

Clinician's View of the Diagnosis of Dementia in the Elderly

David S. Knopman MD, Professor of Neurology, Mayo Clinic, Rochester MN

Disclosures: Dr. Knopman serves as Deputy Editor for *Neurology*[®]; served on a Data Safety Monitoring Board for Lilly Pharmaceuticals; will serve on a Data Safety Monitoring Board for Lundbeck Pharmaceuticals and for the DIAN study; served as a consultant to TauRx Pharmaceuticals, was an investigator in clinical trials sponsored by Baxter and Elan Pharmaceuticals in the past 2 years; and receives research support from the NIH. None of these are relevant to this presentation.

It is well known that dementing illness is a major public health problem. Accurate diagnosis is key to improving care of persons with dementia. The diagnosis of cognitive impairment involves two steps. The first is establishing whether cognitive impairment is present or not. The second step is determining the etiology of the cognitive impairment.

The foundation of the diagnosis of cognitive impairment in the elderly is the clinical history and neurological examination. Cognitive impairment is the core symptom, and that can be ascertained by interview of the patient, interview of an informant who knows the patient well, a mental status examination and the rest of the neurological examination. Technology plays no role in establishing whether cognitive impairment is present or not. Cognitive impairment may manifest itself either in changes in activities of daily life or on direct assessments such as a mental status examination administered "at the bedside" by a clinician or a battery of standardized tests administered in the neuropsychology laboratory (or both). We distinguish two severity levels of cognitive dysfunction, the milder form referred to as mild cognitive impairment (MCI) and the more impaired form as dementia. In both, there is objective evidence of cognitive impairment that is clearly distinct from the patient's presumed prior level of functioning. In MCI, however, daily functioning is largely preserved, whereas in dementia, daily functioning is clearly impaired. The boundaries between cognitive normality, MCI and dementia are unfortunately indistinct. Across the range of functioning from manifestly normal to obviously demented, cognitive ability represents a continuum. Clinical expertise becomes necessary for making diagnoses of cognitive impairment, because judgment is required to weigh information from different sources: the informant about daily living and the patient on the mental status examination. "Cut-off scores" for mental status examinations, while appealing in their objectivity and simplicity, impose an artificial and sometime erroneous separation between "normal" and "abnormal" mental status. That said, a skilled clinician can usually be confident in diagnosing someone with mild cognitive impairment or dementia.

Determining the etiology of the cognitive impairment is very challenging on clinical grounds alone. It is in this second aspect of diagnosis that imaging studies as well as other laboratory aids play a pivotal role.

Based on extensive clinical-pathological experience over the past 30 years, the universe of etiologies of cognitive disorders in late life is reasonably well understood. There are six major classes of etiologies:

- 1) Alzheimer's disease (β -amyloidosis + mixed tauopathy)
- 2) Cerebrovascular disease (mainly arteriolosclerosis)
- 3) Lewy Body disease (α -synucleinopathy)
- 4) Frontotemporal degenerations (3R or 4R tauopathies or TDP43 proteinopathies)
- 5) Rapidly progressive illnesses (Creutzfeldt-Jakob disease, a prionopathy; or noninfectious autoimmune encephalopathies)
- 6) Rarer and heterogeneous (normal pressure hydrocephalus, neoplasms, metabolic disorders, toxic disorders, nutritional disorders)

The first four account for roughly 95% of dementia in the elderly. Identifying the presence of one or more of those four is the first order of business for clinicians.

Note that I said "identifying the presence of one or more" and not "diagnosing one of them." Unlike diagnosis in younger people, Occam's razor represents the wrong conceptual model for late life dementia. Instead, late life cognitive disorders most often represent the additive effects of multiple pathologies.

Clinical features are of variable utility in detecting the presence of dementia etiology. As a brief overview, the prototypical presentation of dementia due to Alzheimer's disease (AD) is that of a purely cognitive disorder that begins gradually and then progressively worsens. In AD dementia the most profoundly impaired cognitive function and the first one to become impaired is that of learning and short-term memory. As the disease progresses, other domains of cognitive functioning such as language, spatial cognition and reasoning also become impaired. Cerebrovascular disease (CVD) causing cognitive impairment is traditionally diagnosed when there is a history of a stroke, and especially when there was a clear temporal relationship between the stroke and the onset or worsening of the cognitive impairment. Findings on the neurological examination that are typically associated with strokes, such as hemiparesis or hemianopia, may be used as evidence for a cerebrovascular etiology. Lewy Body disease has a number of distinctive clinical features that make its detection easier than AD or CVD: the presence of parkinsonism on neurological examination and the presence of distinctive alterations in sleep such as REM sleep behavior disorder are two features that have valuable predictive accuracy for α -synucleinopathy. Certain variants of primary progressive aphasia are highly predictive of frontotemporal degenerations, as is the often distinctive clinical syndrome of behavior variant frontotemporal dementia. With some exceptions, all of the above etiologies tend to produce clinical syndromes that evolve slowly over time. In contrast, when cognitive and behavioral difficulties appear over a matter of weeks or months, Creutzfeldt Jakob disease becomes a strong consideration.

While prototypical cases certainly exist, the reality of clinical practice is that syndromic presentations are often messier and include elements supporting more than one etiology. Some clinical symptoms such as memory impairment can occur as a result of many different pathophysiologies. And, equally importantly, clinical features are insensitive, in that clinical features are often absent or atypical in the presence of a particular etiology. From an etiological perspective, we clearly need more information than can be provided by the clinical history and examination.

With that whirlwind tour of the clinical diagnosis of the major etiologies behind late life dementia, the role for neuroimaging is major and growing. Here is my view of where neuroimaging fits in:

- 1) Alzheimer's disease - Structural MR of hippocampus, cortical regions; FDG PET, Amyloid PET, Tau-PET
- 2) Cerebrovascular disease – Structural MR for WMH, infarcts, microbleeds.
- 3) Lewy Body disease – the disorder with the least available valuable imaging. α -synuclein imaging would be a game-changer.
- 4) Frontotemporal degenerations – invaluable for structural imaging changes; tau PET may have a dramatic impact on diagnosis.
- 5) Rapidly progressive illnesses - structural MR is critical
- 6) Rarer and heterogeneous – structural MR is critical

Given the limited time available, therapeutics will not be discussed. Hopefully in the future, contributions to accurate diagnosis will pay dividends in improved therapeutic success in the dementing illnesses.

Rochester Minnesota

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