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INSIDE

*Doxycycline
treatment for
multiple
sclerosis*
Page 59

*Neurologic
sequelae of
inflammatory
bowel disease*
Page 60

*Cataplexy:
a laughing
matter?*
Page 61

Financial Disclosure:

Neurology Alert's physician editor, Matthew Fink, MD, reports no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study. Peer reviewer M. Flint Beal, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company having ties to this field of study.

Traumatic Brain Injury: A Modern Epidemic of "Shell Shock," Revisited

ABSTRACT & COMMENTARY

By **Matthew E. Fink, MD**

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Dr. Fink reports no financial relationships relevant to this field of study.

Synopsis: Mild TBI may be associated with brain microhemorrhages and white matter disruption, even with mild or absent symptoms of a postconcussion syndrome.

Sources: Hähnel S, et al. Prevalence of cerebral microhemorrhages in amateur boxers as detected by 3T MR Imaging. *AJNR Am J Neuroradiol* 2008;29:388-391; Hoge CW, et al. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med* 2008;358:453-463; Kraus MF, et al. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain* 2007;130(Pt 10):2508-2519; Meares S, et al. Mild traumatic brain injury does not predict acute postconcussion syndrome. *J Neurol Neurosurg Psychiatry* 2008;79:300-306.

TRAUMATIC BRAIN INJURY (TBI) IS A SIGNIFICANT PUBLIC HEALTH problem (incidence is between 180 and 500 per 100,000 population per year), and is the most common neurological cause for hospital admission.¹ The Iraq war has refocused U.S. physicians on this problem, as the military and veterans' health services in this country have been overwhelmed by returning soldiers with serious brain injuries who have survived their bodily injuries. It is estimated that as many as 18% of returning soldiers (of 1.5 million deployed) have suffered at least a mild head injury, with persistent postconcussion symptoms such as irritability, memory problems, headache, and difficulty concentrating.¹ These numbers represent a staggering demand on our health care system, and the recently published studies that we will review in this issue, shed additional light on how we, as neurologists, might approach this problem.

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VOLUME 26 • NUMBER 8 • APRIL 2008 • PAGES 57-64

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Hoge and colleagues from the Walter Reed Army Institute of Research screened 2525 infantry soldiers 3–4 months after their return from year-long deployment in Iraq. Of these soldiers: 124 (4.9%) reported injuries with loss of consciousness (LOC), 260 (10.3%) reported injuries with altered mental status, and 435 (17.2%) reported other injuries during deployment. Of those reporting LOC, 43.9% met criteria for post-traumatic stress disorder (PTSD), compared with 27.3% of those who reported altered mental status, 16.2% with other injuries, and 9.1% with no injuries. Soldiers who had mild TBI and reported LOC were more likely to report poor general health and missed work days, but after adjustment for PTSD and depression, mild TBI was no longer associated with poor physical health outcomes. Based on their survey, the authors concluded that mild TBI is associated with poor health outcomes only in those patients who develop PTSD or depression. They questioned the validity of “postconcussion syndrome” as a specific neurological diagnosis, and suggested that these symptoms might be part of a psychological disorder.

Meares et al studied a consecutive group of 90 patients admitted to a level 1 trauma unit with mild TBI who were diagnosed with postconcussion syndrome (PCS). Using a checklist of symptoms, and comparing the TBI group with 85 non-brain injured hospitalized controls, they looked at the variables that predicted the development of persistent PCS (headache, dizziness, fatigue, anxiety, irritability). They found that the diagnosis of PCS was not specific to patients with TBI; it occurred in 43.3% of those

with TBI and in 43.5% of controls. The strongest predictor of PCS after any type of injury was the presence of a previous affective or anxiety disorder. Females were 3.33 times more likely than males to have PCS.

The studies by Hoge et al and Meares et al only used a symptom screening checklist to diagnose PCS after mild TBI; what would we observe with advanced imaging? Hähnel and coworkers studied 42 male amateur boxers with 3T MR imaging. They paid special attention to the gradient echo sequences, and compared the findings to MR imaging in 37 healthy non-boxing males. The boxers neither participated in fights in which they lost consciousness or required hospitalization, nor had PCS; however, the boxers had a higher prevalence of cerebral microhemorrhages on MR imaging than did the control group.

Finally, Kraus et al used one of the most advanced imaging techniques, diffusion tensor imaging (DTI), to study white matter integrity in a mixed group of patients with TBI. They studied 20 patients with mild TBI, 17 with moderate to severe TBI, and 18 controls. They then examined the relationships between white matter integrity and cognition. Fractional anisotropy was the primary measure of white matter integrity, and they examined 13 regions of interest that encompassed all of the major white matter tracts in the cerebral hemispheres. Cognitive domain scores were calculated from executive, attention, and memory testing. Decreased fractional anisotropy was found in all 13 regions of interest for the moderate and severe TBI group, but only in the corticospinal tract, sagittal stratum, and superior longitudinal fasciculus for the mild TBI group. White matter abnormality load was negatively correlated with all cognitive domains. The investigators felt that irreversible myelin damage occurred in moderate and severe TBI, but reversible axonal injury occurred in patients with mild TBI.

■ COMMENTARY

There are dramatic contrasts between the papers of Hoge et al and Meares et al, who used screening tests of symptoms, compared to the more objective imaging studies of Hähnel et al and Kraus et al. There is a huge difference in their implied conclusions, based on what type of diagnostic study was used. The screening tests seem to suggest that PCS — a constellation of symptoms that includes headache, fatigue, dizziness, anxiety, irritability, insomnia, and cognitive impairments — is a function of psychological disorders, including PTSD, anxiety, and depression. Yet, when advanced imaging is performed in patients with mild TBI, who have minimal

Neurology Alert, ISSN 0741-4234, is published monthly by AHC Media LLC, 3525 Piedmont Road, NE, Building 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/
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ASSOCIATE PUBLISHER: Lee Landenberg.
SENIOR MANAGING EDITOR: Suzanne Thatcher
GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to *Neurology Alert*, P.O. Box 740059, Atlanta, GA 30374.
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Questions & Comments

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or no complaints, microhemorrhages and white matter disruption is discovered.

How do we explain these contradictions, and what does this mean for us as neurologists? First, it is worth restating a fundamental principle: the mind and the brain are the same. So called neuropsychological symptoms, such as PTSD, come from a brain disorder, whatever the etiology; it is perfectly plausible to attribute such symptoms to TBI, not to a vague psychodynamic cause. The DTI study by Kraus shows that there is a continuous inverse relationship between the degree of white matter injury and cognition, but this can only be appreciated if patients are studied with MR imaging and DTI. A screening test of symptoms tells us only about symptoms, not whether the brain has been structurally altered by trauma. I believe it is a disservice to patients who have sustained TBI, in the military or civilian population, to dismiss their complaints as “psychological” without a more intensive investigation with modern imaging.

I wonder what would be found if the soldiers returning from Iraq, who sustained mild TBI, underwent brain imaging studies with MR and DTI? ■

Reference

1. www.braintrauma.org. Accessed 3/18/08.

Doxycycline Treatment for Multiple Sclerosis

ABSTRACT & COMMENTARY

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Dr. Caporaso reports no financial relationships relevant to this field of study.

Synopsis: Addition of doxycycline to interferon-beta therapy in patients with relapsing-remitting multiple sclerosis might improve control of inflammatory lesions.

Source: Minagar A, et al. Combination therapy with interferon beta-1a and doxycycline in multiple sclerosis: an open-label study. *Arch Neurol* 2008;65:199-204.

IN MULTIPLE SCLEROSIS (MS), IT IS BELIEVED THAT autoreactive lymphocytes in the systemic circulation cross the blood-brain barrier (BBB) to induce inflammatory demyelination in the central nervous system.

These lymphocytes express matrix metalloproteinases (MMPs) that proteolyze the extracellular matrix of the BBB, thus facilitating cellular transmigration. Doxycycline has been demonstrated to inhibit MMP-9 activity in laboratory studies. With this in mind, Minagar and colleagues examined the effects of adding doxycycline to the treatment regimen of MS patients who were experiencing breakthrough relapses on interferon beta-1a (IFN beta-1a). In an open-label trial, 15 patients with relapsing-remitting MS (RRMS) who had experienced a relapse within the preceding 2 months were first assessed during a 3-month pretreatment phase while on IFN beta-1a alone and then for a 4-month treatment phase in which doxycycline (100 mg/day) was added.

The mean patient age was 44 years, and 80% of patients were women. Their median duration of RRMS was 4.0 years, with a median expanded disability status score (EDSS) of 3.5 (range 3.0-4.5, consistent with mild disability). The addition of doxycycline was associated with a 39% reduction in gadolinium-enhancing brain lesions, from a pre-treatment median of 8.8 lesions to a post-treatment median of 4.0 lesions. The median decrease in EDSS was 2.3 points. No significant change in serum MMP-9 levels was observed. However, the transendothelial migration of monocytes *in vitro* was reduced in the presence of post-treatment patient's serum compared to pre-treatment serum. These results raise the possibility that the addition of doxycycline to interferon-beta therapy might afford greater anti-inflammatory effects than interferon-beta alone in patients with RRMS. Further, they suggest that doxycycline might mediate these effects by inhibiting the migration of immune cells across endothelial barriers.

■ COMMENTARY

Tetracycline antibiotics such as doxycycline and minocycline have been receiving much attention as possible treatments for a variety of neurological disorders, including stroke, amyotrophic lateral sclerosis (ALS), Huntington's disease, and, of course, RRMS. Their efficacy in these diseases has been mixed to date, with positive treatment effects described for some (e.g., stroke) and negative effects for others (e.g., ALS). The present study by Minagar et al suggests that the addition of doxycycline to interferon-beta might be beneficial to patients with RRMS who continue to experience breakthrough relapses while on interferon alone. However, their findings should be viewed in light of several weaknesses in their study design, the most significant relating to the statistical phenomenon

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