Published in final edited form as:

JAMA Pediatr. 2021 October 01; 175(10): 1001–1003. doi:10.1001/jamapediatrics.2021.2038.

Advances in understanding the association between pediatric traumatic brain injury and attention-deficit/hyperactivity disorder

Keith Owen Yeates, PhD[1], **Jeffrey E. Max, MD**[2], **Megan E. Narad, PhD**[3,4]

[1]Department of Psychology, Alberta Children's Hospital Research Institute, and Hotchkiss Brain Institute, University of Calgary, Alberta, Canada

[2]Department of Psychiatry, University of California, San Diego, and Rady Children's Hospital, San Diego

[3]Division of Behavioral Medicine & Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

[4]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

Traumatic brain injury (TBI) is the leading cause of acquired disability in children, while attention-deficit/hyperactivity disorder is one of the most common neurodevelopmental sources of disability. The association between TBI and ADHD has been a topic of controversy, which Asarnow, Newman, and Weiss (this issue) tackle in their systematic review and meta-analysis. They focus on whether the risk of ADHD increases after TBI, but also present data bearing on the question of whether ADHD is itself a risk factor for TBI. Importantly, their analysis shows a "dose-related" association between TBI severity and post-injury ADHD, with a significantly elevated risk of ADHD among children with severe TBI compared to other-injured children (OIC) and children with mild TBI before 1-year post-injury, and to non-injured children (NIC), OIC, and children with mild TBI after 1-year post-injury. In addition, their analyses show no increase in postinjury ADHD in children with concussion, mild TBI, or moderate TBI compared to NIC or OIC. They also show that the rate of pre-injury ADHD is higher in children with TBI than in the general population, although not higher than among samples of NIC or OIC. These findings have important clinical implications, highlighting the need to assess for ADHD in children with TBI, especially those with severe injuries, but also to take a careful history to determine whether symptoms of ADHD predate the injury.

The Asarnow et al. study has several strengths. These include the largest number of studies included in a systematic review on this topic to date (n = 24), and a substantial number of participants, including 12,374 unique patients with TBI and 43,491 unique controls. Another strength is the modern Bayesian meta-regression analysis, which considers prior probabilities in an explicit fashion, as well as the sensitivity analyses, which addressed potential concerns about pooled severity groups for TBI samples, the effects of less

Corresponding author contact information: Keith Owen Yeates, PhD, RPsych, ABPP, FCAHS, Ronald and Irene Ward Chair in Pediatric Brain Injury, Professor and Head, Department of Psychology, University of Calgary, 2500 University Dr. NW, AD254, Calgary, AB T2N 1N4 Canada, kyeates@ucalgary.ca, Phone: 403-220-2928, Fax: 403-282-8249.

informative priors, and whether the results were driven by specific studies. One minor shortcoming is that the estimates in the meta-analysis do not take diagnostic method for ADHD into account. The sensitivity analyses suggest that diagnostic method can have a substantial influence on estimates of ADHD prevalence. A specific comparison of estimates using gold standard structured psychiatric interviews to those using symptom rating scales or unstructured clinician diagnoses would have been informative. Another minor shortcoming was the absence of a specific test of the dose-response relationship between severity of TBI and ADHD. The inclusion of a specific linear contrast for this purpose would have been instructive.

The findings from the systematic review and meta-analysis point to several important observations. One is the need for appropriate comparison groups in research on TBI. The seminal UCLA study of mild TBI showed that children with mild TBI differed significantly from NIC in their post-injury outcomes, but not from OIC, suggesting that some effects attributed to mild TBI in the past were a non-specific consequence of injury in general or reflected pre-injury differences.[1] Children with mild TBI and OIC likely share similar outcomes because they are well-matched demographically, share similar risk factors for injury, and have both experienced traumatic injuries necessitating medical attention. Notably, in their meta-analysis, Asarnow et al. found that the rate of pre-injury ADHD in children who sustained TBI was higher than in the general population but did not differ significantly from OIC. These results are consistent with evidence that ADHD is a risk factor not only for TBI, but for injury more generally.[2] An interesting question for the future with practical implications for prevention is whether an increased risk of injury for children with ADHD arises because of heighted impulsivity or inattention or both.[2]

Another noteworthy conclusion from the meta-analysis, as noted by the authors, is that mild TBI is not associated with an increased risk of ADHD. This is an important finding given the growing concern about the potential consequences of concussion and mild TBI in children and is consistent with other recent reviews.[3] However, we would caution that not all mild TBI are alike. The classification of mild TBI continues to be a topic for debate,[4] but collective variations in acute clinical status, based on factors such as loss of consciousness, Glasgow Coma Scale score, and trauma-related intracranial abnormalities, are demonstrably linked to symptom outcomes after mild TBI.[5] In the future, more nuanced analyses taking such factors into account are needed to address anecdotal clinical examples of low but elevated base rates of ADHD among children with mild TBI.

The study findings also indicate that, although the risk of ADHD is elevated after TBI, most children with TBI do not exhibit the onset of novel ADHD. Even after severe TBI, only about 19% show new-onset ADHD, compared to 16% of children with TBI having ADHD pre-injury. Thus, symptoms of ADHD after a TBI are almost as likely to have been present pre-injury as they are to have arisen after the injury. Of course, just as not all mild TBI are alike, the same is true of severe TBI. The categorization of TBI severity as mild, moderate, and severe using the Glasgow Coma Scale has been bemoaned for years, because it fails to capture the complex pathophysiology underlying TBI.[6] Future research using more exact and multidimensional measures of TBI severity may help generate more precise estimates of which children with TBI are at elevated risk for ADHD. However, the

predictors of secondary ADHD are likely to extend well beyond just the severity of injury to include factors such as pre-injury psychosocial adversity, focal lesions, family functioning, socioeconomic status, and comorbid disorders such as personality change due to TBI.[7,8]

A categorical approach to the diagnosis of ADHD may also obscure important observations about the association of TBI with attention problems. Studies using a categorical approach typically exclude children with pre-injury ADHD and treat outcome as a dichotomy, limiting our understanding of how pre-injury attention problems and TBI may interact to yield post-injury attention problems. A dimensional approach, by contrast, has shown that children with more pre-injury attention problems show a more pronounced increase in attention problems post-injury compared to OIC.[9,10] Moreover, most studies using a categorial approach treat all cases of ADHD alike, and do not examine specific subtypes, although research indicates that most cases of so-called secondary ADHD are primarily inattentive.[7] On the other hand, dimensional approaches do not necessarily document clinical levels of impairment. Thus, a combination of dimensional and categorical approaches may be needed to better understand the role of inattentive versus hyperactive-impulsive symptoms of ADHD, both as predictors and outcomes in children with TBI.[9]

The Asarnow et al. systematic review and meta-analysis points to several other important directions for future research. One is to determine whether secondary ADHD, arising after TBI, is best viewed as a phenocopy of primary or developmental ADHD. Further studies are needed to compare children with primary ADHD to those with secondary ADHD in terms of neural substrates, using structural and functional neuroimaging and neuropsychological testing;[11] common co-morbidities;[7] and response to treatment.[12] Asarnow et al. point out similarities between primary and secondary ADHD, but other research has found important differences in domains such as response to reward contingencies.[13] Notably, a family history of ADHD is not associated with an increased risk of secondary ADHD,[7] and recent evidence suggests that the genetic predisposition to primary ADHD does not put children with TBI at increased risk for secondary ADHD.[14] These findings suggest that ADHD symptoms have different etiologies in TBI versus NIC.

In fact, secondary ADHD is by no means limited to pediatric TBI but is a common occurrence in other childhood disorders affecting the brain, including low birthweight, fetal alcohol spectrum disorder, epilepsy, and various inflammatory disorders.[15] Indeed, historically, one of the first recognitions of this association was the observation of symptoms of so-called ‘minimal brain damage’ reported in association with children who survived the encephalitis epidemic in 1917–18. Thus, we may have come full circle: ADHD likely represents a final common pathway for childhood neurological impairment and provides an excellent example of equifinality. In that regard, we wonder whether secondary ADHD will become an unfortunate consequence of COVID in children, at least for those with neurological sequelae.[16] We applaud Asarnow et al’s contribution to answering this historically vexing question in children with TBI.

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