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Accurate Etiologic Diagnosis of Dementia Contributes to Better Clinical Care

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In current clinical practice, the assessment of patients with progressive cognitive complaints often concludes with a diagnosis of dementia without further investigation of the underlying neuropathological etiology. This approach arises from a number of different considerations. Since the majority of elderly patients with dementia have some contribution of Alzheimer disease (AD) pathology, clinicians may treat dementia and AD as largely synonymous and thus settle upon AD as the *de facto* etiology when making a diagnosis of dementia. This view is compounded by the challenge of distinguishing between different dementing etiologies, which can be difficult and time-consuming, particularly at later stages of disease, with few obvious additional benefits. In particular, since most FDA-approved medications for dementia target AD, many clinicians may prescribe symptomatic anti-AD therapeutics [such as acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine, and galantamine) or memantine] for their dementia patients, irrespective of the possible underlying etiology. Finally, since such medications are viewed as relatively ineffective, there is a greater focus on the general management of functional decline and behavioral disturbances that are less specific to individual neurodegenerative diseases.

Unfortunately, these attitudes lag behind ongoing diagnostic advances in dementia. Recent research demonstrates the utility of cerebrospinal fluid (CSF) and positron emission tomography (PET) imaging biomarkers for amyloid and tau for both the diagnosis of AD and for distinguishing between different dementing illnesses¹. Likewise, there is an increasing understanding of the deposition and propagation of abnormal protein aggregates and how they disrupt neural networks in dementia. Together, these discoveries are fueling the development of novel therapeutic approaches that target the individual proteinopathies associated with neurodegenerative disease. Progress in the diagnosis and treatment of such conditions is closely intertwined, underscoring the importance of accurate etiologic diagnoses for guiding more specific and efficacious treatment for patients with these

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diseases. Below, we delineate some of the key benefits of incorporating more specific diagnoses into the management of patients with dementia.

Patients with cognitive concerns prefer etiologic diagnoses

Patients with cognitive concerns, along with their families and caregivers, are often anxious about the potential causes of their symptoms. While the identification of a dementia or major neurocognitive disorder is a critical first step, prior work suggests that patients and their families want more than an objective confirmation of their cognitive dysfunction; they also want to know the underlying etiology². This information offers important immediate benefits, such as the psychological relief that may arise from having a clear diagnosis without having to wonder whether additional tests are needed to exclude potentially treatable causes of dementia. Furthermore, an etiologic diagnosis can also address concerns regarding the heritability of the underlying condition and any associated risk for other family members of developing similar symptoms.

Etiologic diagnoses assist in prognostication for dementia syndromes

More definitive diagnoses are also valuable for prognostic information that can help answer a common question posed by patients and families: “What can we expect in the future?” Different dementias have different implications for the timing of long-term medical planning (more pragmatic estimations of risk and benefit for procedures and hospitalizations), legal responsibility (power of attorney and conservatorship), and finances (preparing for potential progressive deterioration and provisioning for higher levels of long-term care). While all neurodegenerative dementias, regardless of etiology, are progressively debilitating, they can be distinct in their manifestations and time-course. Early etiologic diagnosis can thus appropriately shape future expectations for disease progression, particularly when supported by biomarker evidence. While patients with AD are likely to have disproportionate memory and visuospatial difficulties at earlier stages of their disease course, those with dementia with Lewy bodies (DLB) are more likely to experience visual hallucinations and Parkinsonism. Likewise, patients with behavioral variant frontotemporal dementia (bvFTD) may have relatively spared memory function, yet make extremely poor decisions and exhibit profoundly inappropriate social behaviors, while those with primary progressive aphasia (PPA) will struggle in their communication. Additionally, while it may be difficult to accurately predict the prognosis for individual patients with dementia, broad overall trends suggest longer survival times after diagnosis with AD relative to other etiologies³. As such, each of these conditions will require a different constellation of supportive resources, which may need to be planned for accordingly.

Etiologic diagnoses guide treatment decisions

Different dementias may also require different specific pharmacological or behavioral interventions. Currently, there are few effective medications for dementia, but the bulk of evidence supports the efficacy of FDA-approved symptomatic agents such as acetylcholinesterase inhibitors and memantine in AD. While the effects of these medications on cognition, behavior, and function can be subtle, Medicaid data suggest that early

initiation of such treatments in AD may result in a modest but significant delay in institutionalization and achieve corresponding cost savings⁴. However, these medications are also frequently used off-label to treat other forms of dementia, such as vascular dementia, FTD, and DLB, despite the relative paucity of evidence to support their efficacy in these conditions. Indeed, acetylcholinesterase inhibitors may worsen behavioral outcomes in bvFTD⁵ and memantine does not appear to be effective for behavior or cognition in either FTD⁶ or DLB⁷. These data reinforce the importance of correctly identifying patients with non-AD dementias, for whom treatment with standard symptomatic anti-AD therapies is not likely to be beneficial and may even be harmful. For while correctly diagnosing and treating AD at early stages can result in decreased health care expenditures⁴, misdiagnosis of non-AD conditions as AD can result in increased health care expenditures⁸.

Appropriate non-pharmacological treatments can also be driven by more specific dementia diagnoses. Speech therapy provides compensatory communication strategies in PPA. Physical therapy improves mobility in dementia syndromes that include parkinsonism, such as DLB and progressive supranuclear palsy. Occupational therapy can target limb apraxia that emerges in corticobasal degeneration and atypical AD variants. Behavioral management classes can be particularly valuable in helping caregivers handle specific difficult behaviors, such as those that characterize bvFTD.

The real-world effects of more accurate etiologic diagnoses for dementia on patient management are currently being evaluated in the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study (NCT02420756), which is sponsored by the Centers for Medicare & Medicaid Services (CMS) Coverage with Evidence Development (CED) program. Recently reported preliminary results indicate that amyloid PET imaging results (used to determine whether patients with mild cognitive impairment or dementia had underlying AD) changed clinical care plans in almost 70% of cases, with the greatest impact seen on the prescription of anti-AD medications⁹.

Etiologic diagnoses will become increasingly important with disease-modifying therapies

Advances in our understanding of the molecular pathology in individual types of dementia increase the promise of targeted and disease-modifying therapies. This in turn demands precise etiologic diagnoses to identify appropriate patients for inclusion in clinical trials and eventual clinical usage when novel interventions are approved. Future therapeutic strategies will target the underlying proteinopathies that appear to be the proximal cause for different dementing illnesses. The approach that is furthest along focuses on the amelioration of β -amyloid ($A\beta$) pathology in AD, which accumulates in the earliest stages of the disease. In preliminary studies, aducanumab (an anti- $A\beta$ antibody) significantly reduces both $A\beta$ deposition and cognitive/functional decline in patients with mild cognitive impairment or mild dementia due to AD¹⁰. Importantly, because aducanumab specifically targets $A\beta$, the inclusion criteria for this study required confirmation of cerebral $A\beta$ accumulation with amyloid PET imaging. Since the failure of prior trials of anti- $A\beta$ AD therapeutics has been attributed in part to the inclusion of patients who were clinically diagnosed with AD but

lacked detectable A β pathology, current Phase III trials of A β -specific interventions now require PET or CSF confirmation of elevated brain A β levels. If such interventions prove to be both safe and effective, future initial treatment decisions in neurodegenerative disease will be primarily predicated on the specific identification of underlying AD (i.e., A β) pathology.

While AD will likely to be the first neurodegenerative dementia to have both disease-specific biomarker assays and proteinopathy-targeted disease-modifying treatments, investigational PET imaging agents have been developed that target tau (which accumulates in specific regional patterns not only in AD but also in FTD, progressive supranuclear palsy, corticobasal degeneration, and chronic traumatic encephalopathy) and α -synuclein (which accumulates in DLB). Therefore, it is conceivable that as additional disease-modifying therapies emerge, etiologic diagnoses will also become increasingly essential for non-AD dementias. While some might argue that etiologic diagnoses for dementia are unnecessary prior to the approval of such specific disease-modifying therapies, the development of proteinopathy-specific interventions is intrinsically linked to and fundamentally driven by the correct etiologic diagnosis of patients bearing such proteinopathies.

Summary

Clinicians may be tempted to lump different types of dementia together given their symptomatic overlap, generally poor long-term outcomes, and the current limited symptomatic treatment options. However, it is clear that accurate etiologic diagnoses of dementia already deliver tangible benefits for patients and their families and promise to have an even greater therapeutic impact in the future. Such diagnoses play an important role in both current patient care and future drug development. We foresee that, as more specific disease-modifying therapies emerge, etiological diagnoses will become the standard of care for patients with cognitive and behavioral disorders.

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