Large Autopsy Study Estimates Prevalence of “LATE” Neuropathologic Change

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Many older people at the end of life may have a pattern of protein deposits in the brain associated with memory loss called limbic-predominant age-related TDP-43 encephalopathy neuropathologic change, or LATE-NC, a recent study published in *Acta Neuropathologica* suggests.

Combining autopsy data from 13 international cohorts, a team of researchers found that LATE-NC was present in almost 40% of more than 6000 individuals with advanced age who volunteered to donate their brains after death. The neuropathology was often—but not always—observed in combination with Alzheimer disease brain changes, a finding the researchers say supports LATE as its own type of amnestic dementia.

Peter Nelson, MD, PhD, the study’s corresponding author and an experimental neuropathologist at the University of Kentucky, said the results continue to establish LATE and its pathology as a public health and research priority.

“This is a condition that is clearly very common and very impactful,” Nelson said in an interview with *JAMA*. “But it’s also understudied and underappreciated.”

Yet some experts are skeptical that LATE represents a separate condition from Alzheimer disease and other neurodegenerative disorders.

**Collaboration Was Critical**

In 2019, a working group of clinicians and researchers including Nelson and many of the new article’s coauthors, met and agreed on diagnostic criteria for LATE, characterizing it as a distinct form of dementia.

According to their definition, which was published in *Brain*, deposits of transactive response DNA-binding protein 43, or TDP-43, that progress from the amygdala to the hippocampus to the middle frontal gyrus of the brain are the hallmarks of LATE neuropathology. The deposits are often also found in the brains of people with Alzheimer disease and—like the misfolded β-amyloid deposits that characterize Alzheimer disease—buildup of TDP-43 is associated with memory loss.

For the new analysis, Nelson and collaborators combined results from longitudinal studies conducted in the US, the UK, Brazil, Finland, and Austria to establish the prevalence of LATE-NC in a larger and more representative group than has previously been possible. The pooled data included autopsy results for 6196 participants, whose average age at death was 88 years. The study drew from both community-based and population-based cohorts, with the latter including individuals recruited from different subgroups within geographic areas.

Many of the investigators from the cohort studies collaborated on the new analysis. Their willingness to share and combine data was essential, Nelson said. Although information from dementia clinic and hospital cohorts is available, these populations tend to have a higher concentration of genetic risk factors for dementia, unusual subtypes, and early-onset diseases, making studies of these data less generalizable.

Because the new estimate of LATE-NC is based on several population-based studies from multiple countries, “it gives us a better sense of confidence about how common it is,” Nina Silverberg, PhD, director of the Alzheimer Disease Research Centers program at the National Institute on Aging (NIA), said in an interview. The NIA is part of the US National Institutes of Health, a major funder of the research.

About 15% of the study’s participants had early-stage LATE-NC, which is not associated with cognitive symptoms, while another 25% had later-stage LATE-NC, which has been linked with cognitive impairment. However, the authors expressed caution in extrapolating the results to the general population. Based on the study design, the findings could apply to people who live, on average, into their late 80s and agree to donate their brains posthumously. The researchers also noted that White individuals were overrepresented in their analysis. (Nelson and 2 additional study authors are *Acta Neuropathologica* editorial board members and another author is the journal’s editor in chief; none were involved in the article’s editorial handling.)
An Evolving Understanding

The study confirmed that LATE-NC frequently exists in combination with Alzheimer disease neuropathology: about 55% of brains with severe Alzheimer disease pathology had LATE-NC as well. However, 27% of brains without any Alzheimer disease pathology also had LATE-NC. For Nelson, the difference in prevalence is evidence that Alzheimer disease and LATE are 2 separate entities.

Scientists have begun to recognize in the past few decades that dementias can be a constellation of different disorders. "The message is that not everything is Alzheimer’s," Silverberg said. "We’re understanding that there are these differences and that people can have more than one [type of dementia]."

TDP-43 was initially linked to diseases including amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) in 2006. Soon after, researchers found TDP-43 deposits in the brains of people older than 80 years who did not have ALS or FTLD. The pathology was often present in tandem with Alzheimer disease and hippocampal sclerosis, a condition in which hippocampal cells die off.

"It turns out that TDP pathology is much less specific than they thought at that time," Nelson said. "There are something like 20 different conditions that have TDP pathology, and LATE is just one of them."

To Nelson, the key to making progress in Alzheimer disease and dementia research is embracing the intricacy of the diseases. "Until we grapple with that complexity and give things names so they can be put into boxes and treated differently, we’re not going to be successful," he said. He compared the field to oncology, where the subcategorization of cancers has led to what are often effective, targeted therapies.

Silverberg, who was not involved with the recent study, said it should spur physicians to help raise awareness that patients can participate in dementia research, not just by enrolling in clinical trials but also by joining community-based studies or volunteering to be brain donors after death. "There’s other research where people don’t necessarily have to take an unknown medication," she said.

Skeptics Remain

Some experts who did not work on the study are skeptical that the pattern of TDP-43 brain lesions, sometimes referred to as "inclusions," qualify LATE as its own form of dementia.

"We have a long way to go in understanding what these inclusions mean," William Hu, MD, PhD, said in an interview. In 2019, Hu, an associate professor and chief of neurology at Rutgers Biomedical and Health Sciences, coauthored an editorial that opposed establishing LATE as a dementia subtype. At the time, he encouraged the dementia research community to defer using the name "LATE" until the biology behind the pathology was better understood.

Little new data have been published since then to change his position. He said that LATE is largely defined by pathology and that the link with cognition depends on whether TDP-43 is present with other pathologies. In his view, "LATE" instead represents 3 established conditions: Alzheimer disease, late-onset FTLD, and hippocampal sclerosis.

One of Hu’s coeditorialists, Karl Herrup, PhD, a professor of neurobiology at the University of Pittsburgh School of Medicine, also remains unconvinced. He echoed the need for more research into the biological effect of TDP-43 deposits. "I think it would really help if we took a step back and looked at our basic science," he said in an interview.

To advance the research, both Hu and Silverberg said that clinical biomarkers are needed for TDP-43, which currently is only identifiable on autopsy. Blood markers would be ideal, Silverberg said, but any ability to detect TDP-43 in living people would be helpful. "We know now that people quite commonly do have both Alzheimer’s and TDP-43 proteinopathy," she said. "If we can’t tell who has one or the other or both, it makes all the research a lot harder."