

Chronic Traumatic Encephalopathy

Neuropathology • mechanisms • diagnostic interpretation

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Learning objectives

- Explain the relationship between repetitive head trauma and CTE pathology
- Recognize the lesion distribution and associated tissue changes
- Distinguish neuropathologic CTE from research criteria for TES
- Appraise clinical uncertainty, comorbidity, and diagnostic limitations

Three levels of interpretation

Repetitive head impacts: Exposure

Traumatic encephalopathy syndrome: Research clinical construct

CTE: Neuropathologic diagnosis at autopsy

These are distinct categories, not an obligatory sequence

CTE is a distinctive chronic traumatic tauopathy

- Classically described after repeated head trauma
- Associated with a variable dementing or neurobehavioral syndrome
- Distinguished by the location and cell types of abnormal tau deposits
- Its neuropathologic diagnosis is not equivalent to a history of concussion

Historical terminology: Dementia pugilistica

- Older literature used “boxer’s dementia” or “dementia pugilistica”
- The name reflected recognition in repeatedly exposed boxers
- CTE now encompasses exposures beyond boxing
- The historical term does not adequately describe the full pathologic spectrum

Where repetitive head impacts occur

FEATURES / EVIDENCE

Contact and collision sport exposure

Military service with repetitive head trauma

INTERPRETATION / LIMITS

Occupational or civilian repetitive trauma

Exposure settings do not confer equal or individually predictable risk

Repetitive exposure is not a neuropathologic diagnosis

- A history of impacts may identify a risk-bearing population
- Not every exposed individual develops CTE pathology
- CTE cannot be confirmed by exposure history alone
- Evidence must be evaluated at the population and individual levels

Concussion and CTE should not be conflated

FEATURES / EVIDENCE

Concussion is an acute clinical syndrome after head injury

CTE refers to a chronic neuropathologic tauopathy

INTERPRETATION / LIMITS

Symptoms after a concussion may resolve without subsequent CTE

CTE-related pathology may follow years of cumulative exposure

Impacts can occur without diagnosed concussion

- Repetitive head impact exposure includes symptomatic and asymptomatic impacts
- Concussion counts are therefore an incomplete exposure metric
- Research criteria consider the nature and duration of exposure
- No universal exposure-to-disease conversion factor is established

Duration of exposure as a crude surrogate

Longer participation in repetitive-impact activity



Potentially higher cumulative frequency of impacts



Association with pathologic severity in autopsy series



Correlation does not yield an individual diagnostic threshold

Why cumulative exposure is difficult to reconstruct

- Activity duration does not encode number of impacts per year
- Impact force and rotational mechanics vary
- Recall-based concussion history can miss unrecognized events
- A years-played measure is a proxy, not a physical dose

Individual susceptibility remains incompletely defined

- Uncertainty about who ultimately develops encephalopathy
- An exposed population contains individuals with heterogeneous outcomes
- Exposure associations should not be presented as destiny
- Prediction requires validated longitudinal evidence

Acute structural injury and chronic degeneration

FEATURES / EVIDENCE

Contusions: Immediate focal tissue destruction or hemorrhage

Diffuse axonal injury: Mechanical injury of white matter axons

INTERPRETATION / LIMITS

CTE: Delayed or progressive accumulation of characteristic tau lesions

A single scan cannot substitute for a neuropathologic tissue diagnosis

Rotational acceleration can injure axons

- Diffuse axonal injury may occur with marked angular acceleration
- Axoplasmic flow changes produce axonal swellings
- Susceptible sites include deep white matter and brainstem pathways
- These acute observations provide context but are not CTE criteria

Different time scales after head trauma

Impact and mechanical deformation



Acute neuronal, axonal, or vascular response



Variable recovery or persistent post-traumatic syndromes



In a subset, chronic neurodegenerative pathology may be found

Clinical presentation is heterogeneous

- CTE-associated cases have cognitive, behavioral, mood, and motor features
- The relative prominence of these domains varies
- Clinical symptoms are not specific to a single underlying proteinopathy
- Pathologic and clinical descriptions must remain conceptually separate

Cognitive manifestations: What is impaired?

- Memory complaints may form part of the phenotype
- Executive dysfunction can affect planning and organization
- Cognitive decline may eventually interfere with daily functioning
- The same domains are affected by several competing disorders

Executive dysfunction in the TES construct

- Reduced planning, flexible thinking, and inhibition may be reported
- Consensus research criteria prioritize objective cognitive impairment
- Episodic memory and executive function are specified core domains
- Symptoms should represent a change from baseline

Behavioral symptoms require careful characterization

- Irritability or impulsivity may feature in reported histories
- Altered emotional regulation can accompany frontal network dysfunction
- Symptoms also occur in psychiatric and other neurologic illnesses
- Behavior alone cannot confirm CTE pathology

Neurobehavioral dysregulation in research criteria

- TES criteria describe loss of behavioral or emotional control
- Examples include explosive anger, impulsivity, and emotional lability
- These are research constructs requiring progressive course and exposure
- Assess them in context rather than labeling them pathognomonic

Mood symptoms are diagnostically nonspecific

- Anxiety and depressive symptoms have many potential causes
- The 2021 TES consensus does not make mood symptoms alone a core criterion
- Mood symptoms may be supportive or coexisting features
- Psychiatric assessment remains important regardless of CTE concern

Motor manifestations overlap with other disorders

- Motor impairment can accompany reported CTE cases
- Parkinsonian signs or gait abnormalities require broader differential diagnosis
- Motor symptoms do not localize a specific tau lesion
- Their presence warrants standard neurologic evaluation

Clinical heterogeneity versus lesion specificity

FEATURES / EVIDENCE

Clinical cluster: Shared across many disorders

Neuropathologic lesion: Defined by abnormal tau topography

INTERPRETATION / LIMITS

Repetitive exposure raises suspicion but lacks tissue specificity

Clinical criteria are research-oriented;
Tissue examination remains definitive

Frontal and temporal cortical vulnerability

Repeated mechanical loading of the brain



Greatest stress and deformation near select sulcal regions

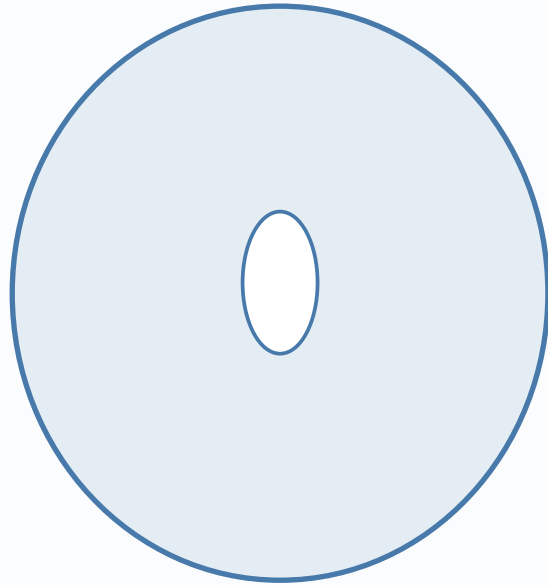


Predilection for frontal and temporal cortical pathology

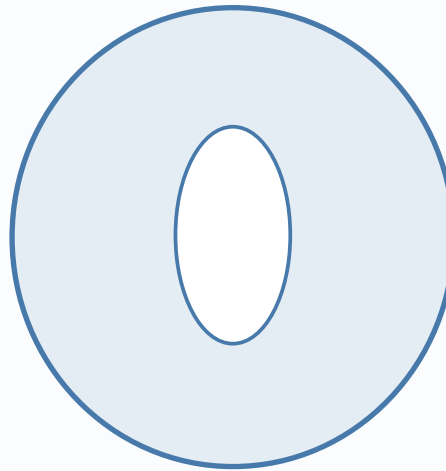


A proposed mechanical link, not a complete molecular mechanism

Global atrophy and ventricular enlargement



Reference schematic



Atrophic schematic

Schematic illustration — not an anatomical specimen

Grossly affected brains can be atrophic

Loss of tissue volume may accompany ventricular enlargement

Neither finding is unique to CTE

A brain-volume change alone cannot establish its etiology

Gross morphologic patterns are supportive, not diagnostic

- Cortical and other regional atrophy can be present
- Enlarged ventricles can accompany overall parenchymal loss
- Similar macroscopic findings occur in several neurodegenerative states
- Microscopic lesion verification is indispensable

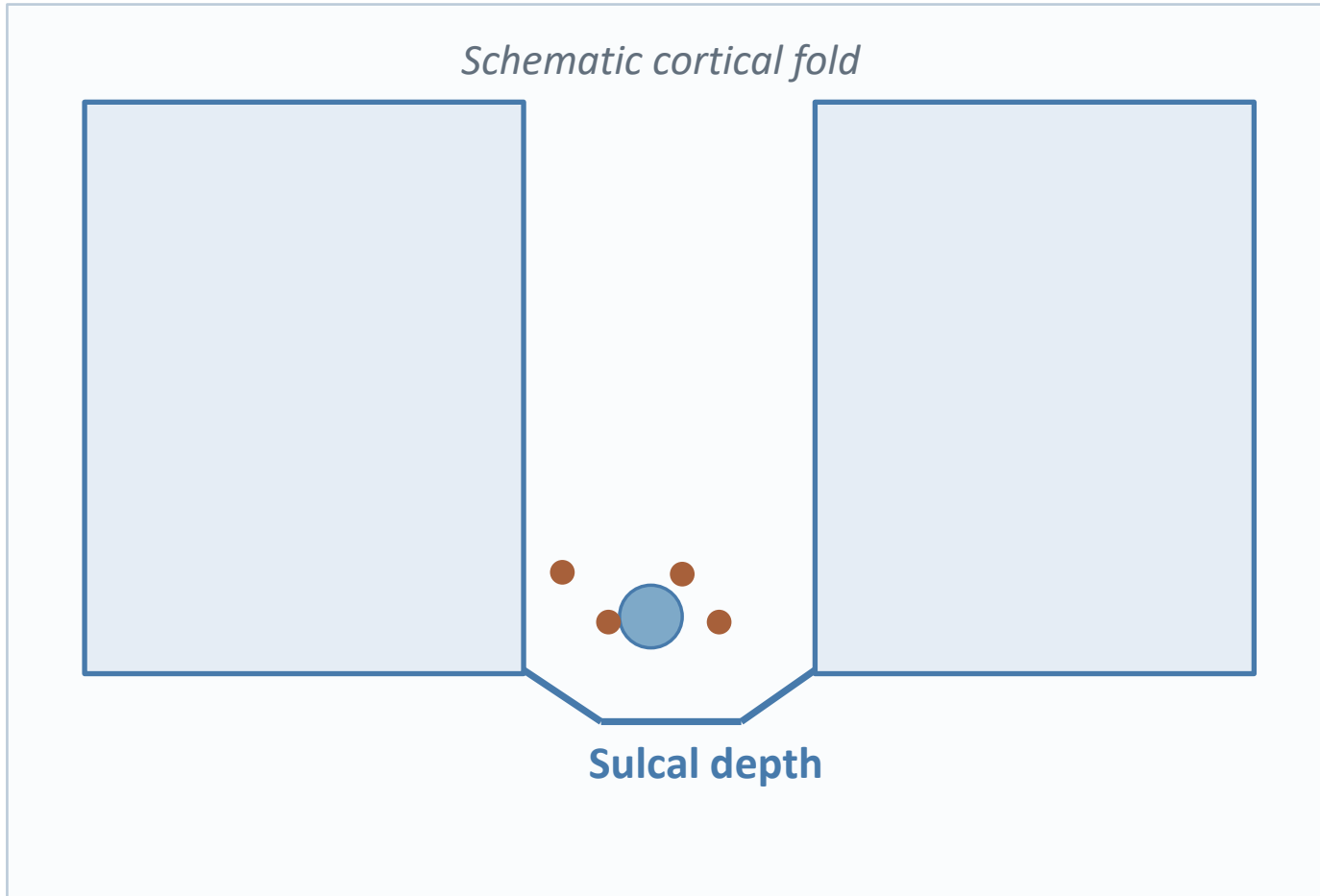
Tau is the principal aggregating protein

- Tau-containing neurofibrillary tangles
- Tau aggregation is a broader feature of several tauopathies
- The spatial organization of deposits distinguishes CTE
- Total tau burden alone is not a CTE diagnostic criterion

Neurofibrillary tangles represent abnormal tau accumulation

- Abnormally phosphorylated tau is detected by immunohistochemistry
- Intraneuronal aggregates can accompany degenerative neuronal injury
- Tangles by themselves are not specific for CTE
- Regional and microscopic relationships establish pathologic identity

Why cortical sulcal depths matter



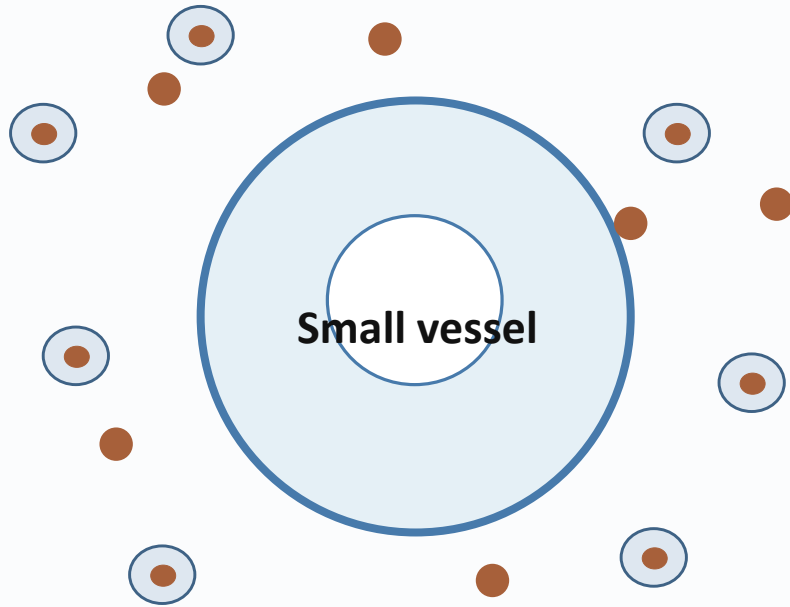
CTE lesions preferentially involve depths of cortical sulci

Robbins relates the distribution to impact-associated physical stress

A sulcus is an anatomic fold, not a tau-specific structure

Location must be combined with cellular and perivascular findings

Perivascular clustering: An essential spatial clue



P-tau+ neurons

Schematic — not a histology image

Abnormal neuronal p-tau lies around small cortical vessels

The pattern is patchy rather than uniform

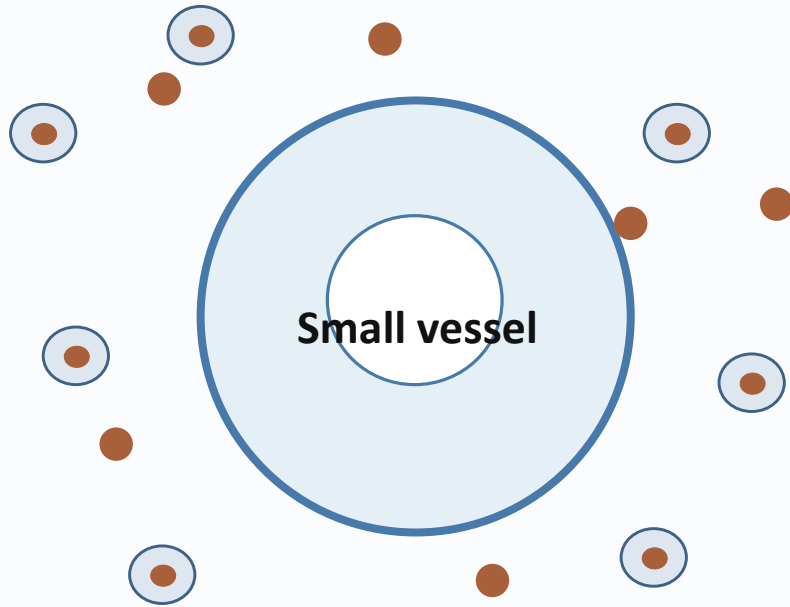
The defining focus lies in sulcal depths, including deeper cortical layers

A vessel alone is not sufficient without neuronal tau pathology

Irregular distribution differs from diffuse tau deposition

- The p-tau pattern is focal and spatially irregular
- Low-power survey may reveal scattered cortical clusters
- Diffuse or superficial tau staining alone is not equivalent to the lesion
- Examine anatomic context before labeling deposits

The pathognomonic lesion: Integrate three elements



P-tau+ neurons

Schematic — not a histology image

Neuronal phosphorylated tau aggregates

Perivascular accentuation around small vessels

Localization at the depth of a cortical sulcus

The lesion is judged as a tissue pattern, not a stain result

2021 consensus: Neuronal tau is required

- Pathognomonic p-tau must involve neurons
- Thorn-shaped astrocytes may or may not accompany the neuronal deposits
- Purely astrocytic perivascular staining does not meet the definition
- This refinement prevents confusion with aging-related tau astrogliopathy

CTE lesion versus astrocytic sulcal tau

FEATURES / EVIDENCE

CTE: Perivascular neuronal p-tau at sulcal depths

ARTAG: Astrocytic tau can involve sulcal and subpial tissue

INTERPRETATION / LIMITS

Pure astroglial lesions without neuronal aggregates are insufficient

Similar location alone does not prove the same disease

Consensus refinement in neuropathologic diagnosis

2015 panel defined a recognizable p-tau lesion



Subsequent independent blinded reviews tested reproducibility



2021 consensus emphasized neuronal involvement in deeper sulcal cortex



Diagnostic protocols standardized sampling and assessment

Minimum pathologic threshold

- The 2021 panel endorsed a single cortical pathognomonic lesion
- The focus must meet location, cell-type, and vessel criteria
- Additional tau deposits may support broader disease burden
- Sampling and disease extent should be recorded separately

Diagnostic lesion is not the same as severity

- Identifying one defining focus answers whether CTE pathology is present
- Extent elsewhere answers a different question: Distribution and burden
- Severity schemes do not replace the core lesion requirement
- Clinical impairment should not be inferred solely from one focus

Phosphorylated tau immunostaining

- Antibodies such as AT8 demonstrate phosphorylated tau deposits
- Survey architecture at low magnification, then inspect cellular localization
- Preserve awareness of cortical layers and sulcal geometry
- Immunopositivity without correct pattern is insufficient

A systematic sampling strategy

Cerebral cortical regions with sulci



Medial temporal structures and other relevant gray matter



Selected subcortical nuclei and brainstem



Expand sections when pathologic suspicion or differential requires it

Focal pathology creates sampling limitations

- A pathognomonic focus may occupy a restricted cortical region
- Inadequate tissue sampling risks under-recognition
- A negative limited panel does not equal proof of universal absence
- Interpret the result in light of the sampling protocol

Supportive cortical laminar findings

- Tau tangles and pretangles may preferentially involve superficial cortex
- Laminar distribution differs from classic Alzheimer patterns
- This is supportive rather than the defining lesion
- Interpret laminar findings alongside sulcal perivascular foci

Hippocampal tau can provide supportive context

- Consensus descriptions include involvement of CA2 and CA4
- This contrasts with the commonly emphasized CA1/subiculum pattern in Alzheimer disease
- Hippocampal findings alone are not diagnostic of CTE
- Coexisting hippocampal disease can complicate attribution

Subcortical disease in more extensive cases

- P-tau involvement may extend into subcortical and brainstem nuclei
- These regions are important when documenting widespread burden
- Subcortical tau without a qualifying cortical lesion is not sufficient
- Distribution and differential diagnosis remain central

White matter rarefaction may accompany CTE

- Loss or reduction of white matter substance
- This is not equivalent to the defining cortical tau lesion
- Axonal and myelin pathology may contribute to neurologic dysfunction
- White matter change is not unique to chronic traumatic disease

TDP-43 inclusions can coexist

- Hippocampal neuronal TDP-43-positive inclusions
- TDP-43 is a distinct aggregation-associated protein
- Its presence is supportive in some cases, not required for CTE
- Consider other TDP-43 proteinopathies and age-related co-pathology

Hippocampal sclerosis is a possible associated lesion

- Neuronal loss and gliosis can affect hippocampal regions
- Clinical correlates may include memory dysfunction
- Hippocampal sclerosis also occurs outside CTE
- Do not infer a unique cause from this lesion alone

Defining lesion versus accompanying changes

FEATURES / EVIDENCE

Defining: Cortical perivascular neuronal p-tau at sulcal depth

Accompanying: Atrophy and ventricular enlargement

INTERPRETATION / LIMITS

Accompanying: White matter rarefaction or hippocampal sclerosis

Possible co-pathology: TDP-43 or other age-related degeneration

A β plaques: Interpret the Robbins statement carefully

- Tau, not β -amyloid plaques, as the CTE signature
- A β deposition is not part of the pathognomonic CTE lesion
- Coexisting Alzheimer neuropathologic change can be present in an individual
- Absence of A β should not be imposed as a universal exclusion criterion

Mixed pathology changes clinicopathologic attribution

- CTE pathology may occur with Alzheimer neuropathologic change
- Multiple lesions can contribute to observed cognitive symptoms
- Neuropathologic reporting should describe concurrent disorders
- Avoid attributing all impairment to a single detected lesion

CTE and Alzheimer disease: Lesion topology

FEATURES / EVIDENCE

CTE: Neuronal p-tau clustered around small vessels at sulcal depth

Alzheimer: Characteristic amyloid and tau pathology distributed by region

INTERPRETATION / LIMITS

Tangles occur in both, so tau positivity alone does not separate them

Co-pathology should be assessed rather than assumed absent

CTE and ARTAG/PART: Common confusion

FEATURES / EVIDENCE

ARTAG: Astrocytic tau may be subpial or perivascular

PART: Neuronal tau pathology associated with aging, without requisite CTE geometry

INTERPRETATION / LIMITS

The 2021 CTE criterion demands perivascular neuronal tau in deep sulcal cortex

A tau-positive older brain therefore requires topographic assessment

CTE and frontotemporal degeneration

- Behavioral symptoms may overlap clinical FTLD syndromes
- Tau and TDP-43 disorders can produce disparate molecular lesions
- The CTE-defining cortical focus should be demonstrated independently
- Clinical syndrome alone cannot differentiate the etiologies

Low and high neuropathologic CTE

FEATURES / EVIDENCE

Consensus staging attempts to stratify severity of tissue involvement

Low burden: Fewer or more localized p-tau abnormalities

INTERPRETATION / LIMITS

High burden: Broader and more extensive regional involvement

These categories describe pathology and are not clinical dementia stages

Cautions when interpreting neuropathologic staging

- A stage depends on a defined protocol and sufficient sampling
- Changing criteria over time limit naive comparison of published stages
- Regional co-pathology may inflate apparent overall burden
- Do not assume a direct one-to-one stage-to-symptom relationship

Clinical phenotype versus pathology burden

FEATURES / EVIDENCE

A pathologic diagnosis concerns microscopic brain lesions

Symptoms reflect multiple functional networks and possible comorbidity

INTERPRETATION / LIMITS

The same symptom cluster can arise from different substrates

Clinical severity cannot replace histologic staging

Traumatic encephalopathy syndrome is a research construct

- TES criteria attempt to standardize a clinical syndrome
- TES is not an in-life tissue-confirmed diagnosis of CTE
- The criteria were developed primarily for research and require validation
- Communicate uncertainty explicitly in clinical documentation

TES research criteria: Stepwise logic

Substantial repetitive-head-impact exposure



Specified core cognitive or neurobehavioral features with progression



Symptoms not fully explained by an alternative condition



Then characterize the level of functional dependence

TES core cognitive features

- Episodic memory impairment and/or executive dysfunction
- Neurobehavioral dysregulation may also meet the core feature definition
- The symptom complex represents decline from prior functioning
- Progression is part of the research case definition

Progression and alternative explanations

- Progressive course distinguishes TES criteria from many static sequelae
- Assess primary psychiatric, sleep, substance-related, and other neurologic causes
- Coexisting disorders do not automatically exclude TES
- The question is whether they fully explain the clinical findings

Functional dependence in TES research criteria

- Functional levels range from independent to severe dementia
- Function is a separate axis from anatomic lesion confirmation
- Support needs and safety assessments remain clinically actionable
- Severity labels do not determine CTE pathology without autopsy

Disease-specific biomarkers remain unvalidated

- No routinely established in-vivo biomarker can confirm CTE pathology
- Existing amyloid or tau biomarkers target different biologic signals
- MRI atrophy patterns are not pathognomonic
- Research tools must not be presented as clinically definitive tests

Clinical attribution is limited by common comorbidities

- Depression, sleep disorders, medications, and substance use may affect cognition
- Other neurodegenerative and vascular conditions can coexist
- Focused examination and neuropsychology can characterize impairments
- Neither a symptom checklist nor a scan proves CTE

Brain-bank samples require selection-bias awareness

- Autopsy donations are often nonrandom samples of exposed populations
- Symptomatic cases and publicized histories may be overrepresented
- Observed lesion frequencies need not equal population prevalence
- Do not transform convenience-sample proportions into personal risk

Association does not establish individual inevitability

- Correlation between exposure duration and autopsy stage
- Risk determinants and susceptible subgroups remain incompletely resolved
- Effect estimates depend on sampling, exposure ascertainment, and follow-up
- Population association is not a diagnostic certainty for one person

A defensible clinical evaluation pathway

Document exposure chronology and specific complaints



Characterize cognitive, mood, behavioral, and motor domains



Evaluate alternative causes and functional impact



Use TES terminology carefully; Avoid claiming pathologic proof

Clinical case: Symptoms after years of play

CLINICOPATHOLOGIC SCENARIO

A retired collision-sport participant reports worsening planning and irritability

Examination reveals executive deficits, but MRI is nonspecific

Question: Can CTE be diagnosed definitively during life?

What competing explanations must be evaluated?

Clinical case debrief

FEATURES / EVIDENCE

A relevant exposure history raises the research question

The syndrome requires progression and alternative-cause assessment

INTERPRETATION / LIMITS

No established clinical test proves CTE tau pathology in life

Document observed deficits and diagnostic uncertainty

Autopsy case: Focal p-tau at a sulcal depth

CLINICOPATHOLOGIC SCENARIO

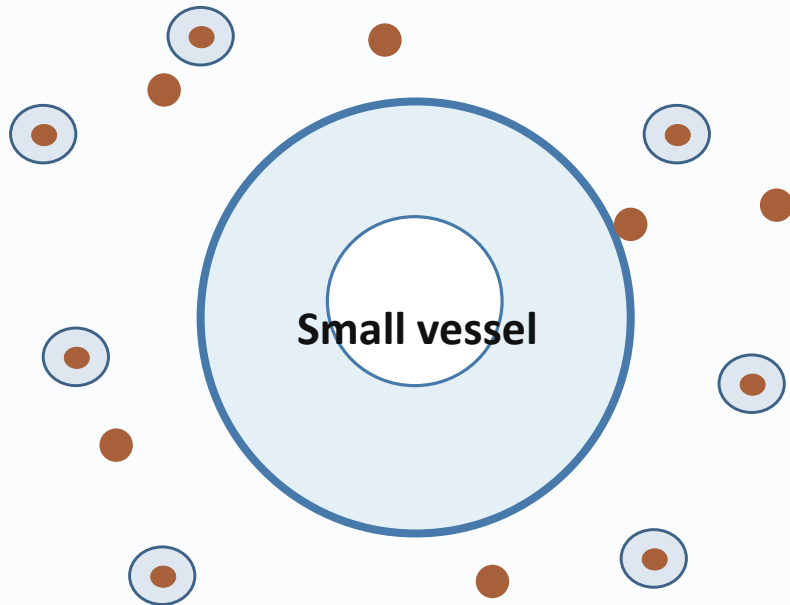
AT8 reveals neuronal p-tau surrounding a small cortical vessel

The focus lies in deeper cortex at the depth of a sulcus

Elsewhere, sparse age-related astrocytic tau is present

Question: Which finding meets the defining criterion?

Autopsy case debrief: The lesion is topographic



P-tau+ neurons

Schematic — not a histology image

Neuronal tau plus small-vessel relationship plus sulcal depth supports CTE

Unrelated astroglial tau does not substitute for the cortical lesion

Further sampling documents distribution and co-pathology

Interpretation requires an actual specimen, not the educational schematic

Other long-term sequelae after traumatic brain injury

- Posttraumatic epilepsy can follow injury
- Posttraumatic hydrocephalus may follow disturbed CSF resorption
- Infection risk can be increased after certain traumatic injuries
- These outcomes are distinct from the CTE-defining tauopathy

High-yield diagnostic distinctions

FEATURES / EVIDENCE

Repetitive head exposure: Risk history, not a neuropathologic diagnosis

TES: Research clinical criteria, not pathologic confirmation

INTERPRETATION / LIMITS

CTE: Perivascular neuronal p-tau at cortical sulcal depth

Atrophy, symptoms, and nonspecific tau cannot independently establish CTE

Knowledge check: Identify a genuine CTE lesion

- A: Isolated diffuse hippocampal tau tangles
- B: Perivascular neuronal p-tau at the depth of a cortical sulcus
- C: Purely astrocytic subpial p-tau with no neuronal lesion
- D: Cortical atrophy with no qualifying tau focus

Knowledge check: Rationale

FEATURES / EVIDENCE

Correct pattern: Perivascular neuronal p-tau at sulcal depth

Hippocampal tau and atrophy are not site-specific lesion criteria

INTERPRETATION / LIMITS

Astrocyte-only tau can represent ARTAG

The diagnostic unit is the combined histologic architecture

Selected references

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