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ABSTRACT & COMMENTARY

Significance of Brain Microbleeds After Traumatic Brain Injury

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

SYNOPSIS: Traumatic microbleeds are common in patients with any severity of traumatic brain injury and may be a useful biomarker to predict clinical outcomes.

SOURCE: Griffin AD, Turtzo LC, Parikh GY, et al. Traumatic microbleeds suggest vascular injury and predict disability in traumatic brain injury. *Brain* 2019;142:3550-3564.

Traumatic brain injury (TBI) is common. Each year, there are approximately 2.5 million emergency department visits for TBI in the United States alone.[1] Although many patients with TBI recover, more than 3 million Americans live with disability due to TBI.[2] Given the heterogeneity of severity, etiology, and type of TBI, it often is difficult to predict who will develop disability, especially among patients with mild TBI in whom initial clinical examination and computed tomography (CT) scans may be normal. Therefore, discovering novel biomarkers that may aid in the diagnosis and prognosis of TBI is essential and may lead to targeted therapies to improve outcomes.

In this prospective, observational study, Griffin et al evaluated the prevalence and significance of traumatic microbleeds on brain magnetic resonance imaging (MRI) among patients with TBI. Specifically, the authors sought to 1) evaluate the frequency of traumatic microbleeds among patients with TBI; 2) evaluate whether traumatic microbleeds were associated with disability after TBI; and 3) elucidate the underlying pathology of traumatic microbleeds. The study included all patients with TBI who received a head CT; they were enrolled within 48 hours of injury and received research MRI. The Glasgow Outcome Scale-Extended was used to evaluate disability (defined as a score of ≤ 6) at a

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30- or 90-day follow-up visit. Binary logistic regression was used to evaluate the association between the presence of traumatic microbleeds and disability after adjustment for trauma severity, Glasgow Coma Scale (GCS) score, time to MRI, and presence of injury on CT.

A total of 439 patients were included in the study: 365 (83%) had mild TBI, 55 (13%) had moderate TBI, and 19 (4%) had severe TBI. Traumatic microbleeds were defined as small foci of hypointensity seen on the initial T2*-weighted MRI. Two types of microbleeds — punctate and linear — were found. Microbleeds were found in 27% of patients with mild TBI, 47% of patients with moderate TBI, and 58% of patients with severe TBI. Not surprisingly, injury severity, GCS at time of arrival, and evidence of injury on the initial CT all were significantly associated with the presence of traumatic microbleeds. Among the 250 (55%) patients who had a 30- or 90-day follow-up visit, the presence of traumatic microbleeds was associated with disability at the time of follow-up (odds ratio, 2.5).

To better understand the underlying etiology of traumatic microbleeds, the investigators performed an autopsy with postmortem brain imaging on a single patient with severe TBI who had evidence of traumatic microbleeds on MRI. Interestingly, when the investigators evaluated the tissue histopathology that correlated to the area of traumatic microbleed on MRI, there was no evidence of axonal injury. Instead, the investigators found evidence suggesting that traumatic microbleeds may represent vascular injury. The microbleed seen on brain MRI may merely represent a small fraction of the tissue-level vascular injury that is too microscopic to visualize on present-day brain imaging.

■ COMMENTARY

The authors of this prospective, observational study demonstrated that traumatic microbleeds are common in TBIs of all severity. In addition, the authors suggested that traumatic microbleeds may be a useful biomarker to predict clinical outcomes, although these results are limited by selection bias and likely by residual confounding. Further studies will be necessary to evaluate the significance of traumatic microbleeds and whether their presence may explain why patients with TBI who have grossly normal clinical exams and head CT scans go on to have significant neuropsychological disability.

Finally, the investigators reported intriguing findings that challenge the currently accepted belief that traumatic microbleeds represent diffuse axonal injury. Instead, the investigators purported that traumatic microbleeds could represent vascular injury. If replicated, further study of vascular injury, and conceivably therapeutics, to promote vascular recovery could be implemented in patients with TBI. ■

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ABSTRACT & COMMENTARY

Neuropathology and Dementia in Football Players With CTE

By Nitin K. Sethi, MD

Associate Professor of Neurology, Weill Cornell Medical College; Director, Weill Cornell Concussion and Brain Injury Center

Dr. Sethi reports no financial disclosures relevant to this field of study.

SYNOPSIS: The authors of a cross-sectional study involving analysis of data from the ongoing Understanding Neurologic Injury and Traumatic Encephalopathy (UNITE) study found that dementia is likely a result of neuropathologic changes associated with repetitive head injury as well as non-head trauma-associated vascular pathologic changes in patients with chronic traumatic encephalopathy.

SOURCE: Alosco ML, Stein TD, Tripodis Y, et al. Association of white matter rarefaction, arteriolosclerosis, and tau with dementia in chronic traumatic encephalopathy. *JAMA Neurol* 2019; Aug 5. doi: 10.1001/jamaneurol.2019.2244. [Epub ahead of print].

There is increasing evidence that repetitive concussive and subconcussive brain trauma (repetitive head injury) leads to chronic traumatic encephalopathy (CTE) in U.S. football players. CTE presents with cognitive and neuropsychiatric disturbances that can progress to dementia. The pathways that lead to dementia remain to be elucidated scientifically, and it is suggested that tau and non-tau pathologies are involved.

Alosco et al conducted a cross-sectional study involving analyses of data from the ongoing Understanding Neurologic Injury and Traumatic Encephalopathy (UNITE) study, which includes brain donors from the Veterans Affairs–Boston University–Concussion Legacy Foundation brain bank between 2008 and 2017. The study included 180 men who had played football and were neuropathologically diagnosed with CTE. Men younger than 40 years of age and those with missing data were excluded. The mean age at death was 67.9 years. The number of years of football play acted as a proxy for repetitive head impacts.

The investigators conducted neuropathological assessment of white matter rarefaction and arteriolosclerosis severity; number of infarcts, microinfarcts, microbleeds, and phosphorylated tau accumulation determined by CTE stage; and semiquantitative rating of dorsolateral frontal cortex (DLFC) neurofibrillary tangles (NFT). Informant-based retrospective clinical interviews determined dementia diagnoses via diagnostic consensus conferences. Of the 180 patients, 120 (66.7%) were found to have dementia prior to death. Moderate to severe white matter rarefaction (84 of 180 [46.6%]) and arteriolosclerosis (85 of 180 [47.2%]) were common, but infarcts, microinfarcts, and microbleeds were not common. Using a simultaneous equations regression model that controlled for age and race, they found that more years of play was associated with more severe white matter rarefaction and greater phosphorylated tau accumulation. White matter rarefaction and DLFC NFTs were associated with dementia. Arteriolosclerosis and years of play were not associated with dementia, but arteriolosclerosis was independently associated with dementia.

■ COMMENTARY

Physicians evaluating and treating athletes, especially those involved in contact sports such as U.S. football, are concerned by the increasing evidence that repetitive concussive and subconcussive brain trauma leads to CTE. Patients with CTE present with cognitive and neuropsychiatric disturbances that can progress to dementia in some cases.[1] It is unclear whether dementia in CTE patients is the result of neuropathologic changes associated with repetitive head injury or if other non-head trauma-associated pathologic changes also contribute. To confound matters, post-traumatic proteinopathies have similarities to dementias such as Alzheimer's disease (AD). So, while it is difficult to disentangle the neuropathological changes induced by repetitive head trauma from those induced by a progressive neurodegenerative disorder such as AD, the mechanism by which head trauma can trigger neurodegeneration increasingly is understood. Diffuse axonal injury disrupts microtubule function, providing the potential framework for pathologies of tau and amyloid to develop. While CTE only can be identified confidently at postmortem, imaging biomarkers, such as magnetic resonance imaging and positron emission tomography, and fluid biomarkers, such as neurofilament light, can be used to characterize endophenotypes associated with distinct types of post-traumatic neurodegeneration. It is likely that football players who suffer repetitive head trauma and also have multiple vascular risk factors for cerebrovascular disease are most at risk for developing dementia in association with CTE. Clinical trials addressing some of these factors with neuroprotective and disease-modifying treatments are needed. ■

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ABSTRACT & COMMENTARY

Fluctuating Cognition: An Often-Neglected Feature of Lewy Body Dementias

By Silky Pahlajani, MD

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

SYNOPSIS: Clinical identification of fluctuating cognition is challenging. A better understanding of potential etiological mechanisms can allow for optimization of clinical assessment tools and targeted therapeutic approaches.

SOURCE: O'Dowd S, Schumacher J, Burn DJ, et al. Fluctuating cognition in the Lewy body dementias. *Brain* 2019;142:3338-3350.

Dementia with Lewy bodies (DLB) is the second most common type of neurodegenerative dementia in older adults (after Alzheimer's disease). Per the 2017 consensus diagnostic criteria, one of the core clinical features of DLB is fluctuating cognition (FC), typically accompanied by parkinsonism, visual hallucinations, and REM sleep behavior disorder.

O'Dowd et al reviewed data related to potential etiological mechanisms of FC in DLB in correlation with clinical features. Alterations in attention and alertness are the primary manifestations of FC. A key distinguishing feature is that it demonstrates a spectrum of severity (lasting seconds or minutes to days of altered attention or drowsiness) due to an internally mediated process resulting in a spontaneous, periodic, and transient quality. Comparatively, fluctuations in Alzheimer's disease generally are a consequence of interactions or changes in the external environment, with memory failure as a prominent symptom. Data collated from various studies revealed that prevalence rates of FC are lower (29-39%) and less heterogeneous in patients with possible DLB and mild cognitive impairment (MCI) compared to those with probable DLB (45-90%). Cognitive fluctuations in DLB are not necessarily associated with poorer prognosis or greater overall cognitive decline based on results of two cross-sectional studies. Fluctuating cognition in patients with non-amnestic MCI was a predictor of conversion to DLB and a characteristic feature of prodromal DLB.

Of the four clinical scales used for assessment of fluctuating cognition, the Dementia Cognitive Fluctuation Scale[1] was found to accurately distinguish between DLB, Alzheimer's disease, and vascular dementia, especially in patients with mild or moderate dementia. It also demonstrated good test-retest and inter-rater reliability and had two versions, a full 17-item questionnaire for use in research studies and a shorter four-item version for use in clinical practice.

Although several theories have been postulated to explain the underlying mechanisms of FC, there is evidence for two broad mechanistic etiologies: cognitive fluctuations due to disturbance in attentional circuitry (as a consequence of hypocholinergic etiology or alterations in large-scale networks) or due to a disorder of sleep/arousal. Attentional circuitry perturbations can be caused by a loss of cholinergic neurons in nucleus basalis of Meynert (NBM), involved in transmitting "bottom-up" signals of attention, and shown to correlate with reduced cortical choline acetyltransferase levels in DLB. This theory is supported by improvement in FC after treatment with cholinesterase inhibitors. Complex functional disturbances in large-scale neuronal networks can occur via various mechanisms. These include: 1) atrophy of regions containing von Economo neurons involved in the integrity of attentional circuits; 2) dysfunction at various levels of the default mode network; and 3) abnormal perfusion in motor areas followed by decreased perfusion in partial areas correlating with cognitive fluctuations. There is strong evidence to support that subcortical thalamic cholinergic denervation is associated with FC because alpha-synuclein pathology has a prominent impact on the reticulo-thalamo-cortical activating system, which is critical for mediating consciousness. Fluctuating cognition might be a manifestation of disrupted sleep-wake homeostasis. This is based on the affinity of Lewy bodies for the hypothalamus in DLB and Parkinson's disease, as well as very poor sleep efficiency and distortions in sleep-wake architecture in advanced DLB. Some studies have suggested a correlation between multiple sleep latency tests and polysomnography parameters, whereas others have not. These findings further support that fluctuations may have two distinct aspects, one associated with arousal/alertness and another with attention.

EEG techniques, in addition to functional neuroimaging, also have helped better understand functional disturbances associated with FC. Distinct EEG patterns that correlate with cognitive fluctuations in DLB include the presence of prominent posterior slow-wave activity and an increase in dominant frequency variability and slowed dominant EEG rhythm compared to pre-alpha/fast theta activity. Studies show that these EEG abnormalities correlate with severity of FC in DLB and are identifiable in the MCI stage, potentially preceding symptoms of FC.

For symptomatic treatment, studies demonstrate that cholinesterase inhibitors, specifically donepezil, can improve fluctuating cognition, as measured by clinical assessment scales and EEG abnormalities. Memantine is more efficacious for targeting attention in DLB. There is conflicting evidence regarding the therapeutic effect of deep brain stimulation and the use of modafinil and armodafinil.

■ COMMENTARY

There are limited treatment options available to patients with DLB. Identification and appropriate therapeutic management of fluctuating cognition in DLB can improve a patient's quality of life and ability to perform activities of daily living and reduce caregiver burden. Better understanding of mechanistic theories can be useful in clinical practice, especially when considering medication trials for symptoms of cognitive fluctuations vs. attentional deficits in DLB. It also increases the neurologist's

awareness to screen for a constellation of symptoms, potentially leading to more accurate identification of FC, therefore obtaining targeted and pertinent tests. ■

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ABSTRACT & COMMENTARY

Submentalis REM Sleep Muscle Activity: A Potential Biomarker for Synucleinopathy

By Daniel A. Barone, MD, FAASM

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Dr. Barone reports he is on the speakers bureau for Jazz Pharmaceuticals and is a consultant for Molecule Mattress.

SYNOPSIS: Objective findings during polysomnography (REM sleep without atonia), as diagnosed with submentalis EMG recordings, may be a biomarker for synucleinopathies, such as Parkinson's disease and multiple system atrophy.

SOURCE: McCarter SJ, Feemster JC, Tabatabai GM, et al. Submentalis rapid eye movement sleep muscle activity: A potential biomarker for synucleinopathy. *Ann Neurol* 2019;86:969-974.

Parkinson's disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), grouped as "parkinsonism" syndromes, often have overlapping symptoms, which can complicate diagnosis. This is unfortunate because the prediction of treatment response, prognostic counseling, and use of disease-modifying therapy rely on such accuracy. Currently, diagnosis of parkinsonism is based on clinical evaluation with limited biomarkers.

Tau accumulation is associated with PSP and CBD (so-called tauopathies), whereas alpha-synuclein accumulation is associated with PD and MSA (so-called synucleinopathies). Rapid eye movement (REM) sleep behavior disorder (RBD) consists of a history of dream enactment behavior (DEB) in conjunction with REM sleep without atonia (RSWA) noted during polysomnography (PSG) testing. RBD strongly correlates with alpha-synucleinopathy, but much less with tauopathies. Despite this clear difference, clinical DEB is not specific for parkinsonism etiology. Thus, the authors aimed to determine whether quantitative RSWA testing distinguishes probable synucleinopathy and tauopathy subtypes of parkinsonism, using electromyographic (EMG) analysis in the submentalis and anterior tibialis muscles in parkinsonian patients.

The authors analyzed RSWA in 97 patients at the Mayo Clinic between 2008 and 2015. Patient groups included 53 probable synucleinopathy patients (meeting clinical diagnostic criteria for PD [n = 33] and MSA [n = 20]) and 24 probable tauopathy patients (meeting clinical criteria for PSP [n = 17] or CBD [n = 7]). These groups were analyzed against 20 age- and sex-matched controls. Of note, while both visual scoring (by standard American Academy of Sleep Medicine standards) and automated scoring (via HypnoLab software) were used and compared, the automated scoring method demonstrated more cases of RSWA and was more precise in that it allowed for a REM atonia index (RAI).

Comparing RAI across the four parkinsonian conditions, elevated submentalis EMG activity was highly sensitive (70-77%) and specific (95-100%) in distinguishing synucleinopathy from tauopathy, whereas with anterior tibialis EMG, synucleinopathy discrimination was poor. The authors concluded that elevated submentalis EMG activity in RSWA appears to be a potentially useful biomarker for presumed synucleinopathy etiologies in parkinsonism.

■ COMMENTARY

With this paper, the authors have opened a new door for further research into RSWA and RBD, an ever-growing subset of neurology and sleep medicine. The authors mentioned that among the 97 patients, the use of quantitative scoring demonstrated more cases of RSWA than qualitative scoring by visual inspection, and there was poor correlation between the quantitative and qualitative methods. This is important, as often in clinical practice, RSWA typically is scored through visual inspection and thus, per this study, may be missed. Perhaps in the future, automated/universal scoring of EMG (especially in REM sleep) will allow for more uniform data analysis, with positive implications for both clinical and research endeavors.

Another element worth discussing is that in clinical practice, isolated RSWA without DEB is considered a PSG finding of unclear significance. The authors compared RSWA in cases both with and without DEB, and found

the association that RSWA can distinguish synucleinopathy from tauopathy regardless of DEB. This finding adds to the growing literature that suggests that isolated RSWA may be a harbinger of synucleinopathy and requires further investigation. ■

ABSTRACT & COMMENTARY

Stereotactic Radiosurgery for the Treatment of Cerebral Cavernous Malformations

By Susan C. Pannullo, MD, and Swathi Chidambaram, MD

Dr. Pannullo is Associate Professor of Clinical Neurological Surgery, Weill Cornell Medical College; Adjunct Assistant Professor of Neurological Surgery, Columbia University College of Physicians and Surgeons; and Associate Attending Neurological Surgeon, NewYork-Presbyterian Hospital. Dr. Chidambaram is Fellow in Neurological Surgery, Weill Cornell Medical College.

Dr. Pannullo and Dr. Chidambaram report no financial relationships relevant to this field of study.

SYNOPSIS: In this comprehensive review of studies comparing treatments for cerebral cavernous malformations, there were no randomized or blinded outcome trials, and the most effective treatment remains uncertain.

SOURCE: Poorthuis MHF, Rinkel LA, Lammy S, Al-Shahi Salman R. Stereotactic radiosurgery for cerebral cavernous malformations: A systematic review. *Neurology* 2019;93:e1971-e1979.

Cerebral cavernous malformations (CCMs) are intracranial vascular malformations found in 0.15-0.44% of the population. Often, CCMs are incidental findings on computed tomography (CT) and magnetic resonance imaging (MRI) scans. However, these lesions may present with seizures, neurological deficits, or intracerebral hemorrhages. The goal of treatment is to prevent these complications. Patients with CCM are managed conservatively with observation or treated with surgical excision or stereotactic radiosurgery (SRS). The role of SRS for CCM remains controversial, as randomized, controlled trials have not been performed, and no observational studies at low risk of bias have shown meaningful associations between treatment of CCM with SRS and better outcomes.

Poorthuis et al performed a systematic review of the literature to quantify clinical outcomes after SRS for CCM and compare them to microsurgical excision or conservative management to further explore the efficacy of SRS for treatment of CCMs. They searched Ovid Medline and Ovid EMBASE from inception until June 1, 2018, for peer-reviewed publications describing clinical outcomes after SRS for ≥ 10 people with CCM in cohorts with or without a comparison group treated with neurosurgical excision or conservative management. Two reviewers independently extracted data from the included studies to quantify cohort characteristics and the incidence of the primary outcome and secondary outcomes. The primary outcome was death attributed to CCM or its treatment. The secondary outcomes were incident nonfatal symptomatic intracranial hemorrhage (ICH), incident nonfatal and non-hemorrhagic persistent focal neurologic deficits (FND), a composite outcome (death attributed to CCM or its treatment or nonfatal ICH or nonfatal and non-hemorrhagic persistent FND), seizures, adverse radiation effects, and functional outcome.

From screening 361 references and excluding ineligible studies and smaller overlapping reports of included studies, 30 studies involving a total of 1,576 patients undergoing SRS for CCM were included. Of these, three studies compared SRS to neurosurgery, one study compared SRS to neurosurgery and conservative management, one study compared two cohorts receiving different types of SRS, and 25 cohort studies examined SRS alone. In general, included studies were at medium to high risk of bias. None of the studies were randomized, none concealed treatment allocation, and none used blinding of allocation or outcome assessment.

Four nonrandomized studies compared SRS to other treatment modalities, but did not demonstrate dramatic associations. The authors reported pooled estimates of the risks of SRS for CCM over approximately four years after treatment that they assert can be applied to clinical practice, especially for patients with CCM that have caused ICH. The risks after SRS appear similar to the untreated clinical course of CCM, by indirect comparison with the overall five-year risk of ICH found in a patient-level meta-analysis (15.8%; 95% confidence interval, 13.7-17.9). The authors concluded that it is not possible to be confident regarding the beneficial effects of SRS for CCM because of the shortage of comparative studies at low risk of bias, leaving reassurance only from indirect comparisons with untreated clinical course or neurosurgery. Outcomes did not differ by CCM location or type of SRS. The authors reported that after SRS for CCM, the annual incidences of death, ICH, and FND are < 5% and seem comparable to outcomes without SRS.

They concluded that randomized trials of SRS for CCM are needed.

■ COMMENTARY

In this systematic review of SRS for CCM, the authors did not find any randomized trials, but included 30 observational studies involving a total of 1,576 patients (median sample size 34, age 40 years, 91% presented with ICH, 65% infratentorial CCM, and follow-up 48 months). This study reinforces the lack of clarity when choosing treatment options for CCMs. As the authors pointed out, randomized trials and higher-quality observational studies are needed to further investigate the role of SRS vs. surgery or observation in treating CCMs. In current clinical practice, SRS can be a reasonable option for CCMs in cases in which the patient is experiencing progressive neurological decline, intractable seizures, or multiple recurrent hemorrhages and simultaneously is not amenable to surgery. In such cases, a multidisciplinary team can guide the decision-making process regarding which management approach is optimal in any particular case. ■

ABSTRACT & COMMENTARY

Does a Repeat Course of IVIg Help in Severe Guillain-Barré Syndrome?

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports he is a consultant for Merck Sharp & Dohme Corp.

SYNOPSIS: In an open-label, non-randomized clinical trial using a second course of intravenous immunoglobulin (IVIg) to treat patients with Guillain-Barré syndrome, no benefit was observed. A single course of 2 g/kg of IVIg should be administered. No additional treatment is helpful.

SOURCE: Verboon C, van den Berg B, Cornblath DR, et al. Second IVIg course in Guillain-Barré syndrome with poor prognosis: The non-randomised ISID study. *J Neurol Neurosurg Psychiatry* 2019; Oct 5. doi:10.1136/jnnp-2019-321496. [Epub ahead of print].

Despite current treatment, Guillain-Barré syndrome (GBS) remains a severe disease. Artificial ventilation will be required for days to months in 25% of patients, about 20% will be unable to walk after six months, 5-10% will have incomplete recovery, and 3-10% will die. Depending on preferences, availability, contraindications, and risk factors, intravenous immunoglobulin (IVIg) or plasma exchange are equally efficacious and of proven benefit for GBS when administered within weeks of disease onset. However, sequential treatment using plasma exchange followed by IVIg offers no additional benefit. Corticosteroids, either alone or in combination with IVIg, are to be avoided. For severe GBS patients unlikely to regain independent ambulation as identified by the modified Erasmus GBS Outcome Score (mEGOS), does a second course of IVIg have benefit in the treatment of severe GBS, if no significant response was obtained after an initial round?

Using the database of the prospective, observational, International Guillain-Barré Syndrome Outcome Study (IGOS), which included GBS patients within the first two weeks of onset, a comparison was made, with respect to disease course, of patients treated with one course of IVIg, 2 g/kg IVIg over two to five consecutive days, vs. two courses. Exclusionary criteria included patients who died or were lost to follow-up within the first week of study entry, those who received a second course of IVIg as a result of a reported treatment-related fluctuation observed by the local physician, and children younger than 6 years of age, for whom mEGOS is not validated. Patient data were collected at entry, and at weeks 1, 2, and 26, and included GBS disability score, Medical Research Council (MRC) sum score, and the presence of sensory deficits, facial weakness, and prior diarrhea. Improved functional outcome on the GBS disability scale after four weeks was the primary endpoint. Secondary endpoints included improvement of ≥ 1 score on the GBS disability scale at four and 26 weeks, GBS disability score at 26 weeks, median change in the MRC sum score at four and 26 weeks, ability to walk independently at 26 weeks, ventilation need at any time during follow-up, time admitted to the intensive care unit, time on a ventilator, and GBS-related mortality at six months. Statistical analysis comprised the Mann-Whitney U test, and one-way ANOVA or Kruskal-Wallis tests, with a two-sided P value < 0.05 considered significant.

Among 1,300 patients enrolled in IGOS, 831 initially received IVIg. Poor prognosis (mEGOS 6-12) was predicted in 260, of which 237 satisfied inclusionary criteria. Among these, 199 received a single course of IVIg, while 20 received a second course within one to two weeks, and 18 within two to four weeks after start of initial IVIg. Those receiving two courses were more disabled at baseline and week 1 compared to those receiving one course, and a second course of IVIg did not significantly affect the primary endpoint GBS score four weeks after

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study entry. GBS disability score at 26 weeks, a secondary endpoint, also was unaffected. No serious complications from the second IVIg course were reported, but no benefit accrued.

■ COMMENTARY

Weakness, sensory loss, fatigue, and pain are the most common residual deficits in GBS, requiring patients to modify their work, lifestyle, and social activities. Often overlooked, prolonged and intensive physical rehabilitation can improve prognosis. In a retrospective analysis of 51 GBS patients seen between 2003 and 2017 at the Neurological Unit of Sant'Andrea Hospital, La Spezia, Italy, 40 patients underwent intensive physical rehabilitation for an average of two months while inpatients, of which 31 continued for an additional three months as outpatients. Mean MRC sum score and GBS-Disability scale improved significantly in the intensive physical rehabilitation group, compared to the medical therapy. Intensive physical rehabilitation should be performed in patients with severe GBS.[1] ■

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CME QUESTIONS

1. **A 34-year-old man is brought to the ED after being hit in the head with a baseball. He was wearing a helmet, and his neurological exam and CT scan are normal. He is diagnosed with a concussion. Which of the following is true?**
   a. The brain MRI in patients with concussion or mild traumatic brain injury will not show evidence of traumatic microbleeds.
   b. The brain MRI in patients with concussion or mild traumatic brain injury may show evidence of microbleeds.
   c. The brain MRI in patients with concussion or mild traumatic brain injury always will show evidence microbleeds.
   d. The brain MRI in patients with concussion or mild traumatic brain injury will not show evidence of traumatic microbleeds if the CT scan is normal.
2. **Which therapeutic treatment has demonstrated efficacy in specifically targeting attentional disturbances in dementia with Lewy bodies?**
   a. Donepezil
   b. Deep brain stimulation of nucleus basalis of Meynert
   c. Amantadine
   d. Memantine
3. **Which of the following statements regarding chronic traumatic encephalopathy (CTE) associated dementia is most true?**
   a. Dementia in CTE is likely the result of neuropathological changes associated with repetitive head trauma as well as non-head trauma-associated neuropathology, such as arteriolosclerosis.
   b. Dementia in CTE is likely the result of neuropathological changes associated with repetitive head trauma alone.
   c. Dementia in CTE is likely the result of non-head trauma-associated neuropathology, such as arteriolosclerosis alone.
   d. CTE is not associated with dementia.
4. **Polysomnography can help in the diagnosis of various neurodegenerative diseases such as:**
   a. amyotrophic lateral sclerosis.
   b. multiple systems atrophy.
   c. Duchenne muscular dystrophy.
   d. Alzheimer's disease.
5. **What is the most effective treatment for cerebral cavernous malformations?**
   a. Surgical excision
   b. Stereotactic radiosurgery
   c. Watchful waiting
   d. Unknown
6. **Which of the following statements is true regarding intravenous immunoglobulin (IVIg) for Guillain-Barré syndrome (GBS)?**
   a. Where no significant response was obtained after an initial round of IVIg for GBS, a second course of IVIg does not appear to be beneficial.
   b. Two sequential courses of IVIg always should be administered to newly diagnosed GBS patients.
   c. One course of IVIg followed by plasma exchange always should be administered to newly diagnosed GBS patients.
   d. One course of plasma exchange followed by IVIg always should be administered to newly diagnosed GBS patients.

[IN FUTURE ISSUES]

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