CLINICAL VIGNETTE

Limbic Predominant Age-Related TDP-43 Encephalopathy (LATE) in an Elderly Patient

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Case Report

An 89-year-old, college educated female presented with her daughter for a complaint of cognitive deficits. She has been in good health without any hospitalizations in the last 50 years. She is widowed and lives alone in an apartment. Her daughter lives a few miles away, speaks to her daily and visits several times a week. The patient was an unreliable historian and history was obtained from her daughter. The patient had prior alcohol use but quit 12 years ago when she relocated from out-of-state to be closer to family. She stopped driving about 8 years ago, and is unable to navigate public transportation due to "difficulty locating places" and requires transportation assistance from her family. She reports problems with concentration and memory loss. No depression, personality, or behavioral changes were noticed by family. Past medical history was negative for stroke, traumatic brain injury, frequent falls, tremors, seizures, and depression. There is no history of wandering or getting lost outside her home. She had no family history of dementia and had never been on any medications for her memory. The patient eats well when family is present but, when her family is not there, she does not feel hungry, forgets, and does not go to the refrigerator for food. Regarding functional status, she is independent in her basic activities of daily living but requires assistance for all instrumental activities of daily living. She is not taking any prescription medications.

Physical exam was unremarkable but cognitive exam was abnormal. Due to time constraints in clinic, a mini-mental status exam (MMSE) was performed. The patient's score was 18 out of 30 with deficits in orientation, delayed recall, naming, and sentence repetition. Clock draw test was abnormal with inaccurate spacing of the number 1 and imprecise drawing of the hands of the clock. Depression screening was negative. Labs for reversible causes of dementia were notable for both vitamin B12 and folic acid deficiencies. She started on B12 and folic acid supplementation. Evaluation also revealed aortic atherosclerosis. Magnetic resonance imaging (MRI) of the brain without contrast showed an incidental dural-based mass in the left cerebellopontine angle measuring 1.5 x 1.2 cm, likely a meningioma. There was also left temporal pole volume loss suggestive of semantic dementia. There was no hemorrhage, infarct, midline shift or abnormal intra-axial fluid collection. A subsequent flurodeoxyglucose (FDG)-positron emission tomography (PET) brain in conjunction with MRI findings, indicated either a temporal-predominant form of frontotemporal dementia (FTD) or, in this patient's age-group, Limbic-predominant Age-related TDP-43 Encephalopathy (LATE). The patient was referred to a neuropsychologist for further testing but declined. She was referred to a neurologist who found impairments in short-term memory, word finding and facial recognition with preservation of organizational and executive skills. FTD was unlikely in this patient because she had no behavioral changes, and LATE was considered the probable etiology of her dementia.

Discussion

Limbic-predominant age-related TDP-43 encephalopathy (LATE) is an under-recognized form of dementia which may be more common than expected.[1] It is characterized by the accumulation of misfolded TAR-DNA-binding Protein 43 (TDP-43) aggregates in older adults, typically over age 80.[1,2] TDP-43 is a nuclear RNA/DNA-binding protein involved in the regulation of RNA processing.[3] Abnormal cytoplasmic aggregation of TDP-43 in affected neurons is a pathological hallmark of many neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease (AD), Lewy body disease (LBD), and LATE.[1,2,4] In LATE, the accumulation of abnormal TDP-43 is usually found in the limbic system, which is involved in memory, emotion, and behavior.[1] TDP-43 aggregates are found in amygdala in the first stage of LATE, and in both the amygdala and hippocampus in the second stage of LATE. In the third stage of LATE, TDP-43 inclusions are found in the amygdala, hippocampus and middle frontal gyrus.[3] The brain changes that occur in autopsy-confirmed LATE are called LATE-neuropathologic change (LATE-NC).[2]

LATE often coexists with other brain pathologies including amyloid-beta plaques and tauopathy.[1] In a demographic analysis study with autopsy confirmation, the frequency of LATE was highest in the LBD+AD subtype, followed by AD subtype, then LBD subtype and, lastly, aging subtype.[2] The hippocampal distribution of LATE is different between LATE-LBD and LATE-AD.[2] LATE is also often associated with hippocampal sclerosis of aging.[2,5] Another study combined data from 13 community-based or population-based longitudinal cohorts from 5 countries, with 6,196 participants found about 25 % had "pure" LATE-NC with no or minimal AD-neuropathologic change (AD-NC).[6] "Mixed" LATE-NC is present in about 50% of brains with moderate / severe AD-NC.[1] Lastly, another longitudinal study, the 90+ Study, reported presence of hippo-

campal sclerosis (HS) is associated with increased odds of developing dementia.[5]

Risk factors for LATE include advancing age, genetics (five genes with risk alleles for LATE-NC: *GRN*, *TMEM106B*, *ABCC9*, *KCNMB2*, and *APOE*)[1,7] presence of other neurodegenerative disorders like AD or LBD, hippocampal sclerosis, cerebrovascular disease, and arteriosclerosis.[2,5] LATE typically affects adults over age 80.[1,8] Since the "oldest-old" are at greatest risk for LATE and are a rapidly growing demographic group in many countries, LATE has an expanding but under-recognized impact on public health.[1] There is currently no specific biomarker for LATE, and it is definitively diagnosed post-mortem via autopsy. However, clinical history, MRI and PET findings can be used to suggest LATE. On MRI, there is atrophy both within and outside of the medial temporal lobes.[1] Post-mortem MRI research also shows atrophy in the inferior frontal, anterior temporal and insular cortices.[1] On FDG-PET scan, the ratio of inferior to medial temporal metabolism was elevated in autopsy-proven LATE with hippocampal sclerosis compared to autopsy-proven AD lacking LATE-NC.[1]

Clinical features of LATE overlap with those of AD. It is characterized by an amnestic dementia syndrome and symptoms can include memory loss, word finding difficulties, and other impairment in episodic memory, semantic memory, and working memory.[1] It also causes impairment in basic and instrumental daily activities of living. "Pure" LATE is associated with a slower rate of clinical decline than AD alone or FTD alone.[2] However, when there is mixed pathology with coexisting AD and /or LBD, the rate of cognitive decline is more rapid and severe.[2] Patients with LATE do not have features of FTD, but commonly have arteriolosclerosis.[2] LATE is estimated to cause about 15-20% of all dementias.[1] There is currently no cure for LATE. However, some studies suggest Vitamin B12 may be a potential therapeutic target for TDP-43-associated proteinopathies.[4] Research studies are underway to study the prevalence, clinical course, and impact of LATE pathology.[1,2,5]

Conclusion

LATE is an under-recognized form of dementia that should be considered in the differential diagnosis of dementia patients over age 80. It can mimic amnestic-AD but is associated with a slower clinical decline than AD alone.[1] In large community-based autopsy series, LATE-NC is present in > 20% (up to 50%) of individuals over age 80.[1] It frequently coexists with AD and "mixed" pathology is associated with more rapid cognitive decline.[1,2]

In this patient, the neurologist noted bilateral hippocampal atrophy as well as more left-sided focal insular and temporal pole atrophy on imaging. Her cognitive exam, MRI and FDG-PET brain imaging were concerning for LATE. Her evaluation also revealed aortic atherosclerosis and Vitamin B12 deficiency, for which supplementation was started. The neurologist recommended a trial of appetite stimulant in this patient due to her anorexia and mild weight loss. She started on mirtazapine, but because of her forgetfulness, it was difficult for her to remember taking her medication. Her family was encouraged to actively participate in her medication management. After discussion with the patient's family about LATE and its clinical course, they deferred a trial of acetylcholinesterase inhibitors or N-methyl-D-aspartate (NMDA) receptor antagonists, as they had concerns for potential adverse side effects of these medications. Raising the awareness of LATE as a separate dementia is important since it is more common than previously thought and can have a huge public health impact. Ongoing research is needed for its prevention, diagnosis, and treatment.[1]

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