Balancing Underdiagnosis and Overdiagnosis:

The Case of Mild Traumatic Brain Injury

Jeffrey B. Ware, MD, Saurabh Jha, MD

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Mild traumatic brain injury (m-TBI) is a public health problem, particularly in veterans and athletes. Often synonymous with "concussion," m-TBI is head injury accompanied by acute-phase characteristics, such as alteration of consciousness. m-TBI can lead to chronic neuropsychological symptoms, known as postconcussive syndrome (PCS), and has been linked to chronic traumatic encephalopathy, a progressive neurodegenerative disorder.

Managing patients with m-TBI is challenging because of the difficulty in predicting outcomes. Furthermore, it is challenging to distinguish between the effects of m-TBI and the psychiatric conditions which frequently coexist.

Advanced neuroimaging can identify structural brain damage related to m-TBI which is not detectable with conventional brain magnetic resonance imaging. The most promising techniques are diffusion-based, such as diffusion tensor imaging (DTI), which detects changes in the diffusion properties of the white matter that reflect microstructural injury.

There are significant differences in scalar diffusion metrics in patients with m-TBI compared with controls (1), and these differences correlate with axonal damage in animal models of m-TBI (2). Diffusion measurements correlate with symptoms, objective measures of neurocognitive function, and outcomes. The research, thus far, induces hope that diffusion imaging techniques will identify individuals with structural brain injury and complement clinical decision making. Although the need for further standardization and refinement of these techniques before clinical implementation in m-TBI is recognized (3), it is timely to speculate on their potential impact in the real world.

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From the Diagnostic Radiology, Hospital of the University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104. Received May 26, 2015; accepted May 27, 2015. **Address correspondence to:** J.B.W. e-mail: jeffrey.ware2@uphs.upenn.edu

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The detection of disease at an earlier state, when more amenable to intervention, risks identifying disease which does not truly exist or will not impact the patient. This is known as overdiagnosis, which is widely recognized in screening for cancer, but also in nonneoplastic medical conditions.

Neuropsychiatric disorders, such as m-TBI, are particularly prone to overdiagnosis because the diagnostic criteria are often subjective and imprecise. The implications of falsely labeling individuals as having m-TBI or worse permanent "brain damage" have been recognized as problematic in this field (4).

What are the consequences of the mislabeling? In combat-related m-TBI, overdiagnosis can stigmatize and reduce expectations, which affects self-confidence leading to poorer outcomes. Resultant pursuit of ineffective or inappropriate treatment is accompanied by the risk of side effects and tremendous frustration. The overdiagnosed can overuse the disability status, which will reduce resources for those truly in need. A combination of overdiagnosis and a reductionist clinical approach can stop physicians from seeking underlying psychiatric comorbidities. With regard to sports-related m-TBI, overdiagnosis can restrict, unnecessarily, athletic participation, with career-destroying consequences for professional athletes. Thus, the underdiagnosis–overdiagnosis trade-off must be confronted before widespread adoption of diffusion imaging for m-TBI.

As DTI detects diffusion changes consistent with structural injury in the absence of clinical symptoms and at levels of trauma below the threshold for concussion (5), it is touted to be highly sensitive for white matter injury. However, diffusion changes are correlated with the traumatic exposure, the cause, as opposed to anatomic pathology, a verification standard, and so its true sensitivity is less certain. However, this vexing problem must be mitigated by quantifying the intensity of the trauma, the cause, in a standardized manner.

Attention must be paid to methodology so that imagers are speaking a common language across vendors and institutions. The effect size of m-TBI on conventional diffusion is too small for visual appreciation. This has implications, notably

that rigorous quantitative analysis and complex statistics are required. There is spatial heterogeneity of diffusion changes in m-TBI. To achieve reasonable sensitivity in individuals, multiple regions of the brain are measured. There must be rigor in measuring to avoid detecting the spurious. The key point is that consistency and consensus will reduce variability.

However, it is the specificity and the discernment which are the most problematic. Worryingly, studies have found that the neuropsychiatric disorders which coexist and enter the differential diagnosis of symptoms of m-TBI and PCS, have been associated with similar diffusion changes (6). Mere knowledge of this fact is important as imagers must never generate reports in a clinical vacuum.

The tendency to give objective criteria on imaging undue deference, particularly when there is clinical uncertainty coupled with the "rule out disease" diagnostic mentality which is so pervasive in our medical culture, induces false positives and leads to overdiagnosis even in rare entities such as arrhythmogenic right ventricular dysplasia (7). Paradoxically, unbound reliance on diffusion imaging for the diagnosis of m-TBI or PCS might lead not only to overdiagnosis but also to underdiagnosis because it can lull clinicians into believing that brain damage does not exist in the absence of abnormal diffusion measurements.

There is little doubt that diffusion imaging techniques hold potential to improve the care of patients with m-TBI by revealing insights into *in vivo* neurobiology. However, the neuroimaging community must learn from the mistakes made with other imaging tools, which have overshot the underdiagnosis chasm to a bloated state of overdiagnosis.

The lessons are as follows. Different thresholds for defining disease must acknowledge the underdiagnosis–overdiagnosis trade-off and consider the implications equitably. Vitally, trade-offs, as realities in medical imaging, must not be denied. In practice, the barriers to using these specialized techniques must be high and there must be a discussion between the referring clinician and the neuroradiologist who, among other things, must ask about psychiatric comorbidities. The reports generated must be contextualized clinically, in much the same way as reports for oncological positron emission tomography imaging are. Note, clinical contextualization is not the same as clinical correlation. The burden of the former falls on the imager, and this is where the burden should lie, whereas the burden of the latter falls on the referring clinician.

A task force must convene annually to reassess imaging thresholds in lieu of emerging evidence and, more importantly, experience in the trenches. A psychiatrist practicing in the community and/or at a Veterans Administration Medical Center must be on such a task force.

TBI causes great suffering but could be a setup for imaging overdiagnosis as well as a medicolegal landmine. It is important that imagers exert prudence in how this condition is assessed.

REFERENCES

1. Hulkower MB, Poliak DB, Rosenbaum SB, et al. A decade of DTI in traumatic brain injury: 10 years and 100 articles later. AJNR Am J Neuroradiol 2013; 34(11):2064–2074.
2. Mac Donald CL, Dikranian K, Bayly P, et al. Diffusion tensor imaging reliably detects experimental traumatic axonal injury and indicates approximate time of injury. J Neurosci 2007; 27(44):11869–11876.
3. Wintermark M, Sanelli PC, Anzai Y, et al., on behalf of the American College of Radiology Head Injury Institute, . Imaging evidence and recommendations for traumatic brain injury: advanced neuro- and neurovascular imaging techniques. American Journal of Neuroradiology 2015; 36(2): E1–E11.
4. Hoge CW, Goldberg HM, Castro CA. Care of war veterans with mild traumatic brain injury—flawed perspectives. New England Journal of Medicine 2009; 360(16):1588–1591.
5. Davenport EM, Whitlow CT, Urban JE, et al. Abnormal white matter integrity related to head impact exposure in a season of high school varsity football. Journal of Neurotrauma 2014; 31(19):1617–1624.
6. Daniels JK, Lamke J-P, Gaebler M, et al. White matter integrity and its relationship to PTSD and childhood trauma–a systematic review and meta-analysis. Depress Anxiety 2013; 30(3):207–216.
7. Christiansen J, Looi KL, Edwards C, et al. Utility of cardiac magnetic resonance in the evaluation of unselected patients with possible arrhythmogenic right ventricular cardiomyopathy. Clinical Medicine Insights: Cardiology 2012;153.