Cognitive ability, traumatic brain injury and dementia: the opportunities of register-based studies

Gonzalo Arrondo

Mind-Brain Group, Institute for Culture and Society (ICS), University of Navarra, Pamplona, Spain

Email: garrondo@unav.es

Orcid: 0000-0003-3085-8959

This article was later accepted for publication in the **European Journal of Neurology** in **November 2019**, but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as **doi: 10.1111/ENE.14122**

Both reduced cognitive ability and traumatic brain injuries (TBIs) have been proposed as risk factors for dementia later in life. Moreover, a 2008 case-control study comparing 55 controls to 197 TBI patients from the Vietnam War indicated that higher intelligence could offer protection from dementia after a penetrating brain injury [1]. However, gathering sufficient data concerning the moderating effect of cognitive ability on the increased risk of dementia after TBI is challenging, as TBIs are not common and follow-up times after the lesion have to be on the order of decades.

Register-based studies, based on complete and updateable listings of subjects [2], have led to important advances in the fields of neurology and psychiatry. Recent discoveries include the finding of differential risks of serious infections associated with disease-modifying treatments for multiple sclerosis [3], support for the efficacy and safety of acute endovascular reperfusion treatments for stroke patients with large-vessel occlusions [4], and evidence that medications for attention deficit hyperactivity disorder reduce the risk of unintentional injuries, including TBIs [5]. Register-based studies are ideal for untangling the relationship between cognition, TBI and dementia, as registries potentially have large sample sizes, limited selection or attrition bias, long follow-ups and the possibility of adjusting for critical confounders. However, these strengths do not come without limitations. Among these, a key problem is the restriction of the study variables or population to those already existing in the registry [2].

In this issue of the *European Journal of Neurology*, Osler and colleagues report results of a register-based nation-wide study on 658,447 Danish men who were cognitively evaluated at military conscription and followed for 40 years for TBI and dementia [6]. Cognitive testing was carried out using a standardized Danish battery that combines information from verbal and non-verbal reasoning items, and included close to 90% of men born between 1939 and 1959. After adjusting for psychiatric comorbidity (depression and alcohol abuse), education, cognition and accident proneness, TBI increased the risk of early onset dementia (hazard ratio, HR= 5.49; confidence interval, CI=4.97-6.06) and the risk of dementia after age 60 (hazard ratio, HR= 2.85; confidence interval, CI=2.63-3.10). Importantly, this risk was not reduced by higher cognitive abilities at study entry or by more years of education.

Inherent limitations and advantages of register-based studies can be found in the study at hand. First, data was limited to males as they were the only ones recruited for military service. Even if there is no ground to think that results found do not apply to women, in truth such a generalization cannot be made. Nevertheless, it will be hard to carry out a similar study in the short-term. The study merits recognition for its huge sample size with almost complete representativeness of the country's male population, its forty-year follow-up, and the use of a validated cognitive battery. It might be argued that because the study is correlational a causal relation between TBI and dementia cannot be proven. However, potential confounders such as psychiatric comorbidity or education were taken into account. In addition, the accumulation of evidence in the scientific literature concerning a dose-dependent relation between

dementia and the number and severity of lesions certainly points towards a causal mechanism [7].

The major discovery of the study is a negative finding. Although correlation does not prove causation, lack of correlation is a step away from causal explanations. The fact that there was no evidence for a protective effect of cognitive abilities and education on the increased risk of dementia after TBI is a major blow to cognitive reserve theories. This negative finding cannot be attributed to a lack of statistical power. Moreover, the existence of a standard cognitive measure and a validated definition of dementia for the Danish National Patient Registry minimizes the risk that poor data quality is driving the lack of significance. It can be concluded that whereas education and cognitive ability are related to a reduced risk of dementia, this effect disappears after a major brain injury.

In summary, the work by Osler and colleagues provides further evidence for a causal relationship between brain damage and the later risk of dementia, especially early-onset dementia. Additionally their work could become a landmark study on cognitive reserve in the specific case of brain lesions. More generally, the present work exemplifies the power of register-based studies, highlighting their limitations as well as their special strengths for the neurological scientific community.

References

[1] Raymont V, Greathouse A, Reding K, et al. Demographic, structural and genetic predictors of late cognitive decline after penetrating head injury. *Brain* 2008; 131: 543–58.

[2] Thygesen LC, Ersbøll AK. When the entire population is the sample: Strengths and limitations in register-based epidemiology. *Eur J Epidemiol* 2014; 29: 551–558.

[3] Luna G, Alping P, Burman J, et al. Infection Risks Among Patients With Multiple Sclerosis Treated With Fingolimod, Natalizumab, Rituximab, and Injectable Therapies. *JAMA Neurol*. Epub ahead of print 7 October 2019. DOI: 10.1001/jamaneurol.2019.3365.

[4] Truelsen T, Hansen K, Andersen G, et al. Acute endovascular reperfusion treatment in patients with ischaemic stroke and large-vessel occlusion (Denmark 2011-2017). *Eur J Neurol* 2019; 26: 1044–1050.

[5] Ruiz-Goikoetxea M, Cortese S, Aznarez-Sanado M, et al. Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: A systematic review and meta-analysis. *Neurosci Biobehav Rev* 2018; 84: 63–71.

[6] Osler M, Rozing M, Eliasen M, et al. Traumatic brain injury and risk of dementia at different levels of cognitive ability and education. *Eur J Neurol*.

[7] Mendez MF. What is the Relationship of Traumatic Brain Injury to Dementia? *J Alzheimers Dis* 2017; 57: 667–681.