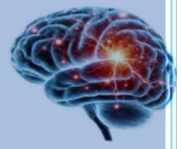
The Canadian Concussion Centre
12th Annual Concussion Research Symposium

Update on Research and Care for the Concussion Spectrum of Disorders
Friday, May 23, 2025
Hybrid: Zoom & In-Person BMO Education and Conference Centre at Toronto Western Hospital



QUO VADIS CTE?

*

CRITICAL REAPPRAISAL OF NEUROPATHOLOGY

GABOR G. KOVACS MD PhD FRCPC

Professor, Department of Laboratory Medicine and Pathobiology and Department of Medicine/Division of Neurology University of Toronto ;

Consultant Neuropathologist, Laboratory Medicine Program, University Health Network;

Principal Investigator, UofT Tanz Centre for Research in Neurodegenerative Disease (CRND), Krembil Brain Institute;

Faculty/Neurologist, Edmond J. Safra Program in Parkinson's Disease and Co-Director Rossy Program for PSP research

Forensic Science International 160 (2006) 207–216

*

Head injuries of Roman gladiators

Fabian Kanz [a,*], Karl Grossschmidt [b,1]

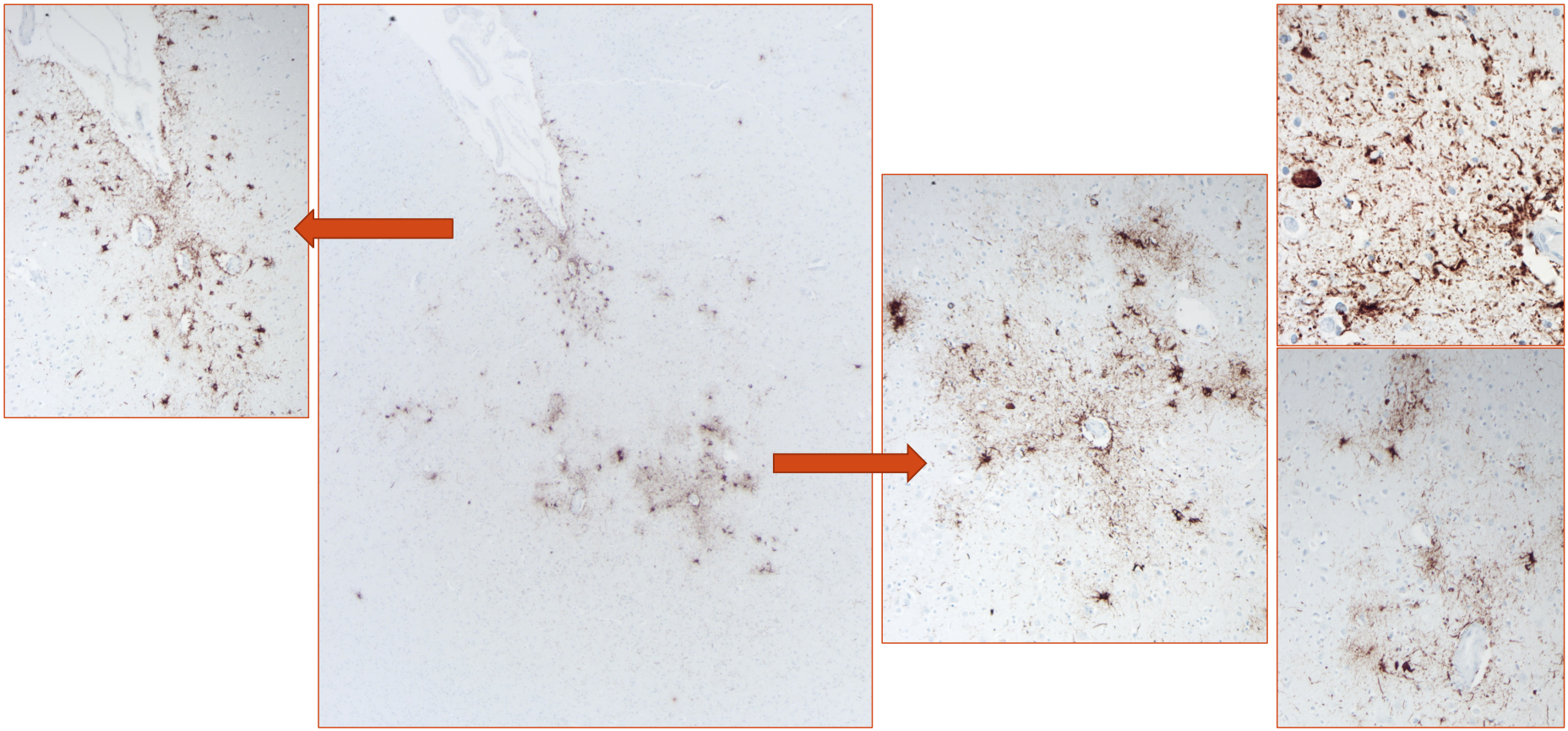
OBJECTIVES

- Evolution of the definition of CTE-NC
- CTE beyond contact sports
- Other tau pathologies seen in mTBI cases
- Is it only Tau-related neurodegeneration?
- Conclusions

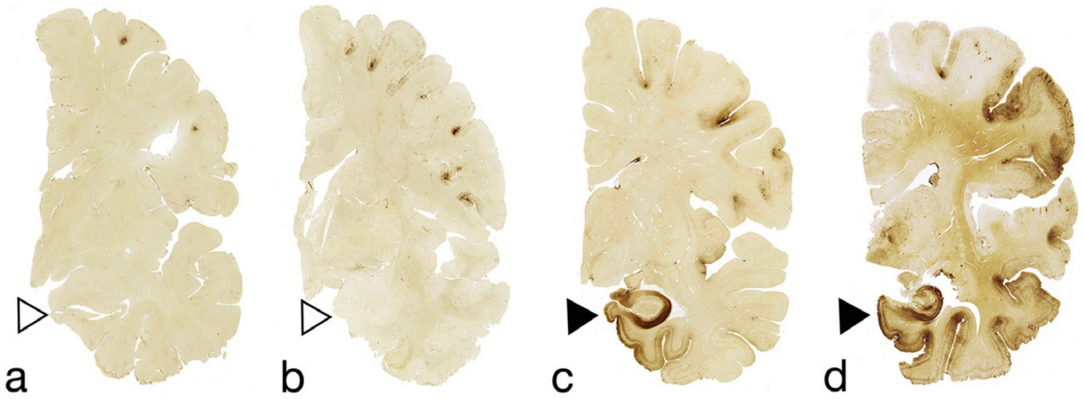
CHRONIC TRAUMATIC ENCEPHALOPATHY

- CURRENT DEFINTION: Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with exposure to repetitive head impacts, including those sustained in contact and collision sports
- Descriptions of the clinical features of CTE include nonspecific cognitive, neuropsychiatric, and motor impairments, progressing to functional dependence and dementia. Research diagnostic criteria termed clinical symptoms as traumatic encephalopathy syndrome (TES).

CTE NEUROPATHOLOGY: TAU



CHRONIC TRAUMATIC ENCEPHALOPATHY: SEQUENTIAL DISTRIBUTION OF PATHOLOGY



doi:10.1093/brain/aws307 Brain 2013: 136; 43–64 | 43

BRAIN
A JOURNAL OF NEUROLOGY

The spectrum of disease in chronic traumatic encephalopathy

Ann C. McKee,[1,2,3,4,5] Thor D. Stein,[1,5] Christopher J. Nowinski,[2,4,6] Robert A. Stern,[2,3,4,7] Daniel H. Daneshvar,[2,4] Victor E. Alvarez,[2,4] Hyo-Soon Lee,[3,4] Garth Hall,[8] Sydney M. Wojtowicz,[1,2] Christine M. Baugh,[2,4] David O. Riley,[2,4] Caroline A. Kubilus,[3,4] Kerry A. Cormier,[1] Matthew A. Jacobs,[2,4] Brett R. Martin,[9] Carmela R. Abraham,[2,10] Tsuneya Ikezu,[3,4,11] Robert Ross Reichard,[12] Benjamin L. Wolozin,[3,4,11] Andrew E. Budson,[1,3,4] Lee E. Goldstein,[2,3,4,12,13,14,15] Neil W. Kowall[1,3,4,5,*] and Robert C. Cantu[2,6,7,16,*]

Sequential involvement of anatomical areas are recognized

Four stages are proposed (awaits widespread application):

CTE Stages I and II are characterized by the progressive involvement of the cerebral cortex, with extensive cortical and subcortical involvement in Stages III and IV.

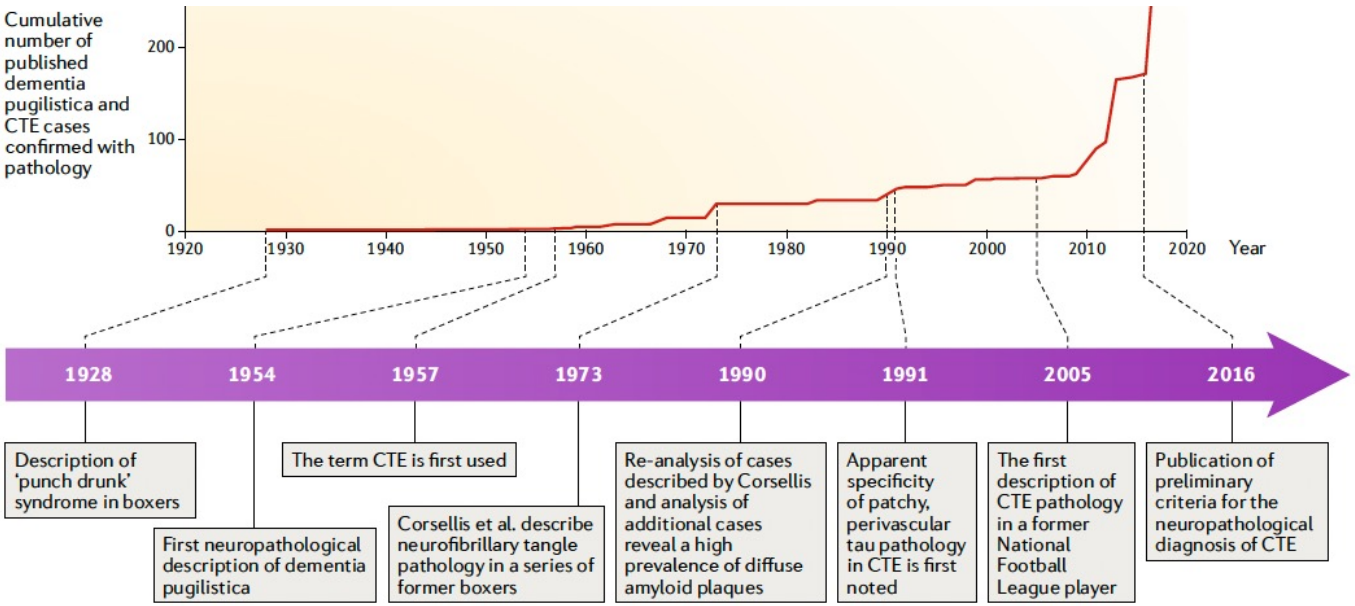


Fig. 1 | **Historical timeline of developments and the cumulative number of published cases of dementia pugilistica and CTE.** The association between exposure to brain injury in boxing and the risk of neurodegenerative disease was first reported in 1928. Since the first description of the pathology in a former American National Football League player in 2005, a marked increase in case identification and reporting has been seen. Nevertheless, the cumulative number of unique chronic traumatic encephalopathy (CTE) cases reported is currently just over 300.

OPINION

Chronic traumatic encephalopathy — confusion and controversies

Douglas H. Smith, Victoria E. Johnson, John Q. Trojanowski and William Stewart

Acta Neuropathol (2016) 131:75–86
DOI 10.1007/s00401-015-1515-z

CONSENSUS PAPER

The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy

Ann C. McKee[1,2,3,4,5] · Nigel J. Cairns[6] · Dennis W. Dickson[7] · Rebecca D. Folkerth[8] · C. Dirk Keene[9] · Irene Litvan[10] · Daniel P. Perl[11] · Thor D. Stein[2,3,4,5] · Jean-Paul Vonsattel[12] · William Stewart[13] · Yorghos Tripodis[3,14] · John F. Crary[15] · Kevin F. Bieniek[7] · Kristen Dams-O'Connor[16] · Victor E. Alvarez[1,2,3,4] · Wayne A. Gordon[16] · the TBI/CTE group

2016-------2021

J Neuropathol Exp Neurol
Vol. 80, No. 3, March 2021, pp. 210–219
doi: 10.1093/jnen/nlab001

ORIGINAL ARTICLE

The Second NINDS/NIBIB Consensus Meeting to Define Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy

Kevin F. Bieniek, PhD, Nigel J. Cairns, PhD, FRCPath, John F. Crary, MD, PhD, Dennis W. Dickson, MD, Rebecca D. Folkerth, MD, C. Dirk Keene, MD, PhD, Irene Litvan, MD, Daniel P. Perl, MD, Thor D. Stein, MD, PhD, Jean-Paul Vonsattel, MD, William Stewart, PhD, FRCPath, Kristen Dams-O'Connor, PhD, Wayne A. Gordon, PhD, Yorghos Tripodis, PhD, Victor E. Alvarez, MD, Jesse Mez, MD, Michael L. Alosco, PhD, Ann C. McKee, MD, and the TBI/CTE Research Group

Table 2 Preliminary NINDS criteria for the pathological diagnosis of CTE

Required for diagnosis of CTE
1. The pathognomonic lesion consists of p-tau aggregates in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci
Supportive neuropathological features of CTE
p-Tau-related pathologies:
1. Abnormal p-tau immunoreactive pretangles and NFTs preferentially affecting superficial layers (layers II–III), in contrast to layers III and V as in AD
2. In the hippocampus, pretangles, NFTs or extracellular tangles preferentially affecting CA2 and pretangles and prominent proximal dendritic swellings in CA4. These regional p-tau pathologies differ from the preferential involvement of CA1 and subiculum found in AD (Fig. 3)
3. Abnormal p-tau immunoreactive neuronal and astrocytic aggregates in subcortical nuclei, including the mammillary bodies and other hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum, and isodendritic core (nucleus basalis of Meynert, raphe nuclei, substantia nigra and locus coeruleus)
4. p-Tau immunoreactive thorny astrocytes at the glial limitans most commonly found in the subpial and periventricular regions
5. p-Tau immunoreactive large grain-like and dot-like structures (in addition to some threadlike neurites) (Fig. 2h)
Non-p-tau-related pathologies:
1. Macroscopic features: disproportionate dilatation of the third ventricle, septal abnormalities, mammillary body atrophy, and contusions or other signs of previous traumatic injury
2. TDP-43 immunoreactive neuronal cytoplasmic inclusions and dot-like structures in the hippocampus, anteromedial temporal cortex and amygdala (Fig. 4)
Age-related p-tau astrogliopathy that may be present; non-diagnostic and non-supportive [22]
1. Patches of thorn-shaped astrocytes in subcortical white matter
2. Subependymal, periventricular, and perivascular thorn-shaped astrocytes in the mediobasal regions
3. Thorn-shaped astrocytes in amygdala or hippocampus [22]

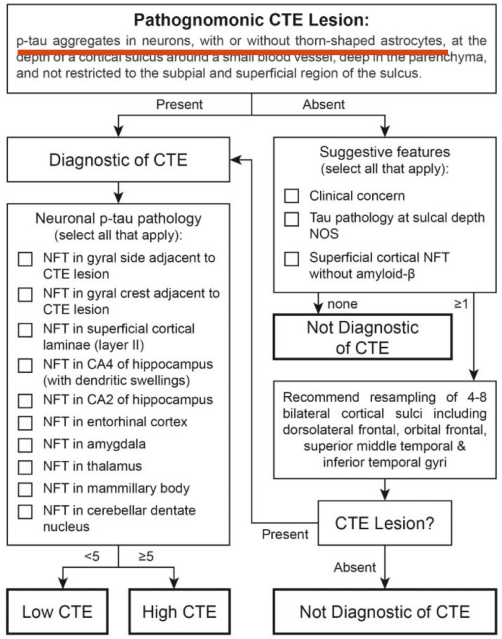


FIGURE 3. Working protocol for the diagnosis of chronic traumatic encephalopathy (CTE).

The pathognomomic lesion consists of p-tau aggregates in **neurons, astrocytes**, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci.

2016

P-tau aggregates in **neurons, with or without thorn-shaped astrocytes**, at the depth of a cortical sulcus around small blood vessel, deep in the parenchyma, and not restricted to the subpial and superficial region of the sulcus.

2021

CONDITIONS WHERE CTE-NC HAS BEEN DESCRIBED

- Boxers
- Autistic patient with repetitive head-banging behaviors
- head banging, poorly controlled epilepsy, rugby union, rugby league
- American National Football League (NFL) players
- Canadian Football League players
- Australian Rules football players
- Professional wrestlers
- Soccer
- Military veterans with known blast exposure or concussive injury
- Ice hockey
- Bull rider
- Some Hospital/Community/Brain Bank based studies identified occasional cases: they usually included some kind of head trauma

Acta Neuropathologica (2023) 146:803–815
https://doi.org/10.1007/s00401-023-02646-1

ORIGINAL PAPER

Check for updates

The neuropathology of intimate partner violence

Kristen Dams-O'Connor[1,2] · Alan C. Seifert[3] · John F. Crary[4,5,6] · Bradley N. Delman[3] · Marc R. Del Bigio[7,8] · Gabor G. Kovacs[9,10] · Edward B. Lee[11] · Amber L. Nolan[12] · Ariel Pruyser[1] · Enna Selmanovic[1] · William Stewart[13,14] · Emma Woodoff-Leith[4,5,6] · Rebecca D. Folkerth[15,16]

Received: 8 May 2023 / Revised: 14 October 2023 / Accepted: 14 October 2023 / Published online: 28 October 2023

"only limited neurodegenerative proteinopathies were encountered in the oldest subjects, ***none meeting consensus criteria for CTE-NC****"*
(14 NY + 70 other cases included)

NO

Acta Neuropathologica (2024) 148:1
https://doi.org/10.1007/s00401-024-02757-3

CORRESPONDENCE

Chronic traumatic encephalopathy (CTE) in the context of longstanding intimate partner violence

M. Tiemensma[1,2] · R. W. Byard[3,4] · R. Vink[5] · A. J. Affleck[6,7] · P. Blumbergs[3] · M. E. Buckland[6,7]

2 cases, Australia

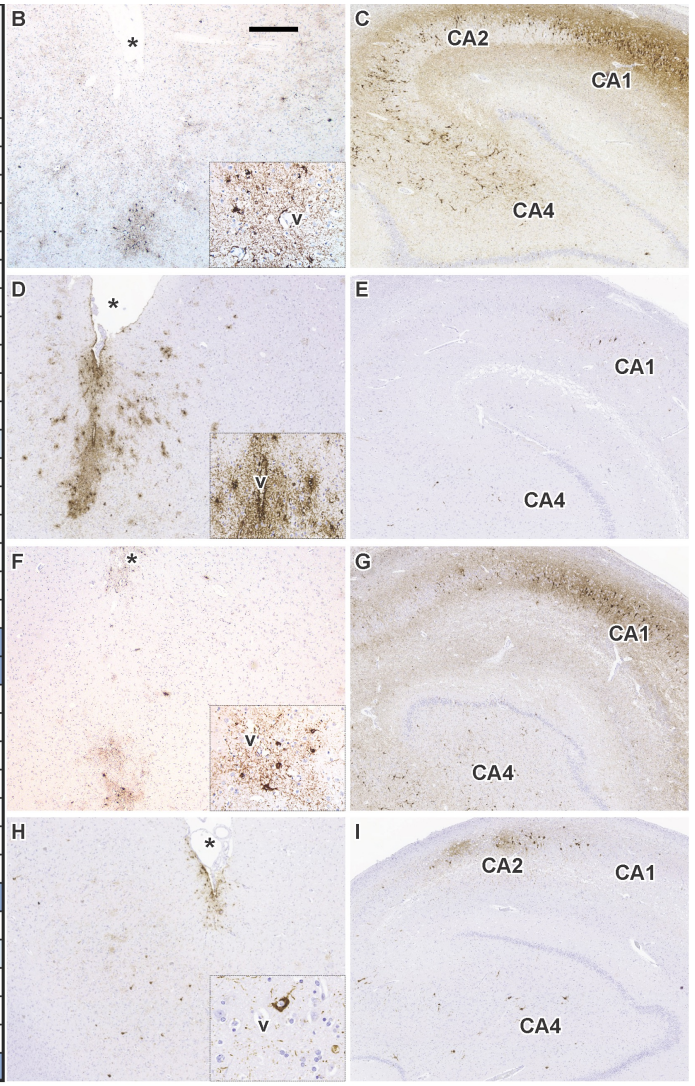
YES

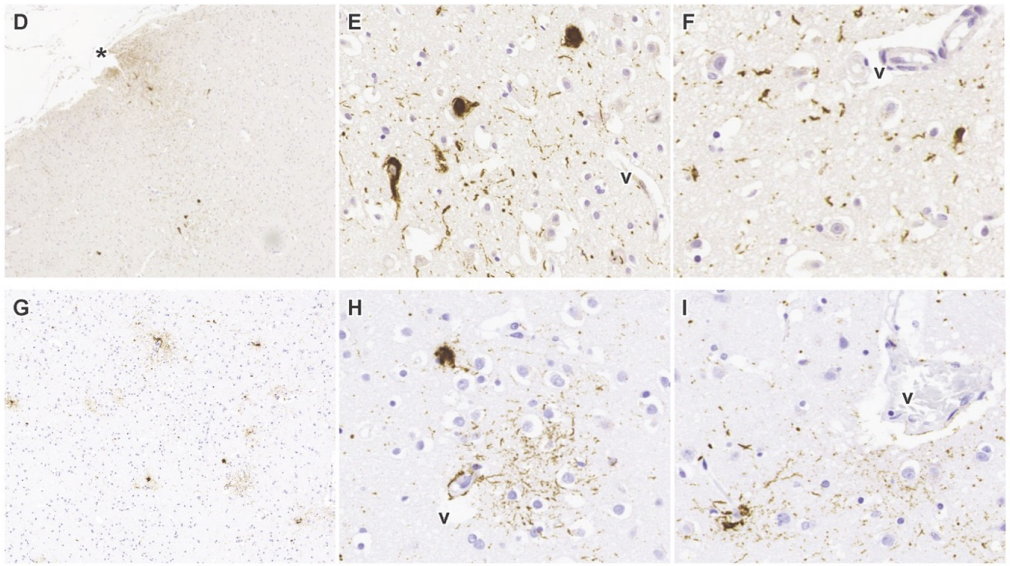
- **34** consecutively collected homeless individuals that came to autopsy between November 2017 and February 2018 at the Department of Pathology, Forensic and Insurance Medicine of Semmelweis University were included in this study. The cases were part of a previously charactered **homeless population in Central Europe (Hungary).**
- Cases ranged from **41 to 67 years of age** (57 ± 7 years) and comprised **5 females** (56 ± 7 years; females: 59 ± 5 years).
- **Alcohol and toxicology screenings** were performed on blood samples in all cases, and on urine samples when available.
- Cases with drug abuse, neoplastic, vessel pathologies, contusion, histological signs of acute and chronic intracranial hemorrhages, and inflammatory disorders of the brain were **excluded**.
- Professional sport or military veteran status was not present.

4 out 34 = 11.7%

A

Case	Age range	Sex	NFT stage	Aβ Phase	Lewy stage	CAA	CTE
1	51-55	F	I	1	–	+	-
2	51-55	F	I	0	–	–	-
3	56-60	F	I	1	–	+	-
4	61-65	F	I	1	–	–	-
5	66-70	F	III	2	–	–	-
6	41-45	M	I	0	–	–	-
7	41-45	M	II	0	–	–	-
8	46-50	M	I	0	–	–	-
9	46-50	M	I	0	–	–	-
10	46-50	M	I	0	–	–	-
11	46-50	M	II	1	–	–	-
12	51-55	M	I	0	–	–	*
13	51-55	M	I	0	–	–	-
14	51-55	M	I	0	–	+	-
15	51-55	M	I	0	–	–	-
16	51-55	M	I	0	–	–	-
17	56-60	M	II	0	–	–	-
18	56-60	M	1b	0	4	–	-
19	56-60	M	III	0	–	–	+
20	56-60	M	I	0	–	–	+
21	56-60	M	I	0	4	–	-
22	56-60	M	I	0	–	–	-
23	56-60	M	II	1	–	–	-
24	56-60	M	I	0	–	–	-
25	56-60	M	I	0	2	–	-
26	56-60	M	I	1	–	–	-
27	61-65	M	I	0	–	–	-
28	61-65	M	III	1	–	–	+
29	61-65	M	0	0	–	–	-
30	61-65	M	II	0	–	–	*
31	61-65	M	I	0	–	–	-
32	61-65	M	II	0	–	–	-
33	61-65	M	II	1	–	+	-
34	66-70	M	II	0	–	–	+





Two cases with neuropathological features reported in CTE although both cases did not fulfill neuropathological consensus criteria

Acta Neuropathologica (2025) 149:28
https://doi.org/10.1007/s00401-025-02867-6

CORRESPONDENCE

Chronic traumatic encephalopathy neuropathologic change in homeless

Krisztina Danics[1] · Shelley L. Forrest[2,3] · Gabor G. Kovacs[1,2,3,4,5]

Received: 14 March 2025 / Revised: 14 March 2025 / Accepted: 15 March 2025

"Violent behavior and various mental illnesses reported in homeless might not be only the cause, but also the consequence of CTE-NC. The presence of a progressive repetitive trauma-related neurodegenerative disorder in homeless has implications for the care system and for legal practice evaluating consequences of violent behavior."

CTE-NC can be observed in various cohorts but mostly studied in North American contact sports.

Not everyone shows CTE-NC in the same cohorts reported from various countries

Some studies did not apply the verbatim definition of CTE-NC and might have reported cases in the community having CTE that do not have according to strict criteria

JAMA Neurology | Original Investigation

Association of *APOE* Genotypes and Chronic Traumatic Encephalopathy

Kathryn Atherton, BA; Xudong Han, MS; Jaeyoon Chung, PhD; Jonathan D. Cherry, PhD; Zachary Baucom, MA; Nicole Saltiel, BA; Evan Nair, BA; Bobak Abdolmohammadi, BA; Madeline Uretsky, MS; Mohammed Muzamil Khan, MS; Conor Shea, BA; Shruti Durape, MBBS, MPH; Brett M. Martin, MS; Joseph N. Palmisano, MS; Kurt Farrell, PhD; Christopher J. Nowinski, PhD; Victor E. Alvarez, MD; Brigid Dwyer, MD; Daniel H. Daneshvar, MD, PhD; Douglas I. Katz, MD; Lee E. Goldstein, MD, PhD; Robert C. Cantu, MD; Neil W. Kowall, MD; Michael L. Alosco, PhD; Bertrand R. Huber, MD, PhD; Yorghos Tripodis, PhD; John F. Crary, MD, PhD; Lindsay Farrer, PhD; Robert A. Stern, PhD; Thor D. Stein, MD, PhD; Ann C. McKee, MD; Jesse Mez, MD, MS

- Among brain donors with RHI exposure, ***APOE* ε4 was significantly associated with CTE stage** and quantitative and semi-quantitative measures of p-tau pathology

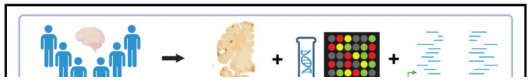
Two genetic studies suggesting why not everyone in the same sport develop CTE-NC

Cell Reports
Medicine

Article

A structural haplotype in the 17q21.31 *MAPT* region is associated with increased risk for chronic traumatic encephalopathy endophenotypes

Graphical abstract



Authors

Xudong Han, Yichi Zhang, Jillian N. Petrosky, ..., John F. Crary, Ann C. McKee, Jesse Mez

- The ***MAPT* H1β1γ1 haplotype was significantly associated with dementia and semi-quantitative tau burden** in multiple cortical and medial temporal regions commonly affected in CTE.
- H1β1γ1 differential expression analyses in dorsolateral frontal cortex implicated *cis*-acting genes and inflammatory pathways.
- The **H1β1γ1 haplotype may help explain CTE heterogeneity** among those with similar RHI exposure.

ASTROCYTES….*WITHOUT* P-TAU….

Babcock *et al.*
Acta Neuropathologica Communications (2022) 10:52
https://doi.org/10.1186/s40478-022-01358-z

Acta Neuropathologica Communications

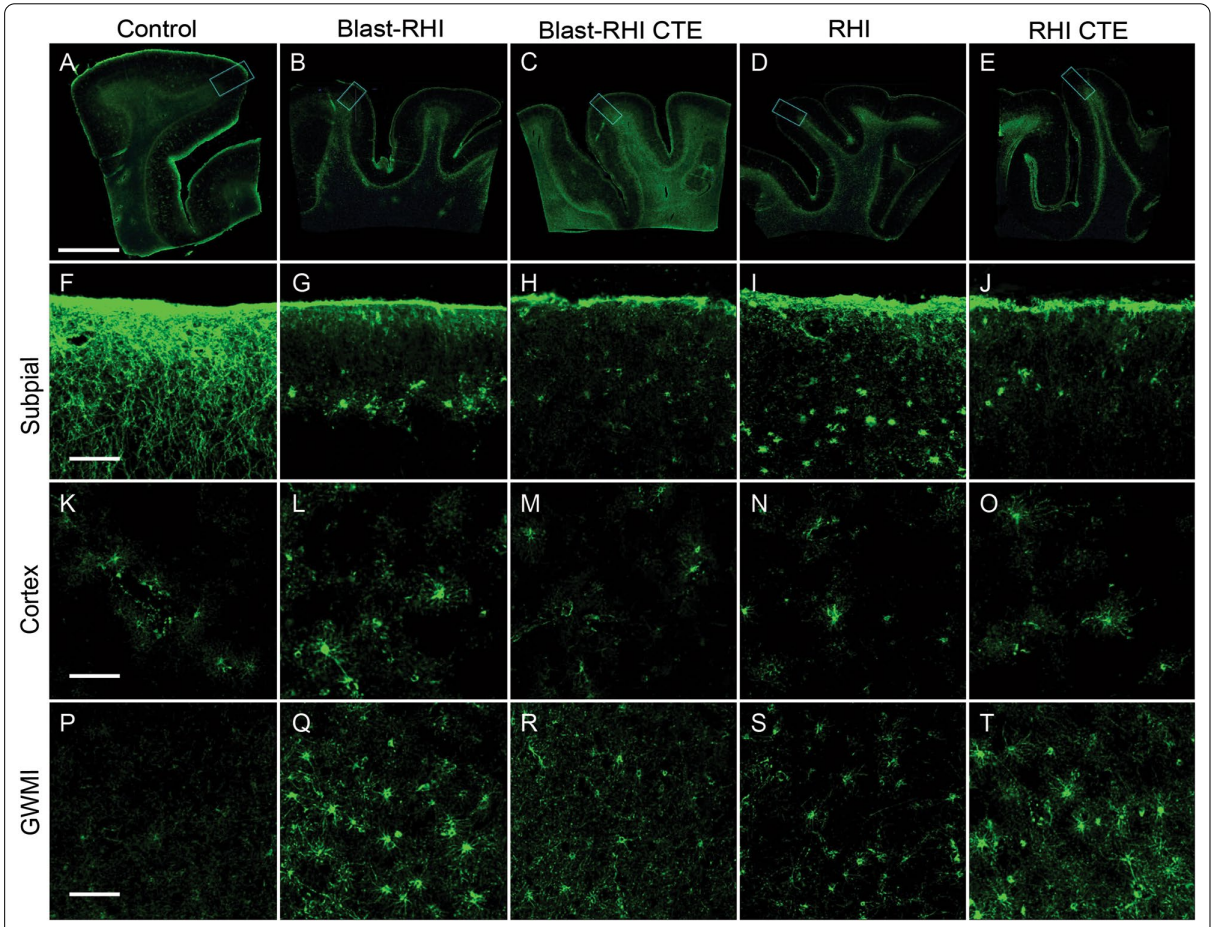
RESEARCH Open Access

Interface astrogliosis in contact sport head impacts and military blast exposure

Katharine J. Babcock[1,2,3], Bobak Abdolmohammadi[3,5], Patrick T. Kiernan[3], Ian Mahar[3,5], Jonathan D. Cherry[2,3,4,5], Victor E. Alvarez[2,3,5,6,7], Lee E. Goldstein[3,5,8,9], Thor D. Stein[2,3,4,7], Ann C. McKee[2,3,5,6,7] and Bertrand R. Huber[2,3,5,6,7*]

Astrocytes of the glial limitans superficialis demonstrate intralaminar astrocyte processes that extend down from the subpial surface into cortical layers I-II in controls.

In all forms of neurotrauma there is a dropout of interlaminar astrocytic processes, however, changes indicative of reactive astrocytosis can be seen throughout the cortex.



ASTROCYTES….*WITH* P-TAU….

Acta Neuropathol (2016) 131:75–86
DOI 10.1007/s00401-015-1515-z

CONSENSUS PAPER

The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy

Ann C. McKee[1,2,3,4,5] · Nigel J. Cairns[6] · Dennis W. Dickson[7] · Rebecca D. Folkerth[8] · C. Dirk Keene[9] · Irene Litvan[10] · Daniel P. Perl[11] · Thor D. Stein[2,3,4,5] · Jean-Paul Vonsattel[12] · William Stewart[13] · Yorghos Tripodis[3,14] · John F. Crary[15] · Kevin F. Bieniek[7] · Kristen Dams-O'Connor[16] · Victor E. Alvarez[1,2,3,4] · Wayne A. Gordon[16] · the TBI/CTE group

Table 2 Preliminary NINDS criteria for the pathological diagnosis of CTE

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	g superficial layers (layers II–III), in contrast to layers III and
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	rtical nuclei, including the mammillary bodies and other hypo- ntum, and isodendritic core (nucleus basalis of Meynert, raphe
	found in the subpial and periventricular regions
	some threadlike neurites) (Fig. 2h)

1. Macroscopic features: disproportionate dilatation of the third ventricle, septal abnormalities, mammillary body atrophy, and contusions or other signs of previous traumatic injury
2. TDP-43 immunoreactive neuronal cytoplasmic inclusions and dot-like structures in the hippocampus, anteromedial temporal cortex and amygdala (Fig. 4)

Age-related p-tau astrogliopathy that may be present; non-diagnostic and non-supportive [22]	
1.	Patches of thorn-shaped astrocytes in subcortical white matter
2.	Subependymal, periventricular, and perivascular thorn-shaped astrocytes in the mediobasal regions
3.	Thorn-shaped astrocytes in amygdala or hippocampus [22]

Acta Neuropathol (2016) 131:87–102
DOI 10.1007/s00401-015-1509-x

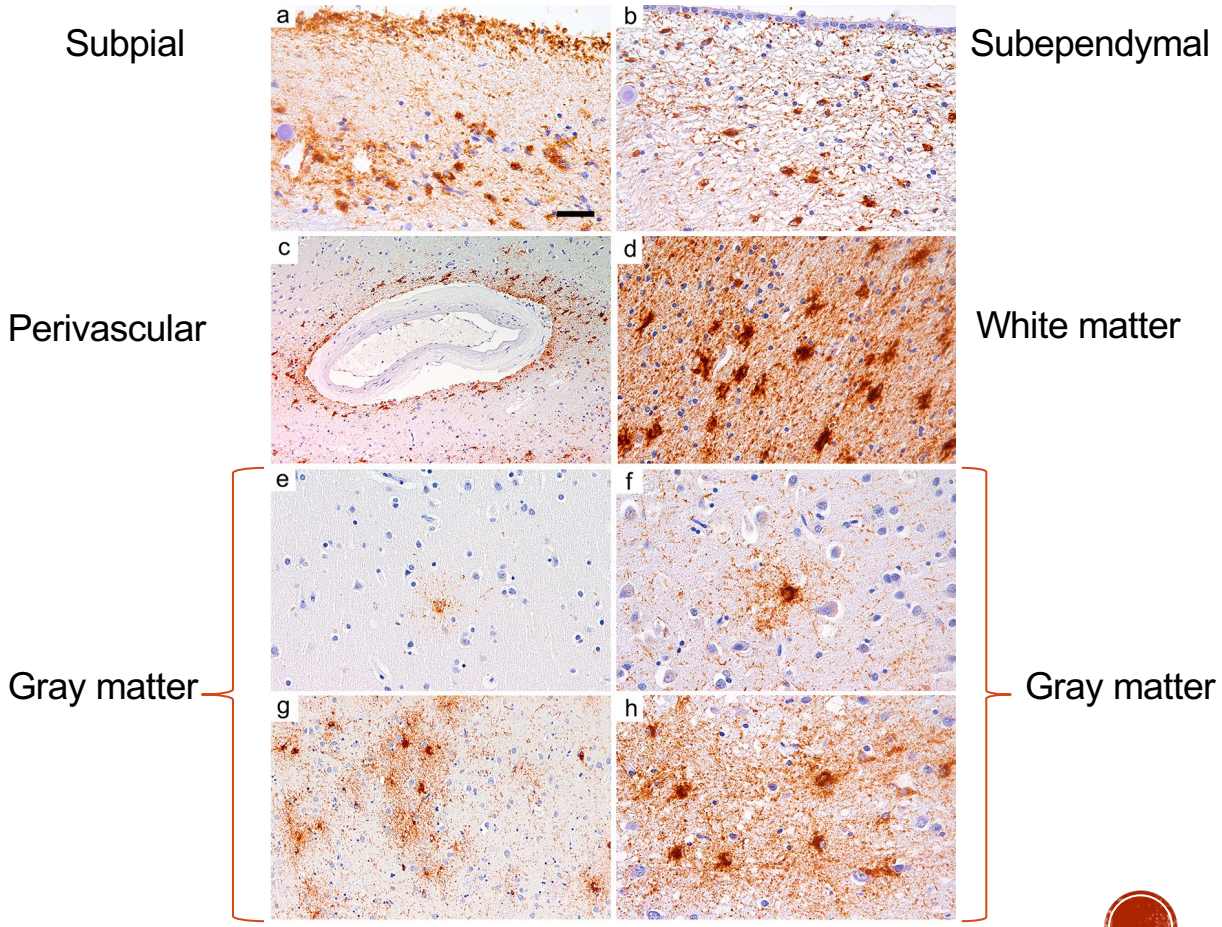
CrossMark

CONSENSUS PAPER

Aging-related tau astrogliopathy (ARTAG): harmonized evaluation strategy

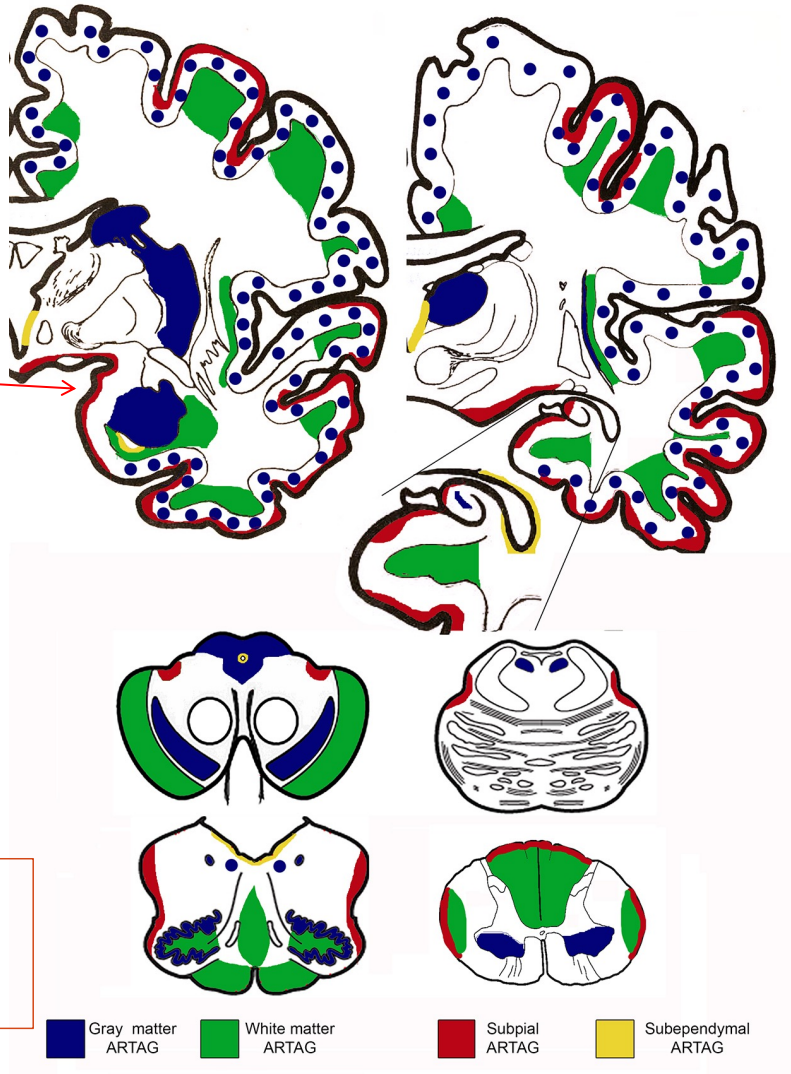
Gabor G. Kovacs[1] · Isidro Ferrer[2] · Lea T. Grinberg[3,4] · Irina Alafuzoff[5] · Johannes Attems[6] · Herbert Budka[7] · Nigel J. Cairns[8] · John F. Crary[9,33] · Charles Duyckaerts[10] · Bernardino Ghetti[11] · Glenda M. Halliday[12] · James W. Ironside[13] · Seth Love[14] · Ian R. Mackenzie[15] · David G. Munoz[16] · Melissa E. Murray[17] · Peter T. Nelson[18] · Hitoshi Takahashi[19] · John Q. Trojanowski[20] · Olaf Ansorge[21] · Thomas Arzberger[22] · Atik Baborie[23] · Thomas G. Beach[24] · Kevin F. Bieniek[17] · Eileen H. Bigio[25] · Istvan Bodi[26] · Brittany N. Dugger[24,27] · Mel Feany[28] · Ellen Gelpi[29] · Stephen M. Gentleman[30] · Giorgio Giaccone[31] · Kimmo J. Hatanpaa[32] · Richard Heale[6] · Patrick R. Hof[33] · Monika Hofer[21] · Tibor Hortobágyi[34] · Kurt Jellinger[35] · Gregory A. Jicha[36] · Paul Ince[37] · Julia Kofler[38] · Enikö Kövari[39] · Jillian J. Kril[40] · David M. Mann[41] · Radoslav Matej[42] · Ann C. McKee[43] · Catriona McLean[44] · Ivan Milenkovic[1,45] · Thomas J. Montine[46] · Shigeo Murayama[47] · Edward B. Lee[20] · Jasmin Rahimi[1] · Roberta D. Rodriguez[48] · Annemieke Rozemüller[49] · Julie A. Schneider[50,51] · Christian Schultz[52] · William Seeley[3] · Danielle Seilhean[10] · Colin Smith[13] · Fabrizio Tagliavini[31] · Masaki Takao[53] · Dietmar Rudolf Thal[54,55] · Jon B. Toledo[20] · Markus Tolnay[56] · Juan C. Troncoso[57] · Harry V. Vinters[58,59] · Serge Weis[60] · Stephen B. Wharton[37] · Charles L. White III[32] · Thomas Wisniewski[61,62,63] · John M. Woulfe[64] · Masahito Yamada[65] · Dennis W. Dickson[17]

Aging-related tau astrogliopathy (ARTAG), a term that refers to a morphological spectrum of astroglial pathology detected by tau immunohistochemistry, especially with phosphorylation-dependent and 4R isoform-specific antibodies. ARTAG occurs mainly, but not exclusively, in individuals over 60 years of age.



WHERE WAS ARTAG SEEN?

Amygdala:
Hotspot!



J Neuropathol Exp Neurol
Vol. 0, No. 0, 2016, pp. 1–19
doi: 10.1093/jnen/nlx007

ORIGINAL ARTICLE

Evaluating the Patterns of Aging-Related Tau Astrogliopathy Unravels Novel Insights Into Brain Aging and Neurodegenerative Diseases

Gabor G. Kovacs, MD, PhD, John L. Robinson, BS, Sharon X. Xie, PhD, Edward B. Lee, MD, PhD, Murray Grossman, MD, EdD, David A. Wolk, MD, David J. Irwin, MD, Dan Weintraub, MD, Christopher F. Kim, Theresa Schuck, BA, Ahmed Yousef, BA, Stephanie T. Wagner, Eunran Suh, PhD,Vivianna M. Van Deerlin, MD, PhD, Virginia M.-Y. Lee, PhD, and John Q. Trojanowski, MD, PhD

Clinical, neuropathological, and genetic (eg, APOE ε4 allele, MAPT H1/H2 haplotype) data from 628 postmortem brains from subjects were investigated; most of the patients had been longitudinally followed at the University of Pennsylvania.

Kovacs et al. Acta Neuropathologica Communications (2018) 6:50
https://doi.org/10.1186/s40478-018-0552-y

Acta Neuropathologica Communications

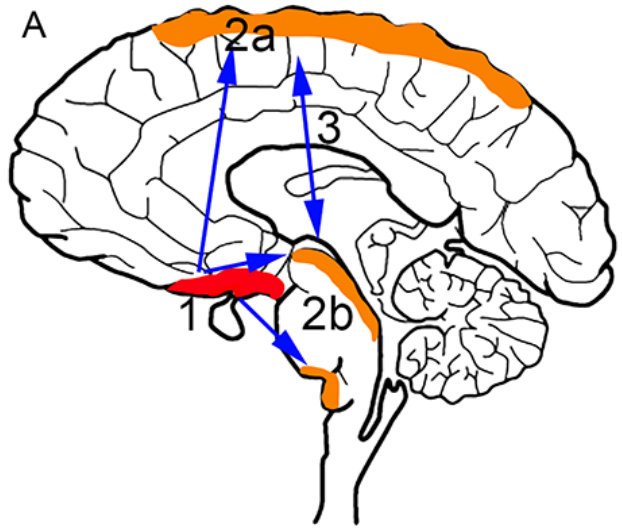
RESEARCH Open Access

Sequential stages and distribution patterns of aging-related tau astrogliopathy (ARTAG) in the human brain

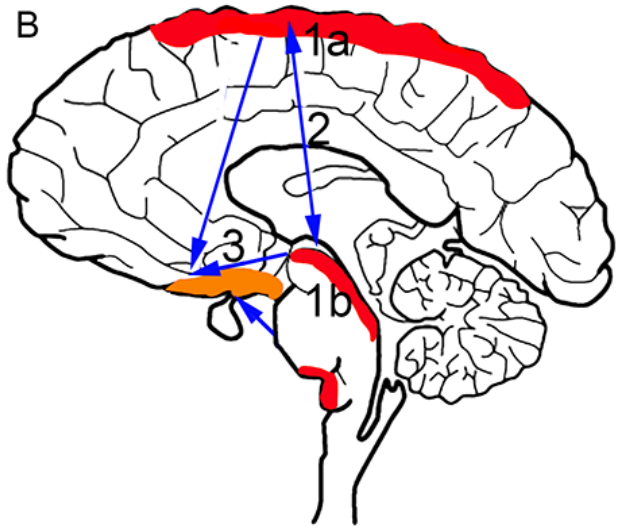
Gabor G. Kovacs[1,2*], Sharon X. Xie[3], John L. Robinson[2], Edward B. Lee[2], Douglas H. Smith[4], Theresa Schuck[2], Virginia M.-Y. Lee[2] and John Q. Trojanowski[2*]

PREDICTING SEQUENTIAL INVOLVEMENT OF BRAIN REGIONS

SUBPIAL ARTAG



Subpial ARTAG
Pattern 1



Subpial ARTAG
Pattern 2

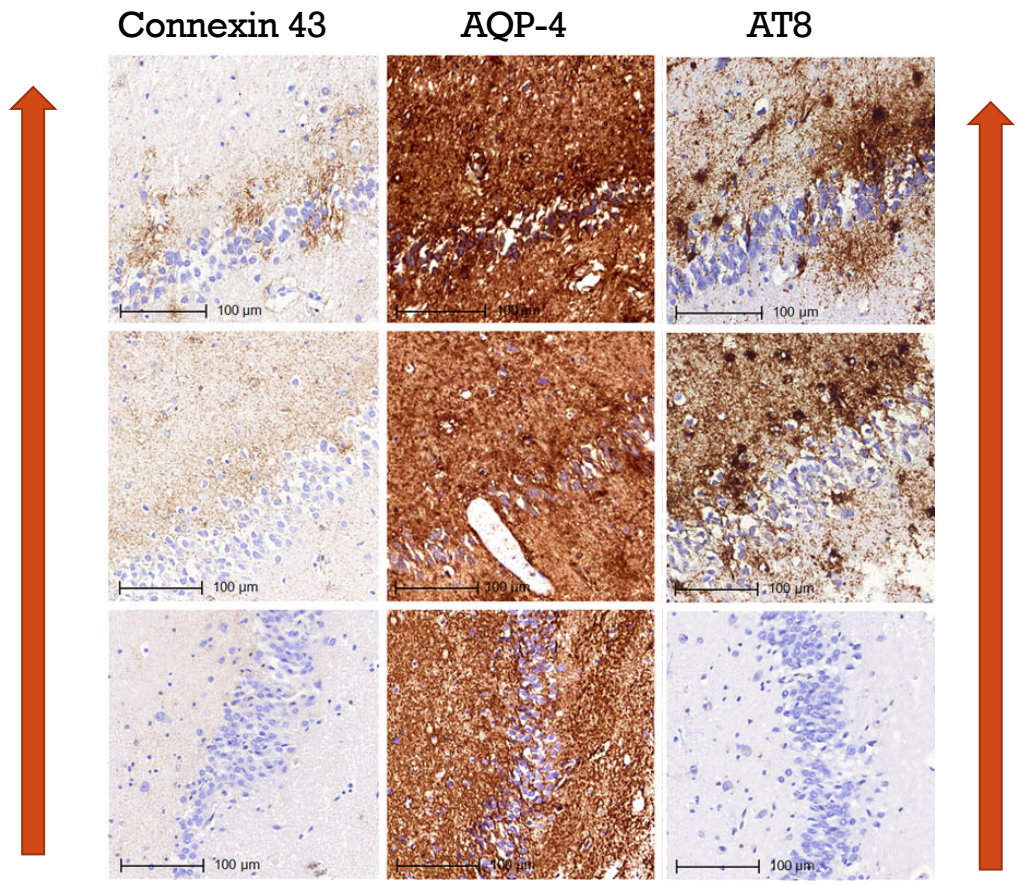
suggest a disease mechanism related to the circulation of the cerebrospinal fluid

TRAFFIC JAM

suggest a local inducing factor (i.e., mechanical)

LOCAL PRESSURE

ARTAG - GAP JUNCTION - AQUAPORIN



Neuropathology and Applied Neurobiology (2018), **44**, 491–505 doi: 10.1111/nan.12427

Connexin-43 and aquaporin-4 are markers of ageing-related tau astrogliopathy (ARTAG)-related astroglial response

G. G. Kovacs*,†,[1], A. Yousefi,[1], S. Kaindl*, V. M. Lee† and J. Q. Trojanowski†

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Increased and expression Connexin-43 & AQP4 expression

Blood Brain Barrier dysfunction?

JOURNAL ARTICLE ACCEPTED MANUSCRIPT

Traumatic brain injury or head impacts from contact sports are associated with tau astrogliopathy

John D Arena , William Stewart , Gabor G Kovacs , Edward B Lee , John L Robinson , Virginia M-Y Lee , John Q Trojanowski , Andrea L C Schneider , Douglas H Smith , Victoria E Johnson ✉

Brain, awaf073, https://doi.org/10.1093/brain/awaf073

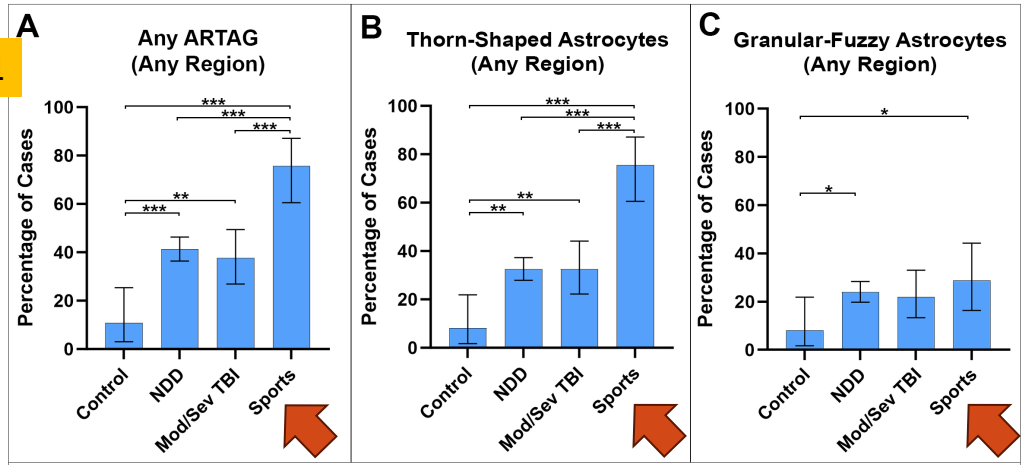
1

P-Tau+ Thorn-shaped astrocytes (TSA) were observed more frequently in contact sports participants (75.6%) versus controls with (32.5%; p<0.001) and without (8.1%; p<0.001) NDD.

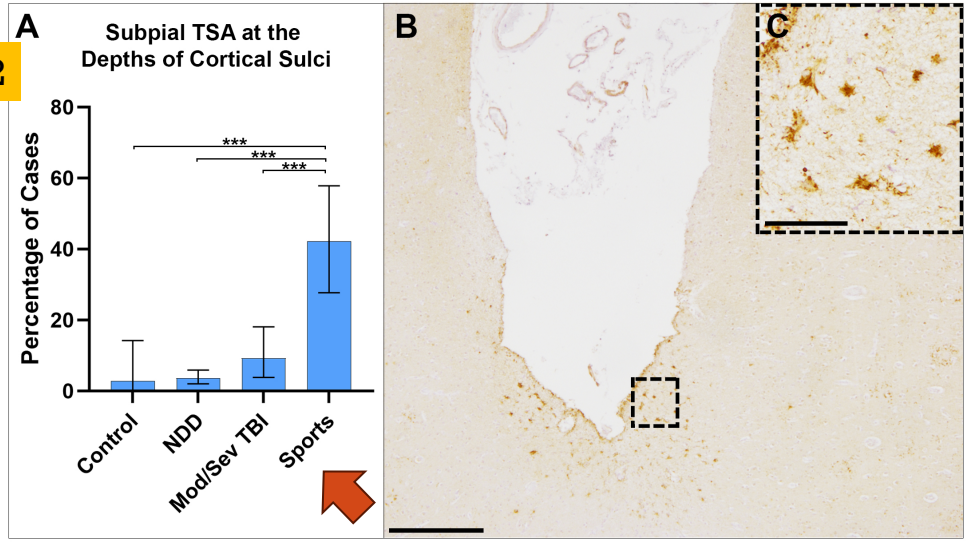
2

P-Tau+ subpial TSA at sulcal depths were occasionally observed in aged controls with (3.6%) and without (2.8%) NDD, this pathology was considerably more common following RHI/TBI (42.2%; p<0.001).

1



2



FREQUENCY OF CORTICAL TAU PATHOLOGY IN THE COMMUNITY

J Neuropathol Exp Neurol
Vol. 0, No. 0, 2019, pp. 1–8
doi: 10.1093/jnen/nlz017

ORIGINAL ARTICLE

OXFORD

Chronic Traumatic Encephalopathy (CTE) Is Absent From a European Community-Based Aging Cohort While Cortical Aging-Related Tau Astrogliopathy (ARTAG) Is Highly Prevalent

Shelley L. Forrest, PhD, Jillian J. Kril, PhD, Stephanie Wagner, Cand. Med.,
Selma Hönigschnabl, MD, Angelika Reiner, MD, Peter Fischer, MD, and Gabor G. Kovacs, MD, PhD

Feature	Frontal	Parietal	Temporal
Neurofibrillary tangles (NFTs)	26.1	25.5	47.4
NFTs depth of sulci only	**1.3**	**0.3**	**0.6**
Subpial ARTAG	3.5	1.9	5.8
Subpial ARTAG depth of sulci only	**1.3**	**0.3**	**1.0**
Gray matter ARTAG	20.6	16.5	17.1
Gray matter ARTAG depth of sulci	**1.6**	**0**	**0.3**
only	**1.3**	**0.3**	**0.6**
Gray matter perivascular ARTAG	2.6	3.2	5.5
White matter ARTAG	1.3	0.6	1.3
White matter perivascular ARTAG			

GM, grey matter; NFT, neurofibrillary tangle; PV, perivascular; SP, subpial; WM, white matter

TAKE HOME MESSAGES 2

CTE-NC is characterized by neuronal p-Tau pathology but astrocytic is also important

Astrocytic p-Tau pathology is reminiscent of that seen in aged brains (ARTAG), which has a pathogenic aspect related to barrier dysfunction

Pathology 57 (2025) 178–190

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journal homepage: www.pathologyjournal.rcpa.edu.au

NEUROPATHOLOGY: SPECIAL THEME ISSUE

Current concepts and molecular pathology of neurodegenerative diseases

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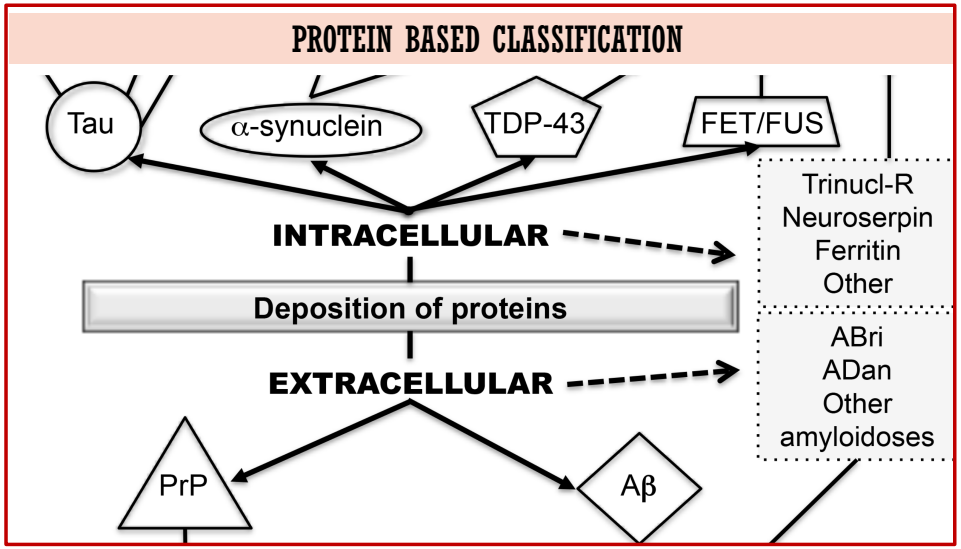
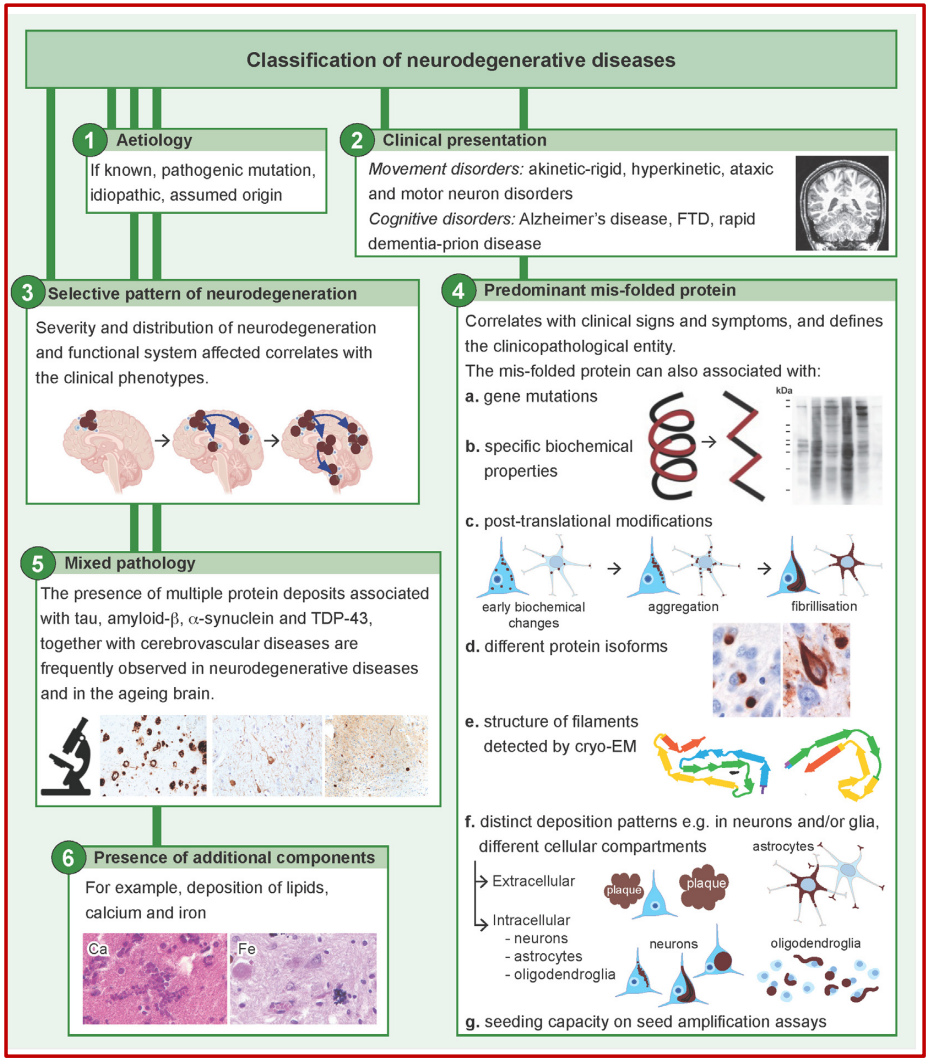




Acta Neuropathologica (2020) 140:495–512
https://doi.org/10.1007/s00401-020-02197-9

ORIGINAL PAPER

Characterizing tau deposition in chronic traumatic encephalopathy (CTE): utility of the McKee CTE staging scheme

Michael L. Alosco[1] · Jonathan D. Cherry[1,2,3] · Bertrand Russell Huber[1,3,6] · Yorghos Tripodis[1,5] · Zachary Baucom[5] · Neil W. Kowall[1,2,3] · Nicole Saltiel[1] · Lee E. Goldstein[1,2,7,8,9,10] · Douglas I. Katz[1,14] · Brigid Dwyer[1,14] · Daniel H. Daneshvar[1] · Joseph N. Palmisano[1,15] · Brett Martin[1,15] · Robert C. Cantu[1,11,12,13] · Robert A. Stern[1,11,16] · Victor E. Alvarez[1,3,4] · Jesse Mez[1] · Thor D. Stein[1,2,3,4] · Ann C. McKee[1,2,3,4]

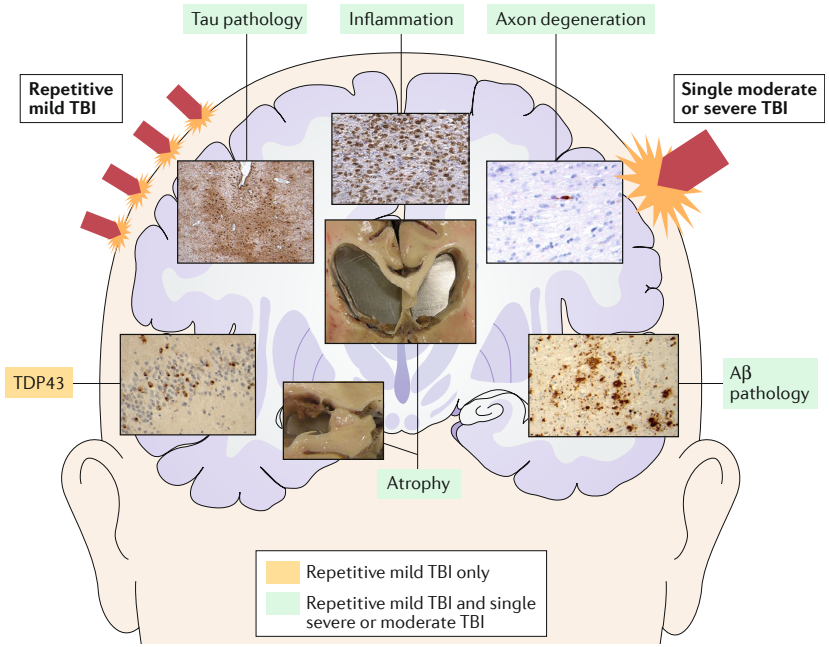
Table 3 Co-morbid neuropathologic characteristics among 366 brain donors with CTE

	Total sample (*N* = 366)		CTE stage I (*n* = 58)		CTE stage II (*n* = 79)		CTE stage III (*n* = 127)		CTE stage IV (*n* = 102)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Alzheimer's disease	54	14.8	2	3.4	6	7.6	10	7.9	36	35.3
Lewy body disease										
Brain stem	28	7.7	3	5.3	2	2.5	7	5.5	16	15.7
Limbic (transitional)	18	4.9	2	3.5	2	2.5	10	7.9	4	3.9
Neocortical (diffuse)	20	5.5	2	3.5	2	2.5	8	6.3	8	7.8
Amygdala	4	1.1	0	–	0	–	0	–	4	3.9
Olfactory	10	2.7	1	1.8	2	2.5	2	1.6	5	4.9
Frontotemporal Lobar Degeneration (FTLD)										
FTLD-Tau	19	5.2	2	3.4	3	3.8	7	5.5	7	7.1
FTLD-TDP-43	23	6.3	2	3.4	5	6.4	1	0.8	15	14.7
Motor neuron disease	17	4.7	1	1.7	6	7.6	8	6.3	2	2.0
Prion disease	2	0.5	0	–	0	–	1	0.8	1	1.0
CERAD neuritic plaque score										
No neuritic plaques	232	63.6	51	89.5	67	84.8	89	70.1	25	24.5
Sparse neuritic plaques	84	23.0	5	8.8	8	10.1	28	22.0	43	42.2
Moderate neuritic plaques	32	8.8	1	1.8	3	3.8	6	4.7	22	21.6
Frequent neuritic plaques	17	4.7	0	–	1	1.3	4	3.1	12	11.8
Thal amyloid phase										
Phase 0	165	45.7	44	77.2	55	70.5	59	46.5	7	7.1
Phase 1/2	48	13.3	3	5.3	8	10.3	24	18.9	13	13.1
Phase 3	42	11.6	8	14.0	6	7.7	15	11.8	13	13.1
Phase 4/5	106	29.4	2	3.5	9	11.5	29	22.8	66	66.7
Braak staging										
Stage 0	84	23.7	36	64.3	32	41.0	12	9.8	4	4.1
Stage I/II	71	20.1	13	23.2	36	46.2	17	13.8	5	5.2
Stage III/IV	141	39.8	6	10.7	5	6.4	80	65.0	50	51.5
Stage V/VI	58	16.4	1	1.8	5	6.4	14	11.4	38	39.2
Atherosclerosis, moderate–severe	64	19.2	3	5.9	7	10.0	20	18.0	34	33.3
Arteriolosclerosis, moderate–severe	161	44.5	20	34.5	19	25.0	59	46.5	63	62.4
White Matter Rarefaction, moderate–severe	167	46.5	17	29.3	20	26.3	57	46.0	73	72.3

OPINION

Chronic traumatic encephalopathy — confusion and controversies

Douglas H. Smith, Victoria E. Johnson, John Q. Trojanowski and William Stewart



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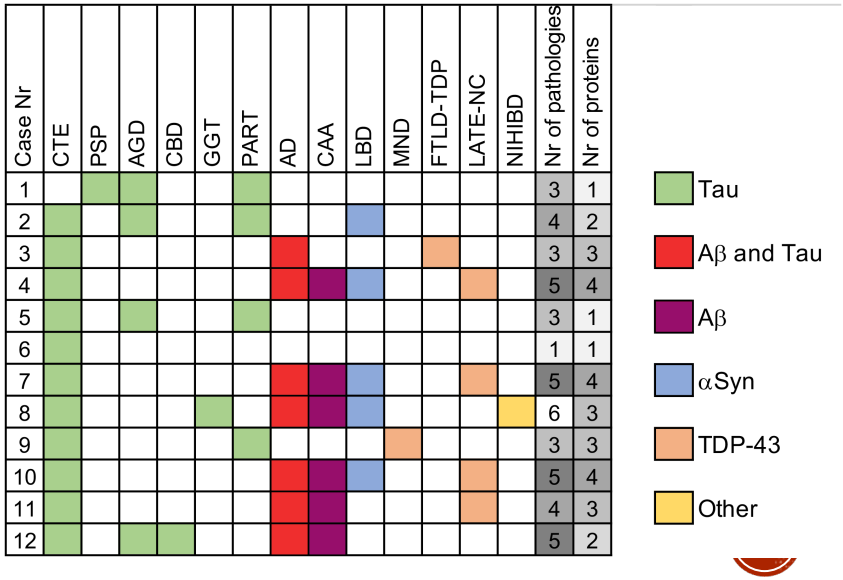
DOI: 10.1111/ene.16259

european journal of neurology

ORIGINAL ARTICLE

Unusual combinations of neurodegenerative pathologies with chronic traumatic encephalopathy (CTE) complicates clinical prediction of CTE

Foad Taghdiri[1] | Mozhgan Khodadadi[2] | Nusrat Sadia[2] | Asma Mushtaque[2] | Olivia F. T. Scott[2] | Veronica Hirsch-Reinhagen[3,4] | Charles Tator[2,5] | Richard Wennberg[2,5] | Gabor G. Kovacs[1,2,5,6,7,8] | M. Carmela Tartaglia[1,2,5]



Case Nr	CTE	PSP	AGD	CBD	GGT	PART	AD	CAA	LBD	MND	FTLD-TDP	LATE-NC	NIHIBD	Nr of pathologies	Nr of proteins
1		■	■			■								3	1
2	■		■			■			■					4	2
3	■						■				■			3	3
4	■						■	■	■			■		5	4
5	■		■			■								3	1
6	■													1	1
7	■						■	■	■			■		5	4
8	■				■		■	■	■				■	6	3
9	■					■				■				3	3
10	■						■	■	■			■		5	4
11	■						■	■				■		4	3
12	■		■	■			■	■						5	2

CASE REPORT OPEN ACCESS

Unprecedented Combination of Rare Degenerative Pathologies in an Octogenarian Ex-Football Player

Shelley L. Forrest[1,2] | Nusrat Sadia[3] | Mozhgan Khodadadi[3] | Charles Tator[3,4] | Robin Green[3,5] | Maria Carmela Tartaglia[3,6] | Gabor G. Kovacs[1,2,7,8]

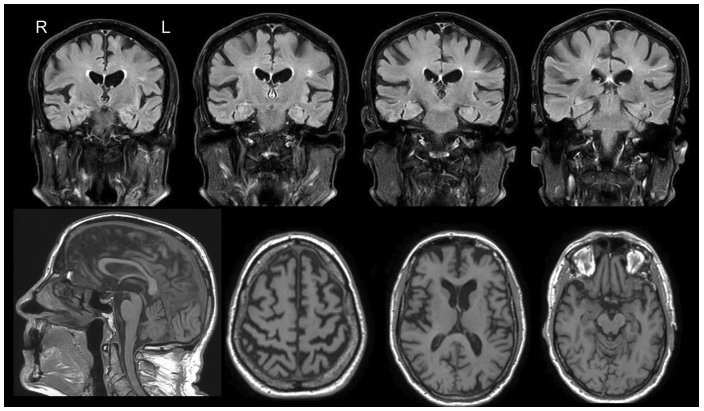
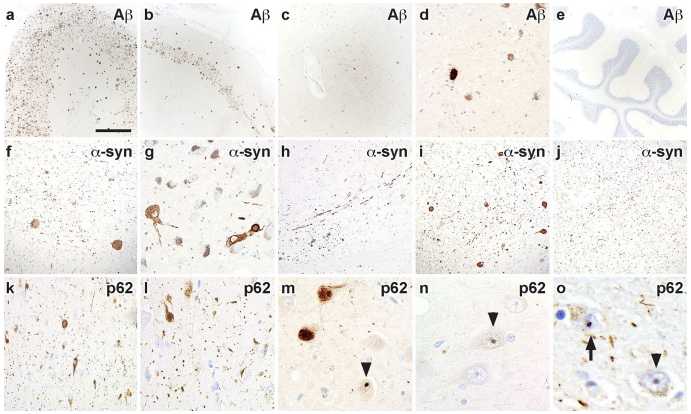
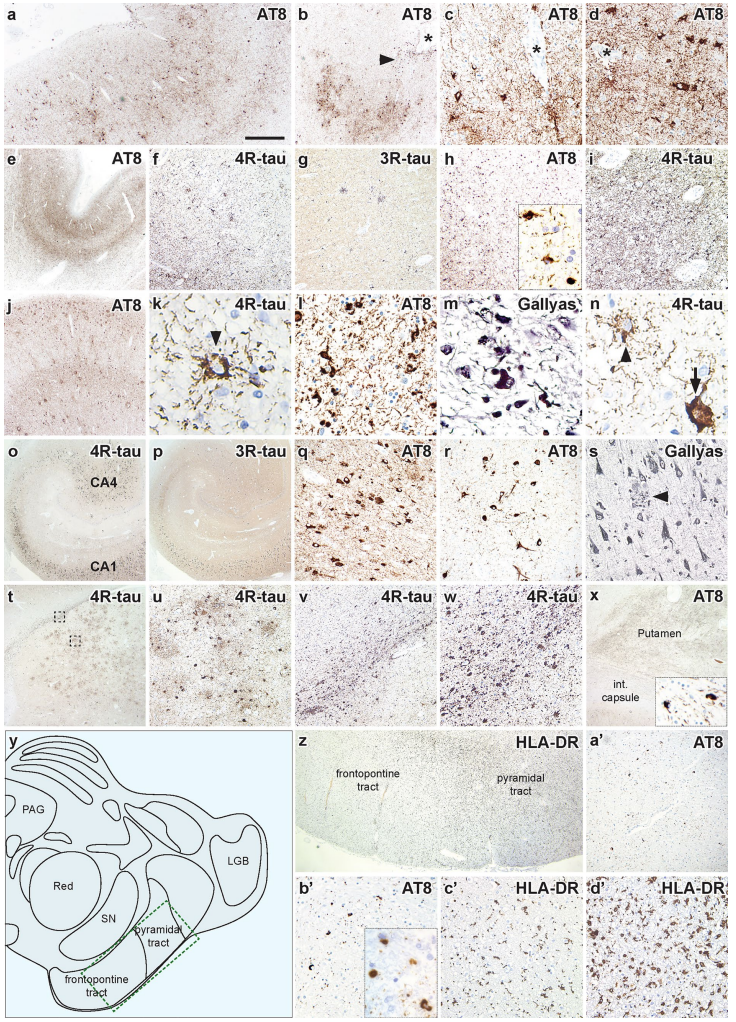


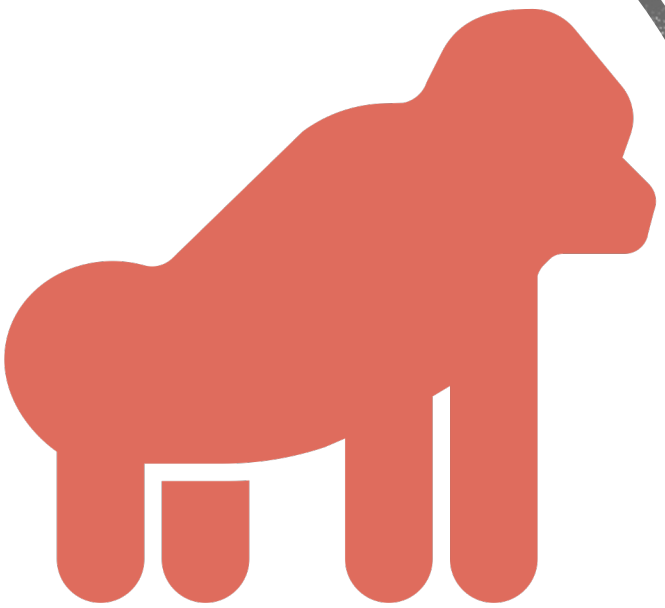
FIGURE 1 | Representative MRI images taken when the patient was aged 81 years. MRI revealed mild asymmetric left greater than right fronto-temporal atrophy and some linear white matter hyperintensity in the left frontal area.





1. Chronic traumatic encephalopathy (CTE, high level)
2. High level Alzheimer's disease neuropathologic change (A3B3C3)
3. Limbic Lewy body disease,
4. Cerebral amyloid angiopathy (type 2)
5. Argyrophilic grain disease (Stage 2)
6. Neuronal intranuclear hyaline inclusion body disease
7. Globular glial tauopathy (Type II).


CAUTIONARY NOTE NR.1.:
NOT EVERYTHING IS DUE TO CTE-NC IN A CONTACT SPORT PLAYER!



Cautionary note Nr.2.

CTE-NC can develop or even be accerelated in a pre-existing neurodegenerative condition in a contact sport player

TAKE HOME MESSAGE

- CTE-NC can be observed in various cohorts but mostly studied in North American contact sports.
- Not everyone shows CTE-NC in the same cohorts reported from various countries: genetic susceptibility factors?
- CTE-NC is characterized by neuronal p-Tau pathology but astrocytic is also important: maybe there is trauma–related astrocytic p-Tau pathology?
- Astrocytic p-Tau pathology is reminiscent of that seen in aged brains (ARTAG), which has a pathogenic aspect related to barrier dysfunction
- Repetitive head injusry is a risk factor for various neurodegenerative diseases not only CTE
- Not every contact sport player who has neuropsychiatric symptoms has CTE-NC