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Unmasking LATE: Understanding a Newly Defined Cause of Memory Loss in Older Adults– A Conversation with Dr. David Wolk

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Navigating Neuropsychology (NavNeuro) is an INS-partnered podcast series that includes conversations with experts in neuropsychology about cutting-edge scientific findings, debates within the field, and the latest in assessment and intervention. You can listen to NavNeuro episodes online or anywhere you listen to podcasts.

The journey into understanding the complexities of age-related cognitive decline recently took a significant turn with the formal recognition and definition of the neurodegenerative condition known as LATE: Limbic-predominant Age-related TDP-43 Encephalopathy. In a recent episode of Navigating Neuropsychology, hosted by Drs. Ryan Van Patton and John Bellone, leading expert Dr. David Wolk discussed this critical, newly described condition. LATE is a clinical-pathological disease resulting in brain dysfunction and cognitive decline in older adults. Critically, LATE often overlaps with Alzheimer's disease (AD) but possesses distinct features that are vital for clinicians and researchers to understand.

At the core of LATE is the aggregation of the protein TDP-43. While its normal function is to regulate RNA processing inside the cell's nucleus, in disease states TDP-43 is cleared from the nucleus and forms clumps, or protein aggregates, in the cytoplasm. This type of pathology was initially recognized in 2006 as a key feature in conditions such as Amyotrophic Lateral Sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). In LATE, the protein aggregates primarily target the limbic system, particularly the hippocampus. This localization makes the medial temporal lobe a "hot spot for neurodegenerative conditions in general."

As the name suggests, LATE is strongly age-dependent, typically affecting the "oldest old cohorts, in the 80s or after." Dr. Wolk noted that estimates suggest that "about 30 to 40% of individuals 80 or over have some degree of LATE."

David Wolk, PhD

This prevalence, particularly in the oldest segments of the population, highlights its immense public health importance.

Because both LATE and AD target the medial temporal lobe, they both cause amnestic (memory-based) syndromes, making clinical differentiation challenging. However, there are key distinctions. AD is generally considered an "amnestic multi-domain syndrome" where memory loss is accompanied by language, visuospatial, and executive deficits. In contrast, LATE typically presents as a "more purely amnestic syndrome" in which memory impairment is the most isolated and salient feature.

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Another important difference is the pace of the condition. Dr. Wolk commented that LATE is "very slow-moving." Clinicians might encounter a patient whose memory has been severely impaired for years, yet other cognitive functions remain relatively spared – a scenario less typical five years into an AD progression. A vital tool for differentiating LATE is structural magnetic resonance imaging (MRI). LATE is associated with pronounced atrophy of the hippocampus. Patients with LATE tend to show more atrophy than expected for their level of memory impairment. This severe hippocampal atrophy is a core feature that shifts the clinical thinking toward LATE.

Due to LATE's prevalence and clinical mimicry of AD, Dr. Wolk and his colleagues recently published clinical diagnostic guidelines. Even without a definitive in vivo biomarker for TDP-43, these guidelines are seen as crucial. Dr. Wolk argues that a disease entity cannot be properly studied until researchers can clinically follow individuals likely affected by it, allowing for richer data collection on genetics and cognitive phenotypes. Furthermore, in the modern era of precision medicine, patients "just want to know what they have," and a clinical label allows for better prognostic information and facilitates inclusion in potential future clinical trials.

The clinical criteria distinguish between two scenarios: LATE as a primary driver of symptoms and LATE co-occurring with AD. To diagnose Probable LATE (where LATE is the primary driver), the patient must have the core amnestic syndrome, evidence of severe hippocampal atrophy (often visible on MRI), and, crucially, be amyloid negative. If a patient is amyloid negative, Dr. Wolk confirms, "now you really kind of know Alzheimer's is highly unlikely to be in the picture."

For patients who are amyloid positive, biomarkers of tau pathology are used. If a patient is amyloid positive but tau negative (meaning they likely have preclinical AD), LATE can still be considered the primary driver of their memory loss because significant tau pathology is generally required for AD symptoms to manifest.

While LATE is currently diagnosed definitively only postmortem, research is rapidly developing new biomarkers. Additionally, the definition of LATE has critical implications for AD treatment. Because LATE frequently co-occurs with AD, this mixed pathology is associated with more rapid cognitive decline than either condition in isolation. Therefore, identifying LATE is vital for prognostication and for understanding how effective anti-amyloid treatments are in people with co-pathologies. Dr. Wolk stresses the importance of studying outcomes in these mixed-pathology patients because "it's incumbent on the field to start to really try to categorize these patients so that we can move the field forward."

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