dementia, which may be partly related to exclusion of some cognitive domains, such as executive function. Given the availability of superior instruments, its use will likely decrease over time. The MMSE may not be sensitive to memory impairment since it only relies on the immediate recall of three words. Expanded versions of the MMSE such as the 3MS might have increased sensitivity. More comprehensive standardized instruments include the Short Portable Mental Status Examination, the Montreal Cognitive Assessment (MOCA) (www.mocatest.org), and the Addenbrooke Cognitive Examination-Revised. The Frontal Assessment Battery evaluates aspects of frontal lobe function, and can be used as a complement to tools such as the MMSE that do not specifically address this cognitive domain. It can assist in the differentiation of AD from frontotemporal dementia and may be useful in assessing parkinsonian disorders.

Neuropsychological testing, which affords a comprehensive, objective, and standardized approach to quantifying cognitive impairment, is helpful for diagnosis and differential diagnosis, but is not available in all settings. It is particularly relevant in mild or questionable cases, in cases where malingering is suspected, or in subjects for whom ceiling or floor effects might obscure interpretation of results on simplified tests (for example, people with very high or very low levels of education). Patients with clear changes and obvious deficits on simpler tests may not require neuropsychological testing. Moreover, it should be borne in mind that subjects may have test scores that are abnormal based on statistical population-based comparison but that this may represent a “normal” score or minimal change for that individual. Neuropsychological tests can be helpful in following change over time. The shorter tests do not necessarily validly assess cognitive subdomains as can be done by neuropsychological batteries, which may be important in differential diagnosis.

**TIPS AND TRICKS**

When should neuropsychological tests be used?

- In patients with worrisome history but good performance on mental status exam.
- In cases where malingering is suspected.
- To distinguish depression with cognitive symptoms from neurodegenerative disease.

**Neurological examination**

A complete general neurological examination is important. On cranial nerve testing, olfactory deficits are common in Lewy body dementia. Visual field defects or higher order visual defects may suggest cerebrovascular disease affecting the visual pathways or a posterior evolving dementia, such as the visual variant of AD or the Heidenhain variant of Creutzfeldt-Jakob disease (CJD). Other cranial nerve examination clues to the etiology of dementia can include vertical supranuclear gaze difficulty suggesting progressive supranuclear palsy. Nystagmus and restricted eye movement can be seen in Wernicke’s encephalopathy, which can
evolve into alcoholic dementia. Gaze-evoked nystagmus is non-specific and be seen with many causes of cerebellar degeneration. Upper motor neuron facial weakness suggests pyramidal involvement. Lower motor neuron facial weakness and involvement of other lower cranial nerves may provide a clue to involvement of the subarachnoid space due to an inflammatory, neoplastic or infectious process. Bulbar difficulties are seen in processes involving the brainstem or upper motor neuron lesions.

Focal weakness with other pyramidal signs can be seen in patients with cerebrovascular disease. Pyramidal signs can also be a clue to the presence of motor neuron disease (amyotrophic lateral sclerosis – ALS), in which features of lower motor neuron dysfunction can also be found (fasciculations, atrophy). Up to 10% of frontotemporal dementia patients can develop features of ALS, which has a substantial impact on prognosis and hence on long-term planning.

Cerebellar dysfunction in dementia might indicate a specific neurodegenerative disorder such as multiple system atrophy, a paraneoplastic disorder, CJD or celiac disease.

Neuropathy can be seen in renal failure, diabetes, vitamin B12 deficiency, alcohol exposure or paraneoplastic disorders. Neuropathy can also be seen in HIV, Lyme disease or hepatitis C infections which can all be associated with cognitive impairment and dementia. In addition, some mitochondrial disorders or disorders of central white matter (leukodystrophies) can be associated with neuropathy. Mitochondrial disorders are also classically associated with myopathy, myoclonus, and seizures.

Gait assessment is critical in patients with dementia. While it is less often impaired in AD, it is commonly affected in PDD, vascular dementia, and dementia with Lewy bodies.

It is important to examine for adventitious movements. The triad of tremor (rest tremor), bradykinesia, and rigidity indicates parkinsonism, as seen in dementia with Lewy bodies or Parkinson’s disease. Chorea would suggest Huntington’s disease, neuroacanthocytosis or another Huntington-like disorder. Dystonia in older adults may suggest a cerebrovascular event, either in the basal ganglia or thalamus. In addition to dystonia, unilateral chorea or tremor in an older adult should lead to consideration of a cerebrovascular event or other lesion, generally involving frontostriatal circuits, which can additionally be involved in cognition.

Myoclonus can be seen in degenerative disorders, including advanced AD and DLB, and more rarely Huntington’s disease and frontotemporal dementia. Focal myoclonus as well as asymmetrical apraxia, parkinsonism, and dystonia is characteristic of corticobasal ganglionic degeneration. Myoclonus is included in the diagnostic criteria of CJD, though it may not be seen early in the illness. When CJD is considered, it is important to keep alternative entities in mind. In terms of systemic illness, myoclonus is most often a manifestation of any cause of encephalopathy, including common disorders such as renal or hepatic disease (asterixis), as well as rarer autoimmune disorders such as steroid-responsive encephalopathies associated with thyroid disease or antibodies to the CNS. Rare disorders such as mitochondrial disease are characterized by myoclonus.

**Laboratory studies**

**Blood and spinal fluid**

Recommended tests for the assessment of dementia include blood work-up, including complete blood count (CBC), glucose, electrolytes (including calcium), renal and hepatic tests and thyroid function. Testing for vitamin B12 or folate deficiency is recommended. In many areas grains are supplemented with folate, making folate deficiency unlikely unless there are other reasons for malabsorption, in which case malabsorption of other B-vitamins should be considered. If indicated, based on the patient’s history, assessment for chronic infections that can cause dementia, such as HIV or syphilis, is indicated.

If the presentation suggests a delirium additional testing should be done to rule out possible causes of delirium such as acute infections (cultures, chest x-ray, urinalysis). Work-up for inflammatory or autoimmune disorders should also be considered. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) or more specific tests such as rheumatoid factors and antinuclear antibodies can provide clues to the presence of an autoimmune disorder. Additional work-up is indicated if specific disorders such as vasculitis, Sjögren’s syndrome, sarcoidosis or a paraneoplastic or non-paraneoplastic autoimmune encephalopathies are being considered.

A complete work-up may include cerebrospinal fluid (CSF) examination, which can also be used to