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Formerly AHC Media

Vol. 37, Issue 10, June 2018
AHCMedia.com

Neurology
[ALERT®]

Evidence-based summaries of the latest clinical neurology research

SPECIAL ISSUE: TRAUMATIC BRAIN INJURY

ABSTRACT & COMMENTARY

Prediction of Persistent Post-concussion Symptoms After Mild Traumatic Brain Injury

By Louise M. Klebanoff, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Persistent post-concussion syndrome may last for more than six months, and risk factors include female sex, neck pain, headache, and post-concussive symptoms at two weeks after the injury.

SOURCE: Cnossen MC, van der Naalt J, Spikman JM, et al. Prediction of persistent post-concussion symptoms. *J Neurotrauma* 2018; Apr 25. doi: 10.1089/neu.2017.5486. [Epub ahead of print].

Mild traumatic brain injury (mTBI), a common condition in the general population, frequently results in persistent post-concussive symptoms (PPCS). Although most patients who develop an acute post-concussive syndrome improve in the days or weeks following the injury, a significant proportion of patients develop persistent cognitive, somatic, and emotional symptoms that can last for six months or longer following the injury. PPCS is associated with reduction in health-related quality of life and with work absenteeism, making it a serious public health concern. Cnossen et al aimed to develop an algorithm to identify patients at risk of developing PPCS based on their initial presenting complaints.

Previous studies aimed at identifying predictors for PPCS have not been validated externally. In addition, these models did not consider the role of acute complaints reported in the ED, such as headache, nausea, vomiting, and neck pain. Using the Dutch multicenter, prospective, observational UPFRONT study, the authors aimed to assess the quality and clinical value of the existing prediction models for six-month PPCS in patients with mTBI and to develop a new model ("The UPFRONT-PPCS model") based on relevant predictors from existing models and complaints at the ED.

The authors reviewed data from a prospective cohort study conducted in three Level I trauma centers in

Financial Disclosure: *Neurology Alert*'s Editor in Chief Matthew Fink, MD; Peer Reviewer M. Flint Beal, MD; Executive Editor Leslie Coplin; Editor Jonathan Springston; and Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

Neurology
[ALERT]

Neurology Alert (ISSN 0741-4234) is published 12 times annually by AHC Media, a Relias Learning company
111 Corning Road, Suite 250
Cary, NC 27518-9238
AHCMedia.com
GST Registration Number: R128870672.
Periodicals Postage Paid at Cary, NC, and additional mailing offices.

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the Netherlands between 2013 and 2015. They included all patients 16 years of age or older with an admission Glasgow Coma Scale (GCS) score of 13-15, post-traumatic amnesia (PTA), or loss of consciousness (LOC) and who had sufficient comprehension of the Dutch language. They excluded patients with drug or alcohol addiction, homelessness, or dementia. All patients had computed tomography (CT) scanning. The medical records were reviewed for prior TBI, education level, LOC, PTA, and ED complaints of headache, nausea/vomiting, and neck pain. Post-concussive symptoms (PCS) were assessed at two weeks and again at six months using the Head Injury Symptoms Checklist (HISC), a 21-symptom questionnaire. Patients were classified as PCS persisting for two weeks and PPCS persisting for six months if they indicated that at least three of the following symptoms were worse than before the injury: headache, dizziness, fatigue, irritability, difficulties falling asleep or staying asleep, concentration problems, memory difficulties, intolerance of alcohol, or anxiety. Post-traumatic stress symptoms were assessed at two weeks with the Impact of Event Scale.

A total of 1,151 patients were included in the UPFRONT study, of whom 591 (51%) completed the six-month HISC. The included patients had a mean age of 51 years, 41% were female, and 16% had intracranial traumatic abnormalities on their initial head CT. At six months following the injury, 370 patients (63%) reported at least one of eight symptoms and 241 (41%) reported three or more symptoms, fulfilling the criteria for PPCS. The most commonly reported symptoms were fatigue (38%), concentration problems (36%), and memory problems (35%).

Backward selection with all variables resulted in the inclusion of three variables: female sex (odds ratio [OR], 1.48; 95% confidence interval [CI], 1.01-2.18), two weeks PCS (OR, 4.89; 95% CI, 3.19-7.49), and two weeks post-traumatic stress (OR, 2.98; 95% CI, 1.88-4.73). The addition of acute complaints in the ED improved the model, but only neck pain was statistically significantly associated with six-month PPCS (OR 2.58, 95% CI 1.39-4.78). In a univariate analysis, there was a statistically significant association between headache and PPCS.

PCS after two weeks was the strongest predictor in the model. Among the 241 patients with PPCS at six months, 192 (80%) reported three or more symptoms after two weeks and almost all (97%) reported at least one symptom after two weeks. Of the 333 patients reporting three or more symptoms after two weeks, only half (192) still reported three or more symptoms after six months. The authors also found that patients with a GCS score lower than 15, patients admitted to the hospital, patients reporting dizziness,

[Mild traumatic brain injury is common in the general population, and persistent post-concussive symptoms cause a significant public health burden.]

and patients having enhanced scores on the symptoms checklist or the hospital anxiety and depression scale after two weeks had higher odds of developing PPCS in both univariable and multivariable analyses.

■ COMMENTARY

Mild traumatic brain injury is common in the general population, and persistent post-concussive symptoms cause a significant public health burden. Because of the complexity in developing a predictive model for PPCS, existing models often underestimate the risk of PPCS and have not been validated externally. The authors sought to improve existing models by the adding factors noted at ED presentation. They found that PPCS at two weeks was the strongest predictor. Of the acute symptoms analyzed, neck pain was statistically associated with PPCS; it is thought that concomitant cervical soft tissue injury contributes to PPCS. It may be helpful to be able to predict patients at higher risk for the development of PPCS. Acute interventions, including physical therapy to reduce neck pain, therapy or medications to reduce psychological complaints, and cognitive remediation, could be introduced more readily to those patients at higher risk for the development of PPCS. ■

ABSTRACT & COMMENTARY

Intracranial Pressure Changes in Mild Traumatic Brain Injury

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: After an exhaustive review of the animal and human studies literature regarding mild traumatic brain injury (mTBI), Haider et al did not reach consistent conclusions regarding evidence for intracranial pressure elevation in human patients who sustain an mTBI.

SOURCE: Haider MN, Leddy JJ, Hinds AL, et al. Intracranial pressure changes after mild traumatic brain injury: A systematic review. *Brain Injury* 2018; Apr 27. doi: 10.1080/02699052.2018.1469045. [Epub ahead of print].

Traumatic brain injury (TBI) is a term generally used for patients who have suffered a severe blow to the head, resulting in injuries such as cerebral contusion or bleeding into the intracranial vault. Hemorrhage may be multi-compartmental, including the epidural, subdural, subarachnoid, and intra-parenchymal spaces. In addition to the coup and contra-coup effects of direct impact and recoil, acute deceleration of the head leads to shear forces, resulting in diffuse axonal injury (DAI). With DAI, there may be coma and persistent neurological deficits despite normal standard brain imaging (although more advanced techniques, such as tensor diffusion imaging, can show disruption of axonal tracts).

Haider et al aimed to examine the role of intracranial pressure (ICP) in mild traumatic brain injury (mTBI) by performing a systematic review of both animal and human literature. The term "mTBI" is not defined clearly, but closely approximates the term "concussion." It is defined as a blow to the head associated with loss of consciousness (LOC), amnesia (both retrograde and anterograde), mental status change (e.g., dizziness or confusion), and focal neurological signs that are transient. Additionally, mTBI should have normal brain imaging, with an absence of a visible contusion on computed tomography or magnetic resonance imaging (MRI).

According to the Monro-Kellie doctrine, ICP is made up of three components: brain, blood, and cerebrospinal fluid. Given that the cranium is a closed compartment, when there is an addition to these components, for example, intraparenchymal clot or brain edema, the ICP will rise. Taking the Monro-Kellie doctrine into account, mTBI would increase ICP only if it would produce brain edema below the detection of standard imaging techniques.

Management of mTBI generally is dictated by symptoms, with return to activity based on resolution of headache, dizziness, or other acute symptoms. If elevated ICP plays a role, there would be a crucial need for surrogate markers to detect this.

In their literature review, Haider et al used a series of search terms, including but not limited to: mild traumatic brain injury, concussion, Glasgow Coma Scale 13-15, ICP, intracranial hypertension, brain edema, and papilledema. Their search yielded 1,067 papers, 55 of which passed initial screen and nine of which met inclusion/exclusion criteria. There were five animal studies (primarily rodent) and four human studies, including 95 total subjects, with variable numbers of controls totaling 67. Methodology of human studies included one prospective cohort, one small randomized, clinical trial, and two case-control investigations.

There was no uniformity in the animal models. The largest study involved dropping a weight (averaging 60-120 g) onto the head of a mouse with varying numbers of repetitions (generally daily, for a range of five to 10 days). Another study included sequential impacts on a rat head (helmeted) using a 50 g projectile at a velocity averaging 11.2 m/sec. One animal study involved direct cortical impact on a rodent using a piston following a small craniotomy, producing focal hemorrhage and edema seen post-mortem. Other animal models mimicked a "blast" injury, using pulses of compressed air when the rat was placed in a "shock tube." Notably, in all of the animal models, the rodent was motionless, with an external force applied, as opposed to much of human head injury, which involves a subject moving at a high velocity and striking an immovable object (e.g., a windshield). Importantly, all of the animal models included direct ICP measurements with invasive probes placed through the cranium. The majority of animal studies included multiple blows. Given this, mTBI can be subcategorized as repetitive mild TBI (rmTBI), which may be a more relevant model than merely an isolated head strike.

Of the five animal studies, two did not show significant ICP increases, but of the three that did, there were consistent data regarding the time course of ICP change. Overall, there was a steady increase in ICP between six and 10 hours post-impact, with a plateau at one day and a trend toward resolution starting at two days and

returning to normal or near normal between three and seven days. This ICP trajectory is typical for the edema patterns seen in cortical contusions. The authors suggested that this may explain the "delayed" symptoms in mTBI patients who have delayed symptoms 12-24 hours or more after a blow to the head. Mechanistically, this is unlikely, since humans with concussions (especially those who are initially normal) do not have the types of brain lesions seen in these significantly injured animals. Nonetheless, the importance of sequential exams is important, as return-to-play decisions in athletes are best made after watchful waiting.

The four human studies provided conflicting results without direct ICP measurements available. Two studies using MRI brain volume showed a decrease in MRI volumetrics in mTBI patients compared to controls, which the authors concluded as evidence of decreases in ICP. One study, using phase contrast MRI methodology with assessment of venous compliance, showed significant increases in mTBI patients compared to controls, but this study was done an average of 11 years after impact. The authors cited one clinical study using 3% hypertonic saline showing benefit for mTBI and characterized this as "indirect evidence" of an ICP increase. "Benefit" was decreased as a 2-point decrease on the Faces pain scale in subjects treated with 3% saline compared to subjects treated with normal saline.

■ COMMENTARY

This "review" of data on mTBI was not amenable to typical meta-analysis methodology and, therefore, could not reach any statistical conclusions regarding mTBI and ICP. On a descriptive, qualitative level, this review was inconclusive overall. Given the mixture of animal and human data, with variable methods of assessing ICP, and the ambiguity of the nature of mTBI itself, there was too much heterogeneity to reach any consistent conclusion.

In the animal models, there was little uniformity in the mechanism used for brain trauma, with the overall severity likely more intense than in human concussion (including a direct piston blow to the cortex following craniotomy). The authors acknowledged that assessment for mild ICP changes in humans could be made only using noninvasive means. Lower brain volumes were seen in head-injured patients compared to controls, but it is unclear how this was related to ICP. More accurate, complex MRI analysis using phase contrast and venography techniques may provide useful data regarding ICP, but the only data were in patients who were years removed from their injury and is of questionable significance. One possible noninvasive surrogate marker of ICP elevations in critically ill subjects is optic nerve sheath diameter as measured by trans-orbital transcranial Doppler. This technique may be useful in detecting ICP increases in mTBI, but may not be sensitive enough for subtle increases in ICP, with a high dependency on the specific diameter cutoff values chosen.

Although these authors did not reach conclusions regarding ICP in mTBI, it is important work, given concerns that repetitive episodes of mTBI (concussion) can lead to accelerated brain degeneration (chronic traumatic encephalopathy). This review draws attention to the significant challenges that remain in understanding of how such mTBI injuries may damage the brain over time. ■

ABSTRACT & COMMENTARY

What Are the Early Predictors for Post-traumatic Epilepsy After Injury?

By Kimberly Pargeon, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Pargeon reports no financial relationships relevant to this study.

SYNOPSIS: Following traumatic brain injury, early (first five days after injury) epileptiform abnormalities on EEG were seen more commonly in patients with subsequent post-traumatic epilepsy (PTE), compared to controls, and were found to be a significant and independent predictor of PTE. The presence of subdural hemorrhage was the only other independent predictor of PTE.

SOURCE: Kim JA, Boyle EJ, Wu AC, et al. Epileptiform activity in traumatic brain injury predicts post-traumatic epilepsy. *Ann Neurol* 2018;83:858-862.

Traumatic brain injury (TBI) is a significant cause of morbidity and mortality for both adults and children, with about 12% resulting in hospitalization or death.[1] Post-traumatic seizures can be a relatively common complication, affecting up to 20% of patients, especially those with more severe injuries requiring surgery and those of younger age.[1] Patients with acute TBIs commonly are placed on prophylactic anti-seizure drugs (ASD), but duration of treatment is often unclear, as is which patients will go on to develop post-traumatic epilepsy (PTE). Kim et al sought to determine if epileptiform abnormalities (EAs) seen on initial EEG and other

demographics could be used as early predictors for development of PTE within the first year after TBI.

The authors retrospectively reviewed records for adult patients presenting with TBI from 2011-2015 to a single tertiary care center in the northeastern United States (Massachusetts General Hospital). All patients underwent EEG monitoring during their initial admission for TBI. Twenty-five consecutive patients were identified who developed PTE, defined as at least one seizure in the two to 12 months post-TBI. Twenty-five age-matched controls also were identified with comparable TBIs (as determined by similar Glasgow Coma Scale [GCS] at admission), but without PTE by one year. EAs on EEG were classified by a standardized nomenclature and were as follows: seizures, sporadic epileptiform discharges (EDs), lateralized or generalized periodic discharges (LPDs or GPDs), and lateralized rhythmic delta activity. The authors also recorded the incidence of generalized rhythmic delta activity, as well as polymorphic generalized and focal slowing, but none of these were considered EAs. The timing of target EEG activity was noted relative to the day of TBI onset. Finally, the authors calculated associations between PTE and certain demographic variables, including age, gender, admission GCS, and the presence of intracranial hemorrhage delineated by type (intraparenchymal, subdural, epidural, or subarachnoid).

Overall, patients with subsequent PTE were monitored longer on EEG, relative to controls. Acute EAs also were nearly twice as common in patients with PTE (64% vs. 36%) when controlling for the presence of subdural hemorrhage (SDH), making EAs a significant and independent predictor of PTE (odds ratio, 3.16).[1] More specifically, when looking at the types of EAs, only EDs showed a significant association with PTE, as did focal slowing, although the latter was not classified as an EA. EDs, when observed, often were seen early, with about half seen at five days or sooner after the TBI. Early seizures and LPDs showed positive associations with PTE development, but neither were statistically significant. The only demographic variable found to be significantly associated with later PTE was the presence of SDH. In fact, the authors found that SDH and EAs, specifically EDs, independently contributed to the risk of developing PTE without a relationship to one another, suggesting these were "independent causal factors."[1]

Kim et al demonstrated a significant association for patients with TBI and SDH for later development of PTE, which has been reported previously. However, this study also suggests that early EAs, particularly EDs, are significantly and independently associated with later PTE, which has not been reported previously. In addition, although not considered an EA, polymorphic focal slowing was significantly associated with later PTE. The authors point to prior evidence demonstrating EEG slowing in areas where the blood-brain barrier was disrupted associated with TBI, more commonly seen in patients with PTE, compared to those who did not develop later seizures.[2] However, the key for the associated EAs is that these often were seen *early*, within the first five days after the TBI in the Kim et al study, so early EEG monitoring could be used to diagnose and even predict patients with TBI at higher risk for later PTE.

[Kim et al demonstrated a significant association for patients with traumatic brain injury and subdural hemorrhage for later development of post-traumatic epilepsy (PTE), which has been reported previously. However, this study also suggests that early epileptiform abnormalities, particularly epileptiform discharges, are significantly and independently associated with PTE.]

One of the limitations of this study is that the sample sizes were small, with only 25 patients included in each group, which likely limited the ability to see effects for relatively infrequent entities, such as LPDs and early seizures, both of which showed a positive association with PTE but were not statistically significant. Further, the authors set their defined period for development of PTE at up to one year after TBI, but some patients in the control group still may have developed PTE after this mark. The authors acknowledged this may not capture all patients with eventual PTE, but believed this would capture the highest risk period.[2] However, the authors of another recent study found an incidence of post-traumatic seizures up to 20.5% by five years after injury.[1] Regardless, Kim et al hope to use EAs as an early biomarker for designing more cost-effective studies for evaluating epileptogenesis in patients with TBIs. ■

REFERENCES

1. Ritter AC, Wagner AK, Fabio A, et al. Incidence and risk factors of posttraumatic seizures following traumatic brain injury: A traumatic brain injury model systems study. *Epilepsia* 2016;57:1968-1977.
2. Tomkins O, Feintuch A, Benifla M, et al. Blood-brain barrier breakdown following traumatic brain injury: A possible role in posttraumatic epilepsy. *Cardiovasc Psychiatry Neurol* 2011;2011:765923.

ABSTRACT & COMMENTARY

Longitudinal tau PET as an Outcome Measure for Clinical Trials

By Gloria C. Chiang, MD

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

SYNOPSIS: tau PET imaging shows progression of brain Alzheimer's pathology over time and correlates with cognitive impairment better than amyloid PET. In future clinical trials, tau PET can serve as a biomarker for Alzheimer's disease progression.

SOURCE: Jack CR Jr, Wiste HJ, Schwarz CG, et al. Longitudinal tau PET in ageing and Alzheimer's disease. *Brain* 2018;141:1517-1528.

Alzheimer's disease is widely prevalent and incurable, and numerous clinical trials aimed at halting disease progression in these patients have failed. A new research framework has been suggested to stage Alzheimer's disease on a continuum, based on the presence or absence of beta-amyloid pathology, tau accumulation, and neurodegeneration.[1] Although the amyloid hypothesis of Alzheimer's pathogenesis remains widely accepted, approximately 20% of cognitively normal older adults have been reported to have positive amyloid PET scans,[2] and amyloid correlates weakly with clinical symptoms.[3] This suggests that amyloid, although an early marker of Alzheimer's pathology, may not be sufficient to produce neurodegeneration and subsequent cognitive decline. Rather, the presence of pathological tau marks the crossover from Alzheimer's pathologic change to true Alzheimer's disease.

In this study, researchers analyzed tau PET scans obtained longitudinally in 126 older adults, ranging from 52 to 94 years of age, who were recruited through the Mayo Clinic Study of Aging, a population-based cohort, and the Mayo Alzheimer's Disease Research Center. Fifty-nine of these subjects were cognitively normal and had negative amyloid PET scans, 37 subjects were cognitively normal and had positive amyloid PET scans, and 30 subjects were cognitive impaired with positive amyloid PET scans. All subjects had two tau PET scans, obtained 12 to 15 months apart.

The researchers found that subjects who were cognitively normal and had negative amyloid PET scans showed no evidence of tau accumulation. Subjects who were cognitively normal but amyloid-positive had low rates of tau accumulation (0.5% per year), predominantly in the temporal lobes but also in the parietal lobes. The cognitively impaired group had the highest rates of tau accumulation (3% per year) in nearly all regions of the brain, although the rates of tau accumulation in the medial temporal lobe were not significantly different from the cognitively normal, amyloid-positive group. Taken together, tau accumulates at greater rates at later stages of Alzheimer's disease. Furthermore, tau accumulation loosely follows the Braak staging system, in which tau accumulates first in the temporal regions before spreading to the remainder of the brain.

The researchers then defined "early" and "late" Alzheimer's meta-regions of interest, based on the brain regions that best separated the three groups. Temporal and whole brain regions of interest also were considered, and all meta-regions were found to correlate highly with each other. The researchers found that the sample size required to detect a 25% therapeutic reduction at 80% power in a clinical trial is significantly smaller using tau PET as an outcome measure instead of cognition. For example, the sample size required for a trial targeting amyloid-positive, cognitively normal individuals would be 1,087 using a tau PET temporal meta-region, compared to 1,360 using cognitive scores. The sample size required for a trial of cognitively impaired individuals would be 282 using the "late Alzheimer's" meta-region, compared to 623 using cognition. Thus, the authors concluded that longitudinal tau PET scans would provide a useful and efficient outcome measurement for clinical trials.

■ COMMENTARY

This is a thoughtfully designed study evaluating longitudinal tau PET across three stages of the Alzheimer's disease continuum, including those without evidence of Alzheimer's pathology (cognitively normal, amyloid-negative), those with early Alzheimer's pathology (cognitively normal, amyloid-positive), and those with Alzheimer's disease with cognitive impairment. Although tau PET is not used clinically yet, its role in clinical trials could be substantial. It has been reported that a quarter of people with a clinical diagnosis of Alzheimer's dementia have no Alzheimer's pathology on autopsy;[4] therefore, the effects of drugs targeting Alzheimer's pathology could be diluted by subjects without the actual disease. Using imaging markers of underlying Alzheimer's pathology, such as amyloid and tau PET scans, would classify subjects more accurately for enrollment in clinical trials. It also is notable that cognitively normal subjects with

negative amyloid PET scans showed no observable tau accumulation. This further supports the amyloid hypothesis of Alzheimer's pathogenesis, in which amyloid is an early event in the disease.

Future studies in larger cohorts with longer follow-up should be performed to validate these findings. As the authors noted, the cognitively impaired group included both subjects with mild cognitive impairment and frank dementia. It would be important to know how the rates of tau accumulation differ with severity of cognitive impairment. The authors also focused on the amnestic form of cognitive impairment, whereas other Alzheimer's subtypes may present with non-memory deficits. The marked heterogeneity of individual tau accumulation trajectories also would be crucial to understand, since group rates of tau accumulation may not be generalizable to individual patients. Finally, although using tau PET as an outcome measure would decrease the number of subjects needed to show a significant effect in a clinical trial, longitudinal PET imaging would markedly increase the cost of the trial, and tau tracers are not yet widely available. ■

REFERENCES

1. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018;14:535-562.
2. Pike KE, Savage G, Villemagne VL, et al. Beta-amyloid imaging and memory in non-demented individuals: Evidence of preclinical Alzheimer's disease. *Brain* 2007;130(Pt 11):2837-2844.
3. Jack CR Jr, Lowe VJ, Weigand SD, et al. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: Implications for sequence of pathological events in Alzheimer's disease. *Brain* 2009;132:1355-1365.
4. Monsell SE, Kukull WA, Roher AE, et al. Characterizing apolipoprotein E e4 carriers and noncarriers with the clinical diagnosis of mild to moderate Alzheimer dementia and minimal beta-amyloid peptide plaques. *JAMA Neurol* 2015;72:1124-1131.

ABSTRACT & COMMENTARY

Anti-MAG Antibodies: Clinical and Therapeutic Aspects

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Anti-MAG antibody-associated neuropathy may present as many disorders, including small fiber neuropathy, sensorimotor neuropathy, Guillain-Barré-like syndrome, and multifocal motor neuropathy. Rituximab appears to be the best therapeutic option.

SOURCE: Svahn J, Petiot P, Antoine JC, et al. Anti-MAG antibodies in 202 patients: Clinicopathological and therapeutic features. *J Neurol Neurosurg Psychiatry* 2018;89:499-505.

Considered to be distinct from chronic inflammatory demyelinating neuropathy (CIDP) because of its resistance to standard immunomodulatory therapies to which CIDP usually responds, distal acquired demyelinating symmetric neuropathy often is associated with an IgM protein, and approximately 50% of these patients also demonstrate anti-myelin associated glycoprotein (anti-MAG) antibodies. It is unclear whether the presence of these antibodies alters the clinical features of this condition.

To address this question and to determine the clinical, pathological, and therapeutic features of patients with low (≥ 1,000 to < 10,000 Bühlmann Titer Units [BTU]), medium (10,000 to 70,000 BTU) or high (≥ 70,000 BTU) anti-MAG antibody titers, a retrospective and prospective analysis of the medical records of 202 patients from 14 neuromuscular centers was undertaken between March 2014 and April 2016 in Lyon, France. Neuropathy was classified as acute (progression < 1 month), subacute (progression over > 1 month but < 6 months), or progressive (progression over ≥ 6 months), and the Overall Neuropathy Limitations Scale score and modified functional impairment scale score, ranging from 0 to 5 at the most severe, were ascertained. Patients were defined as *typical* if they presented with sensory ataxic distal polyneuropathy or sensory or sensorimotor length-dependent polyneuropathy without ataxia. Patients were classified as *atypical* if they presented with a Guillain-Barré-like syndrome, chronic sensorimotor polyradiculoneuropathy, small fiber neuropathy, asymmetric or multifocal neuropathy, or associated motor neuron disease. Where available, electrodiagnostic studies, cerebrospinal fluid, and nerve biopsies were reviewed, and types of treatment were assessed to determine if they were administered for neurologic or hematologic considerations. Statistical analysis comprised Fisher's exact test, the Mann-Whitney test, and the Kruskal-Wallis test, with significance set at $P = 0.05$.

Among 202 patients, 133 men and 69 women, whose data were collected, mean age at symptom onset was

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62.6 years, with a mean of 3.1 years to time of diagnosis as an anti-MAG neuropathy. Anti-MAG antibody titers at diagnosis were low, medium, or high in 11%, 51%, and 38%, respectively. Thirty-four patients (16.8%) presented with an "atypical" phenotype, without significant differences of anti-MAG antibody titers, including a Guillain-Barré syndrome-like presentation in four (2%), chronic sensorimotor polyradiculoneuropathy in 22 (10.9%), multifocal or asymmetric neuropathy in six (3%), and small fiber neuropathy or sensory neuropathy with amyotrophic lateral sclerosis in one each (0.5%). No difference in anti-MAG titers was seen between the typical or atypical variants. Rituximab was the treatment modality used most often (n = 92, 45.5%) and resulted in an objective clinical response in 31.5%, stabilization in 29.3%, and transient, reversible worsening in 12% (n = 11). Other treatment modalities included chlorambucil, cyclophosphamide, fludarabine, and dexamethasone. Anti-MAG antibody titers did not correlate with the clinical spectrum of neuropathy, but rituximab may be beneficial if used early in the course of disease.

■ COMMENTARY

In approximately 75% of polyneuropathy patients with immunoglobulin M (IgM) monoclonal gammopathy, the most common paraproteinemic neuropathy, the monoclonal IgM reacts with MAG, sulfoglucuronyl glycosphingolipid, or other peripheral nerve glycolipids that serve as antigens. When deposited on the myelin sheath with complement, splitting of the myelin lamellae occurs, arguing that these antibodies are pathogenic. Sensory ataxia results when adoptive transfer of patients' IgM is performed on susceptible host animals, further supporting their pathogenicity. Nevertheless, immunotherapy remains disappointing. Chlorambucil, cladribine, cyclophosphamide, and intravenous immunoglobulin may be somewhat beneficial, but rituximab shows the most promise. ■

CME QUESTIONS

1. **Which of the following symptoms is associated with a higher risk of developing persistent post-concussive symptoms after mild traumatic brain injury?**
   a. Neck pain
   b. Female gender
   c. Post-concussive symptoms at two weeks
   d. All of the above

2. **Which of the following statements about mild traumatic brain injury (mTBI) is *false*?**
   a. mTBI is defined as loss of consciousness without brain imaging abnormalities.
   b. Concussion is a type of mTBI.
   c. mTBI may be accompanied by confusion, dizziness, and transient focal neurological signs.
   d. mTBI may cause intracranial bleeding and raised intracranial pressure.

3. **What were the two independent predictors of post-traumatic epilepsy after traumatic brain injury?**
   a. Subdural hemorrhage and lateralized rhythmic delta activity
   b. Subdural hemorrhage and seizures
   c. Subdural hemorrhage and epileptiform discharges
   d. Intraparenchymal hemorrhage and epileptiform discharges

4. **Which of the following statements is true regarding Alzheimer's disease brain imaging?**
   a. Brain MRI does not change over the course of Alzheimer's disease.
   b. tau accumulation documented by PET correlates with cognitive impairment.
   c. Amyloid accumulation documented by PET correlates with cognitive impairment.
   d. Amyloid PET scans are not useful in the diagnosis of Alzheimer's disease.

5. **Which of the following statements is true regarding anti-MAG neuropathy?**
   a. Rituximab is of no benefit in the treatment of anti-MAG neuropathy.
   b. Type of neuropathy correlates with titers of anti-MAG antibodies.
   c. Anti-MAG neuropathy may present with a Guillain-Barré-like syndrome.
   d. Small fiber neuropathy is never associated with anti-MAG antibodies.

[IN FUTURE ISSUES]

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