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DEMENTIA (K.S. MARDER, SECTION EDITOR)

Limbic-Predominant Age-Related TDP-43 Encephalopathy: LATE-Breaking Updates in Clinicopathologic Features and Biomarkers

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Abstract

Purpose of Review Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a recently defined neurodegenerative disease characterized by amnestic phenotype and pathological inclusions of TAR DNA-binding protein 43 (TDP-43). LATE is distinct from rarer forms of TDP-43 diseases such as frontotemporal lobar degeneration with TDP-43 but is also a common copathology with Alzheimer's disease (AD) and cerebrovascular disease and accelerates cognitive decline. LATE contributes to clinicopathologic heterogeneity in neurodegenerative diseases, so it is imperative to distinguish LATE from other etiologies.

Recent Findings Novel biomarkers for LATE are being developed with magnetic resonance imaging (MRI) and positron emission tomography (PET). When cooccurring with AD, LATE exhibits identifiable patterns of limbic-predominant atrophy on MRI and hypometabolism on ^{18}F-fluorodeoxyglucose PET that are greater than expected relative to levels of local AD pathology. Efforts are being made to develop TDP-43-specific radiotracers, molecularly specific biofluid measures, and genomic predictors of TDP-43. LATE is a highly prevalent neurodegenerative disease distinct from previously characterized cognitive disorders.

Keywords Limbic-predominant age-related TDP-43 encephalopathy (LATE) · TAR DNA-binding protein 43 (TDP-43) · Alzheimer's disease (AD) · Magnetic resonance imaging (MRI) · Positron emission tomography (PET) · Biomarkers

Introduction

Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a common, primary neurodegenerative disease in older adults typified by memory impairment and pathological accumulation of transactivation response (TAR) DNA-binding protein 43 (TDP-43), particularly in the medial temporal lobe (MTL) [1••, 2]. Inclusions of TDP-43 were first discovered in FTLD and ALS [3••, 4••], and later in hippocampal sclerosis and amnestic cognitive impairment not associated with FTLD/ALS [5••]. Compared to other neurodegenerative diseases such as *Alzheimer's disease (AD), Lewy body disease (LBD), and vascular contributions to cognitive impairment and dementia (VCID)*, LATE was formally defined much more recently in 2019 as a clinical manifestation of older adults who possess *LATE neuropathological change (LATE-NC)*. LATE-NC describes a pattern of TDP-43 inclusions, either with or without hippocampal sclerosis [1••]. LATE is extremely prevalent with ~ 40% of individuals over 80 with LATE-NC across multiple autopsy studies [6•]. Moreover, the contribution of LATE to late-life

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cognitive impairment is relatively high with some estimates at approximately 20% of the attributable risk vs ~ 40% for AD and 30% for VCID [1••]. While AD is defined by the presence of amyloid-β and neurofibrillary tau [7], AD and LATE are often concomitant disease entities within cognitively impaired older adults. Indeed, estimates across autopsy cohorts suggest that patients with both LATE and AD comprise ~ 55% of patients with AD [6•], with individual study estimates ranging from 25 to 60% [5••, 8, 9, 10].

Hippocampal sclerosis (HS) is the profound loss of pyramidal cells and associated gliosis in the cornu ammonis 1 and subiculum regions of the hippocampus [11•] and a common feature in anywhere from 60 to 95% of cases with LATE [1••]. Given this strong overlap, various biomarkers and genetic risk factors that are associated with HS are also linked to LATE.

Here, we survey the recent literature on LATE and HS focusing on clinical and pathological features as well as emerging biomarkers, such as neuroimaging and biofluid tests.

Clinical Presentation

Older Age

As the name of LATE suggests, LATE is defined by TDP-43 in older adults with limbic neurodegeneration. While *frontotemporal lobar degeneration (FTLD)* and *amyotrophic lateral sclerosis (ALS)* have an earlier age of onset and lower prevalence with more advanced age [12, 13], LATE is enriched in older adults [2]. Indeed, > 30% of autopsied brains over the age of 80 have the presence of TDP-43 and/or severe hippocampal atrophy that is pathologically confirmed as HS [11•]. The coincidence of LATE with AD is also thought to increase over the duration and severity of AD [14].

Memory Impairment

Patients with LATE demonstrate episodic memory impairment, often HS [1••, 11•]. Patients with pure LATE often show an amnestic phenotype with fairly indolent progression relative to AD, while patients with mixed LATE + AD have a faster decline in hippocampal volume and cognition, suggesting a potential additive or synergistic relationship between AD and TDP-43 pathologies [9, 15, 16•]. As might be expected, LATE with HS is associated with worse memory and orientation than LATE without HS [1••, 11•, 17•]. In addition to memory loss, LATE-associated clinical features may involve impairment of semantic memory, such as measured with tests of categorical fluency, particularly in the presence of HS [18], though there is also evidence of deficits of working memory as well [19, 20]. Therefore, when compared to patients with pathologically defined AD alone, the current clinical data on LATE suggests a rather prominent and relatively isolated amnestic presentation that is slowly progressive in isolated LATE. Alternatively, LATE with AD is associated with a more rapid progression, exacerbating memory decline and likely contributing to semantic and perhaps other domains.

Additional Clinical Symptomatology

Compared to LATE with AD, pure LATE may have a slightly higher prevalence of frontal lobe-associated behavioral symptoms while pure AD has a higher frequency of agitation symptoms on the Neuropsychiatric Inventory [21•]. Potential symptoms associated with HS and LATE involve decreased personal care [17•] and inappropriate behavior and apathy [22]. Nevertheless, such behavioral symptoms are much more pronounced in frontotemporal dementia (FTD) syndromes [23].

Differential Diagnosis

The clinical syndrome of LATE should be considered in the differential diagnosis of patients with amnestic cognitive impairment, along with AD and VCID [7]. Clinical suspicion for LATE should be raised in patients with memory loss with negative AD markers for amyloid or tau pathology on imaging or biofluid markers, though mixed disease with concomitant AD and LATE pathologies is common (up to 60% of patients with AD) [8]. More severe hippocampal atrophy also may be suggestive of the condition. While there is some overlap in TDP-43 pathology and potential behavioral symptoms between LATE and FTD, FTD is much less prevalent [23] and does not classically have an amnestic phenotype. Furthermore, behavioral symptoms appear to be unlikely primary salient features in LATE. A relatively slowly progressive and isolated amnestic syndrome without progressive involvement of other domains over time is perhaps more suggestive of LATE than AD, particularly in those over 80 years old. Overall, the symptomatology of LATE is clinically similar with AD and should be considered in patients with amnestic cognitive impairment.

Pathology

TDP-43

TDP-43 is an RNA-binding protein and encoded by the *TARDP* gene. Its function includes the regulation of splicing and transcription of mRNA in the cell nucleus [24]. In the context of neurodegeneration and cellular perturbation,

TDP-43 is aberrantly phosphorylated and ubiquitinated, which promote the misfolding of TDP-43 [3••, 4••], and mislocalization of TDP-43 to the cytoplasm. TDP-43 also forms ribonucleoprotein complexes within stress granules [25], which may serve as a protective response [26]. Ultimately, the mislocalization of TDP-43 aggregates triggers organelle dysfunction and neurotoxic sequelae [27], impairing dendritic integrity [28] and activating neuroinflammatory microglia [29].

In current guidelines, LATE-NC is staged by propagation pattern from the amygdala to the medial temporal lobe (MTL) and beyond: no TDP-43 cytoplasmic inclusions (stage 0), amygdala-predominant (stage 1), extension to the hippocampus and entorhinal cortex (stage 2), and spreading to the middle frontal gyrus and neocortex (stage 3) [1••]. Stages 1 through 3 are roughly similar in prevalence [30]. Neurodegeneration in LATE has a predilection for anterior and limbic areas, including MTL, temporal pole, and orbitofrontal cortex. There is a relationship between asymmetry of the MTL and HS [1••, 20].

Hippocampal Sclerosis (HS)

Patients with LATE either with or without HS do not differ in terms of amyloid, tau, or Lewy body pathology, as well as clinical history of stroke, cardiovascular disease, or epilepsy. Yet, patients with LATE and HS were more likely to have stage 3 neocortical TDP-43 burden than patients with LATE without HS and had a higher burden of cerebral arteriosclerosis and atherosclerosis [17•], suggesting a link with vascular disease.

Additional TDP-43 Proteinopathies

TDP-43 inclusions were first observed in FTLD and ALS. *Frontotemporal lobar degeneration due to TDP-43 (FTLD-TDP)* exhibits at least five different pathologic subtypes (A through E), each with different histopathological characteristics, organellar distribution, and regional spreading patterns [31]. About 50% of FTLD cases display TDP-43 pathology [32]. Outside of rare *SOD1* or *FUS* mutations, ~97% of sporadic ALS and about 90% of familial ALS cases have TDP-43 aggregates [33, 34]. Despite similarities, LATE and FTLD-TDP are considered distinct entities based on a number of differential features, including epidemiology, disease onset, clinical phenotype, and the neuropathological density of TDP-43 inclusions; simple criteria based on density patterns of neocortical TDP-43 immunoreactivity achieve about 90% sensitivity and specificity between LATE and FTLD-TDP [35]. *Perry syndrome* is a rare primary TDP-43 disease with rapidly progressive parkinsonism, hypoventilation, depression, and TDP-43 inclusions in substantia nigra and globus pallidus [36]. Overall, TDP-43 pathology is present in many diseases (Table 1).

Table 1 Comparison of limbic-predominant age-related TDP-43 encephalopathy (LATE) with Alzheimer's disease (AD), frontotemporal lobar degeneration due to TDP-43 (FTLD-TDP), and amyotrophic lateral sclerosis due to TDP-43 (ALS-TDP). Abbreviations: *MCI*, mild cognitive impairment; *MTL*, medial temporal lobe; *PET*, positron emission tomography; *MRI*, magnetic resonance imaging. Footnotes: [a]prevalence estimates in MCI/dementia are based on attributable risk analyses. [b]Recent genome-wide association studies demonstrate > 70 loci implicated in heritable risk for sporadic AD. Additional loci may be present for AD and other neurodegenerative disorders. [c]Additionally, patients with ALS can display spatial patterns of neurodegeneration overlapping both entities

Characteristic	LATE	AD	LATE and AD	FTLD-TDP	ALS-TDP
Protein aggregates	TDP-43	Amyloid-β, tau	TDP-43, amyloid-β, tau	TDP-43	TDP-43
Prevalence[a]	~20% of MCI/dementia[a]	~40% of MCI/dementia[a]	25–60% of AD cases	~50% of FTLD	~90% of ALS
Common genetic risk loci	*TMEM106B*, *RBFOX1*, *APOE, GRN*	*APOE*, *TREM2*, *CLU*, *BIN1*, etc[b]	Similar to those in LATE and AD	*TMEM106B*, *GRN*, *C9orf72*	*TMEM106B*, *GRN*, *C9orf72*, *TARDBP*
Clinical phenotype	Slow progression in memory deficit, possible behavioral changes	Typical memory impairment, but can present with atypical non-amnestic variants	Pronounced amnestic phenotype, rapid functional decline	Behavioral, dysexecutive, and language changes	Upper and lower motor neuron symptoms
Spatial pattern of neurodegeneration	MTL, anterior temporal pole, orbitofrontal cortex	MTL, inferior temporal, lateral parietal, precuneus, posterior cingulate cortex	Similar to those in LATE and AD	Anterior frontal, fronto-insular, and temporal pole	Motor cortex, internal capsule, brain stem, anterior spinal cord[c]
Imaging biomarkers	MRI, ^{18}F-FDG PET	MRI, ^{18}F-FDG, amyloid, and tau PET	MRI, ^{18}F-FDG, amyloid, and tau PET	MRI, ^{18}F-FDG PET	MRI

Genomic Landscape of LATE

Progress in uncovering the genetic architecture of TDP-43 diseases has been steadily mounting. Several genetic risk factors for LATE and/or HS are shared with FTLD and ALS, such as common variants in the progranulin gene *GRN* [37•]. However, mutations in the gene encoding for TDP-43, *TARDBP*, may be associated with ALS-TDP, but not dementia with TDP-43 pathology [38]. The APOE4 allele of the apolipoprotein E gene (*APOE*) is associated with increased risk in a variety of cognitive impairments, including AD [39, 40], VCID [41], and LATE [10, 42, 43•]. Additional risk alleles such as those in *RBFOX1* are also associated with TDP-43 pathology [43•]. The gene *ABCC9* codes for the potassium channel and sulfonylurea receptor SUR2; genetic risk alleles of *ABCC9* are associated with HS [44]. In fact, *ABCC9* polymorphisms are preferentially associated with HS over LATE, while polymorphisms in broader neurodegenerative risk genes *TMEM106B*, *GRN*, and *APOE* are associated with both LATE and HS [45]. While LATE and HS are interrelated, these findings suggest that the potential dissociation of LATE and HS is influenced by certain molecular markers.

Pathology and Genetics of TMEM106B

TMEM106B is a regulator of lysosomal degradation deeply implicated in TDP-43 proteinopathies [45, 46]. A common noncoding variant rs1990622 alters *TMEM106B* expression via local genome topology [47] and is strongly associated with TDP-43 pathology in autopsy cohorts of FTLD-TDP [48••, 49••] and LATE [50•]. Additional *TMEM106B* polymorphisms are also enriched in late-onset AD [51], which may perhaps represent (i) complicated interplay between distinct proteinopathies and risk alleles, (ii) common mechanisms such as degradation and clearance that link several proteinopathies, and/or (iii) pathological heterogeneity within the cohort for genetic sampling [52]. Interestingly, several studies have shown that TMEM106B fibrils are present in a variety of neurodegenerative diseases, including FTLD-TDP [53, 54, 55], so it is possible that TMEM106B deposits may also be present in LATE. The causal relationship between TMEM106B, TDP-43, and neurodegeneration is still unknown, but recent literature demarcates an emerging role for TMEM106B in several neurological disorders.

Non-TDP-43 Copathologies and Interactions

Deposition and misfolding of distinct proteins may interact, producing potential nonlinear combinatorial effects [56]. Autopsy and preclinical studies show the intermingling of TDP-43 with neurofibrillary tau tangles [57] and perhaps intracellular amyloid-β [58]. Associations have been found between TDP-43 burden and vascular disease markers, including robust relationships with arteriolosclerosis and microvascular damage in the basal ganglia and watershed areas [59, 60, 61], with some correlations between TDP-43 and microinfarcts and cerebral amyloid angiopathy [61]. Moreover, there are regional relationships and overlapping prevalence for α-synuclein and TDP-43 pathologies in LATE [9, 62•, 63] and FTLD-TDP [64, 65]. Compared to LATE + AD, LATE + LBD may harbor more frequent TDP-43 inclusions with differential severity in specific hippocampal subfields and earlier spread to dentate gyrus and brainstem [62•]. Note that other pathologies such as FUS may be mutually exclusive with TDP-43 in FTLD and ALS [66]. Such findings highlight intricate interactions of different pathologies to modulate the templating, misfolding, and spreading of other polypathologies. Cumulatively, the synergy between copathologies, or lack thereof, may typify a model of biochemical pathologies and cellular responses as actions and corresponding reactions and illuminate mixed disease contributors.

Emerging Biomarkers

Structural Imaging

Serial structural imaging with magnetic resonance imaging (MRI) offers an ideal platform to assess atrophy patterns associated with LATE. T1-weighted MRI is preferred for overall structural visualization of the brain while T2-weighted sequences can distinguish features in the MTL. Anterior-predominant neurodegeneration is seen in MTL, amygdala, and frontal structures [1••]. The rate of atrophy may be relatively slow in pure LATE as exemplified by the case in Fig. 1. Conversely, a more rapid decline in cognition and volume of limbic structures may be appreciated in cases of LATE mixed with AD (15; 16•). Distortion of amygdalar volume and shape is seen with TDP-43 inclusions [67]. With ex vivo imaging, TDP-43 severity is correlated to MTL thickness [68•, 69•]. Furthermore, anterior–posterior gradients of postmortem TDP-43 burden appear to manifest as greater atrophy in the anterior hippocampus and anterior cortical MTL structures (such as the entorhinal cortex). Indeed, TDP-43 pathology may be correlated with thinner cortex in the anterior MTL [70•] in comparison to tau burden, which may have a greater association with atrophy of the posterior MTL; the ratio of which may allow for distinguishing AD with or without concomitant TDP-43 pathology [70•, 71]. It has also been noted that atrophy rates in anterior brain regions are higher in FTLD-TDP than in LATE or mixed LATE and AD [72].

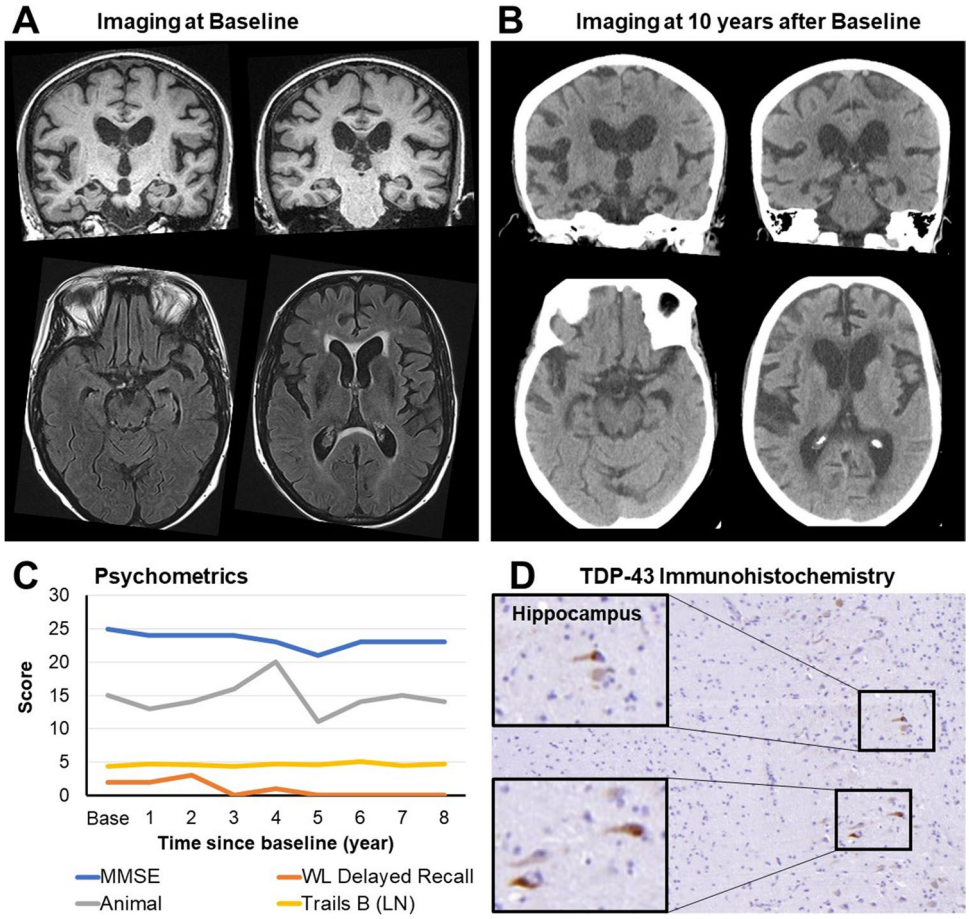

Fig. 1 Example clinical vignette of a patient with LATE. A 78-year-old woman presents with several years of subjective memory loss and was clinically diagnosed with AD. **A** At baseline, T1-weighted coronal MRI (top) shows some volume loss in the bilateral hippocampi and medial temporal lobes, with axial FLAIR sequence scan depicting periventricular white matter hyperintensities corresponding to small vessel ischemia. **B** Ten years after baseline scan, coronal (top) computed tomography (CT) shows mild interval change of limbic structures, with some ventricular dilatation and widening of the lateral fissures compared to prior studies. Small vessel disease is redemonstrated as periventricular hypodensities on axial CT (bottom). **C** Psychometric testing over about nine years shows slow, minimal decline in Mini-Mental Status Examination (MMSE), Animal fluency, Word List (WL) delayed recall, and Trails B time (natural log-transformed). **D** At autopsy, immunohistochemistry of the hippocampus with TDP-43 antibody (1D3, images at × 20 and × 50) reveals TDP-43 cytoplasmic inclusions, consistent with a primary neuropathological diagnosis of LATE-NC. Additional staining showed diagnostic evidence of primary age-related tauopathy and Lewy body disease (amygdala-predominant) and did not reflect AD neuropathologic change

Positron Emission Tomography (PET)

Radionuclide imaging with ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) has shown great promise in identifying in vivo spatial patterns that correlate well with postmortem confirmation of LATE [73••]. By assessing the hypometabolism of the MTL and frontal supraorbital ratio (FSO) relative to the metabolic sparing of the inferior temporal gyrus (I), a measure such as the I/MTL/FSO ratio can distinguish LATE with roughly 80% sensitivity and specificity [74•]. A similar regional ratio based on structural MRI had similar sensitivity but poorer specificity. Together, these studies support the notion that hypometabolism and atrophy on ^{18}F-FDG and MRI can provide probabilistic support for a clinical diagnosis of LATE. Importantly, novel radiotracers that bind to TDP-43 are also being explored [75] and the molecular structure of brain-derived TDP-43 has been discovered [76], though it may be several more years until clinical studies for TDP-43 in vivo imaging are available [77]. Overall, currently available ^{18}F-FDG PET imaging markers provide useful probabilistic prediction of LATE-NC.

Comparison of Imaging Biomarkers to Infer LATE Patterns

Without direct and specific imaging tracers for TDP-43 and other non-AD pathologies, we can infer the presence of unobservable copathologies based on their effects on

observable AD measures. While tau pathology is tightly linked to neuronal loss and hypometabolism in AD [78, 79], additional entities such as non-AD pathologies and resilience factors may drive the decoupling of tau and neurodegeneration. Hence, comparing the amount of neurodegeneration on MRI or ^{18}F-FDG PET expected based on a measure of AD pathology (such as ^{18}F-Flortaucipir PET) has potential to highlight non-AD copathology such as TDP-43-related patterns of neurodegeneration, as well as spatial patterns associated with resilience due to genetic or environmental factors. In a series of studies, our group has shown that mismatch of neurodegeneration relative to tau pathology can predict the presence of non-AD pathologies, such as limbic-associated atrophy and hypometabolism suggestive of mixed AD with LATE [80•, 81•]. On imaging, patients in this group have elevated I/MTL/FSO ratio (Fig. 2). On longitudinal psychometric assessment, the limbic susceptible group has faster cognitive decline and more severe memory impairment than other groups [81•], all congruent with AD and LATE copathology [15, 20].

Biofluid Measures of TDP-43

Assays reflecting TDP-43 pathology are currently in development. Improvements in immunoassays for TDP-43 and phospho-TDP-43 present in cerebrospinal fluid (CSF) and blood have led to some promise as markers of FTLD-TDP [82, 83•, 84•] and ALS-TDP [84•, 85, 86, 87, 88]. TDP-43 is packaged into neuronal and glial exosomes, which may also be detected in plasma [23, 89]. Hence, work is now underway to detect peripheral markers of TDP-43 in LATE cohorts. Since some studies saw an elevation of blood TDP-43 levels in patients with clinically diagnosed MCI or AD [83•, 90], it is possible that such measures may be detecting some TDP-43 pathology in the context of either LATE or mixed LATE and AD.

Additional Neuronal Markers

An array of neuron-specific markers may be dysregulated by TDP-43 pathology. For instance, calsyntenin-1 and neurexin-2a promote cell adhesion by regulating calcium homeostasis and synaptic cleft interactions, respectively. These proteins show lower expression in cerebrospinal fluid (CSF) of patients with FTLD-TDP and negative correlations with TDP-43 burden [91•]. CSF panels including calsyntenin-1 and neurexin-2a promoted the discrimination of FTLD-TDP from AD and FTLD-Tau with areas under the curve around 0.8 [91•]. As an mRNA-binding protein, TDP-43 enables the splicing of Stathmin-2 (*STMN2*) mRNA to its proper, full-length form by suppressing a cryptic polyadenylation site [92, 93]. However, in FTLD-TDP and ALS-TDP, TDP-43 loses this capacity and the cryptic site is unmasked, leading to aberrant accumulation of prematurely truncated *STMN2* mRNA and reduction

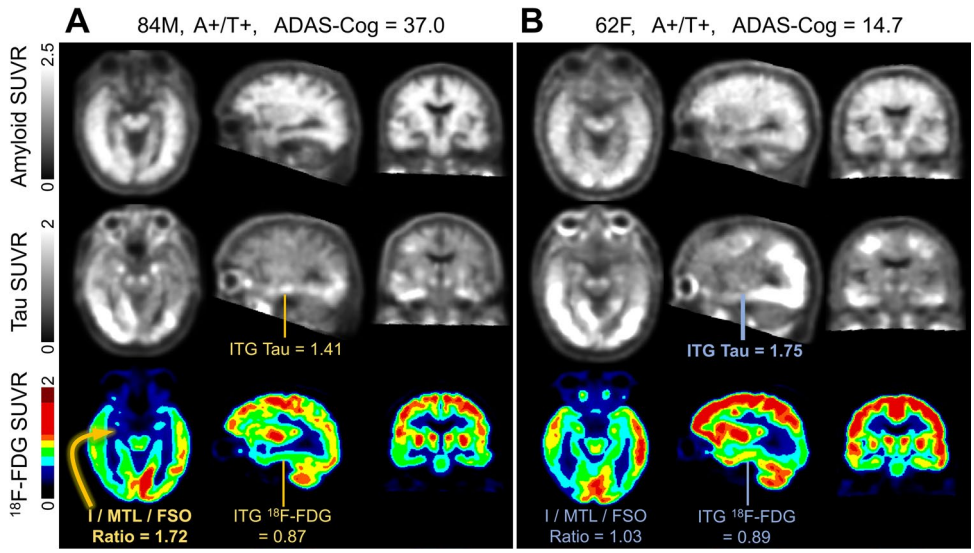

Fig. 2 Limbic PET imaging patterns in susceptible and resilient patients with similar ^{18}F-FDG standardized uptake value ratio (SUVR 0.87 to 0.89) but different tau load (SUVR 1.41 to 1.75) in the inferior temporal gyrus (ITG). ^{18}F-Florbetaben (amyloid), ^{18}F-Flortaucipir (tau), and.^{18}F-FDG PET scans are shown for a **A** cognitively impaired 84-year-old male with amyloid + /tau + status and AD Assessment Scale-Cognitive (ADAS-Cog) score of 37.0 (higher is worse) and a **B** cognitively impaired 62-year-old female with A + /T + status and ADAS-Cog of 14.7. The patient in **A** demonstrates an imaging marker related to LATE seen as the relative sparing of the inferior temporal gyrus (I) relative to medial temporal lobe (MTL) and frontal supraorbital gyrus (FSO), measured by higher I/MTL/FSO than the patient in **B**. Hence, the patient in **A** has evidence concerning for both AD and non-AD (TDP-43) pathology potentially contributing to neurodegeneration not accounted for by tau pathology alone (as in "limbic susceptibility")

in full-length *STMN2* mRNA [94, 95, 96]. Future steps for such biomarkers should determine if expression changes can be detected in additional sample sources. Although such biofluid and neural tissue markers are associated with TDP-43 pathology in FTLD-TDP and ALS-TDP, it is currently unclear if they also translate to LATE. Nevertheless, these encouraging findings support candidate neuronal biomarkers as downstream readouts of TDP-43 function and aggregation.

Clinical Management

Due to the recent definition of LATE as a distinct disease entity, the clinical evidence is still unclear whether symptomatic treatments for AD (such as acetylcholinesterase inhibitors or memantine) have beneficial effects on HS or LATE and potential therapies for LATE and HS are currently under investigation [1••]. For example, *ABCC9*/SUR2 is a potential target given the molecular relationships of *ABCC9* in LATE, HS, and arteriolosclerosis. Sulfonylureas inhibit *ABCC9*/SUR2 and are associated with an increased risk of HS, even when controlling for the presence of diabetes [44]. Thus, *ABCC9*/SUR2 agonists such as nicorandil (NCT04120766) are currently being studied as possible investigational drugs for HS [97].

New therapeutic targets may emerge with increasing recognition of the diagnosis and pathobiology of LATE. Accordingly, greater insight into the natural history and clinical care of patients with LATE may coincide with a more comprehensive diagnosis and clinical trials for AD and other neurodegenerative disorders, as "precision medicine" paradigms are adopted to tailor the management of individual patients across heterogeneous and overlapping disease spectra.

Conclusion

Overall, LATE is a unique and highly prevalent disease process that can also coincide with and accelerate other neurodegenerative diseases. TDP-43 pathology and HS are linked to amnestic phenotype and slow clinical progression when presenting alone and faster decline when interacting with AD pathology. An assortment of genetic and imaging biomarkers exist that can be used to potentially support a diagnosis of LATE. Moreover, additional biomarkers from radiotracer imaging to biofluid assays of proteins and exosomes are on the horizon. Together, LATE is a common neurocognitive disease entity that should be recognized in the clinical setting.

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Declarations

Conflict of Interest David A. Wolk reports grants from Merck, Biogen, Eli Lilly/Avid and additional fees from GE Healthcare, Functional Neuromodulation and Neuronix, all outside of this work. Michael Tran Duong has no conflicts of interest to report.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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