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Vol. 40, Issue 8, April 2021
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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Phospho-Tau217 Blood Biomarker May Help to Diagnose Early Alzheimer's Disease

By Richard S. Isaacson, MD

Associate Professor of Neurology (Education), Weill Cornell Medical College

SYNOPSIS: Serum phospho-tau217, a biomarker of tau protein that can be detected in the blood, is increased in preclinical Alzheimer's disease and may have clinical utility for the early detection of brain pathology.

SOURCE: Janelidze S, Berron D, Smith R, et al. Associations of plasma phospho-tau217 levels with tau positron emission tomography in early Alzheimer disease. *JAMA Neurol* 2021;78:149-156.

For the past decade, the National Institute on Aging/Alzheimer's Association diagnostic criteria have described a broad spectrum of Alzheimer's disease (AD). AD begins at least 20-30 years before the first symptoms occur, and these criteria divide AD into three distinct stages: Stage 1 refers to AD pathology starting in the brain without symptoms (pre-clinical AD); stage 2 refers to mild memory loss, but the person still can perform all of their usual daily activities (mild cognitive impairment [MCI] because of AD); and stage 3 refers to dementia caused by AD. Eventually, effective treatments will be best positioned to have a positive effect if initiated at a preclinical or prodromal stage to offer the most clinically meaningful neuroprotection. As such, it is of pressing need to have cost-effective and minimally invasive biomarker tests to help diagnose the earliest stages of AD. Beginning in 2017-2018, multiple research groups first reported reductions in the serum Aβ42:Aβ40 ratio in patients with brain amyloid. In 2020, plasma phospho-tau181 (P-tau181) was found to predict future progression to dementia caused by AD with high accuracy in patients without dementia. A new study by Janelidze and colleagues aimed to determine whether another serum tau marker (P-tau217) also may be a potential early biomarker of AD.

In this study, 490 subjects with a mean age of 65.9 years (standard deviation, 13.1 years) were included from the Swedish BioFINDER-2 study. Plasma P-tau217 was measured in 314 cognitively

Financial Disclosure: Dr. Isaacson (author) reports he is a consultant for Genentech/Roche and Biogen, Dr. Rubin (author) reports he is a consultant for Merck Sharpe & Dohme Corp., and Dr. Noch (author) reports he is a stockholder in Destroke, Inc. All of the relevant financial relationships listed for these individuals have been mitigated. None of the remaining authors or planners for this educational activity have relevant financial relationships to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Neurology [ALERT]

Neurology Alert (ISSN 0741-4234) is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-9468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Neurology Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-9468.

GST Registration Number: R128870672.

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normal subjects and 176 subjects with MCI caused by AD. All subjects also underwent cerebrospinal fluid (CSF) amyloid and tau biomarker studies, and amyloid and tau positron emission tomography (PET) brain imaging. The study found that plasma P-tau217 levels were increased in cognitively normal subjects with abnormal Aβ-PET but *normal* tau-PET in the entorhinal cortex (ERC). This was an important finding, since prior research has found that increases in biofluid P-tau217 precede changes in tau-PET in the ERC, which is an early region of neurofibrillary tangle formation. In this group, most patients who were discordant for plasma P-tau217 and tau-PET were positive for plasma P-tau217 and negative for tau-PET, which is consistent with the sequence of pathological progression. Event-based modeling predicted that in cognitively unimpaired subjects, and in those with MCI caused by AD, both plasma and CSF P-tau217 would change *before* the tau-PET signal in the ERC, followed by more widespread cortical tau-PET changes.

■ COMMENTARY

These results suggest that plasma P-tau217 becomes abnormal before tau-PET and that plasma P-tau217, thus, may be considered as an early biomarker for AD. The findings also add supportive evidence that fluid biomarkers can detect Aβ-triggered changes in tau phosphorylation and secretion. These types of changes likely precede the aggregation of hyperphosphorylated tau into paired helical filaments (that form the characteristic neurofibrillary tau tangles) and also bind PET tracer ligands. For decades, clinicians have used serum lipid biomarkers (e.g., low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglycerides) to evaluate cardiovascular (CV) risk and measure the effect of pharmacological and lifestyle-based treatments. CV serum tests also have evolved to detect even earlier preclinical stages of atherosclerotic disease (e.g., non-HDL-cholesterol [non-HDL-C] and apolipoprotein B [Apo B]). The future of AD soon will hinge on a parallel path. For example, a recent study reported that increased non-HDL-C in adolescence (ages 12-18 years) had the strongest association with atherosclerotic CV disease in midlife, and it seems only a matter of time for AD to be recognized in a similar way. From a practical clinical perspective, in the coming years serum biomarker tests, such as P-tau217, serum Aβ42:Aβ40 ratio, and others (neurofilament light), will emerge as tools more commonly available in both research and clinical settings. Although current lab specimen processing practices make it difficult for rapid adoption in the clinic setting (e.g., the need for rapid centrifugation, freezing of samples, or immediate need to mail on dry ice), experts in the field remain optimistic that a multi-biomarker panel to risk stratify and follow the longitudinal trajectory of patients in the earliest AD stages is within reach. Similar to CV disease, using these biomarkers not only for early diagnosis but also to evaluate therapeutic response to targeted interventions is a natural step forward for adoption in clinical practice. ■

ABSTRACT & COMMENTARY

Cognitive Deficits in Patients Recovering from COVID-19

By Lisa Ravdin, PhD

Associate Professor of Neuropsychology and Director of the Weill Cornell Neuropsychology Service, Department of Neurology & Neuroscience, New York Presbyterian Hospital/Weill Cornell Medical Center

SYNOPSIS: Hospitalized COVID-19 patients with cognitive complaints demonstrate reduced attention and executive dysfunction on formal cognitive testing consistent with the same frequency and pattern of cognitive changes associated with critical illness.

SOURCE: Jaywant A, Vanderlind WM, Alexopoulos GS, et al. Frequency and profile of objective cognitive deficits in hospitalized patients recovering from COVID-19. *Neuropsychopharmacology* 2021; Feb 15:1-6. doi.org/10.1038/s41386-021-00978-8. [Online ahead of print].

In 2020, hospital settings in pandemic hotspots became real-time clinical laboratories for studying the evolving knowledge of the effects of COVID-19 infection. Among the variety of symptoms associated with COVID-19, central nervous system (CNS) manifestations include headaches, dizziness, delirium, encephalopathy, and stroke. Cognitive complaints also have been reported in COVID-19 patients, yet there have been limited formal studies that incorporate objective cognitive measures to understand the nature of these complaints.

Jaywant and colleagues sought to examine cognitive function in patients who underwent prolonged hospitalization for COVID-19 using objective cognitive measures. Subjects consisted of 57 individuals hospitalized for acute COVID-19 symptoms who also had suspected cognitive dysfunction. Participants were medically stable yet experiencing some form of impairment in mobility or activities of daily living that necessitated acute inpatient rehabilitation prior to discharge.

Cognitive testing consisted of bedside administration of the Brief Memory and Executive Test (BMET), a paper and pencil measure that consists of multiple subtests of memory and executive function, including orientation, five-word immediate recall (working memory), five-word recall (delayed memory), five-word recognition (delayed recognition), rapid letter-number matching (divided attention), motor speed, rapid letter sequencing (visual attention and processing speed), and letter-number switching (mental set-shifting). Scores from the short form of the Activity Measure for Post-Acute Care closest to the time of admission to rehabilitation were collected to assess functional status. Impairment ratings were defined according to age-corrected normative data, with scores < 1 standard deviation (SD) below the mean interpreted as mild/borderline impaired and scores < 2 SD below the mean classified as impaired. Pearson correlations and Chi square analyses were used to examine relationships between cognition and patient variables.

Impairment ratings reflecting mild cognitive impairment were a frequent finding (81%) in this sample of hospitalized COVID-19 patients, with deficits primarily on tasks of complex attention. In terms of memory, working memory (immediate recall) was affected more frequently as opposed to delayed recall, consistent with the pattern often observed in the context of compromised complex attention. The presence of cognitive deficits was not associated with the length of intubation, the time between extubation and assessment, or the presence of psychiatric symptoms. There was no significant association between cognition and preexisting cardiometabolic diagnosis, and the relationship between delirium and cognitive deficits was not statistically significant.

■ COMMENTARY

Jaywant et al expeditiously conducted this study early on at the height of the pandemic in the hotspot of New York City. They provided valuable descriptive information to inform our knowledge of the frequency and pattern of cognitive changes observed in hospitalized COVID-19 patients. The results are consistent with the literature on the rates of cognitive deficits in hospitalized critical care patients, with comparable numbers of patients (approximately 80%) experiencing some form of cognitive dysfunction.

[In terms of memory, working memory was affected more frequently as opposed to delayed recall, consistent with the pattern often observed in the context of compromised complex attention.]

These preliminary data on COVID-19 patients set the stage for empirically designed controlled investigations that can explore the causation of cognitive changes over and beyond those that might be attributable to critical illness hospitalization. The literature suggests hospitalized critically ill patients tend to demonstrate the most significant cognitive deficits at or around the time of discharge, and this can persist for months to years after hospitalization. As in this study, often this occurs in the absence of pre-hospitalization cognitive impairment.

Cognitive complaints also have been reported anecdotally in individuals with much milder symptom presentations of COVID-19 that do not require hospitalization, and this often is described by patients as "brain fog." Studies investigating cognition post-COVID-19 infection should consider that cognitive complaints present at an unprecedented time during a pandemic where factors such as social isolation and change in work routines and daily activities as well as in sleep and mood typically are affected.

In those who have survived the more significant physical effects of infection, the emotional response to serious medical illness also may affect the persistence of post-hospitalization symptoms. Consideration of these potential contributing factors to cognitive complaints can help guide intervention and treatment recommendations. ■

ABSTRACT & COMMENTARY

Polyradiculoneuropathy from Immune Checkpoint Inhibitors

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: Immune checkpoint inhibitors have become an important part of the armamentarium for the medical treatment of cancers such as melanoma and lung carcinomas. A number of immune-mediated neurological complications have been identified during the use of these agents, including polyradiculoneuropathy.

SOURCE: Okada K, Seki M, Yaguchi H, et al. Polyradiculoneuropathy induced by immune checkpoint inhibitors: A case series and review of the literature. *J Neurol* 2021;268:680-688.

Typically, neurologic complications associated with immune checkpoint inhibitors (ICI) develop within three months of initiating therapy, and affect 1% to 14% of patients. The most common complications are headache and peripheral sensory neuropathy, but rarely include myasthenia gravis, posterior reversible encephalopathy syndrome (PRES), aseptic meningitis, transverse myelitis, pancerebellitis, autoimmune encephalitis, and cranial and peripheral neuropathies. Polyradiculoneuropathy, in the form of both Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), also has been reported. What are the clinical characteristics of polyradiculoneuropathy induced by ICIs?

To answer this question, the study investigators performed a retrospective records review of all inpatients with neurological immune-related adverse events treated between January 2017 and December 2019 at the neurology departments of Keio University Hospital, Jikei University Kashiwa Hospital, and Tokyo Saiseikai Central Hospital, Japan. This review was supplemented by a systematic PubMed database literature search of such patients, using keywords GBS, CIDP, polyradiculoneuropathy, polyneuropathy, polyradiculitis, polyradiculopathy, and demyelinating polyneuropathy.

Among a total of 36 patients identified with polyradiculopathy (four inpatients and 32 culled from the literature), the mean age was 61 years. There were 28 men and eight women, of which 27 received ICI monotherapy, and nine received combination ICIs. Melanoma was the predominant cancer (n = 26), with non-small cell lung cancer present in four, renal or gastric cancer in two each, and bladder or nasal cancer in one each. Only three had a prior infection or vaccination. Symmetric limb weakness, more so in the legs than in the arms, was evident in all but two cases, bulbar involvement was present in seven cases, and facial weakness was present in three cases. Among 17 patients, muscle weakness progressed rapidly over two weeks. Demyelinating polyradiculoneuropathy was found on electrodiagnostic studies in 22 patients, with 10 showing an axonal pattern, and cerebrospinal fluid demonstrated elevated protein in all but one, with elevated lymphocytes in 13 patients. Non-neurologic immune-related adverse events were present in 10. Patients responded favorably to corticosteroids, which were used in 25 patients, and intravenous methylprednisolone, used in 15, with intravenous immunoglobulin (IVIG) used in 21 patients in combination with steroids. The following features of polyradiculoneuropathy induced by ICIs were observed: significant motor weakness, manifesting particularly as gait impairment; elevation of both protein and lymphocytes in the spinal fluid; demyelination on nerve conduction studies; and a positive response to corticosteroid therapy. Polyradiculoneuropathy induced by ICIs may be more severe than sporadic GBS and CIDP. Early recognition and treatment are crucial to having a positive outcome.

■ COMMENTARY

ICIs may prove beneficial for the treatment of COVID-19, the acute and severe pneumonia caused by the severe acute respiratory syndrome-associated coronavirus2 (SARS-CoV-2). Patients with COVID-19 exhibit lymphocytopenia and, following a period of T-cell activation, shift to T-cell exhaustion, as well as demonstrate a decrease in the number of natural killer cells, which also express the exhaustion marker, NKG2A. T-cell exhaustion may be a leading cause of severe COVID-19. Of note, cancer patients are usually immunocompromised but may restore their antitumoral immune response when treated with ICIs. Additionally, when infected with virus, mice and men exhibit a T-cell exhaustion, similar to observations following SARS-CoV-2 infection. Among ICIs, some antibodies can block the programmed death-1 pathway, such that when treated with antiprogrammed death antibodies, T-cell competence is restored and efficiently counteracts the viral infection. Currently, clinical trials are underway to examine this potential avenue of COVID-19 treatment. ■

ABSTRACT & COMMENTARY

Brain Cancer and Brain Injury Drive Systemic Immunosuppression

By Evan Noch, MD, PhD

Instructor, Department of Neurology, Weill Cornell Medical College

SYNOPSIS: Glioblastoma-associated immunosuppression is a significant factor associated with poor survival in this disease. Accumulating evidence suggests that mouse models of glioblastoma and other brain cancers induce systemic immunosuppression through dysregulation of a newly recognized brain-thymus axis and that targeting this pathway may promote more effective immune surveillance of these tumors.

SOURCE: Ayasoufi K, Pfaller CK, Evgin L, et al. Brain cancer induces systemic immunosuppression through release of non-steroid soluble mediators. *Brain* 2020;143:3629-3652.

Systemic immunosuppression is a strong determinant of poor prognosis in a variety of human cancers. Glioblastoma patients exhibit decreased immune surveillance, mediated by dysregulation of T-cell repertoires and reduced expression of major histocompatibility complex class II (MHCII) expression, leading to unchecked tumor growth. Consequently, although immunotherapy to promote immune-mediated attack and clearance of tumor cells has benefited other cancer patients, immunotherapy has not shown any long-term benefit in glioblastoma. The biological pathways that mediate systemic immunosuppression in glioblastoma remain incompletely understood, and therapeutic targets to promote immune cell retention and function are unknown.

Ayasoufi et al demonstrated a glioblastoma-thymus-adrenal gland axis that regulates systemic immunosuppression in response to brain tumor and brain injury models. They used a variety of brain tumor models, including the GL261 murine glioma model, a transgenic murine diffuse intrinsic pontine glioma model, and an intracranial B16 murine melanoma model. Tumors from each of these models significantly reduced thymus size and cellularity. Functionally, thymic T-cells from these mice were reduced and exhibited decreased late-stage proliferation, while B-cell numbers were increased in atrophic thymus. Next-generation sequencing of thymus from GL261-bearing mice demonstrated upregulation of T-cell proliferation programs but downregulation of deoxyribonucleic acid (DNA) replication and elongation, providing a likely cause of T-cell loss in these models. Interestingly, pathway analysis showed that ribonucleic acid (RNA) molecules associated with cancer development, particularly that of gliomas, were found among thymic bulk RNA transcripts.

To investigate systemic immunosuppression associated with brain tumor development, the authors measured immune cell numbers and phenotypes in tumor-bearing mice. They found that CD4+ and CD8+ T-cells and MHCII-expressing B-cells and monocytes/macrophages were reduced in these mice, indicating deficits in both innate and adaptive immunity. Using the technique of parabiosis to study circulating factors mediating brain tumor-induced immunosuppression, the authors joined GFP-expressing C57BL/6 mice to wild-type C57BL/6 mice. Although they implanted GL261 cells into the brain of only one parabiont, both mice exhibited thymic involution, reduced peripheral blood CD4+ T-cell counts, and decreased MHCII expression levels. Reinforcing the findings of the parabiotic model, the authors found that serum derived from GL261-bearing mice, but not from GL261 cells grown in vitro, inhibited T-cell proliferation in culture systems.

Expanding their observations from gliomagenesis to models of brain injury, the authors found that thymic involution occurs in response to experimental models of demyelination, lipopolysaccharide-induced neuroinflammation, kainic acid-induced seizures, and even mechanical injury mediated by intracranial phosphate-buffered saline injection. When mice recovered from these acute injuries, the thymus recovered also, resembling those of naïve control mice. Similar to the deleterious effects of sera from tumor-bearing mice on T-cell proliferation in vitro, the researchers found that sera from acutely injured but not recovered mice robustly inhibited T-cell proliferation. These findings indicate the presence of soluble factors that induce immunosuppression in response to brain injury.

Since stress hormones produced by the adrenal glands may mediate the sequelae of brain injury, the investigators studied tumor-induced immunosuppression in adrenalectomized mice. Surprisingly, they found that adrenalectomized mice exhibited increased numbers, but not frequencies, of immune cells in the blood, thymus, and spleen. When they implanted GL261 cells into the brains of mice, they found no evidence of thymic involution, disruptions in T-cell development, or sequestration of T-cells in the bone marrow. However,

this rescue of immune function in adrenalectomized mice did not affect overall survival.

To determine the soluble factors that mediate immunosuppression, they filtered sera from glioma-bearing mice based on molecular weight and added this filtrate to cultured T-cells. Large factors with molecular weights greater than 100 kDa inhibited T-cell growth, but small molecules less than 3 kDa were not immunosuppressive. To confirm that cortisol, a small molecule stress hormone, does not induce adrenal-mediated reduction in thymic function, the researchers tested the effects of serum from wild-type and adrenalectomized mice on T-cell growth in vitro. Serum from both mouse cohorts was equally immunosuppressive, but serum from naïve adrenalectomized mice did not inhibit T-cell growth. These findings suggest that, although adrenalectomized tumor-bearing mice do not show thymic phenotypic changes, these mice exhibit thymus-independent immunosuppression from the action of a large molecular weight soluble factor associated with poor survival.

■ COMMENTARY

Immunosuppression in glioblastoma facilitates tumor escape from immune surveillance. By establishing a new brain-thymus-adrenal gland axis through which brain tumors and brain injury mediate thymic involution, decreased peripheral immune cell counts, and the circulation of immunosuppressive serum-derived soluble factors, the authors of this study have identified a putative target to improve immune function in these patients. Such targeted treatments also could improve the efficacy of systemic immunotherapy in this disease. The identity of the large molecular weight soluble factors mediating immunosuppression remain unknown, so future studies should use a proteomics approach to identify and modulate the effects of these factors to establish their role in brain tumor-associated systemic immune cell dysfunction. ■

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Stroke Alert

By Matthew E. Fink, MD

Tenecteplase vs. Alteplase for Thrombolysis in Basilar Artery Occlusion

SOURCE: Alemseged F, Ng FC, Williams C, et al. Tenecteplase vs alteplase before endovascular therapy in basilar artery occlusion. *Neurology* 2021;96:e1272-e1277.

Basilar artery occlusion is a dangerous clinical syndrome of large artery occlusion that carries a high morbidity and mortality with severe disability in survivors. In multiple trials, alteplase has shown minimal benefit in achieving reperfusion in patients with large artery occlusion, including the basilar artery. Tenecteplase is a modified variant of alteplase that has greater specificity in binding to fibrin, a longer half-life, and can be administered in a single bolus. This makes it operationally easier to use and theoretically more effective.

In the head-to-head trial of tenecteplase vs. alteplase before endovascular therapy in ischemic stroke (EXTEND-IA-TNK), tenecteplase led to a higher rate of reperfusion and improved clinical outcomes compared with alteplase.[1] To assess the benefit in patients with basilar artery occlusion, the authors retrospectively analyzed all of the cases of basilar artery occlusion reported in several studies that compared the use of tenecteplase with alteplase. A total of 110 patients with basilar artery occlusion were included and were treated with either alteplase or tenecteplase for intravenous thrombolysis prior to endovascular therapy. Nineteen patients were treated with tenecteplase and 91 with alteplase. Reperfusion > 50% was successful in 26% of patients treated with tenecteplase vs. 7% of patients treated with alteplase, despite shorter thrombolysis-to-arterial puncture times in the tenecteplase-treated group. The groups were not matched and they were unequal, but the risk ratio for alteplase was 4.0, $P = 0.02$. There was no difference in symptomatic intracranial hemorrhage between the groups. This observational study suggests benefits with tenecteplase above alteplase, and it warrants additional randomized trials of this agent in basilar artery occlusion, as well as other types of large vessel occlusions. ■

REFERENCE

1. Campbell BC, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med* 2018;378:1573-1582.

Tranexamic Acid in Patients with Intracerebral Hemorrhage Does Not Improve Outcomes

SOURCE: Meretoja A, Yassi N, Wu TY, et al. Tranexamic acid in patients with intracerebral haemorrhage (STOP-AUST): A multicentre, randomised, placebo-controlled, phase 2 trial. *Lancet Neurol* 2020;19:980-987.

Primary intracerebral hemorrhage is a major cause of severe neurological disability and carries a high rate of death. Worldwide, it comprises 5% of all human deaths. Patients are treated in multidisciplinary specialized stroke units and neurological intensive care units, with the best possible results, but there are no specific, targeted therapies that are evidence-based and have shown benefit in the treatment of these patients. The major determinants of survival and clinical outcome are the patient's age, level of consciousness at onset, and volume of the hematoma. In addition, it has been demonstrated in multiple studies that the hematoma size increases over the first several hours and up to 24 hours. One approach to therapy has been to prevent hematoma growth by administering a hemostatic agent. Recombinant activated coagulation factor VII was tested in two large trials with 1,240 patients treated within four hours of symptom onset, without showing a significant benefit in outcomes. Tranexamic acid was tested in a study of 2,325 patients with intracerebral hemorrhage within eight hours of symptom onset, but again, did not significantly improve neurological outcome.

The current investigators of the STOP-AUST trial led a prospective, double-blind, randomized, placebo-controlled Phase II trial at 13 stroke centers in Australia, Finland, and Taiwan to determine if administration of tranexamic acid within four and a half hours of symptom onset would reduce hematoma growth and have an effect on neurological outcome. Patients were eligible to be enrolled if they were 18 years of age or older with an acute intracerebral hemorrhage, a Glasgow Coma Scale score > 7, intracerebral brain hemorrhage (ICH) volume less than 70 mL, no secondary cause of hemorrhage, no thromboembolic events in the previous 12 months, no planned surgery, no use of anticoagulants, and the presence of contrast extravasation on computed tomography angiography (spot sign). Infusion of tranexamic acid had to be started within four and a half hours of symptom onset. The primary outcome was growth of the intracerebral hemorrhage at 24 hours. A total of 100 participants were enrolled and randomly assigned to tranexamic acid treatment or placebo. There were 50 participants in each group. The median age was 71 years and the median intracerebral hemorrhage volume was 14.6 mL. The primary outcome, which was growth of hemorrhage at 24 hours, was not significantly different between the two groups. Fifty-two percent of patients in the placebo group and 44% in the tranexamic acid group had intracerebral hemorrhage growth of greater than 33% at 24 hours. There was no difference between the groups in mortality or thromboembolic complications. Although this study did not demonstrate benefit of treatment with tranexamic acid, the investigators suggested that earlier treatment should be studied and might be of benefit. ■

Atorvastatin and Low-Dose Dexamethasone for Treatment of Chronic Subdural Hematoma

SOURCE: Wang D, Gao C, Xu X, et al. Treatment of chronic subdural hematoma with atorvastatin combined with low-dose dexamethasone: Phase II randomized proof-of-concept clinical trial. *J Neurosurg* 2020; Jan 31:1-9. doi: 10.3171/2019.11.jns192020. [Online ahead of print].

Chronic subdural hematoma is a common cause of serious neurological morbidity and mortality in the elderly population and is increasing in prevalence as the result of the aging population and the increasing use of antithrombotic medications. Surgical intervention has been the standard of care, but it carries a significant risk of recurrence and complications (20%). Various drug treatments have been proposed and tried. In recent years, treatment with atorvastatin has been shown to be beneficial in several small, randomized trials. Atorvastatin has both an anti-inflammatory effect and the ability to mobilize endothelial progenitor cells, which assist in vascular repair. The current investigators proposed that adding a low dose of dexamethasone to atorvastatin treatment might enhance the anti-inflammatory benefits without causing the side effects associated with high doses of corticosteroids.

Sixty patients with chronic subdural hematoma were randomized to one of two treatment protocols. Group 1 received a five-week regimen of atorvastatin 20 mg daily, and group 2 received a five-week regimen of atorvastatin 20 mg daily plus dexamethasone starting at 2.25 mg daily for two weeks, followed by 0.75 mg twice a day for two weeks, and then 0.75 mg once a day for one week. The primary endpoint was hematoma reduction assessed by imaging at five weeks of follow-up. Secondary outcomes included neurological improvements. The mean age of patients was 66.6 years, and 25% of the patients were women. Patients treated with a combination of atorvastatin plus dexamethasone had more hematoma reduction by the fifth week compared to the group treated with atorvastatin alone. This difference was noted from the second week onward and persisted until the 12th week of follow-up. Complete recovery of neurological function at five weeks was achieved an 83.3% of patients treated with combination therapy of atorvastatin plus dexamethasone, compared to 32.1% of patients treated with atorvastatin alone. In addition, the investigators measured and identified higher levels of regulatory T-cells and endothelial progenitor cells in the peripheral blood of patients treated with the combination therapy. In this Phase II trial, combination therapy with atorvastatin and dexamethasone appeared to be better than atorvastatin alone, and justifies a larger, Phase III randomized trial with a placebo-controlled arm. ■

CME INSTRUCTIONS

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CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

CME QUESTIONS

1. **Which of the following serum biomarkers eventually may be used to diagnose the earliest pre-symptomatic stages of Alzheimer's disease in clinical practice?**
   a. Serum Aβ42:Aβ40 ratio
   b. Phospho-tau217
   c. Neurofilament light
   d. All of the above

2. **Which of the following statements about the cognitive effects of COVID-19 infection is true?**
   a. Compromised delayed recall is the primary cognitive deficit associated with COVID-19.
   b. Cognitive deficits in hospitalized COVID-19 patients occur only in those with prehospitalization cognitive decline.
   c. The most common cognitive finding in hospitalized COVID-19 patients is mild cognitive impairment.
   d. Time of intubation is directly associated with the presence of cognitive impairment.

3. **Which of the following statements about polyradiculoneurotherapy induced by immune checkpoint inhibitors (ICIs) is *false*?**
   a. Polyradiculoneuropathy induced by ICIs results in significant motor weakness, manifesting particularly as gait impairment.
   b. Polyradiculoneuropathy induced by ICIs is associated with spinal fluid elevation of both protein and lymphocytes.
   c. Polyradiculoneuropathy induced by ICIs is characterized by demyelination on nerve conduction studies.
   d. Polyradiculoneuropathy induced by ICIs does not respond to steroid therapy.

4. **Which of the following statements regarding immunosuppression associated with glioblastoma is true?**
   a. Brain tumors dysregulate thymic function.
   b. T-cells in brain tumor mouse models function normally.
   c. Brain injury does not mimic systemic immunosuppression seen in glioblastoma.
   d. Circulating factors do not inhibit immune function in glioblastoma.

5. **Tenecteplase and alteplase are equally effective for successful thrombolysis in acute stroke patients with large vessel occlusions.**
   a. True
   b. False

6. **Hemostatic agents administered to patients with intracerebral hemorrhage show benefit in terms of limiting hematoma growth and improving neurological outcome.**
   a. True
   b. False

7. **Atorvastatin has been shown to be of benefit in treating patients with chronic subdural hematoma.**
   a. True
   b. False