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Traumatic brain injury: an enduring challenge

See **Series** page 813

See **Series** *Lancet Neurol* 2017; **16:** 721–29

The outcomes of traumatic brain injury (TBI) can vary widely from no lasting effects to devastating and persistent consequences. Detailed understanding of the sequelae of TBI has been limited by the heterogeneity of this disorder and, until recently, there have been few studies of long-term outcomes in particular. However, recent progress in characterising specific consequences and the availability of longitudinal studies of outcomes are providing the basis for improved understanding of TBI sequelae, as highlighted in two Series papers on TBI in *The Lancet Neurology*.[1,2] Meyfroidt and colleagues[1] have focused on the puzzling clinical syndrome of paroxysmal sympathetic hyperactivity (PSH), a specific consequence of severe brain injury, especially TBI, that can last for weeks to months after injury, while Wilson and colleagues[2] have reviewed the growing body of evidence emphasising that TBI should be viewed as a chronic health condition with lifelong consequences for many patients.

As described by Meyfroidt and colleagues,[1] research on PSH and awareness of this condition have been hampered by the many definitions of this disorder and approaches to diagnosis, and variations in study design. Therefore, there is a wide range in reported incidences of PSH; a further challenge to efforts to understand the epidemiology of PSH is that, for many patients, symptoms are unmasked only when analgesics are stopped upon transfer from an intensive care unit (ICU) to a rehabilitation setting. The overall effect of PSH on TBI outcomes is unclear, although the presence of PSH symptoms seems to be linked to prolonged ICU stay and probably also to unfavourable outcomes.[3] In addition to assessment of the presence of PSH, examination of duration of symptoms and presence of medical cofactors might enable identification of stronger relationships between PSH and functional outcomes. The recent establishment of a unifying term—paroxysmal sympathetic hyperactivity—and the development of clear diagnostic criteria and a diagnostic tool (the PSH Assessment Measure) by an expert consensus group should facilitate research into outcomes after PSH.[4]

Progress in understanding of pathophysiology might also be facilitated by a clearer definition and criteria for PSH. No single mechanistic explanation exists, but a reasonable unifying theme is that of a disconnection pathology that separates cortical inhibition from caudal excitatory centres. The recent proposal of an excitatory:inhibitory ratio model might add a construct from which to investigate this dysfunction physiologically.[5]

Few randomised controlled trials of interventions for PSH exist, and treatment decisions are largely based on clinical experience. Moreover, several medications proposed to treat PSH, reported in case series, such as opioids and α2-adrenergic drugs,[1] might have sedative effects and therefore affect progress if used in the rehabilitation setting. Assessment of therapeutic interventions needs to be informed by a clear understanding of the effects of PSH on outcomes. A unifying next step could therefore be to adopt a common set of terms such as the Common Data Elements used in TBI research to describe features of PSH and enable development of outcome metrics. Furthermore, large-scale searches of electronic health records could be used to improve understanding of prognosis and enable identification of potential treatments of PSH for evaluation in rigorous clinical trials.

PSH is one complication of the subacute phase of TBI among a wide range of possible complications, including increased risk of mortality and functional, cognitive, emotional, and pathological changes, which can persist beyond this stage and, in many cases, throughout life.

For more on **Common Data Elements** for TBI see https://www.commondataelements.ninds.nih.gov/TBI.aspx#tab=Data_Standards

TBI has long been suspected to be a chronic health condition by many clinicians, a view that is now supported by a growing body of evidence, as reviewed by Wilson and colleagues.[2] Findings from the TBI Model Systems programme[6] suggested that people with TBI were twice as likely to die than their peers in the general population, and that life expectancy of these patients was on average 7 years shorter than that of their peers. Furthermore, results from a study of patients with TBI admitted to hospital in Glasgow, UK,[7] showed that by 15 years after injury more than a third of patients with mild TBI had died despite the young age at injury (median 39 years). These findings are supported by further data from the TBI Model Systems programme, which revealed that by 5 years after injury 50% of patients had been readmitted to hospital at least once and, of those who survived, more than a third had had functional decline. This decline was apparent across all age groups.[8]

Supporting the idea that TBI should be viewed as a chronic and progressive health condition, evidence is emerging that neurodegenerative diseases are more prevalent after TBI. In work based on a large Californian dataset, Gardener and colleagues[9] noted an increased risk of dementia after a single moderate-to-severe TBI, and this risk was enhanced for those aged 65 years or older at the time of injury. This same group[10] noted that TBI sustained after the age of 55 years was associated with a 44% increased risk of Parkinson's disease. Crane and colleagues[11] also reported an association between TBI and development of Parkinson's disease, although not Alzheimer's disease.

Over the past several years, there has been a striking increase in research on the relationship between exposure to repetitive mild TBI in sports and neurodegenerative disease. For example, Lehman and colleagues[12] reported that risk of mortality from neurodegenerative disease in former American football players was three times that of the general population; however, the overall risk was low. Furthermore, pathological and autopsy-based reports have revealed evidence for chronic traumatic encephalopathy (CTE), a neurodegenerative pathology that seems to be specific to repetitive TBI, in a high proportion of professional, college, and even some high-school American football players;[13] however, crucial comorbid factors could not be fully examined, and such high rates of expression in an exposure-related disease is unusual. By contrast, a study[14] of high-school football players who graduated in Wisconsin, USA, in 1957 did not show an association between playing football and cognitive or mental health outcomes in later life. Most worrisome is the growing recognition that CTE could be the result of subconcussive blows and is not solely linked to clinically apparent concussions. Therefore, population-wide effects on outcome are unclear but concerning.

Detection and mitigation of CTE in patients with TBI while they are alive is a particular challenge. Although guidelines for diagnosis have been proposed, no clearly agreed upon clinical diagnostic criteria exist and CTE remains a post-mortem diagnosis. Understanding of comorbid factors that contribute to the clinical expression of CTE is needed to address this challenge. This aim might be facilitated by careful examination of individuals at the extremes of the outcome range—ie, those with similar exposure who had good outcomes versus those who had poor outcomes—taking into account the complex biopsychosocial factors that influence the clinical picture.

Research progress reported in these Series papers[1,2] has provided a foundation to better understand the complications of TBI. Improved understanding of TBI outcomes and the factors that influence such outcomes could facilitate identification of patients who are at risk of specific problems such as PSH or long-term complications. This work could in turn enable better targeting of treatments or preventive interventions for individual patients. Large-scale international collaborative efforts will be needed to advance this field and move towards targeted management to improve outcomes of TBI.

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A new era of multiple sclerosis rehabilitation: lessons from stroke

See **Personal View** page 848

Just over 20 years ago, no treatments were available for multiple sclerosis, a disease characterised by two overlapping processes of nervous system injury: inflammatory destruction of myelin and neurodegeneration of grey and white matter.[1] Disease-modifying drugs, particularly the new oral medications, have changed the prognosis of multiple sclerosis, contributing to increased periods of disease stability and greater potential for rehabilitative therapies to reduce impairment.[2] In *The Lancet Neurology*, Robert Motl and colleagues[3] argue that exercise can be a beneficial rehabilitation strategy for people with multiple sclerosis, but that three limitations obstruct translation of exercise research into practice: the quality and scope of the evidence, the need for improved understanding of the mechanisms underlying the beneficial effects of exercise, and the need for a framework and toolkit for knowledge translation. Progress in stroke rehabilitation research over the past 15 years could serve as a template to help overcome these limitations and accelerate research in multiple sclerosis rehabilitation.

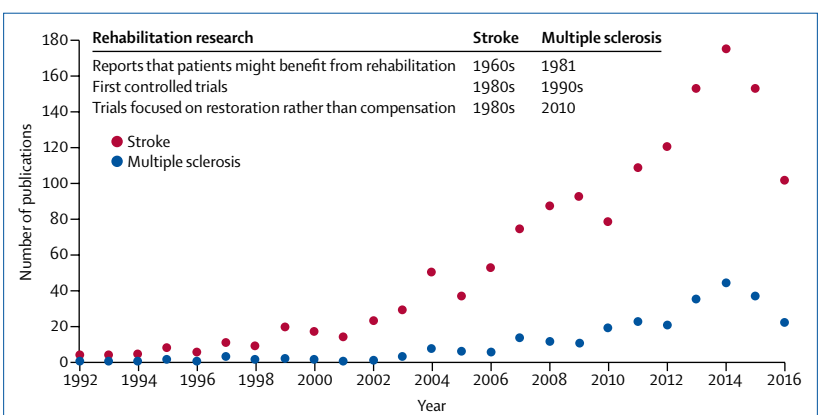

Figure: **Timeline of publications of exercise rehabilitation research in multiple sclerosis and stroke**
I searched PubMed between Jan 1, 1990, and Dec 31, 2016, for relevant publications of clinical trials with the search terms "exercise", "rehabilitation", and "multiple sclerosis" or "stroke". Exercise-induced neuroplasticity in an animal model of stroke was first shown in 1996,[4] whereas exercise-attenuated synaptic and dendritic loss in an animal model of multiple sclerosis (experimental autoimmune encephalomyelitis) was first reported in 2009.[5]

In their Personal View, Motl and colleagues raise concerns about the quality of clinical trials; however, the field of multiple sclerosis suffers most from the small number of rehabilitation trials. For example, the number of clinical trials of exercise rehabilitation in stroke increased about seven times between 2000 and 2015, whereas similar trials in multiple sclerosis barely doubled in that period (figure). A large number of good-quality clinical trials leads to strong systematic reviews and meta-analyses, which in turn lead to detailed evidence-based practice guidelines. Knowledge translation requires not only a conceptual framework and toolkit. What we have learned thus far in stroke rehabilitation[6] is that specific evidence-based guidelines must be available before knowledge translation can take place with toolkits and other techniques.

Motl and colleagues also highlight the need for long-term follow-up in clinical trials, because achieved gains frequently return to baseline after cessation