When Alzheimer's is LATE: Why Does it Matter?

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Recent therapeutic advances provide heightened motivation for accurate diagnosis of the underlying biologic causes of dementia. This review focuses on the importance of clinical recognition of limbic-predominant age-related TDP-43 encephalopathy (LATE). LATE affects approximately one-quarter of older adults and produces an amnestic syndrome that is commonly mistaken for Alzheimer's disease (AD). Although AD and LATE often co-occur in the same patients, these diseases differ in the protein aggregates driving neuropathology (Aβ amyloid/tau vs TDP-43). This review discusses signs and symptoms, relevant diagnostic testing, and potential treatment implications for LATE that may be helpful for physicians, patients, and families.

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Introduction

Dementia is a common clinical syndrome characterized by a progressive decline in one or more cognitive domains that is sufficient to cause functional impairment. With the emergence of therapies that target Alzheimer's disease (AD)/amyloid β (Aβ) amyloidosis,[1] recognition of amnestic dementias that may mimic AD has diagnostic, prognostic, and therapeutic implications.

Among the most prevalent neurodegenerative pathologies seen in aging populations is limbic-predominant age-related TDP-43 encephalopathy (LATE).[2] LATE is a frequent "mimic" of AD in persons of advanced age, with a significant and generally under-recognized impact on public health. Much of the prior literature on LATE has been directed at understanding its pathologic, neuroimaging, and/or genetic features, with relatively little to date describing the disorder as a clinical entity. Available current data suggests LATE has slower and predominantly amnestic decline, which may be of diagnostic and prognostic value. Given the prevalence, impact, and diagnostic significance of LATE in this emerging era of disease modifying therapy for AD, it will become essential that dementia care providers understand this important disease.

This review focuses on LATE from the clinician's perspective. A deeper understanding of LATE will be necessary for meaningful communication with patients and family members about prognosis and treatments. The review will discuss symptoms that could guide a clinician to suspect LATE; how comorbid pathologies influence disease phenotype; which ancillary clinical tests may be most helpful in guiding diagnosis; and the types of information a clinician may wish to provide to an affected patient and their caregiver. Current research breakthroughs inspire hope and also underscore the potential for working toward a precision-medicine based approach to optimize diagnosis, prognostication, and therapies.

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Pathologic Features, Public Health Impact, and Nomenclature

At present, LATE can only be definitively diagnosed at autopsy. The pathologic hallmarks of LATE neuropathologic change (LATE-NC) are so-called "inclusion bodies" comprising misfolded, mislocalized, and aberrantly phosphorylated transactivation response DNA binding protein 43 (TDP-43). The inclusion bodies are distributed predominantly within the medial temporal lobe (MTL). LATE-NC describes a stereotypic anatomic pattern of TDP-43 pathologic inclusions, that sequentially affects the amygdala (stage 1), then the hippocampus (stage 2), and then, in some cases, expands more broadly to involve the middle frontal gyrus at the last stage (stage 3)[2–5]; see Fig S1.

TDP-43 pathology was first described as a disease-related feature in the context of frontotemporal lobar degeneration (FTLD-TDP) and amyotrophic lateral sclerosis.[6] TDP-43 pathology is now known to be present in dozens of other neurologic diseases,[7] and the distribution of TDP-43 pathology in LATE-NC differs from its distribution in those other conditions.[5,8,9] LATE-NC is often, but not always, accompanied by hippocampal sclerosis (HS), a term which implies significant pyramidal cell loss and gliosis in the hippocampal formation.[10,11]

LATE has a large impact on public health. We highlight 3 points: (1) the presence of LATE-NC, with or without comorbid pathologies, is associated with cognitive impairment and dementia, comparable with other conditions, such as AD, cerebrovascular, and Lewy body diseases (LBDs)[12–16] (Fig 1); (2) the prevalence of LATE increases with age, affecting more than a third of persons older than 85 years[15,17]; (3) LATE-NC often co-exists with other pathologies, and, therefore, may be associated with not only a progressive amnesia but also a wider range of clinical features.[18-21] Recognition of LATE as a clinical entity will enable accurate diagnostic and treatment planning.

Areas of uncertainty and disagreement remain for the newly emerging classification and nomenclature for LATE and its "boundary zones" with other neurodegenerative conditions. For a discussion of these issues, readers are referred to relevant publications,[8,9,22,23] and for terms and nomenclature used in this review, see Table 1.

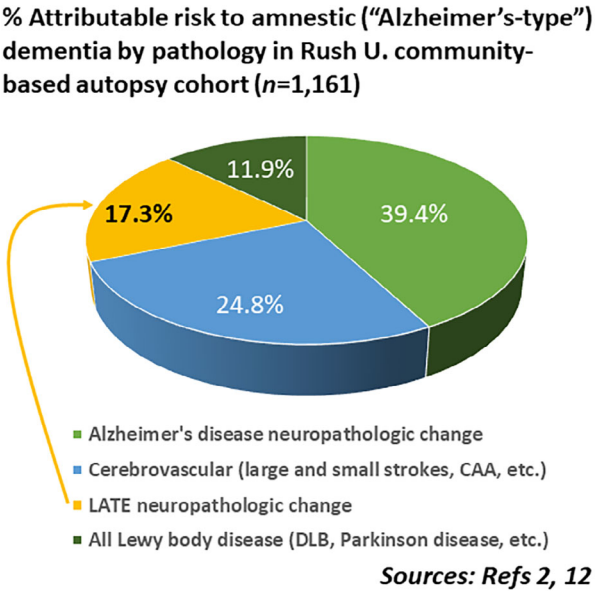

FIGURE 1: A pie chart depicts the relative contributions of different neuropathologic entities to amnestic ("Alzheimer's type") dementia in a large community-based cohort. These data derive directly from an attributable risk analysis, as described in detail in refs. 2 and 12. The research volunteers were from 2 large community-based studies of aging from Rush University (n = 1,161 participants were included); mean age at death was 89.7 years. Multi-variable logistic regression models examined associations between the outcome of Alzheimer's-type (eg, amnestic) dementia with neuropathologic indices. Vascular pathologies included large infarcts, arteriolosclerosis, atherosclerosis in the Circle of Willis, and cerebral amyloid angiopathy. [Color figure can be viewed at www.annalsofneurology.org]

Clinical Presentation of LATE and Other Common Co-Pathologies

LATE-NC can occur in isolation (as the predominant pathology), as observed in approximately 20% of all persons beyond age 85 years with amnestic cognitive impairment; it is often misdiagnosed as AD.[3,16,17] More commonly, however, LATE-NC occurs as a co-pathology with another neurodegenerative condition, such as ADNC (plaques and tangles), Lewy bodies, and/or cerebrovascular disease that often are erroneously presumed to be the sole cause for the dementia syndrome.[3,24] LATE typically presents with memory impairment and significant atrophy of the medial temporal lobes[25] (see Fig 2). Unfortunately, teasing apart the differences between AD and LATE is currently very challenging, if not impossible, based purely on clinical features, particularly at a single visit, but the diagnosis can become more apparent with longitudinal evaluation. Despite the present lack of specific antemortem biomarkers for LATE, available imaging and biofluid biomarkers for AD and other pathologic causes of dementia may be helpful in supporting a diagnosis of LATE (see below).

Clinical Presentation of LATE Alone

In the absence of other pathologies, individuals with LATE commonly present with an indolent amnestic syndrome.[26] Memory loss is consistent with a limbic/episodic amnesia wherein information is lost over time and less facilitated by cueing or recognition testing. Because the clinical picture for LATE is similar to AD, differential diagnosis requires recognition of the nuanced differences

TABLE 1. Notes on Relevant Nomenclature

Terminology	Notes
Amnestic clinical syndrome	Cognitive impairment (MCI or dementia) with predominant memory loss
LATE neuropathologic change (LATE-NC)	A pathologic pattern of TDP-43 proteinopathy predominantly in medial temporal lobe structures
Alzheimer's disease neuropathologic change (ADNC)	Alzheimer's-type Aβ+ amyloid plaques and neurofibrillary tangles (see ref. 10)
LATE-NC versus FTLD-TDP	LATE-NC and FTLD-TDP have the same misfolded protein (TDP-43) but the anatomic, clinical, epidemiological, and genetic features are different
Hippocampal sclerosis (HS)	Cell loss and gliosis in the hippocampal formation, often including subiculum. This is a potentially confusing term because of its historical use in seizure disorders, especially those occurring in children with lengthy and/or repeated seizures. In elderly persons with dementia, HS is associated with severe hippocampal atrophy, usually without seizures. A significant majority of elderly persons with HS have LATE-NC.
LATE	Clinical syndrome, usually amnestic, associated with LATE-NC
AD	Clinical syndrome, frequently amnestic, associated with ADNC
AD + LATE	Clinical syndrome, frequently more aggressive amnestic and multi-domain, associated with concomitant LATE-NC and ADNC

Abbreviation: Aβ = amyloid β; AD = Alzheimer's disease; ADNC = Alzheimer's disease neuropathologic change; FTLD = frontotemporal lobar degeneration; HS = hippocampal sclerosis; LATE = limbic predominant age-related TDP-43 encephalopathy; LATE-NC = limbic predominant age-related TDP-43 encephalopathy neuropathologic change; MCI = mild cognitive impairment.

in presentation and progression. For an overview of the differential diagnosis of common amnestic memory disorders that resemble and include clinical LATE, see Table 2. A patient with progressive cognitive impairment that primarily and severely affects memory throughout the entire disease course supports a diagnosis of LATE. Conversely, a patient with progressive memory impairment with emerging symptoms in other cognitive domains, including language, executive and visuospatial functions, etc., is more likely to have AD.[27,28] Thus, increasing suspicion of LATE may emerge as a patient is followed longitudinally. Whereas episodic memory impairment is highly salient in LATE, mild semantic memory deficits, measured by tests of categorical fluency, also may develop, particularly in the presence of HS (see below), although there is often evidence of deficits of working memory as well in these patients.[27,29–32] Patients with LATE may have frontal lobe-associated behavioral symptoms, but these can also be seen in association with ADNC and other dementias.[31,33] Finally, advanced age (> 80 years old) also increases the likelihood of LATE, as described below.

LATE with Hippocampal Sclerosis

In older adults, HS is associated with dementia, rather than clinical seizures.[34] Most HS in aging is typically a subset of LATE-NC, as evidenced by the presence of the pathologic features of LATE-NC (TDP-43 pathology) and HS (dramatic cell loss and hippocampal atrophy) in the same individuals.[15,25] There appears to be a progression of hippocampal atrophy across the LATE stages, which in some patients culminate in HS. The subset of persons with LATE who have comorbid HS tend to have more profound impairments of episodic memory, but also more global cognitive involvement that is most prominent for semantic memory.[14,35,36] That said, the degree of non-memory domains associated with HS tends to remain less prominent than typical AD. On magnetic resonance imaging (MRI), HS can be observed as severe, particularly anterior, MTL atrophy that can extend into anterior temporal regions (Fig 3). A small minority of persons have HS-like pathology without LATE-NC, perhaps promoted by hypoperfusion, anoxia, hypoglycemia, and/or other vascular or systemic factors.[37]

Clinical Presentation of LATE with AD and Other Neurodegenerative and Vascular Pathologic Conditions

It is common for LATE-NC to co-exist with other dementia-driving pathologies.[18,38,39] These neuropathologic changes may occur in somewhat coherent clusters of

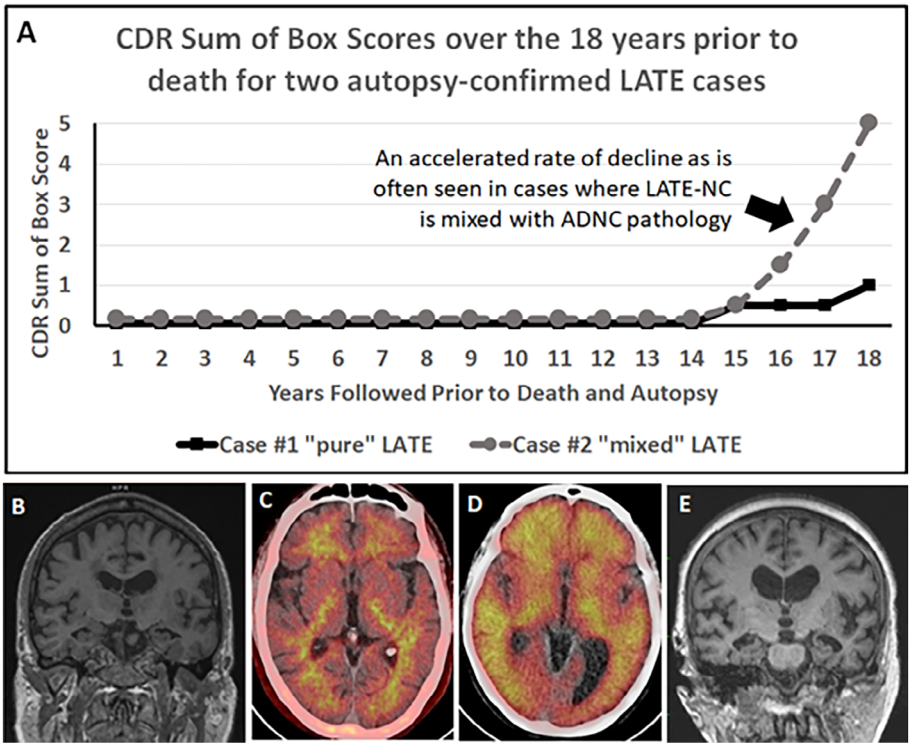

FIGURE 2: Clinical and imaging characteristics of a prototypical "pure" LATE-NC case (#1, age 93 years at death) and a "mixed" ADNC and LATE-NC case (#2, age 90 years at death). (A) Longitudinal CDR-SOB scores show a more severe rate of decline over the 3 years prior to death for Case #2 ("mixed" LATE-NC) compared to Case #1 ("pure" LATE-NC). (B) T1 MRI coronal image in Case #1 ("pure" LATE-NC) at first diagnosis of MCI, 3 years prior to death and autopsy, demonstrating left greater than right hippocampal atrophy. (C) ^{18}F-Florbetapir PET axial image demonstrating no significant amyloid accumulation (SUVr 1.04) 1 year prior to death and autopsy for Case #1 ("pure" LATE-NC), compared to (D) a prototypic AD case with SUVr 1.73. (E) Severe bilateral hippocampal atrophy is seen in a T1 MRI coronal image of Case #2 ("mixed" ADNC and LATE-NC) 1 year prior to death and autopsy. The cerebrospinal fluid ptau-181/Ab42 ratio was 0.15 in Case #2 demonstrating antemortem evidence for Alzheimer's disease/ADNC. Cases presented are from the University of Kentucky AD Research Center (UK-ADRC) cohort. Use of the clinical, biofluid, and imaging data presented in this figure was approved by the University of Kentucky Institutional Review Board. AD = Alzheimer's disease; ADNC = Alzheimer's disease neuropathologic change; CDR-SOB = Clinical Dementia Rating Scale Sum of Boxes; LATE = limbic predominant age-related TDP-43 encephalopathy; LATE-NC = limbic predominant age-related TDP-43 encephalopathy with neuropathologic changes; MRI = magnetic resonance imaging; PET = positron emission tomography; SUVr = standardized uptake value ratio. [Color figure can be viewed at www.annalsofneurology.org]

comorbid neurodegenerative and cerebrovascular disease subtypes.[20] The comorbid conditions are important because the salient clinical/cognitive features may vary in association with the presence of more than a single neurodegenerative disease. Certain diagnostic tools are emerging that may be useful to clinicians in differential diagnoses to provide insights into prognosis, and perhaps in the future, to guide therapeutic decisions.

The combination of Alzheimer's neuropathologic change (ADNC) with LATE-NC is particularly common (Fig 4).[40] Indeed, patients with ADNC have an approximately 2-fold increased odds of LATE-NC relative to those without ADNC.[17] When patients with amnestic dementia have AD + LATE, their progression exhibits a generally more rapid rate of hippocampal atrophy, memory impairment, and overall cognitive decline than in patients with either AD alone or LATE alone.[20,41–43] Data from multiple longitudinal cohorts has demonstrated that AD + LATE is a common combination of copathologies with a large impact on public health.[44] It remains unclear how the presence of LATE might influence outcomes for disease-modifying therapies targeting AD, but one would expect a lower efficacy in mixed AD + LATE for therapies targeting Aβ amyloid. Other therapies, such as immunotherapies, on the other hand, may provide benefit when multiple pathologies or non-AD neuropathologies underlie the amnestic dementia.

A subset of individuals with comorbid ADNC + LATE-NC also have LBD.[45,46] This triple pathology subgroup is important to highlight because the ADNC + LATE-NC + LBD pattern of brain pathologies is more common than would be anticipated based on the individual frequencies of ADNC, LATE-NC, and LBD alone,[20,45] implying pathological synergies. This

TABLE 2. Differential Diagnosis Selected Substrates of Amnestic Dementia

		LATE-NC without ADNC or HS	LATE-NC + HS without ADNC	LATE-NC[a] + ADNC	ADNC with no LATE-NC
Pathologic stain(s)		TDP-43 IHC	TDP-43 IHC + H&E	TDP-43, Aβ, Tau IHC	Aβ, Tau IHC
Approximate attributable risk to amnestic dementia		Approximately 10% of amnestic dementia in older individuals		Approximately 30% of amnestic dementia in older individuals	Approximately 20% of amnestic dementia in older individuals
Common genetic risk factors		*TMEM106B*, *GRN*, and *RBFOX1*	*TMEM106B*, *GRN*, and *ABCC9*	*TMEM106B*, *GRN*, *APOE*, and others	*APOE*, *BIN1*, *PICALM*, *CLU*, etc.
Clinical phenotypes		Slow decline in episodic memory, may also include semantic memory	More severe deficits in episodic and semantic memory, as well as more global cognitive decline, versus LATE-NC lacking HS	More aggressive episodic memory decline than either LATE-NC or ADNC alone with multidomain impairment	Intermediate severity and speed of cognitive impairment
Bio-markers	MRI	Moderate—severe atrophy in MTL, anterior > posterior, can extend beyond MTL with more severe disease	Often severe atrophy in MTL, and extending into anterior temporal and frontal regions later in disease	Additional inferior temporal, lateral parietal, and precuneus atrophy relative to LATE-NC alone	Inferior temporal, lateral parietal, precuneus, less severe MTL atrophy than AD + LATE
	PET	MTL hypometabolism on ^{18}F-FDG-PET, with negative Tau and Aβ PET		Posterior temporal/ parietal hypometabolism and MTL orbitofrontal signal on ^{18}F-FDG-PET plus positive Aβ and Tau PET	Posterior temporal/ parietal hypometabolism on ^{18}F-FDG-PET plus positive Aβ and Tau PET
	Bio-fluids	Negative Tau and Aβ biofluids		Positive Tau and Aβ biofluids	

[a]Includes persons with and without HS.

Abbreviation: Aβ = amyloid β; AD = Alzheimer's disease; FDG = fluorodeoxyglucose; H&E = hematoxylin-eosin stain; HS = hippocampal sclerosis; IHC = immunohistochemical; LATE-NC = limbic predominant age-related TDP-43 encephalopathy neuropathologic change; MRI = magnetic resonance imaging; MTL = medial temporal lobe; PET = positron emission tomography.

hypothesis is supported by the fact that the *APOE* ε4 risk allele for ADNC is also a risk allele for LATE-NC and LBD.[47] Unfortunately, those with ADNC + LATE-NC + LBD have an especially rapid and severe disease course,[45] often with psychoses.[20]

Cerebrovascular pathology is highly prevalent in late life and in persons with AD, LATE, or both. Small vessel disease may be especially important in LATE where there is some evidence of direct and indirect effects of concomitant vascular disease and proteinopathies. In addition, importantly, these vascular co-pathologies have been demonstrated to contribute to clinical decline. Some aspects of vascular disease can be detected and followed over time by MRI and/or vascular imaging methods. Certain MRI sequences, including fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and gradient echo (GRE) sequences are well-suited to detect vascular ischemia, infarcts, and microhemorrhages, whereas contrast-labeled angiography can evaluate the patency of larger vessels. Small vessel disease (microinfarcts and arteriolosclerosis) may be a challenge for clinical detection, as white matter hyperintensities (WMHs), the most commonly used biomarker for vascular disease is nonspecific, especially in those who already are evidencing

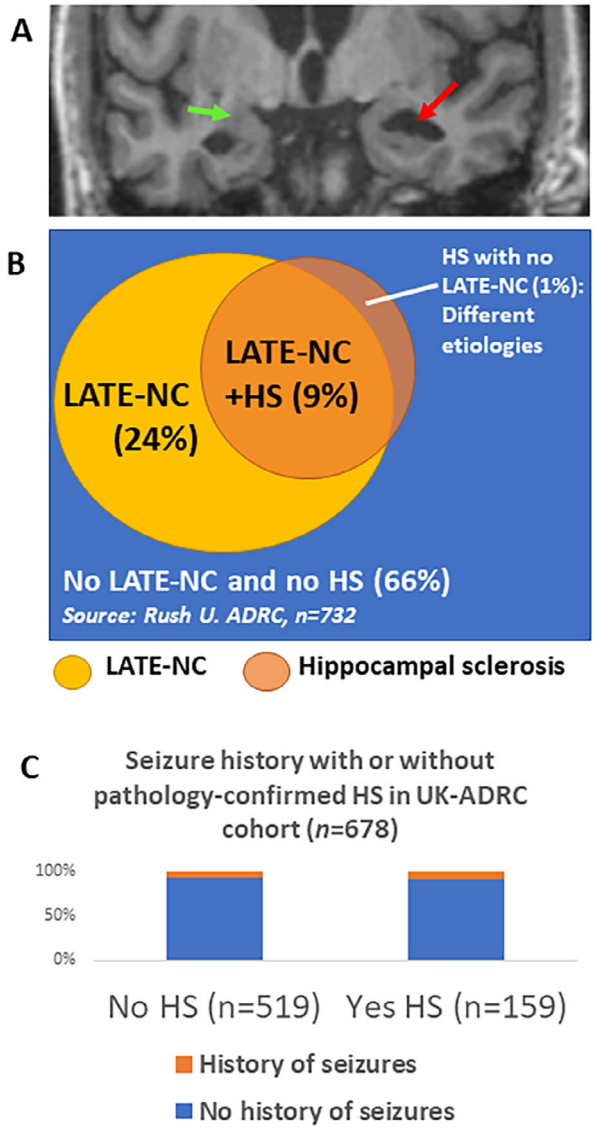

FIGURE 3: Hippocampal sclerosis in aging is associated with LATE-NC and dementia, not with seizure disorders. During clinical workup, the findings on structural MRI (representative example shown in panel A) usually show marked anterior middle temporal lobe atrophy, particularly in the amygdala (green arrow) and anterior hippocampus (red arrow). Most HS in aging is a subset of LATE-NC. In community-based cohorts such as those followed at Rush University Medical Center, approximately one-third of LATE-NC cases show HS at autopsy (see proportional Venn diagram; panel B). A smaller percentage of individuals show HS without LATE-NC; these are different disease categories that may include vascular, metabolic, and anoxic changes. The primary data for this chart were derived from reference.47 HS is not primarily associated with seizures in older subjects. For example, in 678 subjects from the UK-ADRC cohort (panel C), among those with autopsy proven HS, 8.1% with seizure history, whereas in those lacking HS, 7.1% had seizures. As was shown in a larger multicenter cohort previously,[34] this difference was not statistically significant at $p < 0.05$. HS = hippocampal sclerosis; LATE-NC = limbic predominant age-related TDP-43 encephalopathy neuropathologic change; MRI = magnetic resonance imaging; UK-ADRC = University of Kentucky Alzheimer's Disease Research Center. [Color figure can be viewed at www.annalsofneurology.org]

dementia.[48] Controlling for age and other factors, persons with LATE-NC have a relatively high burden of cerebral arteriolosclerosis,[24,49,50] suggesting mechanistic link(s) between LATE and small-vessel vascular disease.

Biomarkers

There currently is no in vivo biomarker known to be specific for TDP-43 pathology or LATE. However, a number of biomarkers may provide inferential support for the presence of LATE-NC.

Structural Imaging

Structural imaging (MRI) is routinely obtained in the assessment of individuals with cognitive impairment. Spatial patterns of atrophy can suggest different neurodegenerative conditions. Ex vivo imaging of individuals with autopsy-confirmed LATE-NC have demonstrated anterior-predominant neurodegeneration in the MTL and orbitofrontal structures.[2,51,52] This pattern largely matches the distribution of TDP-43 pathology in LATE-NC, and the severity of pathology is correlated with MTL thickness.[53,54] More specific distortion of the amygdala volume and shape have also been described with post-mortem imaging.[55]

In vivo studies that are linked to autopsy-confirmed cases have largely aligned with the ex vivo imaging data. Whereas hippocampal volume loss is nonspecific and commonly associated with AD, cases with severe anterior MTL atrophy, such as in Figure 3, are frequently associated with TDP-43 pathology and HS.[30,56–58] Indeed, this gradient of atrophy that is more severe in anterior MTL than posterior contrasts with AD wherein MTL atrophy is more posterior.[30,56–58] A ratio of anterior to posterior MTL atrophy on in vivo MRI had reasonable discrimination for autopsy confirmed AD with versus without concomitant LATE-NC (area under the curve [AUC] = 0.84, 95% confidence interval [CI] = 0.72–0.97).[59] Likewise, LATE appears to have differential effects on hippocampal shape from AD, although standard clinical scans do not provide such data.[51] The longitudinal rate of atrophy tends to be slow in pure LATE; however, when LATE is accompanied by comorbid AD, atrophy rates significantly exceed those of AD alone.[53,60] Nonetheless, because both AD and LATE are predominantly associated with MTL atrophy, for individuals with a primarily amnestic syndrome, severe amygdala and/or hippocampal atrophy in the absence of AD biomarkers (amyloid or tau) is suggestive of LATE.

Positron Emission Tomography

The ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) is a functional biomarker of neurodegeneration that has illuminated patterns of hypometabolism suggestive of LATE.[61-63] By assessing the

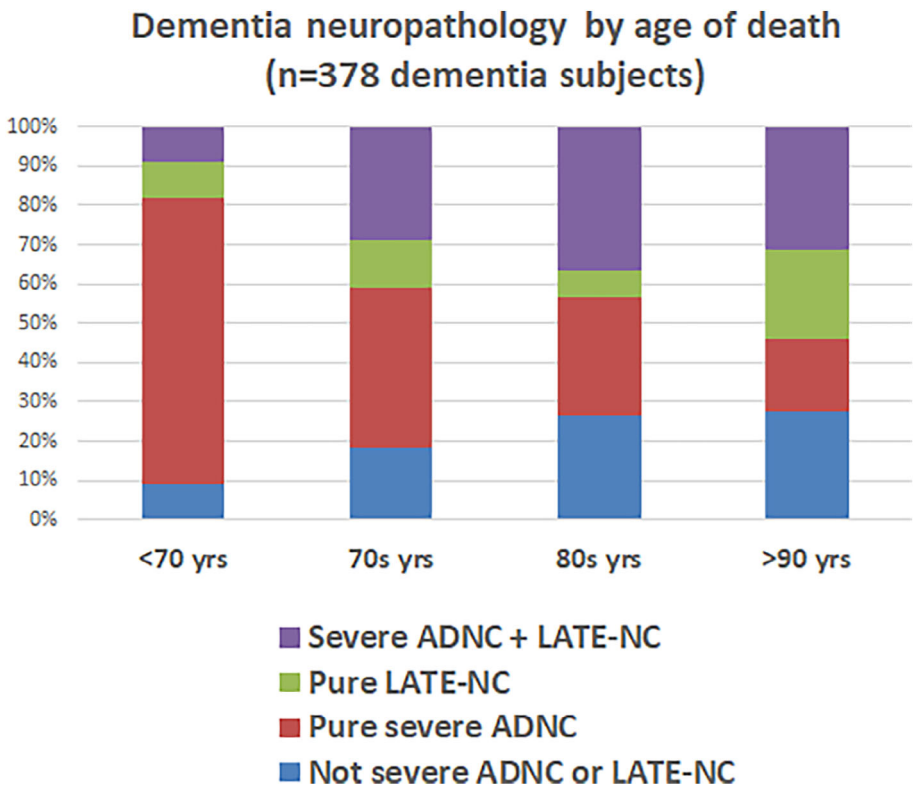

FIGURE 4: A stacked-bar chart helps convey the differences of pathologic features seen in different age groups of dementia patients. Notably, "pure" severe ADNC is predominantly in relatively young individuals, whereas more persons with dementia onset in advanced age have LATE-NC, either with or without comorbid severe ADNC. These data were from the University of Kentucky ADRC autopsy cohort (n = 378 dementia subjects), and are in agreement with prior studies in this and other cohorts.[3,16,17,72,79] ADNC = Alzheimer's disease neuropathologic change; ADRC = Alzheimer's Disease Research Center; LATE-NC = limbic predominant age-related TDP-43 encephalopathy with neuropathologic changes. [Color figure can be viewed at www.annalsofneurology.org]

hypometabolism of the MTL and frontal supraorbital gyrus (FSO) relative to the metabolic sparing of the inferior temporal gyrus (I), the I/MTL/FSO ratio has roughly 80% sensitivity and specificity in distinguishing cases along the AD continuum with and without comorbid LATE.[63] Further, the ratio of I/MTL was able to identify subgroups of patients who were tau-negative (T–) and either amyloid-positive (A+) or negative (A–) on PET. The patients with A+/T+ AD had greater inferior temporal hypometabolism and, thus, a lower I/MTL measure compared to the tau-negative group that was thought likely have LATE-NC with HS. This in vivo PET study was further validated in an autopsy sample. Similar regional ratios based on structural MRI have been found to have similar sensitivity but poorer specificity. Together, these studies suggest that hypometabolism and atrophy on ^{18}F-FDG and MRI can provide probabilistic support for a clinical diagnosis of LATE.

Role of Amyloid and Tau Biomarkers in Differential Diagnosis of LATE

Although specific molecular biomarkers of TDP-43 pathology are not yet available, biomarkers of AD pathology (amyloid and tau) have been broadly used in AD clinical trials and will likely be gaining more wide-spread availability. The absence of positive AD biomarkers in amnestic individuals strongly increases the likelihood of LATE. Particularly, measures of amyloid (amyloid PET or Aβ 42/40 in cerebrospinal fluid [CSF]) and tau-based neurofibrillary tangles (tau PET and CSF p-tau181) can assist in the differential diagnosis of amnestic syndromes. In an isolated amnestic syndrome with MTL atrophy, as described above, the absence of amyloid markers would most likely signify LATE. Indeed, hippocampal volume is most strongly related to AD and LATE pathologies with much less contribution from the other brain pathologies.[64]

A critical challenge is determining when symptomatic patients with AD (A+/T+) have concomitant LATE-NC. Some work has suggested that a disproportionate degree of atrophy or hypometabolism in the MTL may support underlying ADNC + LATE-NC.[65,66] This approach identifies patients with mixed ADNC + LATE-NC co-pathologies from the "mismatch" between observed neurodegeneration on MRI or ^{18}F-FDG PET and expected neurodegeneration based on visible tau burden and is also supported by postmortem analysis.[67]

Using a Combination (Plasma/CSF/Molecular Imaging) to Rule in or out the Diagnosis of LATE and Comorbid Pathologies

Although a definite diagnosis of "pure" LATE is not possible without an autopsy, the clinical presentation with existing biomarkers do allow for a probabilistic classification of LATE. In the appropriate clinical context, approaches to rule out competing diagnoses, as well as rule in LATE may provide the highest clinical certainty. As noted, it would be particularly important to rule out AD with measures of Aβ (and tau if the person is symptomatic). Then, further support may come from a high degree of hippocampal atrophy, particularly with an anterior-to-posterior gradient, and/or an FDG PET quantified by the I/MTL/FSO ratio in support of LATE. In some A+ cases, the absence of tau (T–) and the latter MRI and FDG PET patterns may also lead to suspicion of LATE. Although molecular AD biomarkers are not frequently used in clinical practice, they almost certainly will become more common as AD modifying therapies are brought into routine clinical practice. Further, the emergence of plasma biomarkers (eg, ptau-217 and $A\beta_{42/40}$) may increase the accessibility of biomarker combinations helpful in supporting a LATE diagnosis.

LATE-Specific Biomarker(s): A Critical Unmet Need

Assays reflecting TDP-43 pathology are urgently needed and currently in development. Improvements in immunoassays for TDP-43 present in cerebrospinal fluid and blood have some promise as a marker of TDP-43 neuropathology. In a recent study of human plasma samples, TDP-43 protein was found to be in glial-derived exosomes, which may provide a much-needed blood-based biomarker for LATE-NC.[68] Because some studies saw an elevation of blood TDP-43 levels in patients with clinically diagnosed mild cognitive impairment (MCI) or dementia thought due to AD, it is possible that such measures may be detecting some TDP-43 pathology in the context of either LATE-NC or mixed LATE-NC and ADNC.[52] Novel radiotracers that bind to pathologic TDP-43 are also being explored,[52] but it may be years before clinical in vivo TDP-43 imaging is available.

Risk Factors, Clinical Management, and Clinical Trials

Age of the patient is a key diagnostic consideration as vulnerability to specific subtypes of neurodegenerative diseases differs at different stages of the aging spectrum.[2,69] Recent studies have indicated that ADNC levels off among the "oldest-old"[2,11,27,69,70] after the *APOE* genotype effect is diminished.[27] Further, more pure subtypes

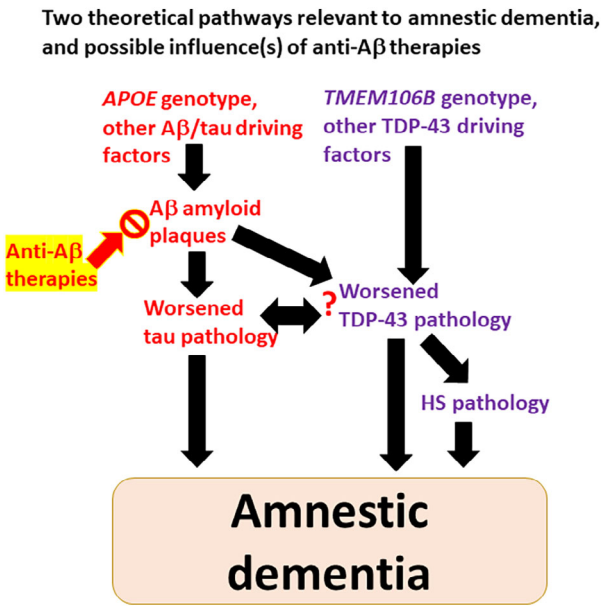

FIGURE 5: A schematic diagram depicts two different perspectives of how LATE-NC may relate to new anti-Aβ therapeutic strategies. In the red text are aspects that may be directly affected by anti-Aβ biological medications. It is credible but presently unknown whether "downstream" TDP-43 pathology will be affected by those new medicines. In the purple text are pathologic features that may still occur despite AD-oriented medicines; these may require new LATE-NC (TDP-43 and/or HS) tailored therapeutic strategies. Aβ = amyloid; AD = Alzheimer's disease; HS = hippocampal sclerosis; LATE-NC = limbic predominant age-related TDP-43 encephalopathy with neuropathologic changes. [Color figure can be viewed at www.annalsofneurology.org]

of pathology become more unusual in advanced old age.[12,13,19]

Unlike AD, the prevalence of LATE is greatest at the final portion of the human aging spectrum.[2,11,71] This is partially conveyed in Figure 4. There is no compelling evidence to date that LATE varies by sex or ethnoracial background.[72] However, because of differential longevity and other factors, a clinician may diagnose more older woman then men with LATE in later life. Family history and genetic testing are not dispositive, because the known genetic risk factors for LATE have incomplete penetrance.[47,73]

Given the relatively slow progression rate of pure LATE, and the more aggressive course of other conditions (such as AD + LATE), it is rational to obtain a rigorous evaluation of patient neurocognitive status for comparison to follow-up assessments. With serial observations, the patterns of cognitive profile may shed light on the diagnosis. At the least, an MRI should be obtained, but other biomarkers, as described above, may be helpful in supporting a tentative diagnosis of LATE.

It is not yet clear whether US Food and Drug Administration (FDA)-approved symptomatic treatments

for AD, such as acetylcholinesterase inhibitors or memantine, would be of benefit in LATE. The basal forebrain (the source of cholinergic innervation to the cerebrum) is affected by LATE-NC,[74,75] suggesting that acetylcholinesterase inhibitors might aid in treatment of LATE, perhaps comparable to the situation in LBD in which involvement of the basal forebrain is affected by α-synuclein, and acetylcholinesterase inhibitors are integral to clinical management. There is no current evidence supporting the use of memantine as a partial NMDA-receptor antagonist in LATE.

Relevance to AD Oriented (Anti-Amyloid) Clinical Trials

Clinical management and prevention efforts in dementia are undergoing a potential sea-change as anti-amyloid (anti-Aβ) AD-targeting therapies come online.[1] The impact of LATE on outcomes, and potential impact of anti-Aβ therapy used for amyloid positive persons, are being investigated by clinical researchers mindful of the fact that LATE-NC is a common pathologic comorbidity. As further evidence is sought, a couple of theoretical possibilities warrant consideration; these are dramatically different but not mutually exclusive (schematically represented in Fig 5).

In the first scenario, Aβ toxicity may be "upstream" of LATE-NC because LATE-NC is more common in brains with AD than in brains lacking AD.[17] Following this logic, if some combination of Aβ and tau pathologies induce LATE-NC pathology, then anti-Aβ therapy could in principle decrease "downstream" LATE-NC pathology as a salutary cross-benefit. Perhaps targeting AD will help halt the onset or progression of LATE?

On the other hand, in persons with comorbid LATE-NC, anti-Aβ therapy may not halt the progression of LATE despite lowering AD pathology. In this scenario, even despite successful target engagement, accumulating LATE pathology would still be associated with progressive cognitive impairment. This scenario might explain the limitations in the degree of disease slowing that has or can be achieved with such drugs.

It is also important to note that the contribution of unidentified comorbid LATE has clear implications for trials of treatment or prevention of AD. This consideration should be factored in when planning sample sizes for both AD- and LATE-oriented clinical trials. In the future, antemortem biomarkers may enable detection of LATE so that trials of disease modifying agents can be confident in establishing whether LATE is present as a targeted pathology or non-targeted comorbid pathology in an effort to more confidently establish potential efficacy of experimental agents.

Targeting LATE and/or LATE-Associated HS in Current and Future Clinical Trials

A primary issue in any clinical trial is the selection of a therapeutic target. Preclinical (animal model) research aimed at TDP-43 pathology provide hope on the horizon.[76] In the meantime, a current clinical trial targeting LATE (NCT04120766), is based on the finding that polymorphisms in the ATP Binding Cassette Subfamily C Member 9 (*ABCC9*) gene are associated with risk for LATE + HS.[47,77] This clinical trial uses the drug nicorandil, a modulator of the *ABCC9* encoded potassium channel, to target LATE + HS, which was operationally defined as persons aged > 75 years, with evidence of MTL atrophy, and an absence of AD biomarkers. Considering the important association of advanced age with LATE, it is theoretically possible that interventions targeting the aging process[78] may also warrant consideration. As we learn more, other molecular targets are likely to be identified that will also warrant consideration as candidates for trials seeking to establish clinical benefit claims for the treatment of LATE.

Opening the Door for Combination Therapy Approaches to Clinical Trials of Comorbid LATE-AD

Given the relatively high prevalence of LATE in AD it is conceivable that a given patient might require anti-Aβ, and, potentially, future anti-LATE therapies. Development of a full antemortem biomarker panel to detect all major co-pathologies (additionally vascular and Lewy body pathology), and then selection of a personalized medicine combination of agents targeting each pathology, may provide the richest return on our investment in therapeutic clinical trials. Alternatively, if these co-pathologies are synergistic in pathophysiological cascade, early detection and intervention of the initial pathology may halt downstream progression. Biomarkers for the various co-pathologies will be critical in addressing these questions in clinical studies.

Discussions with Patients and Caregivers

The diagnosis of LATE as an alternative diagnosis in amnestic impairment, and the rich underlying complexity of pathologies, have become increasingly important for clinicians to recognize for diagnosing, treating, and communicating with patients and their caregivers. The anticipated increase in Aβ amyloid testing required for clinical prescription of anti-Aβ therapies will significantly impact recognition of the number of dementia patients with clinical AD diagnosis that lack cerebral Aβ amyloidosis and likely have LATE. Indeed, in cases screened for such drugs without evidence of amyloid, an expectation of alternative diagnosis will be sought by patients and

families. While we await more directed therapeutic studies to determine management options, there are a number of questions about whether and how to discuss LATE with patients and family members. Given the different clinical course of LATE alone as compared with AD plus LATE, it is desirable to reach a diagnostic best-judgment as early as possible in order to provide an informed prognosis for patients and families. At the least, neuroimaging with MRI and biomarkers of amyloid and tau will be important for such assessments. Distinguishing AD with versus without LATE-NC may also be valuable in discussions around emergent disease-modifying AD-directed therapies. For now, a nuanced conversation will be necessary about current uncertainties in the clinical diagnosis of LATE.

Conclusions

Clinicians treating older adults should be aware of LATE as a potentially dementia-driving disease entity and should be prepared to discuss this condition with patients and their families. LATE is an impactful and highly prevalent disease process that may occur in isolation, or may occur in the presence of, and accelerate, other neurodegenerative disease processes. LATE is linked to an amnestic phenotype with a relatively slow clinical progression when presenting alone and a more rapid decline when accompanied by ADNC and/or other pathologies. An assortment of genetic, imaging, and plasma biomarkers can now be used to potentially support a diagnosis of LATE. Additional biomarkers are urgently needed. The relevance to the current use of anti-Aβ therapies will almost certainly increase the clinical importance of identifying LATE, and we hope that anti-LATE therapeutic strategies will become available in the near future. Despite the many challenges and limitations of current diagnostics, prognosticators, and treatments for amnestic dementias in aging, rapidly expanding knowledge and breakthroughs in dementia research, including evidence of the clinical importance of LATE, point the way toward more optimism and eventually more clinical options for clinicians, patients, and their caregivers.

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Author Contributions

P.T.N., J.A.S., G.A.J., M.T.D., and D.A.W. contributed to the conceptualization and design of the manuscript. P.T.N., J.A.S., G.A.J., M.T.D., and D.A.W. contributed to the collection and interpretation of data included in the manuscript. P.T.N., J.A.S., G.A.J., M.T.D., and D.A.W. contributed to drafting the text and preparing the figures.

Potential Conflict of Interests

D.W. has served as a paid consultant for Eli LIlly, GE Healthcare and Qynapse, and serves on a DSMB for Functional Neuromodulation. He is a site investigator for a clinical trial sponsored by Biogen. Otherwse, the authors declare no conflicts of interest.

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