Lesion analysis in mild traumatic brain injury

Old school goes high tech

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Neurology® 2014;83:1226–1227

Concussion has been a controversial topic in neurology since the beginning of the discipline. Evidence-based diagnostic guidelines have been established,[1] but the diagnosis and treatment are largely grounded in clinical decision-making. Clinical and research issues around sports concussion have even reached the levels of government policy with the White House Healthy Kids & Safe Sports Concussion Summit (May 29, 2014), recently held by President Obama. The field needs objective answers to questions about mild traumatic brain injury (mTBI), its effects, treatment resolution, or long-term sequelae that may only be answered by development of objective measures of mTBI.

At the moderate to severe range of traumatic brain injury, neuroimaging provides well-established, objective pathoanatomical biomarkers of the injury.[2] In contrast, conventional neuroimaging findings in mTBI are typically absent. The cognitive and neurobehavioral symptoms of mTBI overlap with any number of neurologic or psychiatric disorders, providing no definitive marker of injury or for tracking injury effects. Reliable biomarkers of mTBI could lead to better clinical decision-making and potential treatments.

A variety of advanced neuroimaging methods, dominated by magnetic resonance (MR) technology, have been applied to mTBI[3,4] with the goal of identifying potential objective biomarkers.[5] The challenge is that any neuroimaging abnormality must be subtle, or the injury would not meet the threshold required for the mTBI classification. Thus, most pathology will not be visibly identifiable.

Early MRI studies of mTBI were in search of the prototype "lesion."[6] This "Old School" approach assumed that a lesion could be singularly responsible for the effects of mTBI. Although an appealing idea, contemporary understanding of mTBI pathophysiology places the emphasis on a multiplicity of factors, especially disruption in neural networks. It is notable that advanced MR techniques are sensitive to multiple types of pathophysiologic processes: subtle visible abnormalities can be detected, as can an entire array of metrics, based on MR signal characteristics, empirically derived with the objectivity of automated image analysis software. Each MR metric may provide unique and independent information about the effects of mTBI. From these datasets, identification of unique qualifiers that best differentiate mTBI may be derived. How these neuropathologic processes disrupt or damage different networks, and how the brain responds or adapts to the injury, is probably a much better perspective on how to conceptualize neuroimaging findings in mTBI[7] and thus to advance the field.

Given the wealth of data points within contemporary MRI, why not exam all information in mTBI? A potential solution to this richness of MR data is to consider simultaneously all possible MR metrics.[8] Computational techniques of machine learning are suitable for such purposes where ordinal to interval data may be used in a "learning" process to develop algorithms that may lead to successful classification. Machine learning techniques are being applied throughout medicine especially appropriate for complex neurologic disorders.

In this issue of *Neurology*®, Lui et al.[9] capitalized on using various separate MR metrics applied to the development of a machine learning algorithm to differentiate those with mTBI from controls. Although a research study, the MRI-based imaging sequences used by Lui et al. could be routinely performed on patients with mTBI in a clinical setting. This group had already established an innovative method that utilized magnetic field correlation techniques, sensitive to iron deposition that may be altered in mTBI, and other methods for assessing microstructure. Although in previous studies these measures individually differ in patients with mTBI compared to controls, machine learning that considered all of this multifeature imaging information to differentiate individual patients with mTBI from controls had not been done. Using a feature selection approach, 86% accuracy was achieved, dominated by various thalamic metrics.

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

Although machine learning methods utilize all information provided, the importance of identifying select features in the midst of all examined data points yields potentially key information about critical regions of interest most influential in differentiating the individual with mTBI. In the Lui et al.[9] study, both structural and functional measures of thalamic integrity were key elements that contributed the most to the mTBI algorithm.

Deformation-based biomechanical studies of mTBI have shown the thalamus is situated in a particularly vulnerable zone.[10] Tethered to the upper brainstem, yet with complex afferent-efferent connections with the cerebrum along with its own intricate white matter connections, disruptions of thalamic-based networks may be key in understanding mTBI. Obviously, any injury associated with mTBI at the thalamic level has to be subtle by definition, but even subtle impairment at a thalamic level or integrated thalamocortical or corticothalamic tracts may disrupt the central orchestration of a variety of cognitive and neurobehavioral functions sufficient to result in many of the symptoms frequently associated with mTBI.

The patients with mTBI examined by Lui et al. were still within the subacute stage with a mean scan time from injury of 23 days (earliest 5 days postinjury), so no answers are provided on how these findings portend outcome. In addition, clinical correlation cannot be made because these neuroimaging findings were not systematically compared with patient symptoms. The Lui et al. study and others like it show the feasibility of machine learning applied to the vexing problem of defining neuroimaging-based biomarkers of mTBI. If such a biomarker can be established, the centuries-old controversies that surround concussion may be resolved. In addition, this (and similar) techniques are evolving the concept of utilizing image analysis in explaining how multiple areas of subtle brain pathology contribute to the injury in mTBI.

AUTHOR CONTRIBUTIONS

Erin D. Bigler: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Ellen Deibert: drafting/revising the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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