From trauma to tau: the link between traumatic brain injury and neurodegeneration

SINdem meeting
Bressanone, Italy
18-01-18

Steve Gentleman
Prof of Neuropathology
Department of Medicine
Imperial College London

Repetitive mTBI in sport

- A historical perspective
  - Boxers and dementia pugilistica
- Chronic traumatic encephalopathy (CTE)
  - The NFL story
  - Boxers, a contemporary work up
- Unanswered questions
  - ARTAG v CTE
  - Clinicopathological correlations
  - Other sports

Runwell Hospital, Essex

The aftermath of boxing

Psychological Medicine, 1973, 3, 270-303

The aftermath of boxing[1]

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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.

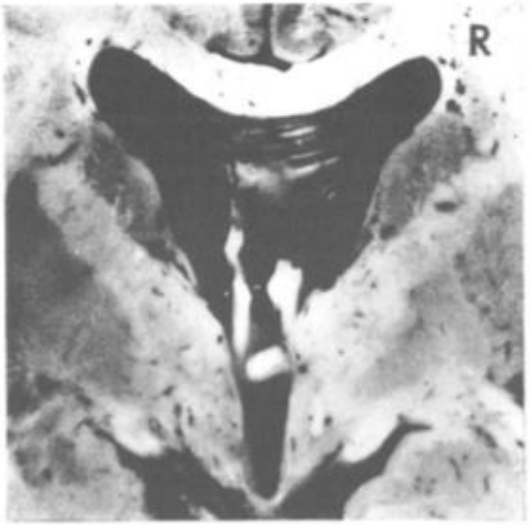


FIG. 12 *Case 6. Widely separated strands of a grossly fenestrated cavum.*

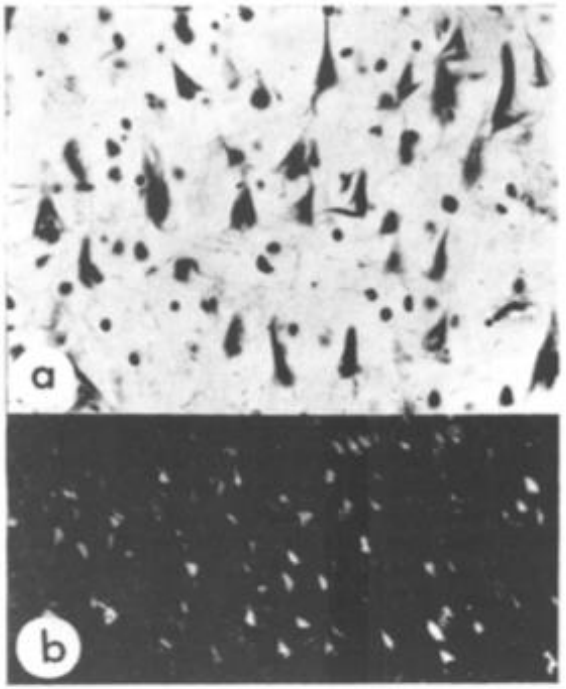


FIG. 7 a. *Case 2. Alzheimer's neurofibrillary tangles affecting large numbers of neurons in the fusiform gyrus. von Braunmühl, × 240.* b. *Congo red stain under polarized light showing the intensity of the neurofibrillary change in the medial temporal cortex of the same case, × 100.*

SCIENCE NOW DISPATCHES FROM FRONT LINES OF SCIENCE, MEDICINE, HEALTH AND THE ENVIRONMENT

Head injuries in one football season cause measurable brain damage

Dartmouth football player Garrett Waggoner, right, intercepts a Princeton pass in a game last month. A new study in Neurology finds that Dartmouth athletes who played football and ice hockey had measurable brain injuries even when they didn't suffer concussions. (Jacob Kupferman / Dartmouth College / November 23, 2013)

Chronic
Traumatic
Encephalopathy.com

doi:10.1093/brain/aws307 Brain 2012: Page 1 of 22 | 1

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,[3,10] Tsuneya Ikezu,[3,4,11] Robert Ross Reichard,[12] Benjamin L. Wolozin,[3,4,11] Andrew E. Budson,[1,3,4] Lee E. Goldstein,[3,4,12,13,14,15] Neil W. Kowall[1,3,4,5,*] and Robert C. Cantu[2,6,7,16,*]

- 85 subjects with history of repetitive mild TBI
- Athletes and military personnel (ages 17-98)
- 68 showed some degree of CTE pathology
- Some with concomitant AD, PD or FTLD

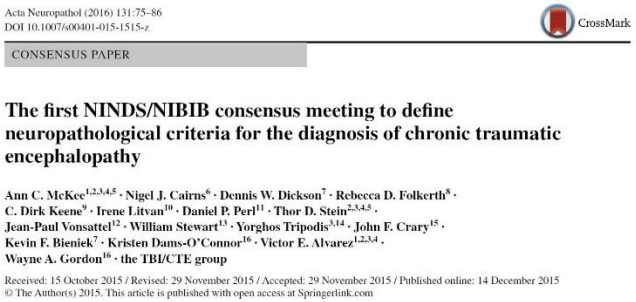
Tau pathology in AD v CTE

Table 1 Distinctions in hyperphosphorylated tau pathology between Alzheimer's disease and CTE

Pathological features	Alzheimer's disease	CTE
Tau protein		
Six isoforms	All six isoforms present	All six isoforms present[a]
3 or 4 repeat tau	3 repeat and 4 repeat tau present	3 repeat and 4 repeat tau present
Cell origin		
Neuronal	NFTs and pre-tangles	NFTs and pre-tangles
Astrocytic	Not present[b]	Prominent astrocytic tangles
Neuronal domain		
Cell body	Prominent	Prominent
Dendrite	Prominent	Prominent
Axon	Sparse	Prominent
Cell Pattern		
Perivascular	Not present	Prominent NFTs and astrocytic tangles
Foci at depths of cerebral sulci	Not present	Prominent NFTs and astrocytic tangles
Irregular, patchy cortical distribution	Not present	Prominent
Cortical laminae	NFTs predominantly in laminae III and V	NFTs predominantly in laminae II–III
Subpial astrocytic tangles	Not present	Prominent
Periventricular astrocytic tangles	Not present	Present
Distribution		
Mild pathology	Braak stages I–III: NFTs in entorhinal cortex, amygdala and hippocampus	CTE stages I–II: NFTs in focal epicentres in cerebral cortex, usually frontal lobe
Advanced pathology	Braak stages IV–VI: High density of NFTs in widespread cortical areas and medial temporal lobe, uniform distribution Low densities of NFTs in basal ganglia and brainstem; none in mammillary bodies. White matter tracts relatively uninvolved.	CTE stages III–IV: High density of NFTs in widespread cortical areas and medial temporal lobe, patchy irregular distribution High densities of NFTs in thalamus, hypothalamus, mammillary bodies, brainstem. Moderate densities of NFTs in basal ganglia, especially nucleus accumbens. Prominent p-tau pathology in white matter tracts.

Definition of CTE pathology

- Presence of:
  - (i) foci of perivascular NFT and astrocytic tangles
  - (ii) irregular cortical distribution of NFT and astrocytic tangles with a predilection for the depths of sulci
  - (iii) clusters of subpial and periventricular astrocytic tangles in the cerebral cortex, diencephalon, basal ganglia and brainstem
  - (iv) neurofibrillary tangles in the cerebral cortex located preferentially in the superficial layers.



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CONSENSUS PAPER

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

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- Research services
  - Clinical trials facility
  - Innovation and intellectual property
  - The Corsellis Collection
    - History
    - Research services
    - Tissue requests
- For patients and the public
- Business development
- Contact R&D

The Corsellis Collection is the largest brain bank in Europe and one of the largest collections of its kind in the world, comprising more than 6,000 specimens.

Started in the early 1950s by Professor John Corsellis at Runwell Hospital, the collection is now managed and maintained by WLMHT.

Our technicians maintain and develop the brain archive, as well as providing a service for researchers by processing and distributing brain specimens for research studies that have ethical approval via the Medical Research Council BRAIN UK network.

The collection contains a large number of brains from patients who had psychiatric and neurodegenerative illnesses, but also a series of brains from patients who did not have any brain disease and who therefore provide a very useful control population.

The collection has been granted a licence by the Human Tissue Authority as an archival brain collection. The collection has now linked its tissue request service with the BRAIN UK database, making it easier for researchers to request tissue for their studies.

RESULTS

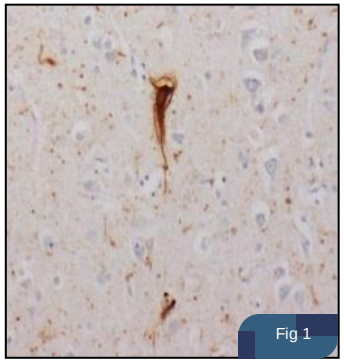
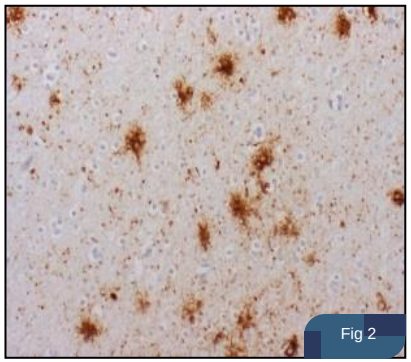


Fig 1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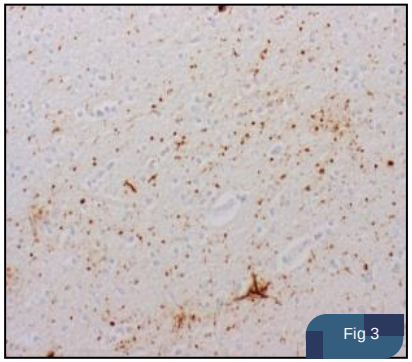
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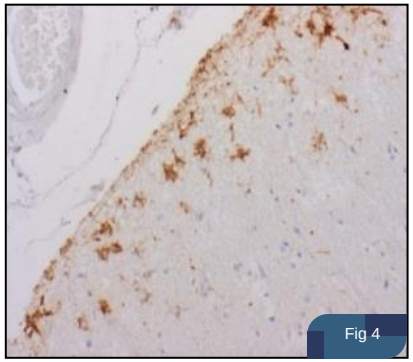
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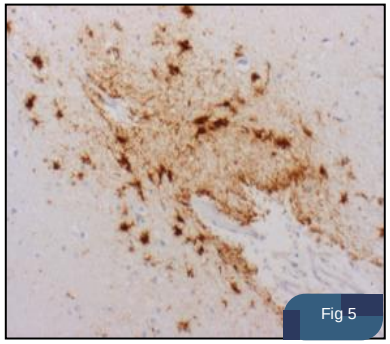
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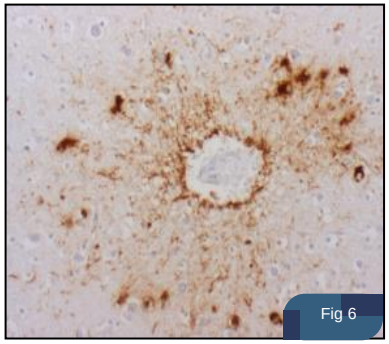
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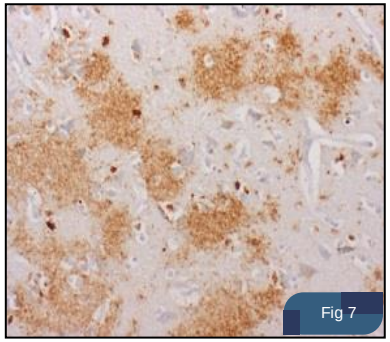
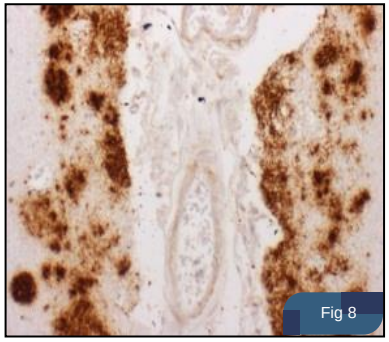


Fig 7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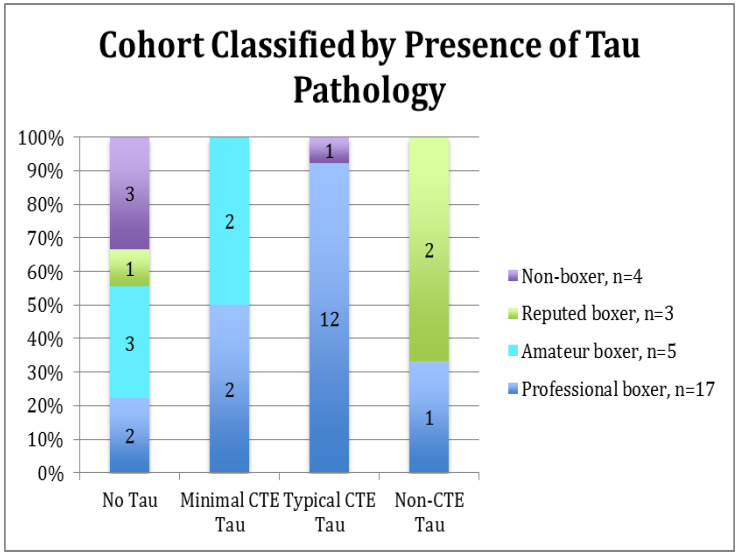
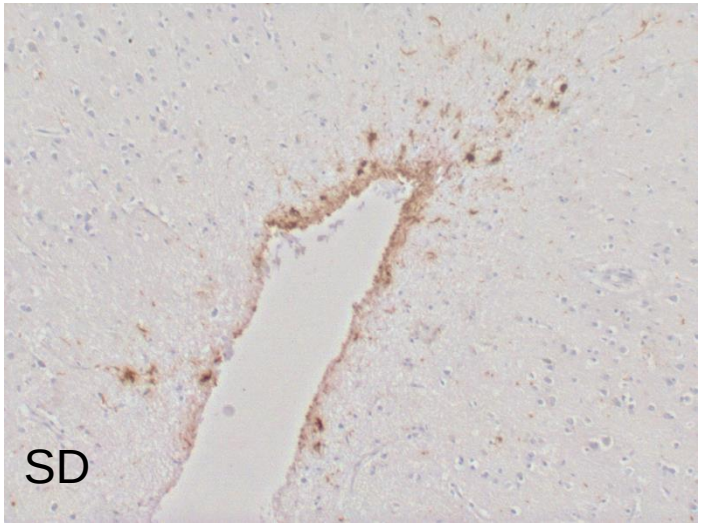
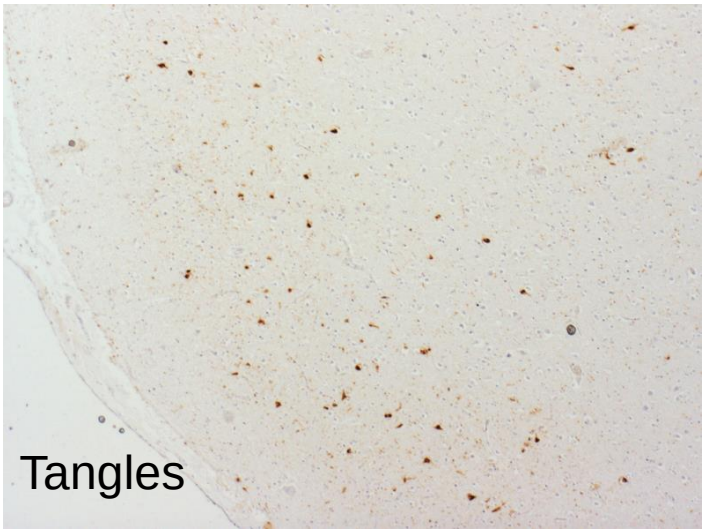
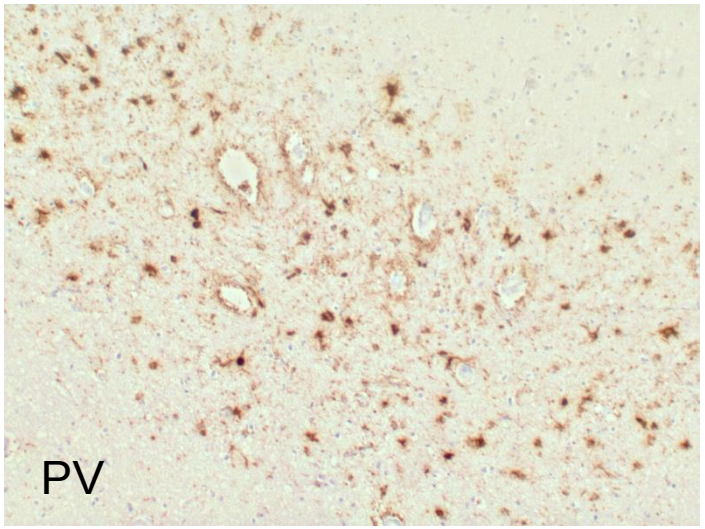


Hyperphosphorylated tau (clone AT8) immunostaining in neurofibrillary tangles (Fig 1, case 6), in astrocytes (Fig 2, case 7) and in puncta within white matter tracts (Fig 3, case 5). Foci of astrocytic tau immunostaining were seen in subpial layers (Fig 4, case 5), at the base of sulci (Fig 6, case 4) and in a perivascular distribution (Fig 6, case 14). A-beta (clone 4G8) immunostaining in diffuse plaques (Fig 7, case 21) and subpial bands (Fig 8, case 1). All photos taken with a X20 stage objective.

64-47 CTE



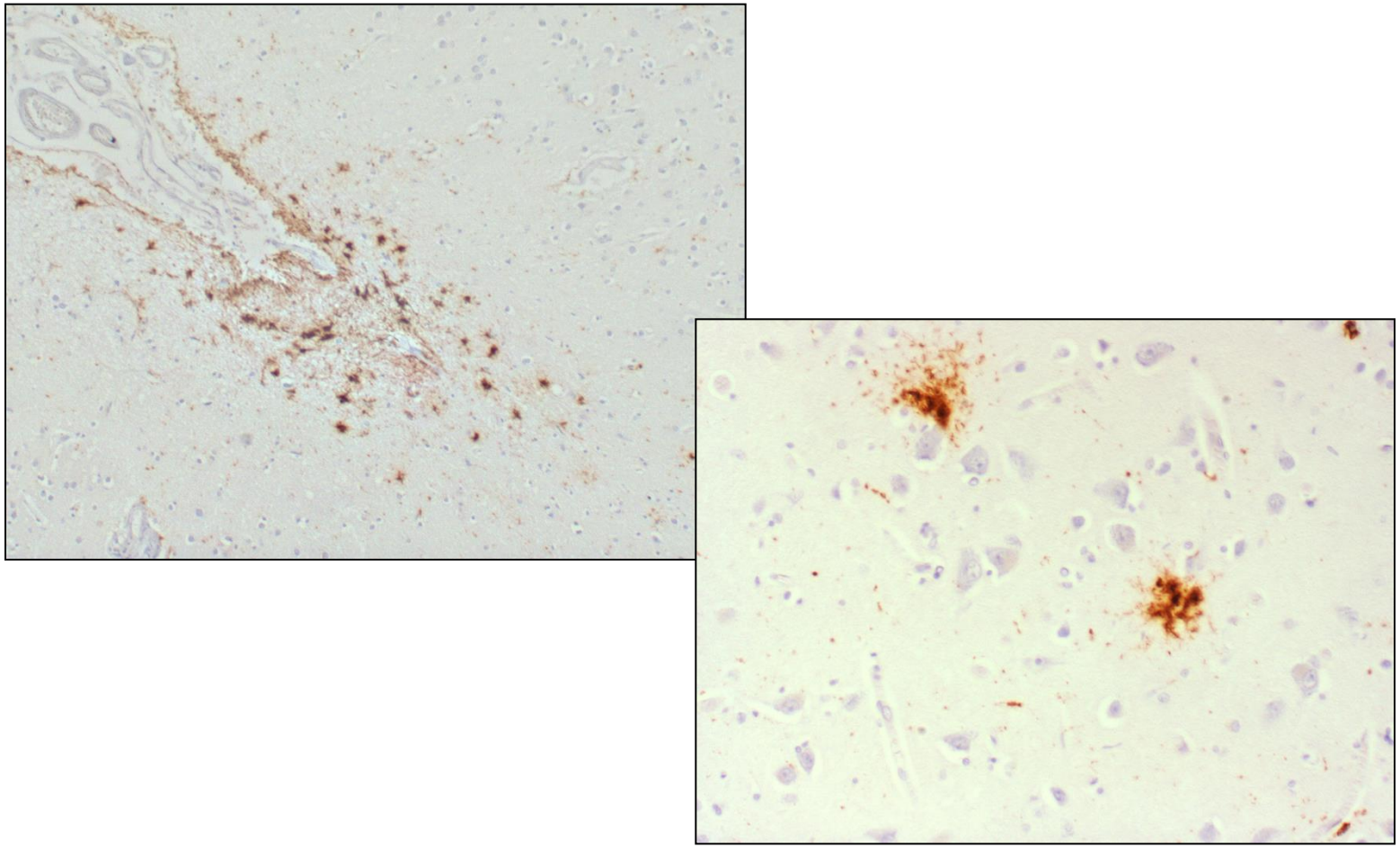




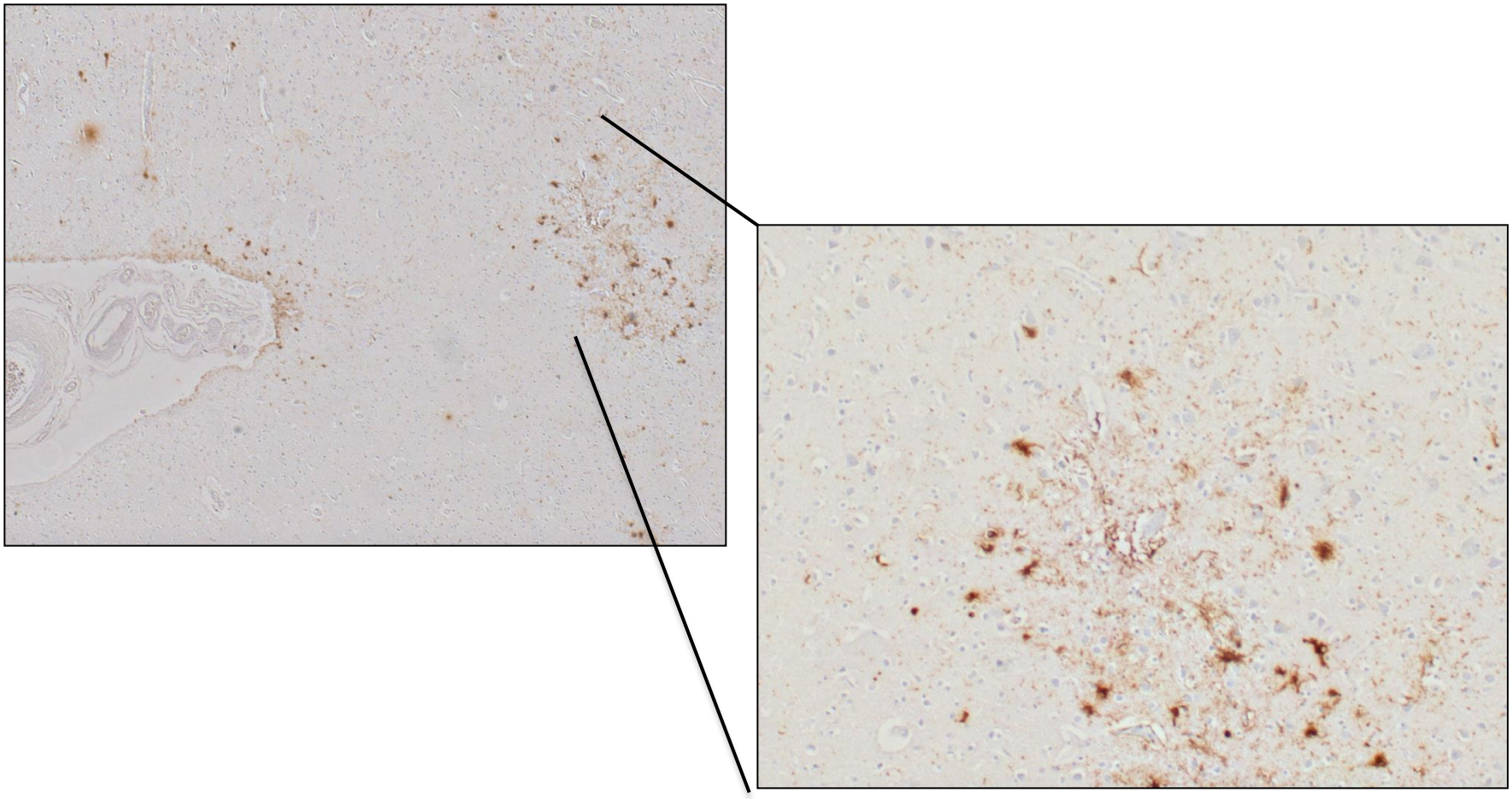
Original cohort

Case No	Age at death	Age of disease onset	Disease duration	Original diagnosis	Cause of death	CTE
57-45	67	40	27	DP		Y
64-47	72	31	41	Pre-senile dementia	Bronchopneumonia	N
70-237	83	32	51	DP	Bronchopneumonia	Y
71-119	77	50	27	DP	Bronchopneumonia	Y
71-120	58			DP	RTA	N
71-122	61				Acute SAH	N
71-123	71	60	11	DP	Coronary occlusion	Y
71-124	62	54	8	DP	Bronchopneumonia	Y
71-125	58	50	8	DP	Bronchopneumonia	N
71-126	91				MI	N
71-127	22				SDH	N
71-153	67					N
71-155	62	30	32	DP		Y
71-47	68	35	33	DP		N
71-54	63	30	33	DP		Y

71-47 PSP



Epilepsy – 19 year old



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CONSENSUS PAPER

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

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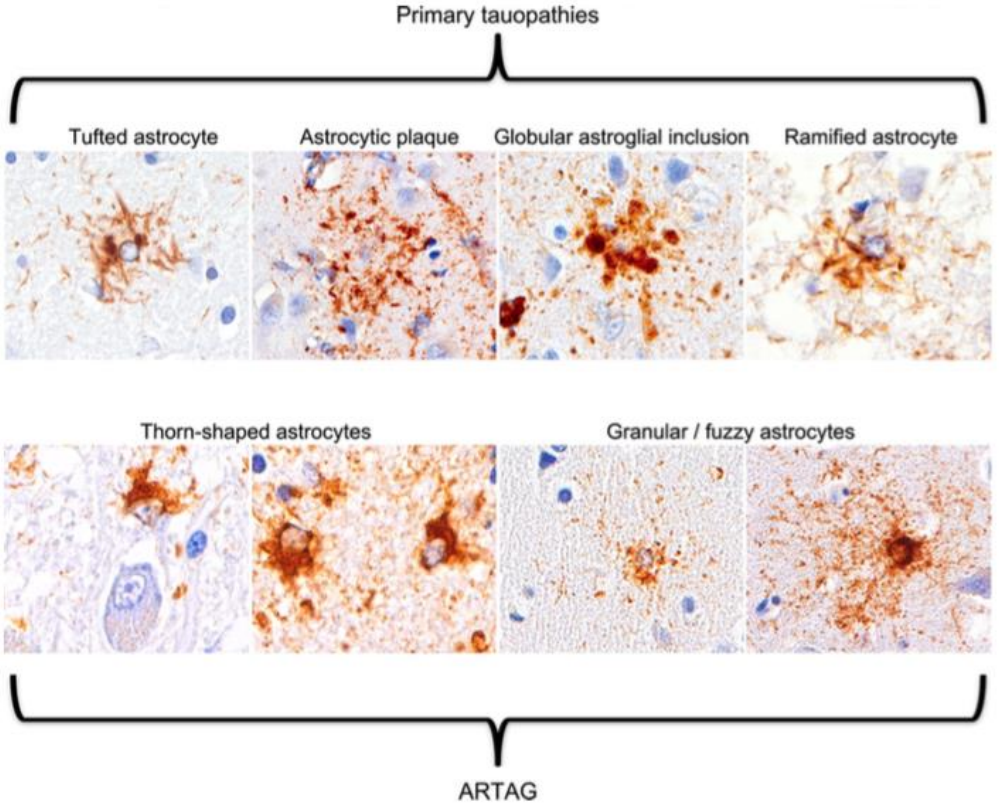

Fig. 1 Comparison of tau (using AT8 antibody) immunoreactivities seen in primary tauopathies with those observed in aging-related tau astrogliopathy (ARTAG)

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doi: 10.1212/WNL.0b013e3182a55f7f
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Clinical presentation of chronic traumatic encephalopathy

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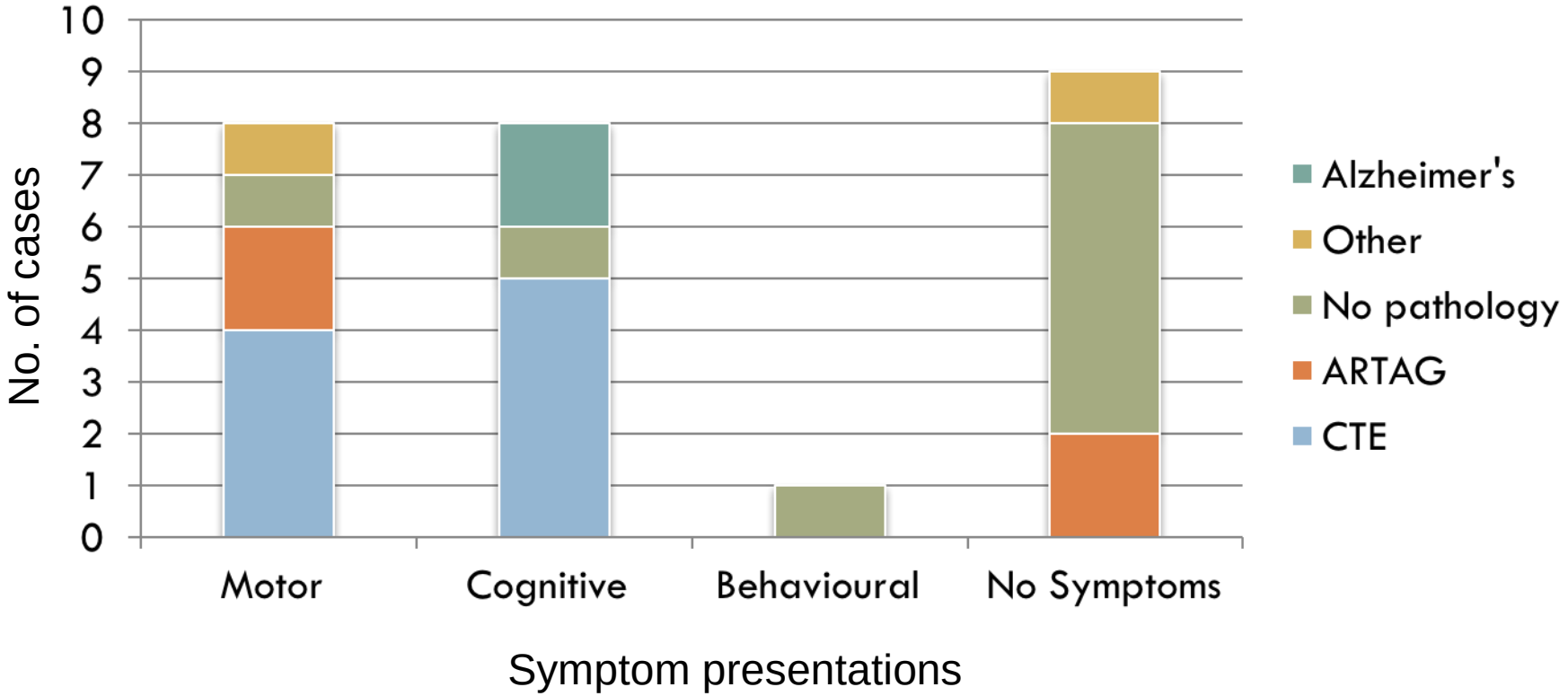
Conclusions:

2 major clinical presentations

- behaviour/mood variants (generally younger onset)
- cognitive impairment (generally older onset)

Symptoms and pathology



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Original Article

ORIGINAL ARTICLE

Chronic traumatic encephalopathy: a potential late and under recognized consequence of rugby union?

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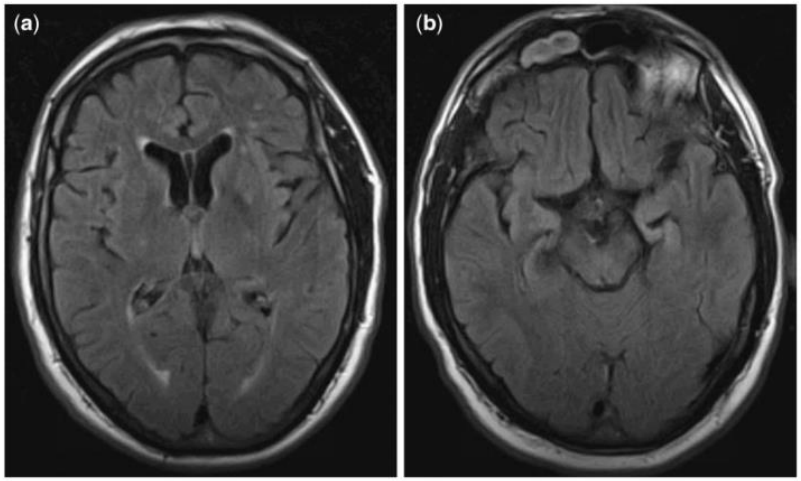

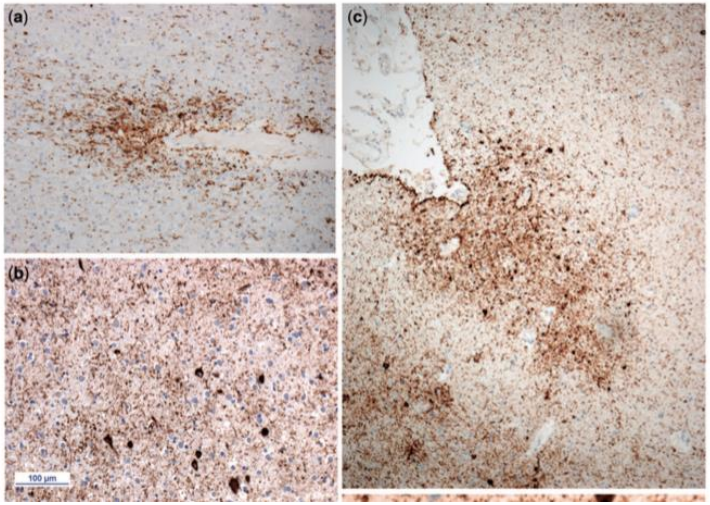

CTE in footballers?

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ORIGINAL PAPER

Mixed pathologies including chronic traumatic encephalopathy account for dementia in retired association football (soccer) players

Helen Ling[1,2,3] · Huw R. Morris[4] · James W. Neal[5] · Andrew J. Lees[1,2] · John Hardy[1,2,3] · Janice L. Holton[1,2,3] · Tamas Revesz[1,2,3] · David D. R. Williams[6]

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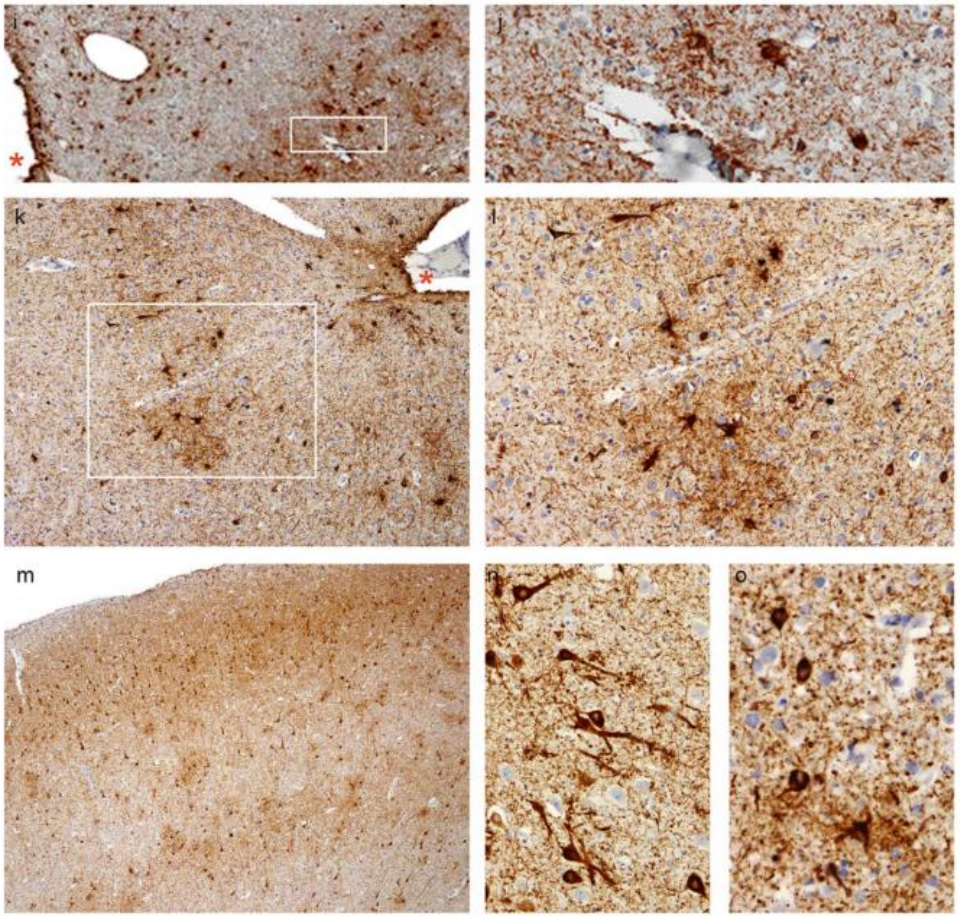
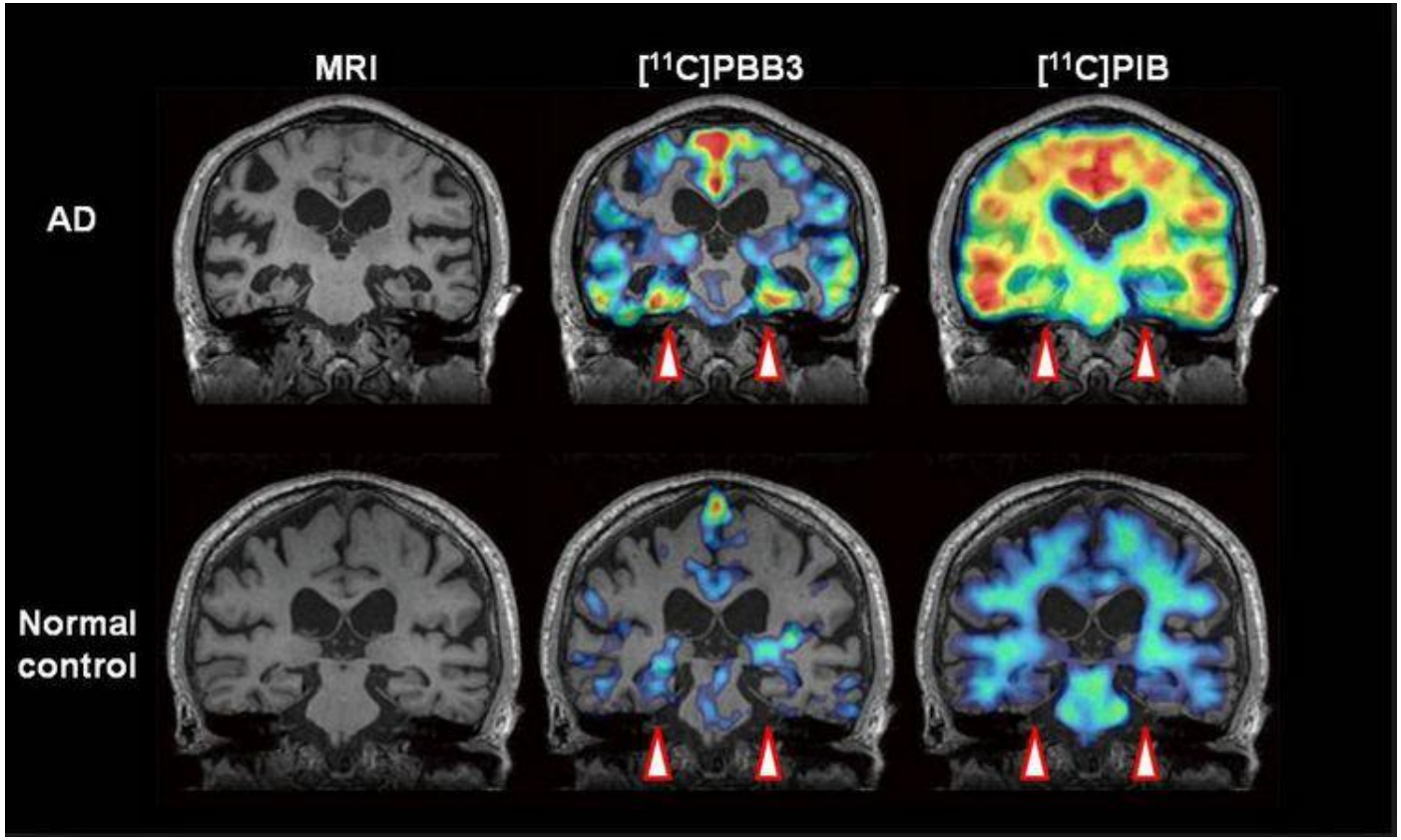


Future directions…



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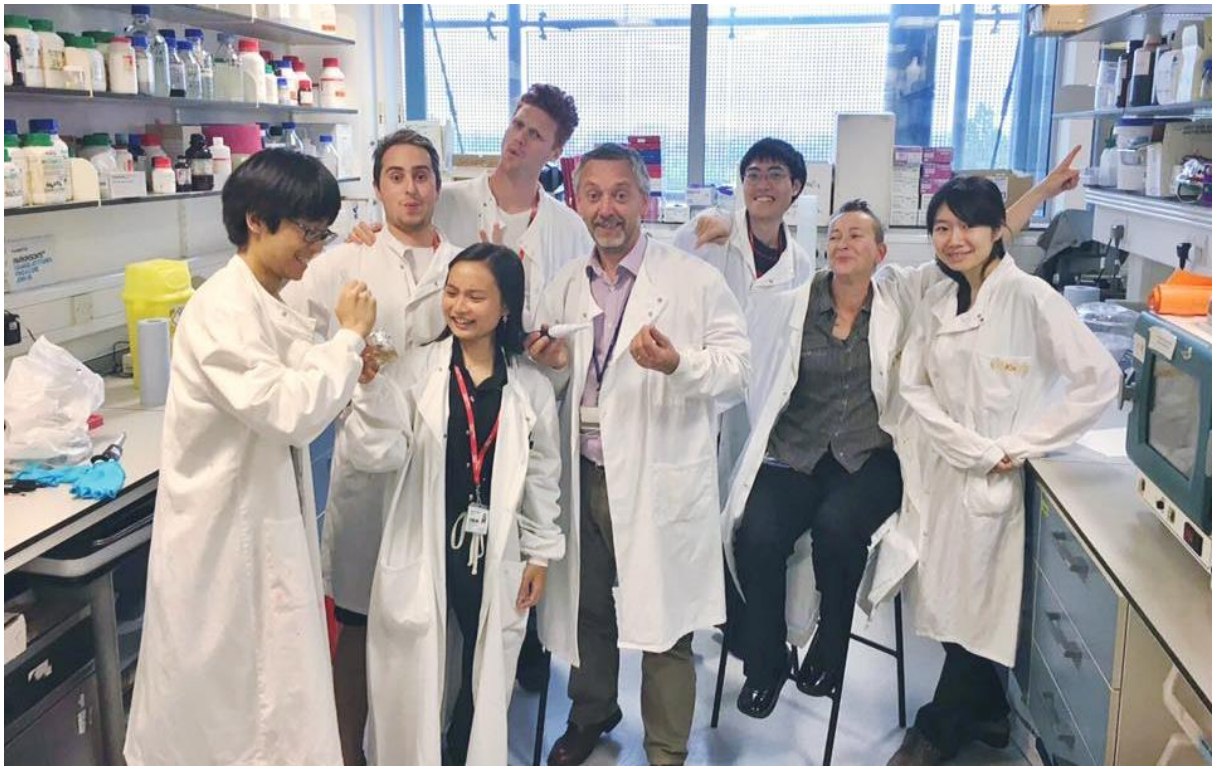

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