Head Trauma in Sports and Risk for Dementia

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Traumatic Brain Injury (TBI) is a major health problem. While severe TBI, rendering the patient unconscious, is often an acute intensive care and neurosurgical issue, the majority (80-90%), of head injury patients have mild TBI (mTBI), which in principle is synonymous with concussion (1). Concussion occurring in conjunction with contact sports, such as boxing, American football and ice hockey, is commonly referred to as a sports-related concussion (2), and have received much attention in recent years, largely due to a much-feared long-term consequence, a chronic brain disorder called chronic traumatic encephalopathy (CTE) (3).

Indeed, it has been known since almost a century that professional boxers after, or at the end of, their career may develop a progressive neurological disorder called "punch drunk syndrome" (4), or "dementia pugilistica" (5). After the recognition of similar types of pathology also in American football players (6), other contact sports athletes (7), as well as in soldiers exposed to explosive blasts (8), both research and public awareness of this condition, which now is known under the more general term CTE, has increased dramatically. At the same time, epidemiological data provide increasing support for an association between TBI and future dementia in people aged >50 years, with recent very large (around 3 million people) nationwide population-based observational cohort studies reporting odds ratios for dementia of 1.24 in Denmark (9), and 1.81 in Sweden (10), with lower risk in individuals with mild TBI, and higher risk in those with repeated TBIs. However, there is a lack of longitudinal clinical studies employing biomarkers, and studies with neuropathology follow-up examinations, to examine the type of pathology underlying the dementia in individual exposed to TBI, as well as its possible relationship or overlap with CTE-type pathology.

To review and update these two connected major health problems, a scientific congress, the Old Servants Symposium on "Head Trauma in Sports and Risk for Dementia", was held in May 2018 at Nobel Forum, Karolinska Institutet, Stockholm, Sweden. The aim of the symposium was to highlight recent findings regarding the long-term risk of dementia after TBIs in participants of contact sports such as ice-hockey, boxing and American football and to bridge recent understanding regarding basic knowledge from animal models, underlying pathogenic mechanisms for nerve cell damage, pathology to epidemiology and clinical aspects, such as diagnosis, biomarkers and prevention

possibilities including prevention of physical injury, clinical management, pharmacological intervention, cognitive rehabilitation and discussions on guidelines for concussion in contact sports. To link the neuroscientific findings and interventions to "real life", we included presentations covering personal experiences from TBIs/CTEs in sports such as boxing, ice-hockey and American football.

In the latest issues of Journal of Internal Medicine (JIM) three review articles covering in depth different aspects of TBI are published: i) Zetterberg et al (ref) discussing the diagnosis including pathology and biomarkers, ii) Marklund et al (ref) discussing the prevention and pharmacological treatment possibilities and iii) Risling et al (ref) discussing the pathology of TBI in animal models. [to be revised by JIM when completed]

Future research needs

Even if recent research advances have given a much deeper understanding on the mechanistic, pathophysiological and clinical characteristics of concussion and its possible long-term sequelae CTE, there are many unresolved issues indicating the need for future research, a number of which are briefly discussed below.

What governs the development of post-concussion syndrome after concussions, and what is the relation between this condition and CTE?

While, by definition, single or repeated concussive and subconcussive head injuries are key players the aetiology of PCS and CTE, increased knowledge on which other factors add to the susceptibility of these long-term consequences are needed. It is not known why a proportion of mTBI patients develop the sub-chronic condition PCS (11). Do these patients have more severe acute brain damage, or is the development of PCS depending on which type of head impact is involved and the subsequent localization of damage? To which degree are psychosocial mechanisms playing a role in making symptoms more chronic?

What is the optimal management of concussion to prevent chronic symptoms and long-term complications?

It is generally recommended that athletes with a concussion should follow strict return-to-play guidelines (12) to prevent long-term symptoms and suffering. However, a recent prospective multicentre cohort study on children and adolescents with acute concussion showed lower incidence of persistent (1 month) post-concussion symptoms in those with early physical activity compared with those having no physical activity (13), and for those symptomatic at one week, rates were lower also for moderate and full-contact activity.

Which severity and frequency of concussions are needed for development of CTE?

Repeated concussions or sub-concussive head impacts underlie the initiation of the chronic and progressive neurodegenerative process leading to CTE pathology (14). In support, a study based on observations in a large brain bank showed that one third of former contact sports athletes had cortical tau pathology consistent with CTE, while no individual without contact sports exposure had CTE pathology (15). At the same time, a recent study on close to 2,700 men who graduated from high school in 1957, of whom more than 800 played American football while the others did not, showed no significant association of playing American football with lowering of cognitive function, increased depression, or secondary outcomes, such as heavy alcohol use (16). Thus, further longitudinal studies are needed to determine which percentage of contact sports athletes will develop either symptomatic or clinically silent CTE pathology, and the relation between severity of pathology and number and severity of concussions, length of career as well as the potential impact of psychosocial factors such as alcohol and drug abuse.

Can we find tools to identify and monitor pathophysiological mechanisms in concussion?

Today, concussion is vaguely defined, and the diagnosis is made in individuals exposed to head injuries having variable symptoms without any clinically identifiable pathological substrate (17). Thus, there is a large need for objective biomarkers to identify and monitor neuronal damage, glial activation and other pathophysiological mechanisms. The glial blood biomarker S100B has been extensively studied, and is currently used regionally in Scandinavia in order to rule out intracranial pathology by CT in mild TBI [ny REF: Unden et al. BMC Med. 2013 Feb 25;11:50] (18). However, S100B has not been able to show adequate efficacy to predict PCS in mild TBI [REF: Prognostic Value of S-100β Protein for Prediction of Post-Concussion Symptoms after a Mild Traumatic Brain Injury: Systematic Review and Meta-Analysis. J Neurotrauma. 2018 Feb 15;35(4):609-622], stressing the

need for novel biomarkers of long-term symptoms. Technical developments have given ultrasensitive methods to measure the axonal proteins such as tau protein (19, 20) and neurofilament light (NFL) protein (21, 22) in blood samples, and these blood biomarkers show promise as tools to monitor axonal damage, one of the central pathophysiologies in mild TBI (23), and thus tentative markers for PCS and other long-term sequalae following mTBI.

Which pathophysiological mechanisms are key players for the progression and development of symptoms in CTE?

While repeated concussions or sub-concussive head impacts are initiating events for the neurodegenerative processes leading to CTE, with end-stage pathology characterized by typical lesion with abnormal tau accumulation in neurons and astroglia irregularly distributed at the depths of cortical sulci (3), little is known on what drives the disease during preclinical and clinical phases. One hypothesis based on preclinical discoveries poses that once initiated, tau pathology spreads to adjacent neurons without additional brain traumas (24). Further, CTE symptoms may be difficult to differentiate clinically from other neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease and depression (25). For the above reasons, we need longitudinal studies on athletes exposed to repeated concussions having early symptoms using biomarkers. This will help to determine the relationship between evolution of brain pathologies and progression of symptoms during the course of CTE. Based on that pathologies overlap between AD and CTE, a shortcut may be to apply biomarkers developed for AD, including not only tau PET (26) and CSF levels of phosphorylated tau (27) for brain tau pathology, but also amyloid PET and CSF Aβ42, which both reflect cortical amyloidosis deposition (28), and CSF total tau and NFL to identify damage to neuronal cells (27).

These and many other important research questions were addressed in the symposium, and are subjects for intense research efforts world-wide.

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References to be added below when ready for publication in JIM:

Zetterberg H et al. Head trauma in sports – clinical characteristics, epidemiology and biomarkers.

Marklund N et al. Diagnosis, treatments and rehabilitation in the acute and chronic state of traumatic brain injury.

Risling M et al. Modelling human pathology of traumatic brain injury in animal models.

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