CLINICAL VIGNETTE

The Evidence-Based Dementia Workup

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Introduction

Dementia is an increasingly common disease involving decline in cognition in one or more cognitive domains: learning and memory, language, executive function, complex attention, perceptual-motor, and social cognition.[1] Dementia of any type is an exacerbating factor for any other existing medical condition, commonly complicating acute medical admissions of all types. Additionally, acute medical illnesses often themselves exacerbate cognitive impairment, leading to diagnostic dilemmas in the inpatient setting. Timely recognition of the ultimate pathology involved is increasingly important as therapeutic strategies evolve.

Among the overall workup in a new diagnosis of dementia, of utmost importance is the early recognition of potentially reversible causes. The differential diagnosis of reversible dementia itself changes based upon patient age, situation, and presence of certain risk factors. The inpatient setting is a common site for initiation of workup for reversible causes of dementia. We present a case of rapidly progressive dementia (ultimately discovered to have had an atypical cause), and discuss the evidence-based workup for newly diagnosed dementia, with a specific focus on reversible causes.

Case Report

A 66-year-old man with a past medical history including peptic ulcer disease, depression, anxiety, remote polysubstance abuse, and undifferentiated dementia syndrome presented with a two week history of progressive dry cough as well as ongoing subacute mental status deterioration, and a four day history of intermittent fevers.

The patient had been living in a skilled nursing facility for approximately five weeks following an admission to an outside hospital for fevers and shortness of breath. Imaging on that admission suggested multiple cavitary lung lesions. The patient had an indeterminate Quantiferon gold assay, but serial acid-fast bacilli stains were negative. Sputum culture was positive for methicillin-resistant Staphylococcus aureus, and the patient was treated with a full course of vancomycin. His cavitary lesions were felt to be likely infected bullae. He ultimately recovered from an acute standpoint, and was transferred to the skilled nursing facility for continued convalescence. With respect to the patient's dementia, he had been noted to have a steady deterioration over an approximate five-month period, manifest as memory disturbance and loss of functional independence. Montreal Cognitive Assessment (MoCA) done five weeks prior to presentation was 11 of 30, corresponding to severe impairment. The patient was evaluated by two outside neurologists with workup including EEG (showing diffuse background slowing consistent with mild diffuse cerebral dysfunction), PET/CT of the brain (suggestive of a neurodegenerative process, most likely dementia of the Alzheimer's type), and routine serologic studies (which were unremarkable). He was started on memantine without appreciable benefit.

He was ultimately referred to a neurologist at our facility for a second opinion just four days prior to hospital presentation. Following that visit, planned workup was to include: MRI of brain, MRA of the brain, brainstem, and carotid arteries, repeat PET/CT of brain to assess for evolution (requested by family), lumbar puncture for prion protein 14-3-3 as well as Alzheimer's disease biomarkers, as well as repeat EEG. Serologic workup was to include serum TSH, RPR, folate, vitamin B12, and HIV testing (none of which had clearly been tested previously).

Shortly after that visit the patient was noted at his skilled nursing facility to develop intermittent fevers along with his more longstanding cough. He was started on levofloxacin but did not respond, and as such was ultimately transferred to our emergency room for evaluation.

On arrival the patient was febrile but hemodynamically stable. Chest imaging did not show an infiltrate. Nevertheless given his history the patient was admitted and started on broad-spectrum antibiotics. The planned neurologic workup was also initiated to expedite diagnosis. On hospital day #2 the patient's HIV testing was noted to be positive. In light of likely immunocompromise the patient was treated empirically for Pneumocystis pneumonia. Ultimately bronchoscopy did confirm active pneumocystis infection. The patient's CD4 count later returned at 3.

The patient had a lumbar puncture, which was generally unremarkable. His rapidly progressive dementia was felt to most likely represent HIV-related dementia, though further workup was planned. The patient improved with targeted antibiotic therapy. His mental status remained at its recent baseline. With overall stabilization the patient was ultimately

discharged back to a skilled nursing facility, with planned close infectious disease and neurology follow up.

Discussion

Dementia is defined in the DSM-5 as impairment in at least one cognitive domain (learning and memory, language, executive function, complex attention, perceptual-motor, and social cognition) representing a decline from prior functioning, occurs in absence of delirium, interferes with independence in daily activities, and is not explained by another disorder.[1] This updated definition is unique when compared to prior versions in that it places equal weight on all cognitive domains, rather than focusing on memory.

The differential diagnosis for dementia is broad. Major dementia syndromes include Alzheimer's disease (which represents approximately 60-80% of cases in patients over 65), dementia with Lewy bodies, frontotemporal dementia, vascular dementia, and Parkinson disease with dementia.[2] Additional precipitants of dementia syndrome include alcohol-related dementia, normal pressure hydrocephalus, chronic traumatic encephalopathy, depression, other central nervous system illnesses (including prion diseases and HIV infection), and metabolic derangements including hypothyroidism and vitamin B12 deficiency.[3]

The initial diagnostic step in suspected dementia involves thorough history, including assessment for certain risk factors, family history, and an assessment of cognitive function. There are numerous available cognitive testing protocols available – the Mini-Mental State Examination (MMSE) is the most widely used cognitive test for dementia in US clinical practice, but other options include the Montreal Cognitive Assessment (MoCA) and the Clinical Dementia Rating (CDR).[4-6] The MoCA offers enhanced sensitivity for mild cognitive impairment, whereas the CDR is precise for ongoing serial assessments of dementia status.

Physical and full neurologic exam is focused on narrowing the differential diagnosis, such as evaluation for evidence of Parkinsonism, focal neurologic abnormalities suggestive of prior stroke, and exam signs of thyroid abnormality.

In our clinical practice, laboratory and neuroimaging approaches appear to differ broadly at times. Nevertheless, the American Academy of Neurology (AAN) makes very clear recommendations regarding the approach to additional testing.[7] According to AAN recommendations, for routine cases of dementia in patients 65 years or older, structural neuroimaging with either non-contrast CT or MRI scanning is appropriate.[7] They recommend against any other imaging procedure (such as PET/CT) in absence of specific clinical concern. EEG is felt to be of low yield as a routine study.

With respect to routine lumbar puncture, the AAN recognizes the development of various CSF biomarkers for Alzheimer's disease (such as CSF tau, β-amyloid$_{1-42}$, and AD7C-NTP), but asserts that evidence does not exist to support routine use in all patients; rather, they advocate for patient-specific consideration of lumbar puncture for these studies.[7] In cases of suspected prion disease, they do recommend use of CSF 14-3-3 protein to assess for Creutzfeld-Jacob Disease (CJD).[7]

Screening for depression, vitamin B12 deficiency, and hypothyroidism should always be performed.[7] The AAN recommends against routine assessment for neurosyphilis in absence of specific clinical suspicion. Finally, the AAN recommends against the routine use of genetic testing in patients with possible Alzheimer's disease (such as testing for apolipoprotein E epsilon 4 allele) in absence of specific characteristic family history.[7]

Studies examining the prevalence of reversible causes of dementia in elderly patients support the AAN assertion that routine broader laboratory investigation is not warranted. A review of studies over a 22-year period ending in 1994 estimated that fully-reversible cause of dementia is discovered in <10% of cases over that time, trending toward <1% in the more recent years.[8] However, in younger patients with dementia, more atypical causes may be discovered. A 2006 analysis of 560 patients differentiated between younger (under age 70) and older patients, and noted that non-degenerative and non-vascular (though not necessarily reversible) causes of dementia were present in 5% of the elderly group, but up to 30% in the younger age group.[9]

Additional workup of dementia should otherwise be guided by the clinical context. As noted, patients with earlier-onset or rapidly progressive dementia tend to have more atypical causes, which would warrant consideration of additional testing as directed by the initial history, physical exam, and workup. For example, the presence of risk factors for HIV would suggest usefulness of HIV testing, in addition to consideration of infectious cause (such as Varicella or Herpes Simplex Virus). Concern for possible seizure would warrant assessment of EEG. Rapid progression would lead to consideration of a prion disease.

Conclusion

All patients with dementia should undergo thorough history and physical with cognitive testing and neurologic exam. They should be imaged with non-contrast head CT or MRI. They should be screened for depression, hypothyroidism, and vitamin B12 deficiency. Any other workup (such as HIV testing, RPR, lumbar puncture, EEG, or additional imaging procedures) should be guided by clinical context, in many cases with the assistance of a neurologist (especially with respect to additional imaging studies and genetic testing for Alzheimer's disease).

Our patient presented at a young age with a fairly rapid progression of dementia. He had a history of polysubstance abuse, which when discussed with family did likely include remote IV drug use. This certainly justified investigation for HIV and broad infectious workup. Indeed, a thorough history, with probing questions about the patient's prior risk factors, may have led to an earlier diagnosis.

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Submitted January 19, 2018