CTE – 1928 to present

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Disclosures

- The speaker:
  - Has provided expert legal testimony in disputes in the US, including cases or issues related to contact sport athletes
  - Receives no research support from any sport organization or players association
  - Does not accept honoraria for presentations
  - Has been occasionally re-imbursed for travel expenses for educational seminars

- The discussion reflects the *speaker's opinions*

Point #1

- CTE in 20th century boxers was a *clinical* entity

PUNCH DRUNK *

HARRISON S. MARTLAND, M.D.
NEWARK, N. J.

For some time fight fans and promoters have recognized a peculiar condition occurring among prize fighters which, in ring parlance, they speak of as "punch drunk." Fighters in whom the early symptoms are well recognized are said by the fans to be "cuckoo," "goofy," "cutting paper dolls," or "slug nutty."

JAMA 1928;91(15):1103-1107

The following case, taken from the series reported by Martland and Beling, is abstracted here as an illustration.

CASE 1.—*History.*—A man, aged 76, while going upstairs, stumbled and struck his head. He became unconscious. He did not vomit. On admission to the hospital he was in coma.

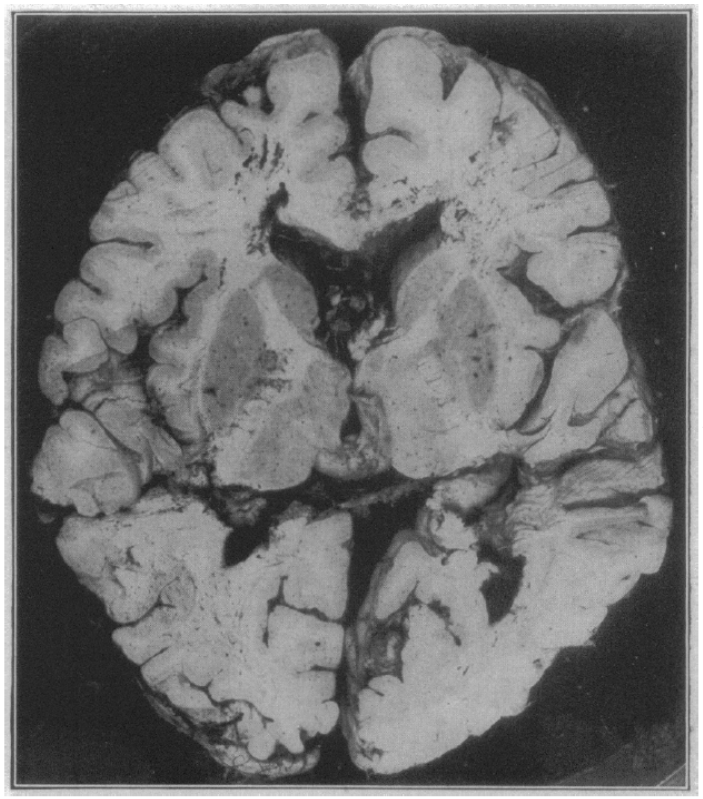


Fig. 2.—Brain in case 1: Multiple punctate concussion hemorrhages may be seen situated chiefly in the corona radiata of both frontal lobes and in the corpora striata. Other brain injury is absent.

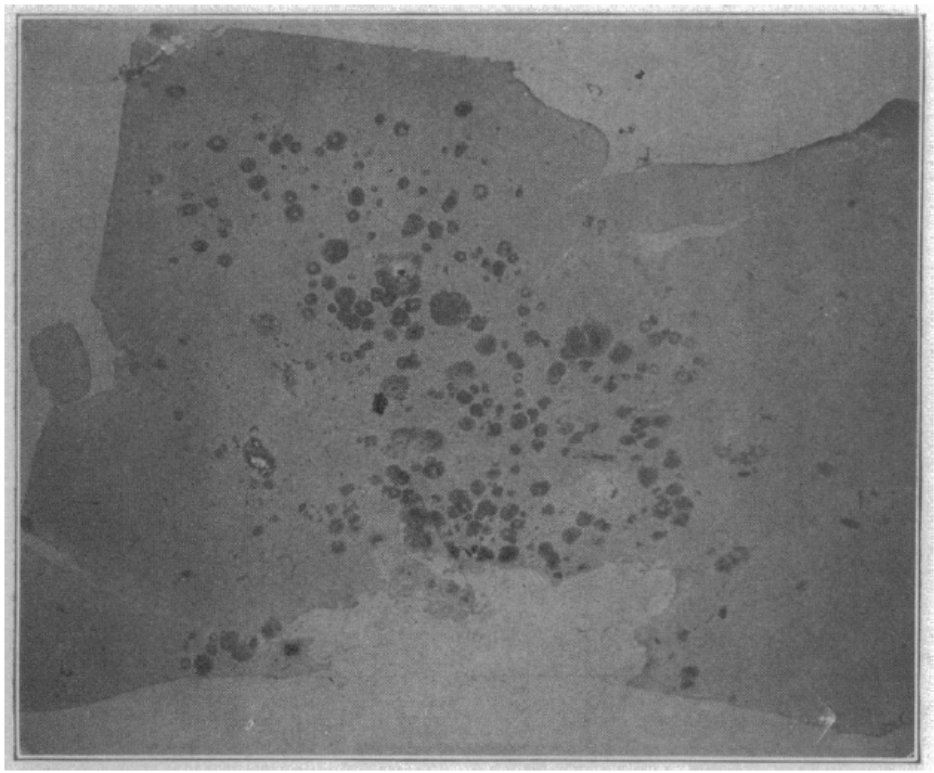


Fig. 3.—Low power photomicrograph of a section through the corpora striatum in case 1: Innumerable "ring hemorrhages" may be noted with their perivascular distribution.

Martland, HS. JAMA 1928;91(15):1103-1107

“CTE” encefalopatia traumatica cronica came to attention because of its *clinical* presentation, obvious even to fans

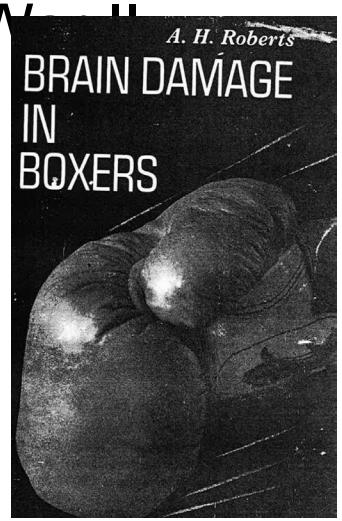
- 1928 Martland – no (boxer) neuropathology
- 1934 Parker – no neuropathology
- 1936 Carroll – no neuropathology
- 1937 Millspaugh – no neuropathology
- 1949 Critchley – no neuropathology

Neurological signs in 20th century boxers (in decreasing order of frequency)
Dysarthria
Memory loss
Abnormal ANDATURA gait, with or without ataxia
Increased reflexes, often asymmetrical
Visual signs – vision loss, eye movement disorders
Tremor
Ataxia
Expressionless or impassive facies FACIES SENZA ESPRESSIONE O IMPASSIBILI
Extensor Babinski sign SEGNO DI BABINSKI DELL'ESTENSORE
Euphoria or fatuousness FATUITA'
Dementia
Positive Romberg
Pathological drooling or dribbling SBAVAMENTO

“CTE” in the 20th century

- A diverse spectrum of *neurological* deficits from repeated *traumatic brain injury,* including moderate to severe TBI TRAUMA CRANICO in some cases.
- Where detailed records exist, athletes were *symptomatic prior to retirement* (i.e, no “latency” or “delay”)
- In many cases, neurological injury could be traced to specific fights INCONTRI.
- Essentially all severely affected boxers PUGILI fought prior to World W[illegible]

> *“Severely disabling degrees of this syndrome were encountered very infrequently, and not at all in those whose professional careers followed the last war” (page 110).*



Roberts A. Brain Damage in Boxers. London: Pitman Medical and Scientific Publishing Co. LTD, 1969.

Is (20th century) CTE ENCEFALOPATIA TRAUMATICA CRONICA a “relic of the past”?

Editorials

(Ex?) Dementia Pugilistica in Ex-Boxers

Like “dementia paralytica” and “dementia praecox,” the term “dementia pugilistica,” first introduced by Millspaugh in 1937 to describe the posttraumatic sequelae of boxing, lacks precision and specificity. The complete disorganization of personality implicit in “dementia” does not occur in all presumed victims of this disorder. Some manifest other psychic disturbances as well as neurologic symptoms. To sharpen accuracy, Critchley suggested the term “chronic progressive traumatic encephalopathy of boxers,” and, more recently, Johnson proposed that the word “progressive” be omitted from the new title, since progression is not an invariable characteristic of the syndrome. Clearly, whatever the present or future designation, the term “dementia pugilistica” has become obsolete.

Having thus established on the basis of recent studies that the ex-boxer’s encephalopathy is a distinct entity, not uncommon among professional fighters, can we be sure that the condition is not an anachronism, a relic of the past? After all, the 15

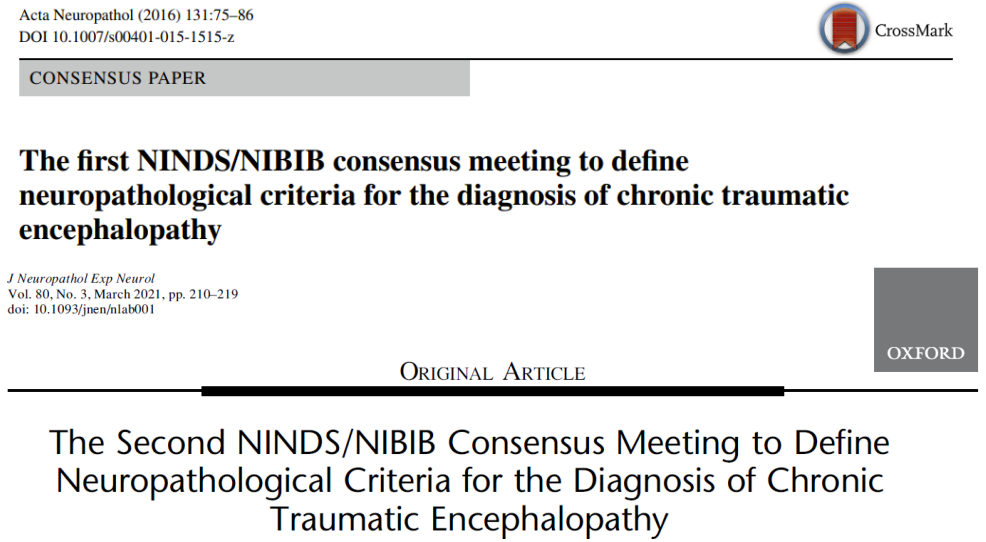
JAMA **1969**;210(12):2272

Point #2 – 21st century CTE is a AUTOPSIA post-mortem finding (CTE neuropathologic change, CTE-NC) CAMBIAMENTO NEUROPATOLOGICO

- No clinical disease has been elucidated
- CTE-NC has no established clinical correlates

(2016) “P-tau aggregates in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci”

(2021) “P-tau aggregates in neurons, with or without thorn-shaped A FORMA DI SPINA astrocytes, at the depth of a cortical sulcus around a small blood vessel, deep in the parenchyma, and not restricted to the subpial SUBPIALE and superficial region of the sulcus.”


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

CrossMark

CONSENSUS PAPER

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

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

OXFORD

ORIGINAL ARTICLE

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

Point #3 – CTE-NC ENCEFALOPATIA TRAUMATICA CRONICA CON CAMBIAMENTO NEUROPATOLOGICO is a research entity

J Neuropathol Exp Neurol
Vol. 80, No. 3, March 2021, pp. 210–219
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OXFORD

ORIGINAL ARTICLE

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

to a strict definition of "pathognomonic CTE lesion." The group endorsed a single pathognomonic lesion in the cortex as the minimum threshold for CTE. The group also endorsed the

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Point #4 – Reseachers struggle to separate CTE-NC from aging (normal variation)

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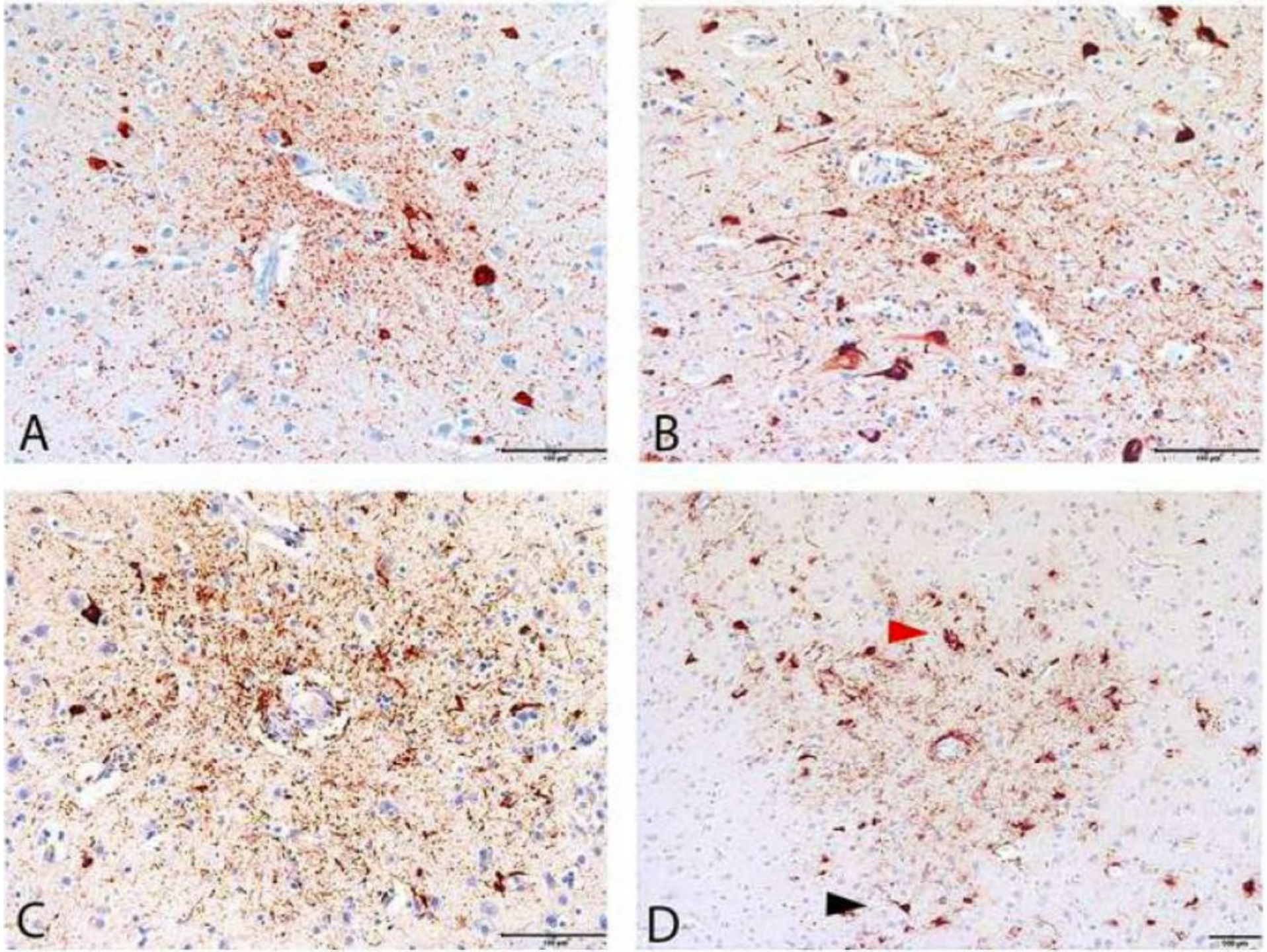
CTE (19, 20, 45–47). Distinguishing CTE from concomitant neurodegenerative and aging-related pathologies represents a topic of interest for future studies, and the consensus committee makes no assertions regarding CTE in the presence of AD or other neurodegenerative disorders at this time. Additional

Page 216


A
B
C
D

- Example, astrocytic tau
  - Involves cerebral cortex
  - Sulcal depths, around small blood vessels
  - Lacks a clinical correlate

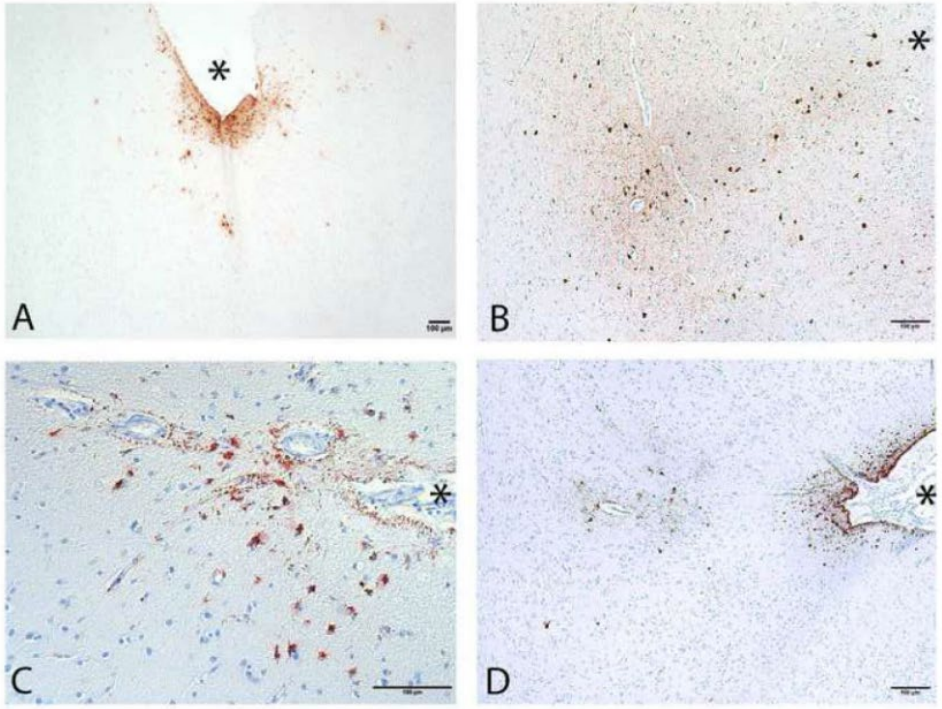
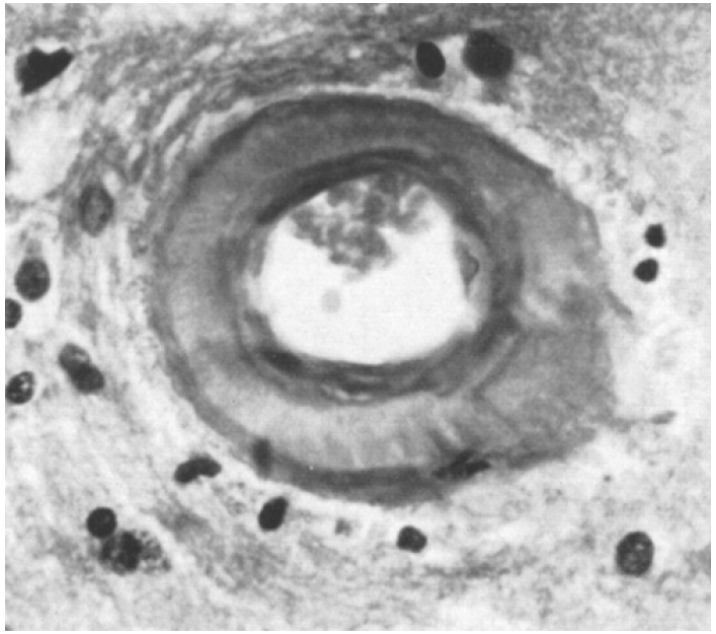


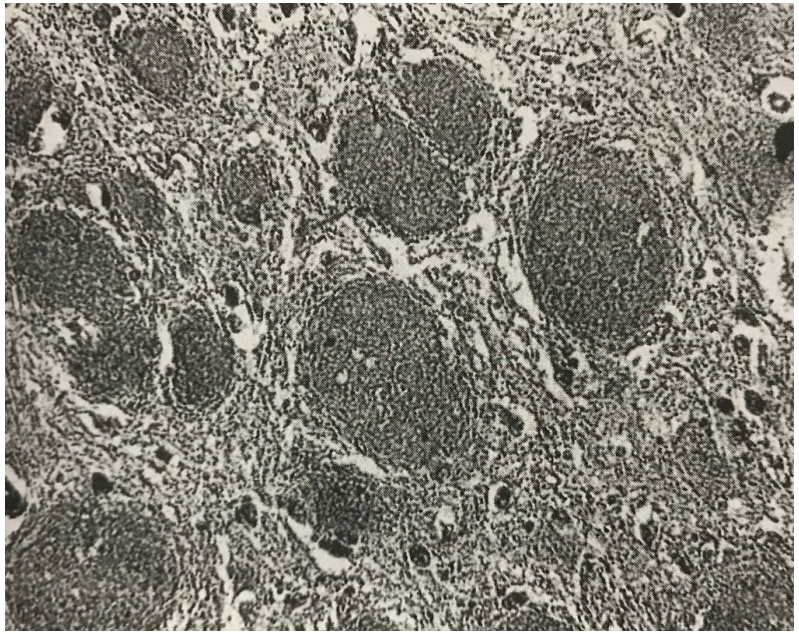
FIGURE 2. ARTAG and CTE p-tau pathology immunolabeled by the anti-phosphorylated tau antibody AT8. **(A)** Subpial ARTAG with superficial astrocytic p-tau pathology, not diagnostic of CTE. **(B)** CTE focus at depth of the sulcus. **(C)** Subpial ARTAG. **(D)** CTE focus at sulcal depth in addition to subpial ARTAG. (Sulcal depths indicated by asterisks; scale bars: 100 μm).

Point #4 – CTE-NC occurs in people with no contact sport or TBI history

- Reviewed in Iverson et al. Brain 2019;142(12):3672-3693
- Bieniek et al. Brain Pathology 2020;30:63-74
  - Basketball – 5.4% with CTE-NC
  - Baseball – 7.8% with CTE-NC
  - Football – 7.9% with CTE-NC
  - Athletes overall – 5%
  - No contact sport – 1.3%
  - “Contact sport” was not associated with any adverse neurological or mental health outcome

Point #5 – Detailed clinicopathological correlations often reveal known conditions (not CTE)

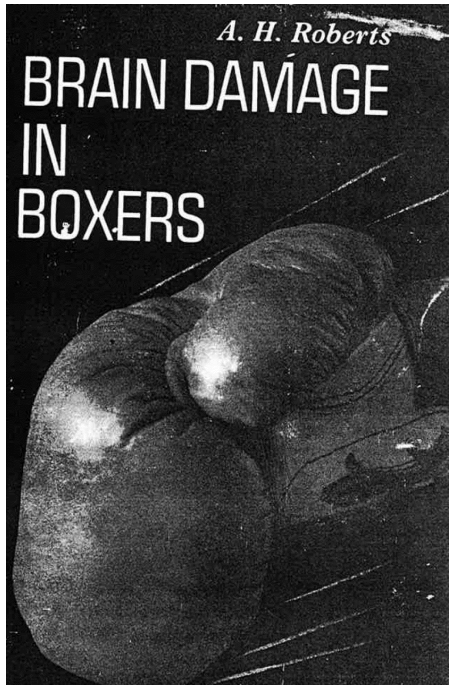




Brandenberg W, Hallervorden J. Dementia pugilistica mit anatomischem Befund. *Arch F Path Anat* 1954;325:680-709

Early onset Alzheimer's disease, probable *PS1* mutation?*

*Castellani R, Perry G. Dementia Pugilistica Revisited. J Alzheimer Dis 2017;60:1209-1221



"…it would appear that the kind of progression indistinguishable from Alzheimer's disease, described in two of the fourteen neuropathological studies so far…must be extremely uncommon. So much so, that the question of the **fortuitous occurrence in boxers of Alzheimer's disease** in these two cases cannot be entirely ignored."

Roberts A. Brain Damage in Boxers. London: Pitman Medical and Scientific Publishing Co. LTD, 1969.

Neubuerger et al, 1959 – Frontotemporal lobar degeneration

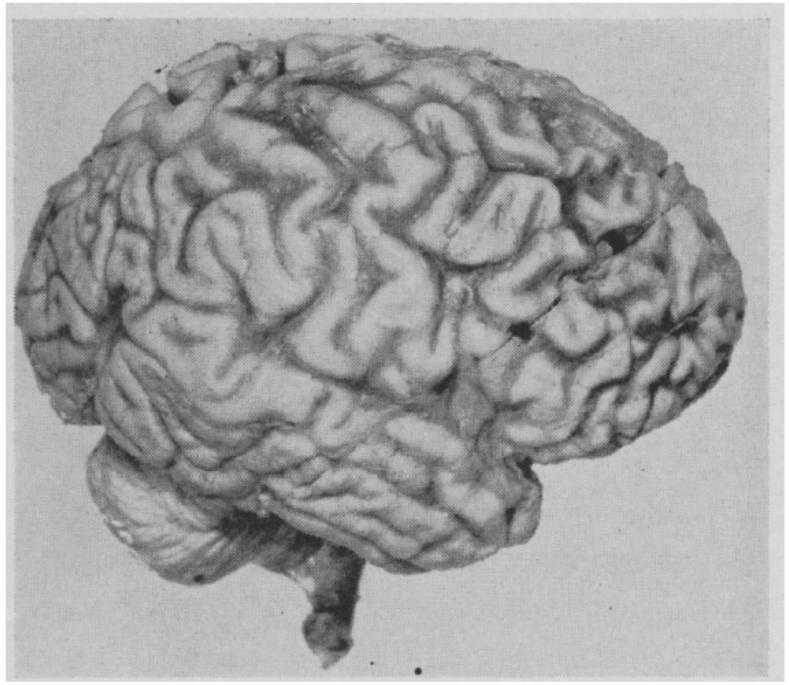
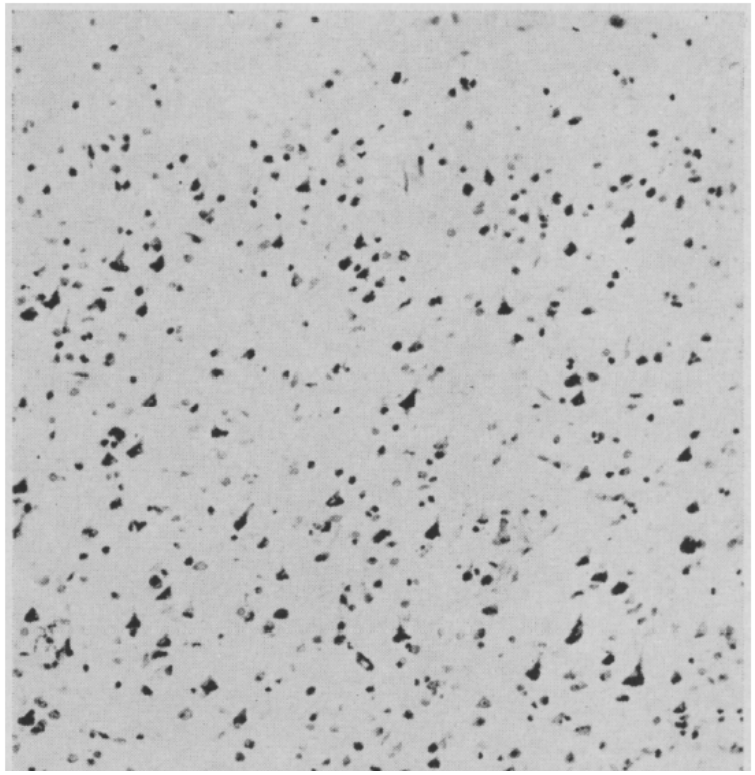


Fig. 2 (Case 2).—Right cerebral hemisphere, showing atrophy, especially of frontal lobe.



Frontal cortex neuronal loss without NFT - today this is called frontotemporal lobar degeneration or frontotemporal dementia

Corsellis et al, 1973

- 15 cases
  - 5 with other diseases (including AD, LBD, PSP)
  - 3 with no findings
  - 7/15 with CTE (20th century version)
- Four changes emphasized
  - Septal abnormalities
  - Cerebellar tonsillar sclerosis
  - Substantia nigra neuron loss
  - Neurofibrillary tangles

*Acta Neuropathologica (2018) 136:973–974

The aftermath of boxing[1]

J. A. N. CORSELLIS, C. J. BRUTON, AND DOROTHY FREEMAN-BROWNE[2]

From the Department of Neuropathology, Runwell Hospital, Wickford, Essex

SYNOPSIS The brains of **15** retired boxers have been studied and the lives of the men concerned have been investigated in retrospect. A characteristic pattern of cerebral change has been identified which appears not only to be a result of the boxing but also to underlie many features of the punch-drunk syndrome.

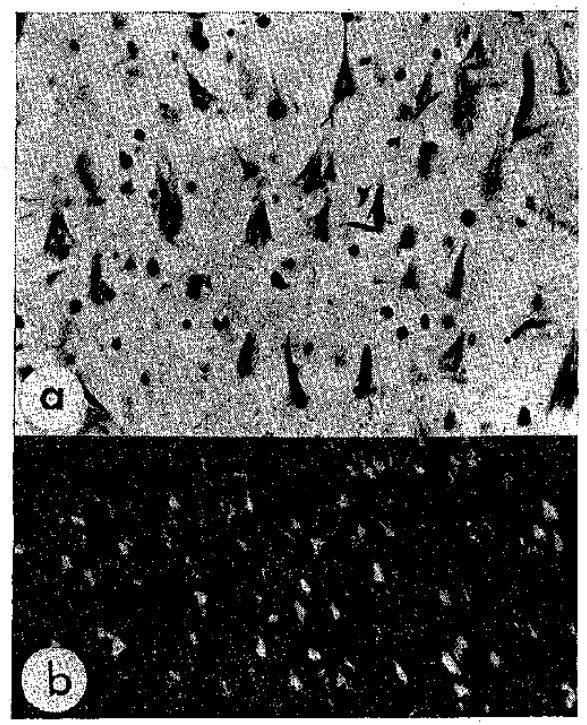
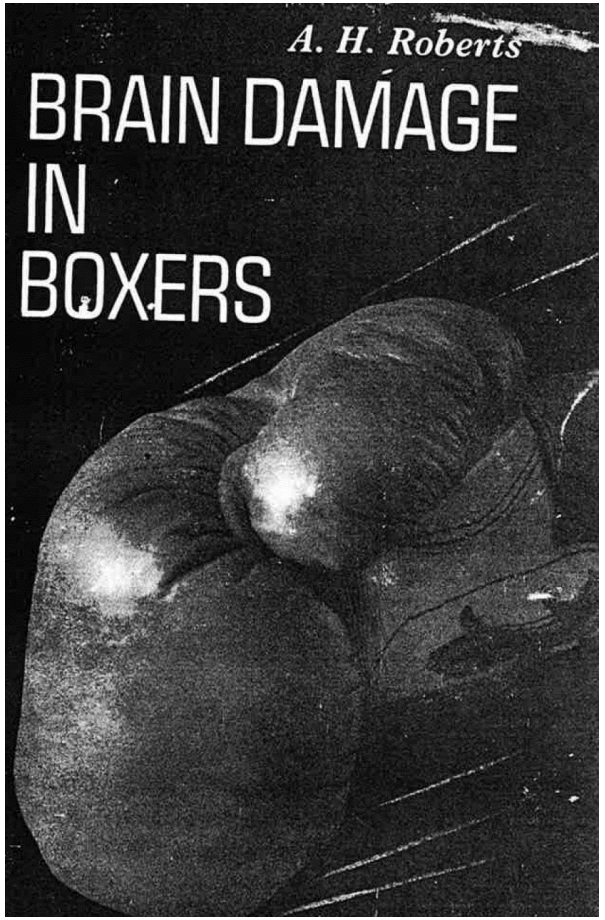


FIG. 7 a. *Case 2. Alzheimer's neurofibrillary tangles affecting large numbers of neurons in the fusiform gyrus. von Braunmühl,* ×240. b. *Congo red stain under polarized light showing the intensity of the neurofibrillary change in the medial temporal cortex of the same case,* ×100.

77 year old, 700 fights

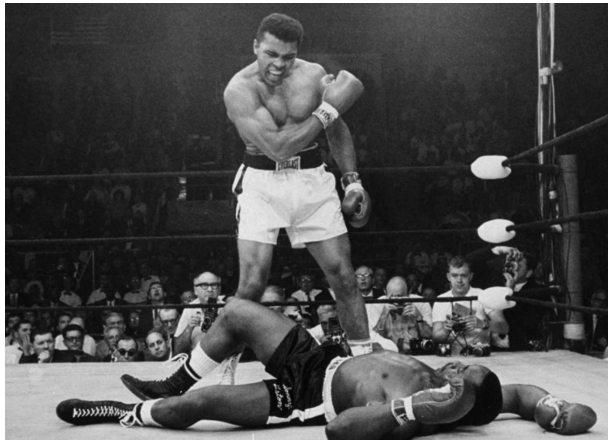
Neuropathology of 20th century boxers

- 37 cases with pathology
  - About 2/3's were either misdiagnoses or had nonspecific or indecipherable findings
  - For the 1/3 of cases consistent with CTE
    - *Neurological* signs at or prior to retirement
    - Co-morbid vascular disease, alcoholism, non-sport TBI
    - Survival for decades following boxing
    - All from early 20th century



*All cases referred to as "neuropathologically verified"
(J Neuropathol Exp Neurol 2009;68(7): 7090-735)

Point #6 – Are anecdotal cases unduly persuasive?



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Viewpoint

ONLINE FIRST

October 24, 2022

Muhammad Ali and Young-Onset Idiopathic Parkinson Disease—The Missing Evidence

Michael S. Okun, MD[1,4]; Helen S. Mayberg, MD[2]; Mahlon R. DeLong, MD[3]

» Author Affiliations

JAMA Neurol. Published online October 24, 2022. doi:10.1001/jamaneurol.2022.3584

SPECIAL REPORT

Chronic Traumatic Encephalopathy in a National Football League Player

OBJECTIVE: We present the results of the autopsy of a retired professional football player that revealed neuropathological changes consistent with long-term repetitive concussive brain injury. This case draws attention to the need for further studies in the cohort of retired National Football League players to elucidate the neuropathological sequelae of repeated mild traumatic brain injury in professional football.

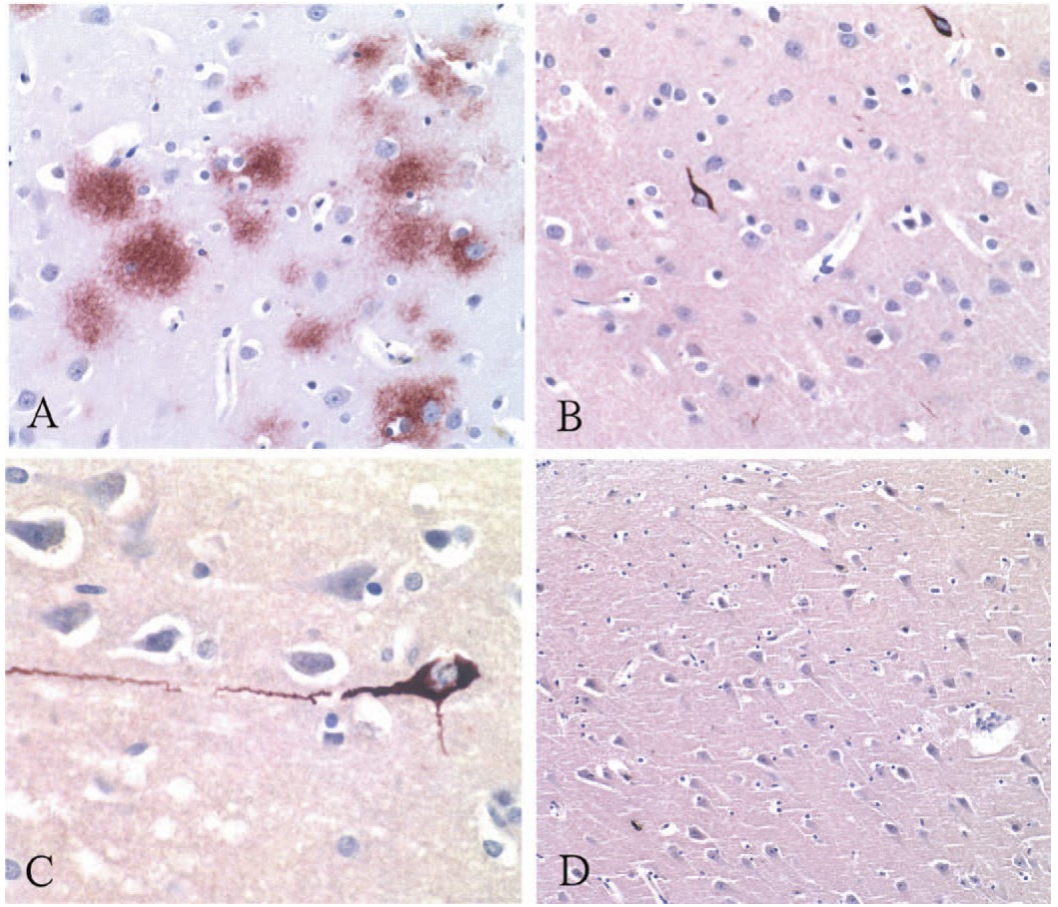
METHODS: The patient's premortem medical history included symptoms of cognitive impairment, a mood disorder, and parkinsonian symptoms. There was no family history of Alzheimer's disease or any other head trauma outside football. A complete autopsy with a comprehensive neuropathological examination was performed on the retired National Football League player approximately 12 years after retirement. He died suddenly as a result of coronary atherosclerotic disease. Studies included determination of apolipoprotein E genotype.

RESULTS: Autopsy confirmed the presence of coronary atherosclerotic disease with dilated cardiomyopathy. The brain demonstrated no cortical atrophy, cortical contusion, hemorrhage, or infarcts. The substantia nigra revealed mild pallor with mild dropout of pigmented neurons. There was mild neuronal dropout in the frontal, parietal, and temporal neocortex. Chronic traumatic encephalopathy was evident with many diffuse amyloid plaques as well as sparse neurofibrillary tangles and τ-positive neuritic threads in neocortical areas. There were no neurofibrillary tangles or neuropil threads in the hippocampus or entorhinal cortex. Lewy bodies were absent. The apolipoprotein E genotype was E3/E3.

CONCLUSION: This case highlights potential long-term neurodegenerative outcomes in retired professional National Football League players subjected to repeated mild traumatic brain injury. The prevalence and pathoetiological mechanisms of these possible adverse long-term outcomes and their relation to duration of years of playing football have not been sufficiently studied. We recommend comprehensive clinical and forensic approaches to understand and further elucidate this emergent professional sport hazard.

KEY WORDS: Chronic traumatic encephalopathy, National Football League, Retired professional football players

Neurosurgery 57:128-134, 2005 DOI: 10.1227/01.NEU.0000163407.92769.ED www.neurosurgery-online.com



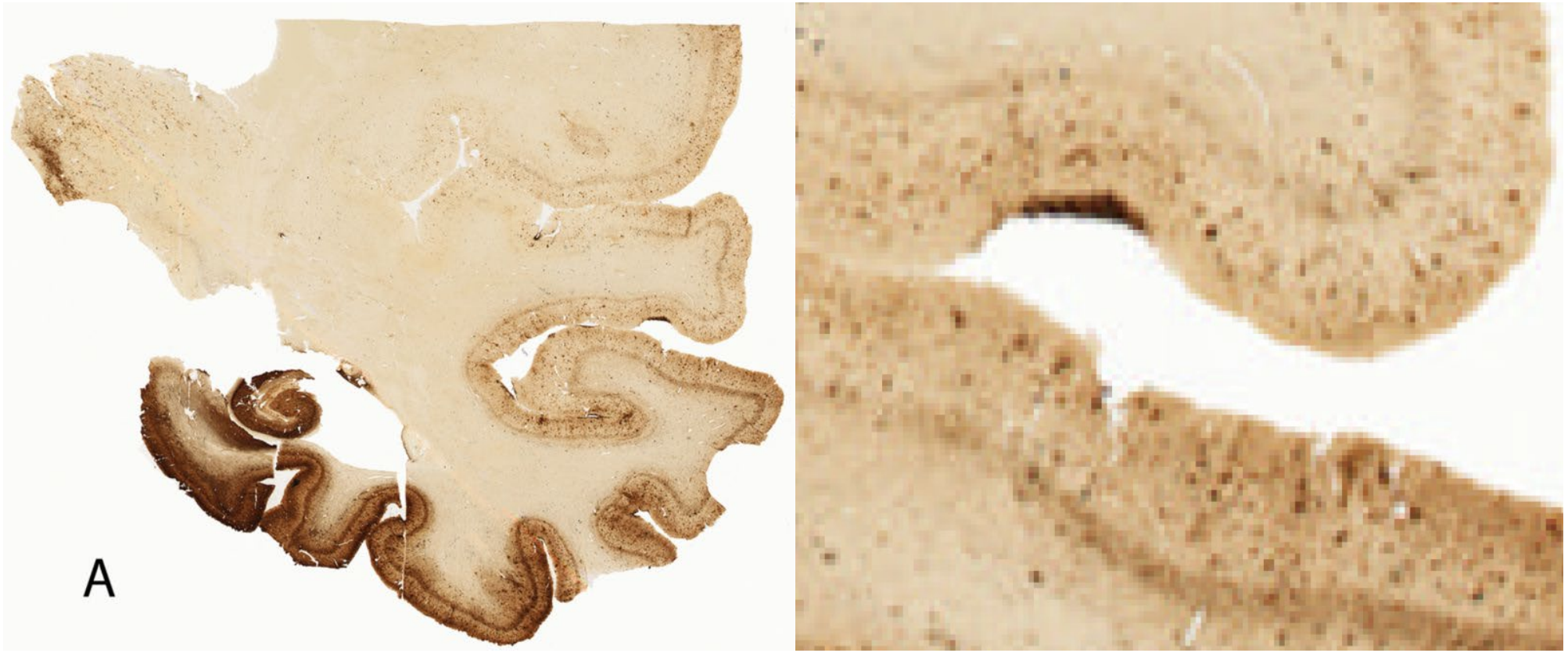
"CTE" described in an NFL athlete in 2005

J Neuropathol Exp Neurol

Vol. 68, No. 7
July 2009
pp. 709–735

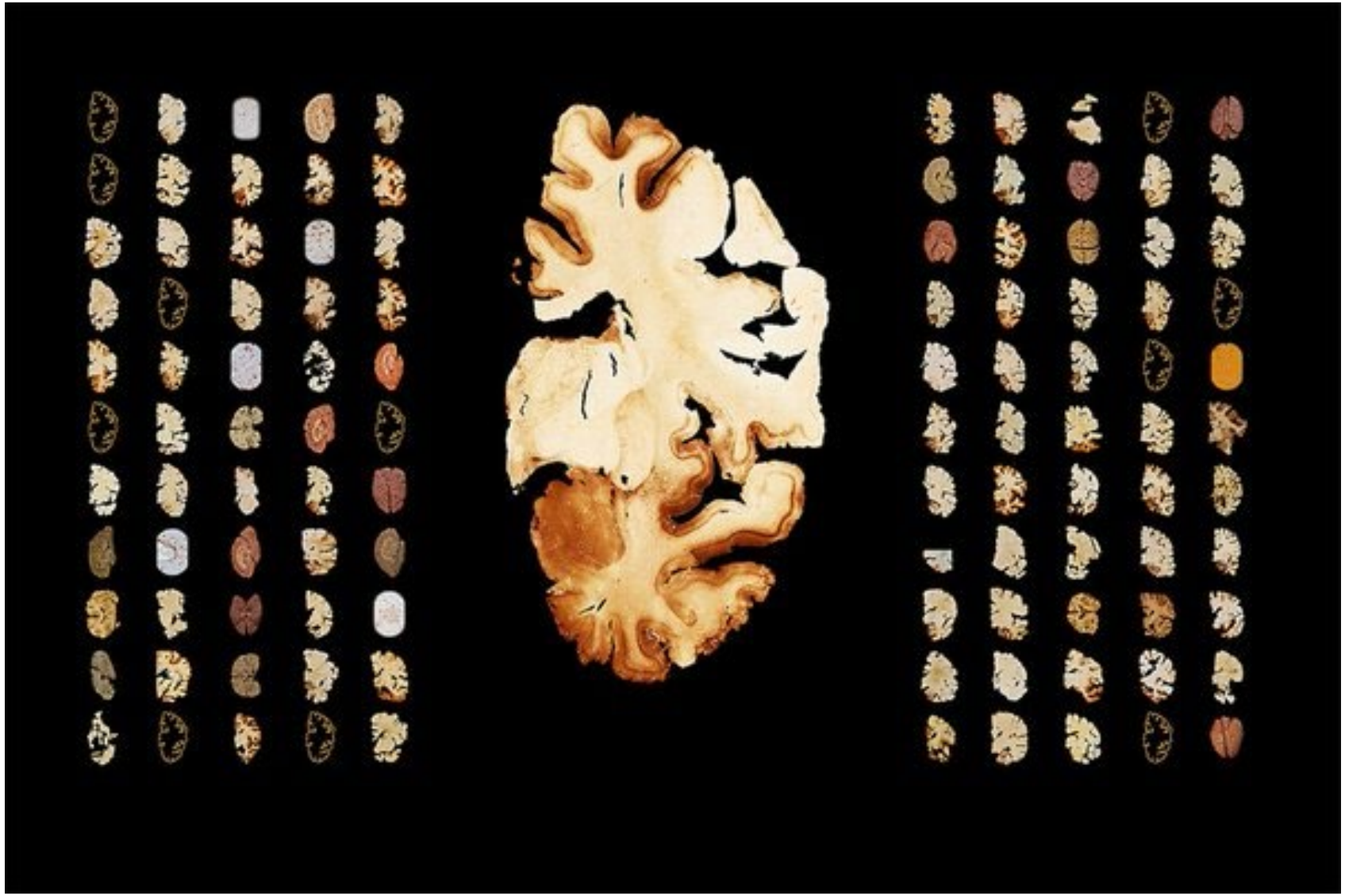
REVIEW ARTICLE

Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury



"Boxers with long-standing CTE are frequently demented (46%) and may be misdiagnosed clinically as AD (47), as occurred in Cases 2 and 3."

The New York Times | SPORTS



Point #7 – CTE as a “neurodegenerative disorder”

INTRODUCTION

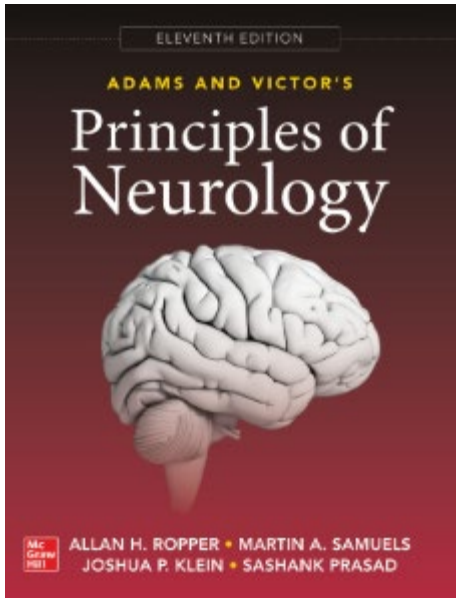
Chronic traumatic encephalopathy (CTE) is a debilitating and enigmatic neurodegenerative disorder associated with

Chronic traumatic encephalopathy (CTE) is a fatal neurodegenerative disease that is closely associated with traumatic brain injury (TBI).[1] Although TBI is typically

Chronic traumatic encephalopathy (CTE) is a progressive neurodegeneration associated with repetitive head trauma.[1-8] In 2013, based on a report of the

“The principle behind what is currently called degenerative disease of the nervous system is a pattern of **progressive neuronal loss** in functionally related cells such as those of the basal ganglia, cerebellum, or cerebral cortex, and so on. These diseases can be identified clinically by a **more or less smoothly progressive loss of neurologic function** referable to the affected system, for example, parkinsonian features, ataxia, or dementia…”

Chapter 38 of Adams and Victor’s Principles of Neurology, page 1082



Cases were often not progressive

- Martland, 1928 - ‘Many cases remain mild in nature and do not progress beyond this point’ (page 1103).
- Parker, 1934 - ‘It is thus possible that a pugilist may be only mildly affected, and may continue to fight to the end of his career, or he may be so disabled that he ultimately has to quit boxing and yet gets no worse in after life’…‘after the patient’s fighting career was over his condition remained stationary or perhaps improved slightly’
- Carroll, 1936 - ‘When these symptoms have once appeared, they will not only persist, but may progress for a period of a year or so when they will naturally become stationary. Thus, punch-drunk is a self-limited rather than a progressive encephalopathy’
- Bowman and Blau, 1940 - “When the symptoms of punch drunk have once appeared, they are persistent and usually progress for a period of a year or more, when the condition usually becomes stationary.”
- Roberts, 1969 - There is a good deal of evidence in the present study to suggest that in most cases the condition remains stationary when the individual has stopped boxing, and indeed there are excellent independent accounts for a few of undoubted improvement after retirement’

Neurodegenerative diseases?

- 20th Century CTE in boxers
  - Progression in boxers was variable and limited
  - Smoothly progressive disease to full blown dementia raised the issue of canonical disease.
- 21th Century CTE-NC
  - Lacks a clinical correlate
  - Most closely aligned with incidental, age-related changes

Of note…

- There are no known environmental causes for Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, or frontotemporal dementia
- All have genetic susceptibilities, *including pathogenic mutations* in some cases
- In general, likelihood of genetic *cause/*pathogenic mutation increases with early onset disease (up to 44% for ALS in one study*)
- Others are strictly genetic – Huntington's disease, spinocerebellar ataxias

National Institute of Neurological Disorders and Stroke

- From the website article entitled '**Focus on Traumatic Brain Injury Research.'**

- **'Chronic traumatic encephalopathy (CTE)** is a delayed neurodegenerative disorder that was initially identified in postmortem brains and, research-to-date suggests, is caused in part by repeated traumatic brain injuries. NINDS supports ongoing efforts to refine diagnostic criteria for both CTE (postmortem diagnosis) and the associated Traumatic Encephalopathy Syndrome (TES; diagnosis in the living).'

- https://www.ninds.nih.gov/current-research/focus-disorders/focus-traumatic-brain-injury-research

The path forward

- Evidence-based medicine
- Transparency in science