Chronic Traumatic Encephalopathy

Provider and Parent Essentials

Concussion Global Cast

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Chronic Traumatic Encephaly (CTE) Working Definition

- **Chronic traumatic encephalopathy is described as a progressive neurodegenerative process associated with one or multiple blows to the head characterized by changes in mood, cognition, and behavioral functioning.**

What's all the fuss?

- Concussion in general has created a media and societal storm.
- CTE is the new buzzword, and typically comes up in every concussion evaluation we perform.
- Internet search results convince parents of the worse case scenarios.
- Scientific journals have published that as high as 17% of athletes with recurrent head injuries will develop CTE.
- To date there are no uniformly accepted definitions or classification systems.
- Will we ever be able to clinically diagnose it?
- Does it actually exist?

Original Case

- **38 year old male retired boxer.**
- **Fought professionally for 7 years since age 16.**
- **History of 2 knockouts (Once >1hr w LOC)**
- **Presented with:**
  - Tremors
  - Gait ataxia
  - Pyramidal tract dysfunction
  - Normal Intelligence
- **Examination was 20 years after sx onset.**
- **Diagnosed with “Paralysis Agitans” (Parkinson’s Disease)**
- ***A promoter had described the “Punch-Drunk” state to a medical examiner who eventually examined 5 of 23.**

Early Studies

- **Roberts et al studied 250 boxers from cohort of 16,781 UK boxers registered between 1929-1955.**
  - CNS lesions present in 37 cases (17%)
  - Severity of the condition directly related to the length of the boxer's career and the # of bouts they had participated in.
  - Many subjects fought in bare knuckles era of late 1800's.
- **Lack of certainty in actual diagnosis published by McCrory et al.**
  - Limitations of studies in 1960's (pneumoencephalograms)
  - Mostly retrospective studies looking at acute symptoms.
  - Applicability to modern day boxers speculated to be low as many rule changes and precautions have taken place.

What is the Tau protein?

- **Tau is a normal protein associated with microtubules in axons.**
- **Here it is NOT toxic and NOT related to neurofibrillary pathology.**
- **Brain trauma causes tau to dissociate likely via mechanisms including:**
  - Intracelluler Ca influx
  - Glutamate receptor mediated excitotoxicity
  - Kinase activation mediating hyperphosphorylation of intracellular tau.
- **Speculated that once phosphorylated, misfolded, aggregated, and cleaved it is more highly neurotoxic.**
- **Also thought to spread and accumulate via multiple routes, increased by multiple traumatic episodes.**

Elevated Tau Not Exclusive To CTE

Other Conditions with high levels of cerebral tau aggregation

- **Alzeimers Disease**
- **Argyrophilic grain dementia**
- **Frontotemporal dementia**
- **Corticobasal degeneration**
- **Creutzfeldt-Jakob disease**
- **Down syndrome**
- **Ganglion cell tumors**
  - (gangliоglioma and gangliocytoma)
- **Gerstmann-Straussler-Scheinker disease**
- **PKAN disease**
- **Inclusion body myositis**
- **Lewy body dementia**
- **Moderate-severe traumatic brain injury**

Multiple system atrophy

Normal aging

Myotonic dystrophy

Neuronal lipofuscinosis

Parkinson disease

Parkinson-dementia complex of Guam

Pick disease

Postencephalitic Parkinsonism

Presenile dementia with tangles and calcifications

Prion protein cerebral amyloid angiopathy

Progressive supranuclear palsy

Subacute sclerosing panencephalitis

Tangle-only dementia

Tuberous sclerosis

Clinical Symptomatology

- **Comprises a broad set of clinical signs and symptoms including:**
  - Neuropsychiatric changes
  - Behavioral changes
    - Depression
    - Mood lability
    - Agitation
    - Impulsivity
    - Aggression
  - Parkinsonism
  - Dysarthria
  - Gait abnormalities
  - Cognitive deficits
    - Memory
    - Attention
    - Executive functioning
    - Language.

Proposed Four Stages of CTE (McKee et al, 2013)

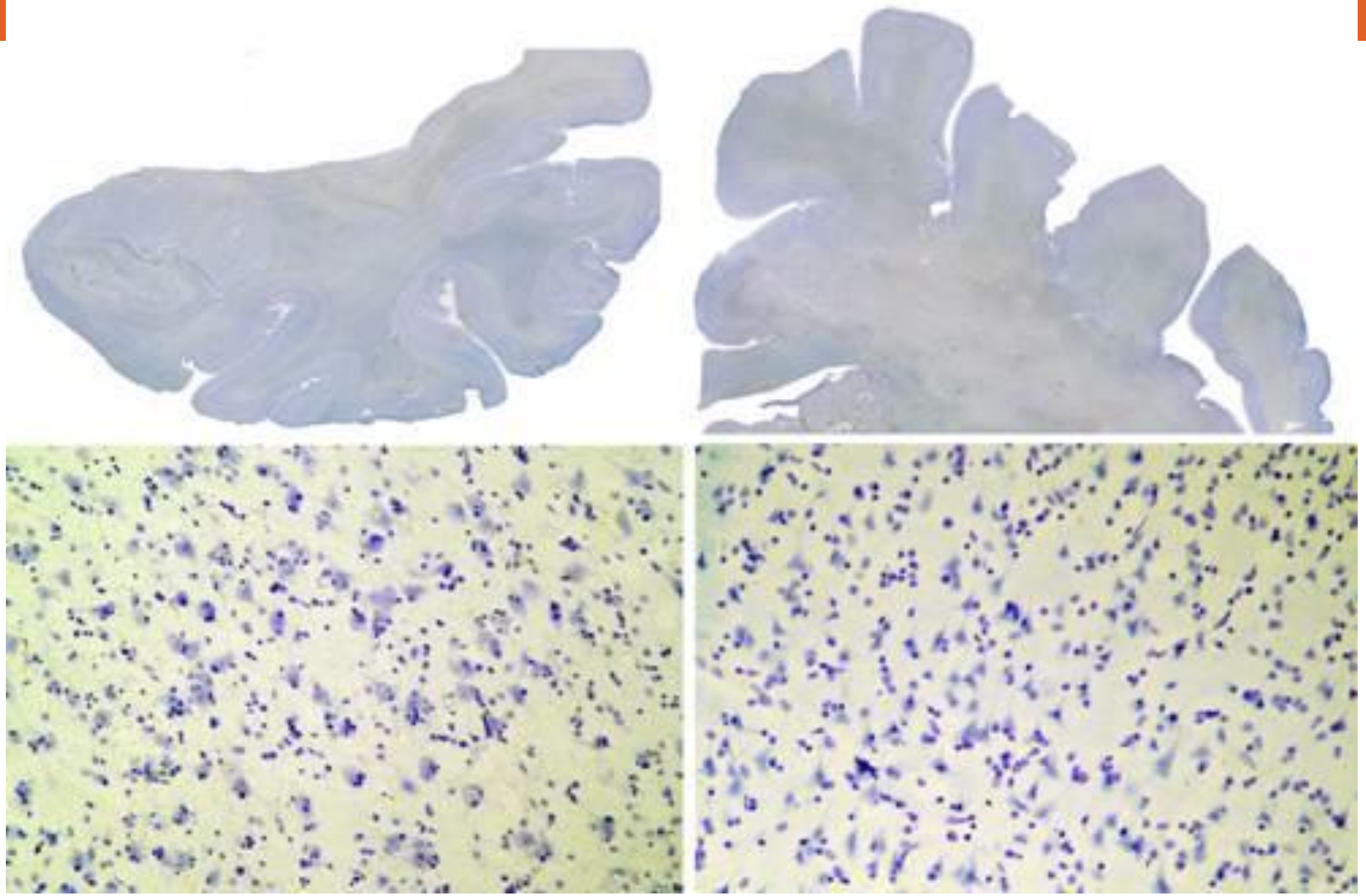
Reference only…Don't try to read in 10 seconds!

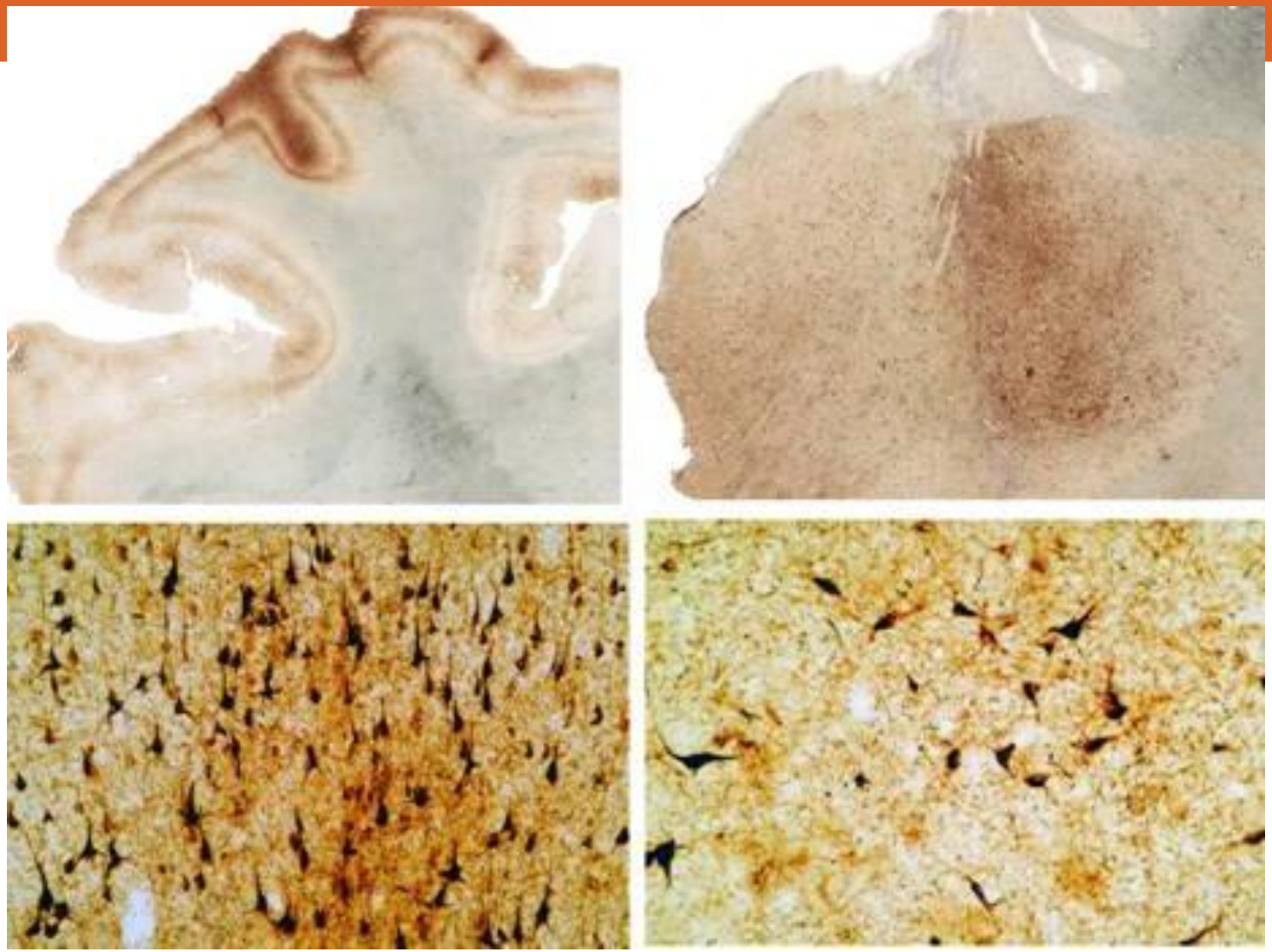
Stage 1 - Perivascular p-tau neurofibrillary tangles in focal epicenters at the depths of the sulci in the superior, superior lateral or inferior frontal cortex.

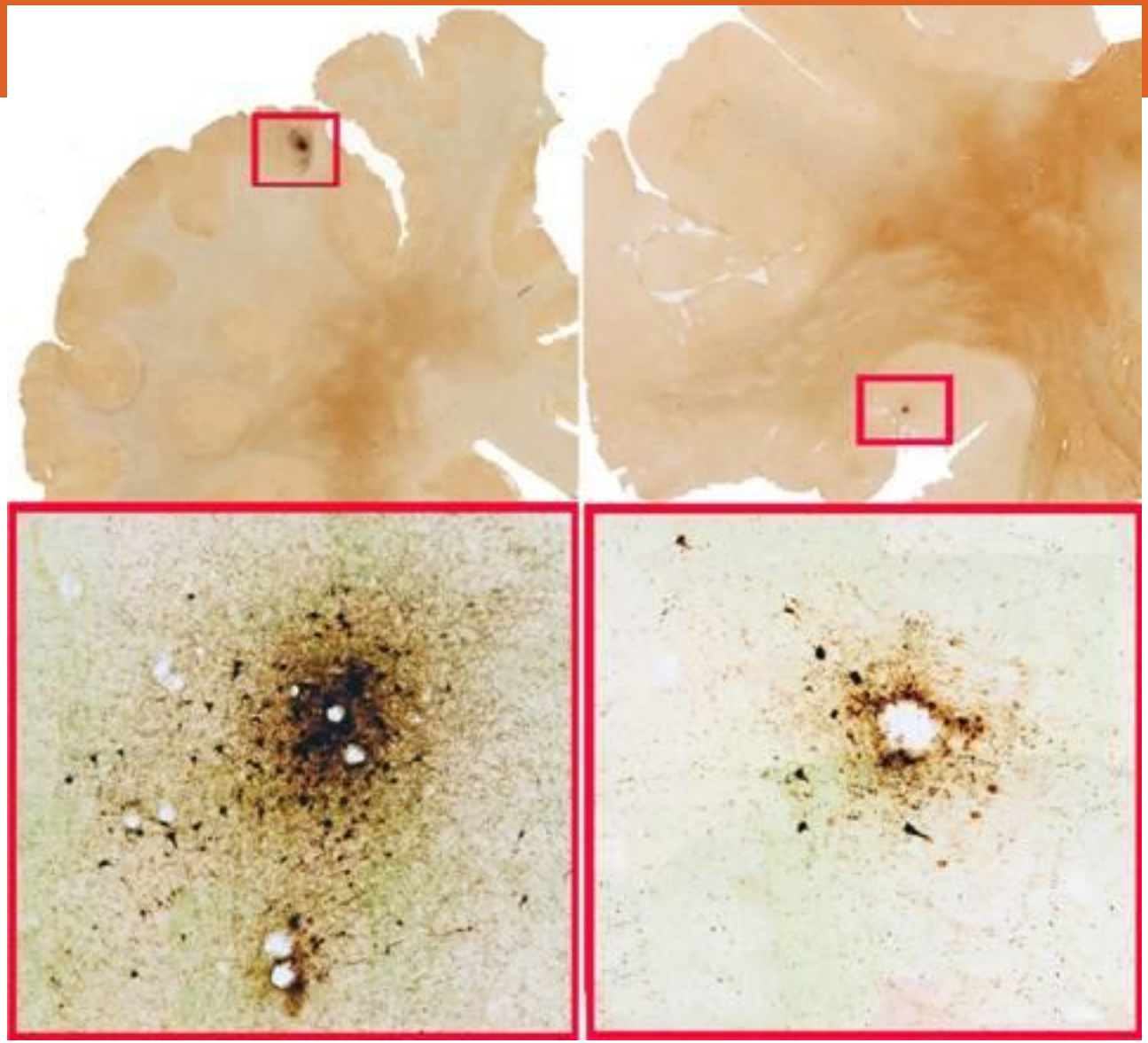
Stage 2 - NF tangles found in superficial cortical layers adjacent to focal epicenters and in the nucleus Basalis of Meynert and locus coeruleus.

Stage 3 - Macroscopic evidence of mild cerebral atrophy, septal abnormalities, ventricular dilation, a sharply concave contour of third ventricle and depigmentation of the locus coeruleus and substantia nigra. Dense p-tau pathology in medial temporal lobe structures (hippocampus, entorhinal cortex and amygdala) and widespread regions of the frontal, septal, temporal, parietal and insular cortices, diencephalon, brainstem and spinal cord.

Stage 4 - Further cerebral, medial temporal lobe, hypothalamic, thalamic and mammillary body atrophy, septal abnormalities, ventricular dilation and pallor of the substantia nigra and locus coeruleus. Microscopically, p-tau pathology involved widespread regions of the neuraxis including white matter, with prominent neuronal loss and gliosis of the cerebral cortex and hippocampal sclerosis.







Corresponding Clinical Manifestations

- **Stage 1**
  - HA
  - Loss of attention and concentration.
- **Stage 2**
  - Depression, mood swings, explosivity, and short-term memory loss.
- **Stage 3**
  - Cognitive impairment with memory loss, executive dysfunction, and visuospatial abnormalities.
- **Stage 4**
  - Uniformly demented, profound short-term memory loss. Most also showed paranoia, depression, impulsivity and visuospatial abnormalities.

Tau Sensitive… Not Specific…

- **Whether the presence of postmortem hyperphosphorylated tau protein alone signifies CTE is debatable.**
- **Abnormal tau protein formation may be sensitive but not specific for CTE.**
- **Hyperphosphorylated tau protein may be also be present in many other neurodegenerative diseases**
  - Even in substance abuse and normal aging.
- **Many comorbitities exist and difficult (if not impossible) to control for these co-variants.**

When will I get it?

- **As stated, confirmation will come post mortem.**
- **CTE has been described as a syndrome that manifests within 1 to 2 decades after retirement from contact or collision sports.**
- **McKee et al and Omalu et al stated that CTE begins 8 to 10 years after retirement.**
- **McCrory reported that symptoms may manifest as late as 10 to 20 years after retirement.**
- **Studies have stated a total of fewer than 7 potential cases of CTE in high school athletes.**
  - Evidence of tauopathy… But questionable clinical manifestations.

But I only had one concussion!?

- **Depending on which camp you subscribe to:**
  - McKee's group believes that a defining characteristic is multiple or recurrent injuries.
  - Omalu feels that even one traumatic injury is enough to eventually develop CTE.

Neuroimaging: Can't we see it on an MRI?

- **Maybe, but not yet. Equivocal results.**
- **Small et al (UCLA) reported that CTE may be diagnosable in vivo using FDDNP-tau marked PET scans.**
  - Found increased FDDNP binding in the amygdala and subcortical regions of 5 retired NFL players (45-73 yo) compared with controls.
  - However, elevated FDDNP signals can be seen in depressive and cognitive symptoms in normal aging.
- **Hart et al (2013) performed imaging studies and measured NP functioning in 34 retired NFL players with an average of 9.7 years of experience.**
  - DTI and fluid-attenuated inversion recovery sequences revealed white matter tract abnormalities, but the authors interpreted these results as being inconsistent with CTE.
  - The NP testing revealed no relationship between the number of years played and the level of cognitive impairment.

Does CTE actually exist?

Randolph concluded that there are:

(1) No established consensus or empirical clinical or neuropathologic criteria diagnosing CTE.

(2) No controlled epidemiologic data related to CTE.

(3) No clinical syndrome unique to CTE on the basis of recent cross-sectional, clinical studies of cognitively impaired retired professional football players.

In his discussion he raised concerns with sample sizes, lack of symptoms as a clinical syndrome, high comorbidities in the analyzed NFL cohort, and lower rates of death in these NFL players.

The wrap up!

- CTE is a a hot topic but wrapped in questions and controversy.
- Tauopathy is very real pathologic finding associated with cognitive decline and dementia.
- Personally, I believe there is likely a pathophysiologic entity that contributes to cognitive decline after recurrent head injuries.
- It is important that we educate our patients on this so that they can make an informed decision on contact and collision sport participation.
- Imperative that we develop databases on longitudinal studies and establish clinical guidelines to better identify

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