Concussion, dementia and CTE: are we getting it very wrong?

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A little less conversation, a little more science please

There has been a large media interest over the recent years in the long-term health effects of concussive injuries sustained by sportsman, culminating in a Hollywood movie ‘Concussion’ starring Will Smith. Hardly a week goes by without further studies being announced in the media and creating considerable interest in social media. The message is that concussion is a dangerous condition that causes a complex neuropsychiatric disorder, chronic traumatic encephalopathy (CTE), with a neuropsychiatric phenotype of mood change, irritability and suicidal behaviour which develops over time into a neurodegenerative disorder and death.1

Increasing alarm has followed, and it has been suggested that this is not just a disorder of elite sportsman but a problem for youth sport and that even heading a football (soccer) may cause dementia,2 a terrifying prospect for those parents trying to decide whether to allow their children to participate in sports.

This journal features, two well-conducted studies examining the outcome of elite rugby and ice hockey players. Both studies offer reassuring messages. Macmillan et al3 study of cognitive outcomes in retired Scottish International rugby players, mean age 54 and a mean of 20 years after retirement, found no significant effects of concussion. The ice hockey cohort4 does not have the same number of years of follow-up but at least in the short term is similarly reassuring, although the authors are appropriately cautious that the long-term follow-up data must be awaited. Both studies used opportunistic cohorts and as such selective sampling, non-participation and choice of controls will be valid criticisms.

But the more important question might be asked, ‘Why are these studies seemingly at such odds with the prevailing wind?’ Part of the problem may be that much of the debate has been played out in mainstream media rather than scientific journals.

To tackle this more objectively, we might examine what evidence is available on the concept of CTE, its relationship to concussion and its neuropsychiatric phenotype; what the evidence on outcome of mild traumatic brain injury (mTBI) in general is and what cohort studies on the risk factors for Alzheimer’s disease (AD) can tell us.

The story has its origins in a case reported by Omalu et al5 on the autopsy of an American footballer. They found that ‘Chronic traumatic encephalopathy was evident with many diffuse amyloid plaques as well as sparse neurofibrillary tangles and tau-positive neuritic threads in necocortical areas. There were no neurofibrillary tangles or neuripil threads in the hippocampus or entorhinal cortex. Lewy bodies were absent. The apolipoprotein E genotype was E3/E3’. They concluded that ‘This case highlights potential long-term neurodegenerative outcomes in retired professional National Football League players subjected to repeated mild traumatic brain injury’.

Unusually for a case report, it became the foundation for the film ‘Concussion’, and it has been widely disseminated that the subject was ‘Iron’ Mike Webster. Consequently, unlike most case reports, there is a lot of biographical material available to review. Some may well be recirculated rumour and innuendo but it is worth highlighting in detail as it is an exemplar of the complexity of identifying neuropsychiatric risks when one works backwards from a pathology slide. Among the more verifiable information, Webster had problems with addiction to opiate and amphetamine drugs after his playing career and a conviction for forging prescriptions. He was successfully treated for lymphoma (one assumes with chemotherapy) and suffered lymphoedema in his leg, and he had alcohol problems.6–8 It is a widely told tale that he had bought a ‘Tazer’, which he used to electrocute himself on a regular basis to aid sleep.6–8 Less certain but potentially highly relevant to his post playing career decline is a suggested family history of primary psychiatric disorder. He was widely rumoured to have used performance-enhancing drugs in his playing career,6–11 but it is important to emphasise that this may simply be idle speculation following a successful athlete. Equally, it would be naïve in the extreme to think that the National Football League (NFL) was free from doping, and given the neurotoxic effect of steroids,12 this must be considered a potential risk, but one that may prove exceptionally difficult to gain reliable data on. Herein lies the problem: scant attention is being paid to other risks to brain’s structural integrity. It is often said in the neuropsychiatry, but seldom considered in this particular literature, that one needs to think more of the nature of the brain which was injured than the nature of the brain injury.

Since this original case report, McKee et al13 have described the first consensus meeting on the neuropathology of CTE. Seven neuropathologists were given digitised images to review on 25 cases of a variety of tauopathies. They were made aware in advance this was a study of CTE and given the proposed criteria for CTE but were blinded to the individual cases. They reported an overall Kappa 0.67 for tauopathies and a Kappa of 0.78 for CTE. One has to read the supplemental tables to find the data this was based on. In the 10 cases of presumptive CTE, the seven neuropathologists (ie, 70 reviews) were classed as being in agreement if they simply identified CTE. There were seven disagreements were one or more reviewer failed to mention CTE which formed the basis of Kappa statistic. However, in a further 36 of the 70 reviews, additional diagnoses were identified which had not been described a priori by the study leads; usually comorbid Alzheimer’s pathology. Given the average age of the cases was 70(100%male: controls average age 80, 46% male), one would have thought that it was essential to be able to distinguish CTE from AD, as the null hypothesis must surely be that it is simply an atypical distribution of AD pathology, or even simply age-related changes.

Maroon et al14 systematically reviewed all published cases of CTE in 2015 and found 153 published cases and noted further 36 of the 70 reviews, additional disagreements were one or more reviewer identified CTE which formed the basis of Kappa statistic. However, in a further 36 of the 70 reviews, additional diagnoses were identified which had not been described a priori by the study leads; usually comorbid Alzheimer’s pathology. Given the average age of the cases was 70(100%male: controls average age 80, 46% male), one would have thought that it was essential to be able to distinguish CTE from AD, as the null hypothesis must surely be that it is simply an atypical distribution of AD pathology, or even simply age-related changes.

They concluded that:

‘the neuropathological and clinical findings related to CTE overlap with many common neurodegenerative diseases. Our review reveals significant limitations of the current CTE case reporting and questions the widespread existence of CTE in contact sports.’

In terms of the neuropsychiatric phenotype of CTE, Lehman et al15 studied rates of neurodegenerative diseases in a large cohort of ex NFL players (n=3349),
They concluded ‘The neurodegenerative mortality of this cohort is three times higher than that of the general US population; that for two of the major neurodegenerative subcategories, AD and amyotrophic lateral sclerosis (ALS), is four times higher.’ This claim is made on the basis of 17 cases of neurodegenerative disorders (AD=7, ALS=7, Parkinson’s disease=3). By contrast, the finding in the same paper, based on all cause mortality of these NFL players (n=334 deaths), was a halving of the standardised mortality ratio compared with national average. This important finding received scant mention, yet as a parent was the figure I want to know most. Put another way, if football were viewed as a drug, it saved 296 lives but at the cost of 17 deaths. A more recent report from the Mayo Clinic failed to show any increase in neurodegenerative disorders among retired footballers.\(^1\)

Regarding the early, wider neuropsychiatric phenotype of CTE, the University of Michigan conducted a large-scale epidemiological study with a notably good sampling frame and case ascertainment, which showed lowered rates of irritability and equivalent rates of depression in retired NFL players compared to the US population,\(^1\) offering little support for the reported clinical phenotype of CTE.

Out with the field of sports medicine, the outcome of mTBI had followed a similar history with small, often poorly conducted, studies making worrying claims of poor outcomes. But in 2004, there was a sea change in the field with the WHO task force report on mTBI.\(^1\) This systematic review offered a different and much more reassuring view of outcome, highlighting that while short-term symptoms in the immediate aftermath of mTBI were common: "There are consistent findings that early cognitive deficits in MTBI are largely resolved within a few months post-injury, with most studies suggesting resolution within 3 months. Since this evidence is based on a variety of study designs, in a number of different MTBI populations and through comparisons with both injured and non-injured control groups, we consider it persuasive and consistent evidence."

When symptoms were prolonged this often related to background psychological and social issues and that litigation had a significant effect on outcome.”

This review was updated in 2014\(^1\) and found "There is a lack of evidence of an increased risk of dementia after MTBI.”

In suggesting that background psychological and social variables were more predictive of prolonged symptomatology, the WHO provided tacit support for a model that many in neuropsychiatry had long believed. As Alwyn Lishman so eloquently described ‘what has initially been based in physiogenic disturbance readily thereafter becomes prolonged, and nonetheless disabling, by virtue of a complicated interplay of psychogenic factors’.\(^1\,\,1\)

This model has subsequently been tested in both general populations\(^2\) and specifically athletes\(^3\) and shown utility. This change in model is important as it provides a potentially more fruitful direction for treatment\(^1\) for patients, and it also highlights that prolonged symptoms in this group of patients may be better thought of as functional disorders which has important considerations for patient assessment\(^4\) and communication\(^5\) both in clinic and in research assessments, emphasising that cognitive examination is not just a case of assessing mean scores on cognitive tests but actually understanding and interpreting what the scores really mean.\(^6\,\,7\)

Since those systematic reviews were published, Sarislan et al\(^2\) published a detailed examination of outcomes of brain injury using Swedish population data. They found convincing evidence that moderate to severe brain injury in childhood and adolescence was associated with an increased rate of psychiatric disorder and receipt of health-related disability benefits in adult life. The results were no surprise to anyone in the brain injury field. But they also found a slight increased risk for the same outcomes associated with both mTBI and, notably, other non-TBI physical injuries. The interpretation of this result is far harder—does childhood mTBI lead to a subtle but nonetheless significant risk in psychiatric disorder? Or are we seeing reverse causality, for instance, that genetic and neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) lead to increased risk-taking behaviour and a consequent increased risk of head injury? The authors accounted as far as possible for this using sibling controls, and the strength of the association diminished but it did not disappear altogether. However, this control methodology is limited as the concordance rate in dizygotic twins for neurodevelopmental conditions such as ADHD is relatively low\(^8\); the jury remains out.

As well as reverse causality, shared risk as a confounder complicates outcome studies of mTBI. A slight increased risk of epilepsy has long been associated with mTBI, but careful review of long-term outcomes by Vaaramo et al\(^9\) suggests this is explained by the confounding effects of alcohol misuse.

A similarly reassuring story of a lack of association between mTBI and neurodegenerative disorders is found in the numerous cohort studies that have examined the risk factors for AD and comment on head injury. Xu et al\(^10\) conducted a meta-analysis of risk factors for AD and found level 1 evidence that head injury was not a risk factor. Since the publication of that study, Crane et al\(^1\) have published one of the most persuasive studies in the literature using data from three large prospective cohort studies on neurodegenerative disorders. This paper offered data on 7130 participants, 865 of whom had head injury with loss of consciousness and found no association between TBI and development of AD. Of note, 213 of the subjects described in this study had subsequently died and gone on to have autopsies. There was no suggestion of an increased rate of Alzheimer’s related pathology. This study did however find an association between severe brain injuries and Parkinson’s disease and accumulation of Lewy body pathology and microbleeds.

Where do we go from here? Review of the available evidence suggests that it is unlikely that concussion is a risk for neurodegenerative disease. Or, in the worst case scenario, if it does increase the risk, it only does so marginally. In weighing the potential risk of this, we need to balance it against the strength of evidence that being a professional NFL player, and participating in sport in general, results in an increased life expectancy. Ideally we need high-quality studies that can give definitive answers to this question which is of considerable public concern. Equally we also have to acknowledge that such studies may not be technically possible to do. Studies examining a connection between sporting head injury and outcome are necessary but its unhelpful when the results are rushed to mainstream media outlets before proper consideration to interpretation, limitations and replication. This is unfair on the public who are often unfamiliar with the technical problems in these studies, such as reproducibility. We need to recognise that fear of CTE has led to recorded suicides (where the autopsy has shown no evidence of CTE),\(^1\) and researchers should exercise appropriate caution and responsibility in how they present, and more importantly disseminate, results.

We need far more recognition of the multitude of confounders that may be causing brain insults. Studies must control for alcohol and substance misuse,\(^1\)
performance enhancing drugs, mood and stress disorders among known problems. The potential neurotoxic effects of performance-enhancing drugs, including those permitted by World Anti-Doping Agency such as tramadol, are the ‘elephant in the room’ which has been seldom discussed in this debate. We also need to be more aware of unknown confounders in terms of genetic and behavioural variables that predispose to head injury occurring. Finally, dare one say it, we may need to be more critical of the reliability and validity of neuropathology, as we would be for any other form of clinical assessment, rather than accepting blindly that it is a ‘gold standard’ because people have always said it is.

In summary, the question concerned parents ask me is ‘what do I advise my own children?’. Tempting though it is, I do not duck the issue; however, I do always begin by cautioning that the evidence is incomplete for all potential harms, although reminding them it is more robust for benefits. I am delighted that my daughter plays and loves hockey and would be equally happy for her to play soccer. My wife has always vetoed rugby, but that is on aesthetic not health grounds; although we would worry about the supplement culture, especially among young players, and the rate of orthopaedic injuries. My real health concern though is my otherwise delightful son who hates sport—but bribery at least lets him get to run a couple of times per week.

Finally for sports governing bodies, if they want to get serious about preventing dementia in their former athletes, it might make more sense to follow the existing evidence base for dementia prevention. Consistent robust findings on the value of being physically, and importantly cognitively, active into old age have been reported. Targeting defined risks rather than speculative ones seems a far better place to start. Many elite athletes leave academic education early as a result of their dedication to sport—why not take the issue of player education on retirement far more seriously? Now that is something that might just make a difference.

Competing interests I have given independent testimony in Court 50% plaintiff, 50% defnder on a range of neuropsychiatric topics including acquired brain injury. I run a free to access, not for profit website www.headinjurysymptoms.com which is a self help guide for patients after mild brain injury.

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References

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