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Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Eculizumab Shows Benefit in a Treatment Trial of NOSD

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Dr. Perumal reports she is a consultant for Genzyme, EMD Serono, and Biogen.

SYNOPSIS: In a randomized, placebo-controlled trial of aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorders, eculizumab demonstrated a decrease in the risk of a relapse. Patients could continue their other stable-dose immune suppressive therapies while enrolled in the trial.

SOURCE: Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *N Engl J Med* 2019; May 3. doi: 10.1056/NEJMoa1900866. [Epub ahead of print].

Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system that preferentially affects the optic nerves and spinal cord. Classic NMO, or Devic's disease, is characterized by concurrent episodes of optic neuritis (ON) and transverse myelitis (TM). NMO spectrum disorder (NMOSD) is diagnosed in patients with isolated ON or TM who have the NMO IgG aquaporin-4 antibody, which is potentially pathogenic and has high specificity for this group of diseases. The anti-aquaporin-4 test is > 80% sensitive and > 99% specific for NMOSD. This distinction of NMOSD from multiple sclerosis is important as the disease course and treatment options for this disease are different from that of multiple sclerosis.

There are no FDA-approved treatments for NMOSD. Empirically, relapses are treated with a course of intravenous (IV) steroids, and steroid-refractory relapses are treated with IV immunoglobulin (IVIG) or plasma exchange. Long-term disease-modifying treatments that have been used in NMOSD include monthly pulse corticosteroids, repeated IVIG, azathioprine, mycophenolate mofetil, and rituximab.

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Eculizumab, a humanized monoclonal antibody, is a complement inhibitor. It binds to complement protein C5, inhibiting its cleavage to C5a and C5b, which cause inflammatory injury. Data suggest that the aquaporin-4 antibody triggers a complement-mediated attack on astrocytes, resulting in injury and neuronal loss. The author of an earlier, small open-label study of 14 NMO patients demonstrated the efficacy of eculizumab in reducing relapses; hence, Pittock et al conducted this larger randomized, placebo-controlled trial.

They enrolled 143 aquaporin-4 antibody-positive patients from 70 international sites. Patients could continue their existing immune-modulating treatment, except for rituximab. Concomitant rituximab use was excluded because of a conflicting mechanism of action; B-cell lysis with rituximab is complement-dependent. The immune-suppressive medications that patients continued included long-term maintenance steroids, azathioprine with or without steroids, and mycophenolate mofetil.

Seventy-six percent of patients in the trial were on other concomitant immune suppressive treatments in addition to the study drug. Patients who had two relapses in the preceding 12 months or three relapses in the preceding 24 months were enrolled. An Expanded Disability Status Scale (EDSS) score of up to 7.0 was inclusive. Patients were randomized in a 2:1 manner to receive either eculizumab or placebo. Eculizumab was administered intravenously over 35 minutes as 900 mg doses every week for four weeks, followed by a maintenance dose of 1,200 mg every two weeks.

The primary endpoint was the first adjudicated relapse. Secondary outcomes included adjudicated relapse rate, quality of life measures, and disability as measured by EDSS. The trial was stopped after 23 of the 24 prespecified relapses occurred. Adjudicated relapses occurred in three of 96 (3%) patients on eculizumab and 20 of 47 (43%) patients on placebo (hazard ratio, 0.06; 95% confidence interval, 0.02-0.20; $P < 0.001$). The annualized relapse rate was 0.02 in the eculizumab group and 0.35 in the placebo group ($P < 0.001$). Other endpoints, although favoring eculizumab treatment, were not statistically significant. In a prespecified analysis of monotherapy with eculizumab, none of the 21 patients who received eculizumab alone had a relapse, while seven of 13 patients in the corresponding placebo arm had relapses. With regard to adverse events, infections were more common in the eculizumab group compared to placebo, and there was a higher incidence of headaches. One person who was on eculizumab and azathioprine died of pulmonary empyema. Prior to treatment, patients were vaccinated against *Neisseria meningitidis* because of the potential risk of this specific infection.

■ COMMENTARY

Currently, there are no FDA-approved treatments for NMOSD. In a disease that is characterized by severe relapses and where the accrual of disability mainly is through residual deficits from relapses rather than progressive disease course, medications that decreases the risk of a relapse are vital in preventing disability. Based on this study, eculizumab was effective in decreasing the risk of a relapse in aquaporin-4 antibody-positive NMOSD patients. As per the study protocol, patients were allowed to continue their existing treatment, except for rituximab. About three-quarters of the patients were on some other immune-suppressive treatment during the trial. However, patients on eculizumab alone appeared to have a lower risk of a relapse as well.

With regard to co-medications, especially since rituximab is used to treat NMOSD, it is important to keep in mind that eculizumab cannot be combined with rituximab because of a conflicting mechanism of action. In addition to a general infection risk with immune suppression, an important specific issue for clinicians to consider is the potential risk of *N. meningitidis* infection with eculizumab, requiring vaccination prior to treatment. The dosing regimen for eculizumab would entail weekly IV infusions during the titration phase, followed after four weeks by a maintenance schedule of infusions every two weeks. Eculizumab treatment requires a significant time commitment from patients, but it offers the advantage of not having to take a medication every day once treatment is completed. In this trial, because of the relatively short duration and study design, long-term disability could not be assessed.

In summary, eculizumab was effective in reducing the risk of relapse in patients with NMOSD, three-quarters of whom

continued their existing treatment. Given its unique mechanism of action, eculizumab offers a new avenue for the treatment of NMOSD. Further studies elucidating the risks vs. the benefits, long-term efficacy, and the optimal treatment regimen of monotherapy vs. combination therapy are warranted. ■

ABSTRACT & COMMENTARY

Neuropathy in Systemic Lupus Erythematosus

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: Systemic lupus erythematosus may be associated with a variety of neuropsychiatric syndromes, including peripheral neuropathy, mostly sensorimotor types. However, all parts of the peripheral and central nervous system may be affected, and careful and repeated neurological evaluation is important.

SOURCE: Bortoluzzi A, Piga M, Silvagni E, et al. Peripheral nervous system involvement in systemic lupus erythematosus: A retrospective study on prevalence, associated factors and outcome. *Lupus* 2019;28:465-474.

Neurologic or psychiatric symptoms occur in 12-95% of patients with systemic lupus erythematosus (SLE). The wide range reflects differences in study design, varied definitional criteria of neurologic and psychiatric disease, and divergent exclusion and inclusion criteria. Common clinical syndromes include cognitive dysfunction, stroke syndromes, seizures, headache, and neuropathy. What is the prevalence of peripheral neuropathic involvement in SLE and what forms does it take?

Medical records of SLE patients, seen between 2000 and 2014, at two tertiary care referral centers in Cona and Cagliari, Italy, were reviewed retrospectively. Inclusion criteria required a diagnosis of SLE based on the 1997 American College of Rheumatology revised classification, and evidence of peripheral nerve involvement was based on recorded clinical and laboratory documentation. Follow-up for at least one year was necessary for inclusion, and sex-matched and disease duration-matched SLE patients, without neuropsychiatric abnormalities, served as controls. Pure compression neuropathies, such as carpal tunnel syndrome, were not included. A statistical analysis comprised the chi-square or Fisher's exact test, as appropriate, and a two-tailed Student's t-test or nonparametric Mann-Whitney U test for continuous variables, with $P < 0.05$ considered significant.

Among 1,224 patients, 85 patients (6.9%) experienced 97 peripheral nervous system (PNS) events. Of these, 61 patients (4.9%) were deemed to have experienced their PNS event as attributable to SLE. Most (67%) PNS events occurred at least three months following SLE diagnosis. However, in two cases it preceded diagnosis, and in 26 patients (31%) it appeared at disease onset. Combined peripheral and central nervous system (CNS) involvement was seen in 47% (n = 40), concomitant in 32.5%, CNS subsequent in 2%, and preceding the PNS event in 65%.

Peripheral polyneuropathy was the most common PNS event (43.3%), sensorimotor in 25% of events, sensory in 13%, and small fiber in 4.1%, with autonomic neuropathy and plexopathy accounting for 1% each. Cranial neuropathy accounted for 30.9% of events, peripheral mononeuropathy for 12.4%, and multiple mononeuropathy for 8.2%. Myasthenia gravis was seen in 3.1%, and no instances of acute or chronic inflammatory demyelinating polyradiculoneuropathy were noted.

Compared to controls, SLE patients with PNS involvement were significantly older at the time of diagnosis and were more likely to have higher scores on SLE Disease Activity Index 2000 and Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index. Sjögren's syndrome was more common in the PNS group, as was livedo reticularis, hypertension, diabetes, and smoking, whereas malar rash and photosensitivity were more common in controls. Careful neurologic evaluation is necessary in SLE, particularly in older patients who are more likely to have neurologic involvement and more aggressive disease.

■ COMMENTARY

Neuropsychiatric lupus, formerly termed lupus cerebritis, occurs in up to 50% of SLE patients, and encompasses a wide range of symptoms and syndromes, including headache, cognitive impairment, acute confusional states, psychosis, memory loss, stroke, and seizures. Some may be related to coagulopathy, but the affective and cognitive manifestations remain poorly understood. Anti-phospholipid antibodies activate platelets and endothelial cells and, with consequent shedding of prothrombotic microparticles, may be the underlying mechanism of thrombosis in the venous and arterial circulation and pregnancy loss. However, neurobehavioral deficits also have been described following their intraventricular injection in mice models. Intrathecal injection

of anti-*N*-methyl-d-aspartate (anti-NMDA) receptor antibodies into mice produce affective and cognitive symptoms, whereas anti-ribosomal P protein antibodies bind limbic structures, thereby affecting memory and mood, and promote inflammation and blood-brain barrier impairment due to production of tumor necrosis factor. Improved understanding of the pathophysiology of neuropsychiatric lupus will be required to best treat its multifaceted manifestations.[1] ■

REFERENCE

1. Schwartz N, Stock AD, Putterman C. Neuropsychiatric lupus: New mechanistic insights and future treatment directions. *Nat Rev Rheumatol* 2019;15:137-152.

ABSTRACT & COMMENTARY

Late Sunsets, Sleep Deprivation, and Adverse Outcomes

By Alan Z. Segal, MD

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

SYNOPSIS: All living organisms have 24-hour circadian rhythms. A body of evidence is accumulating that chronic disruption of this important rhythm may result in poor health outcomes. These negative consequences of disrupted circadian rhythms might be prevented by modifying work and sleep schedules.

SOURCE: Guintella O, Mazzonna F. Sunset time and the economic effects of social jetlag: Evidence from US time zone borders. *J Health Econ* 2019;65:210-226.

Circadian rhythms are present in every living thing. Even simple prokaryotes, such as cyanobacteria, modulate their metabolism based on the wavelength of exposed light. In 2017, the Nobel Prize for Medicine was given to researchers who unlocked the molecular and genetic basis of circadian functions in the drosophila fruit fly. There are multiple determinants of circadian function (known as "zeitgebers," or timekeepers), the most of important of which is blue light. The supraoptic nucleus of the hypothalamus is regulated directly by the intensity and timing of exposure to light. Melatonin (the hormone of darkness) is produced by the hypothalamus and is another important circadian regulator.

Beyond melatonin, multiple hormones cycle on a circadian basis, the most important of which are cortisol and growth hormone. Hypothalamic temperature regulation also follows a circadian pattern, with a typical body temperature nadir occurring three hours before waking. Appetite and weight are linked to circadian function, including the effects of leptin (which promotes satiety) and ghrelin (which increases hunger). Circadian rhythms are widespread, affecting immune and inflammatory regulation and likely modifying the epigenetic modulation of DNA.

Despite these factors, human society has attempted to wrestle control over the circadian clock by creating work schedules (particularly night shifts) that contradict cycles of natural light. While "jet lag" is a transient travel-related disruption in sleep-wake schedules, the process of "social jet lag" is a more chronic process, ingrained in the habits of our daily lives.

Although the Earth's rotation takes 24 hours, experiments in humans deprived of natural light or among the blind who cannot detect any light, show that the circadian cycle actually could extend to 24.5 or even 25 hours. Desynchronization between the circadian and "ultradian" cycles results in a disorder known as "hypernychthemeral syndrome" or "non-24," in which small alterations in cycle length add up from day to day, resulting in significant disruptions in sleep-wake cycles. Research in this area is challenging, as subjects in an experimental "free running" paradigm must spend days sequestered in a state of constant dim light exposure, deprived of TV or any other external cue of day or night.

Time zones are one example of a human construct superimposed on the natural variations of day and night. Within any given time zone, sunset times are not constant, but rather get progressively later as one proceeds westward, with the latest sunset being at the utmost western border of each zone. Over this western time zone boundary, sunset shifts an hour earlier as the clock is turned back. Despite these sunset differences, work, school, and social schedules remain fixed, with rigid morning starting times regardless of location within a time zone. Exploiting these variations, the authors compared sleep times (using data derived from Fitbit-type devices) across each of the four U.S. time zones. Sleep was studied geographically at the county level and ZIP code level, and as a continuous variable across the time zone. Data were derived further from the American Time Use Survey (ATUS) and Behavioral Risk Factor and Surveillance Survey (BRFSS).

Living on the "late sunset" (westernmost) side of a time zone resulted in an average of 19 minutes less sleep per night compared to living at the easternmost sector of the next time zone. Alternatively, using eight hours as an "optimal" sleep duration, the "late sunset" cohort was 8% less likely to achieve the necessary amount of sleep.

The subjects were divided into "employed" (which included students) and "non-employed." Both groups were affected by "social jet lag," but in different ways. Living at the westernmost sections promoted late bedtimes, but this effect was more pronounced in the non-employed. While the employed were 34% more likely to be awake at midnight, the non-employed were 41% more likely to be awake at that hour. For individuals who started work at 7 a.m., their average sleep duration was 36 minutes shorter. Westernmost location promoted late wake-up times, particularly among the non-employed. While employed people were equally likely to be awake at 7:30 a.m. regardless of time zone location, non-employed people in the westernmost locations were 32% more likely to be asleep at that hour.

In addition to sleep times, health outcomes also were affected adversely. Individuals at the western boundary were 11% more likely to be overweight, a difference that reached statistical significance. There were additional nonsignificant trends toward other adverse health outcomes, such as diabetes, cardiovascular disease, and breast cancer. Overall, "self-reported health status" was 2% poorer with late sunsets, but this did not reach statistical significance.

The authors used "back of the envelope calculations" to estimate economic consequences. They determined that circadian misalignment increases healthcare costs by $2 billion. Productivity losses induced by the extra hour of light in the evening were calculated to total 4.40 million days of work nationwide. There was an estimated 3% decrease in income among those living on the western side of a time zone. Total economic losses were estimated to be $2.35 billion (approximately $82 per capita). The authors calculated that a one-hour increase in daily sleep increases productivity to a greater extent than a one-year increase in education.

■ COMMENTARY

There are increasing data showing that sleep plays a key physiological role in the "glymphatic" system of the brain, a "dishwashing" mechanism that widens gap junctions and facilitates the removal of toxins. Multiple studies indicate that high-quality sleep, with increased periods of REM and slow-wave sleep, promotes clearance of substances such as amyloid and tau proteins. Although day-to-day deficiencies in sleep duration promote cognitive loss (impairments in vigilance), more chronic cumulative sleep loss may have more permanent effects, including possibly Alzheimer's disease.

Seasonal differences in light exposure and sleep times may provide quasi-experimental data similar to this time zone investigation. Although daylight duration varies from 14 hours in summer to only eight hours in winter, humans sleep a fixed amount of time. This effect is strongly driven by latitude and perhaps would be less pronounced closer to the equator. It is possible that bears or other hibernating animals behave in a more physiologically favorable manner, being active in summer and sleeping for long periods during the winter, allowing for a cumulative clearance of central nervous system toxins.

As this study suggests, there would be benefits from more flexibility in work schedules. Although banks or public offices may follow a strict 9 a.m. to 5 p.m. day, retail stores maintain potentially more realistic hours, shifted to 10 a.m. to 6 p.m. or possibly an even later interval. While television schedules are modified to broadcast at appropriate times across Eastern to Pacific time zones, there is no such modification of show times within any given time zone. Modern TV practices, with streaming of content and "binge watching," would provide for more flexibility, but may have as yet unrecognized adverse effects on sleep health. ■

ABSTRACT & COMMENTARY

Treatment of Progressive Multifocal Leukoencephalopathy With Pembrolizumab

By Ulrike W. Kaunzner, MD, PhD

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

SYNOPSIS: These authors evaluated the effect of pembrolizumab, a monoclonal antibody that functions as a down-regulator of PD-1 (programmed cell death protein 1), on patients with progressive multifocal leukoencephalopathy. In five of eight treated patients, clinical stabilization or improvement was seen in association with reduced cerebrospinal fluid JC viral load. This is the first reported effective treatment for this disease with a therapeutic agent targeting the JC virus.

SOURCE: Cortese I, Muranski P, Enose-Akahata Y, et al. Pembrolizumab treatment for progressive multifocal leukoencephalopathy. *N Engl J Med* 2019;390:1597-1605.

Progressive multifocal leukoencephalopathy (PML) is an opportunistic, often fatal, infection of the central nervous system (CNS) caused by the polyomavirus JC. Antibodies to the JC virus can be found in approximately 50-60% of healthy adults. In cases of immunodeficiency, the virus can transform into a neurotropic virus, causing PML, with areas of demyelination. Historically, PML was described in leukemia and lymphoma patients; however, more recently, PML has been described in patients with immune-deficiency secondary to immunosuppressant medications given for various autoimmune conditions.

Presenting symptoms can include visual impairment, cognitive dysfunction, and ataxia, but various other neurological symptoms can be associated with PML. The diagnosis of PML is based on MRI findings, the detection of the JC virus in cerebrospinal fluid (CSF), and brain biopsy, which is still the diagnostic gold standard. So far, treatment options for PML are limited, and the predominant focus has been on restoring immune function. Mortality is dependent on the underlying disease and on the degree of immune suppression.

[Overall, this is an elegant approach to explore the blockage of PD-1 and its effect on PML, and might have the potential for a future treatment option in a disease that desperately needs treatment options.]

Programmed cell death protein 1 (PD-1) is an immune checkpoint protein that is expressed on T cell surfaces, and down-regulates immune function. Increased PD-1 expression contributes to decreased immune response to viral infection. PD-1 is up-regulated on CD4 and CD8 T cells in blood and CSF of PML patients and has been shown to be increased in autopsy tissue of PML patients.

Cortese et al tested the hypothesis that blockage of the PD-1 pathway with pembrolizumab, a down-regulator of PD-1 expression, can renew anti-JC virus immune activity in patients with PML. Eight patients with PML were enrolled and all patients had different immunodeficiencies (chronic lymphocytic leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma, idiopathic lymphopenia, HIV). Clinical disability ranged from two to four on the modified Rankin Scale.

Patients received pembrolizumab every four to six weeks, up to a total of three doses. After pembrolizumab administration, down-regulation of PD-1 was seen on lymphocytes in the blood and CSF of all eight patients. Five patients stabilized or showed improvement, and reduction in CSF JC viral count was seen. Four out of these five patients showed persistent reduction of JC viral load and showed clinical stabilization with no recurrence of PML 16-26 months later. MRI showed corresponding reduction in PML lesions, but no PML lesions disappeared fully. Three of eight patients had no positive response to pembrolizumab; one patient had already stabilized and two deteriorated and succumbed to PML. None of the patients developed IRIS.

■ COMMENTARY

This is a landmark study, since no specific medication is available for the treatment of PML, a CNS infection with a high mortality rate. Improving the underlying immunosuppressive disease (e.g., initiating treatment of HIV) is the main approach to PML treatment. For patients on immunosuppressant medications, reconstitution of the immune system is attempted by withdrawing immune-suppressant treatment and adding plasmapheresis. Mirtazapine, a potential blocker of JC virus into cells, has been tried but no benefit on disease outcome has been demonstrated.

In this study, five out of eight patients stabilized clinically, and four out of these five patients showed a persistent reduction of their viral count, which is an impressive result, despite the small study size. An additional benefit is that none of these patients developed IRIS after their immune function improved, which was attributed to continuous low lymphocyte count in the respective patients.

As the authors noted, it would be important to know if these effects are solely secondary to pembrolizumab administration or if improvement of the underlying condition contributed to the outcome. Larger studies or clinical trials would be warranted to assess the efficacy and safety associated with pembrolizumab for different underlying immunodeficient diseases. It also would be important to determine if pembrolizumab has a positive effect on patients on immunosuppressant medications, and if it improves mortality after immune-suppressant medication has been withdrawn. Overall, this is an elegant approach to explore the blockage of PD-1 and its impact on PML, and might have the potential for a future treatment option in a disease that desperately needs treatment options. ■

ABSTRACT & COMMENTARY

Tau PET Is Promising as a Diagnostic Agent in Chronic Traumatic Encephalopathy

By Makoto Ishii, MD, PhD

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

SYNOPSIS: Former NFL players with symptoms consistent with chronic traumatic encephalopathy had increased tau tracer uptake that was associated with years of playing football but not with cognitive or neuropsychological measures.

SOURCE: Stern RA, Adler CH, Chen K, et al. Tau positron-emission tomography in former National Football League players. *N Engl J Med* 2019;380:1716-1725.

The National Football League (NFL) is the most popular sports league in the United States, but chronic traumatic encephalopathy (CTE), a neurodegenerative disease associated with repeated head impacts, is a growing long-term safety concern for its players. Reported symptoms of CTE include cognitive impairment, mood disturbances, and lack of behavioral control. Currently, CTE is defined neuropathologically by the deposition of paired helical filament tau aggregates. These tau aggregates initially form in the frontal, temporal, and parietal cortices before becoming more extensively distributed in a distinct pattern from other tauopathies such as Alzheimer's disease (AD). However, as CTE can be diagnosed formally only postmortem, this limits our ability to accurately diagnose CTE in patients and to develop effective prevention and treatment trials. Therefore, Stern et al sought to use a recently developed positron-emission tomography (PET) tau tracer ^{18}F-flortaucipir to compare brains of living former NFL players with neuropsychiatric symptoms consistent with CTE to asymptomatic controls without a history of head injuries.

Study participants were 26 former NFL players who reported cognitive, mood, and behavioral control symptoms and 31 asymptomatic control participants. All subjects were males 40 to 69 years of age with no history of traumatic brain injury, other than contact while playing football. The former NFL players were recruited from two separate investigator-initiated CTE studies. Eighteen subjects were from a study conducted in Boston (Boston University and Brigham and Women's Hospital) with another eight subjects from a separate study conducted in Arizona (Mayo Clinic Scottsdale and Banner Alzheimer's Institute). Control subjects were from four separate studies, including nine from the CTE study in Boston, one from the CTE study in Arizona, 18 from an earlier Avid-sponsored AD trial, and three from the Alzheimer's Disease Neuroimaging Initiative. The Mini-Mental Status Examination (MMSE) was administered to all subjects. Former NFL players were also administered tests for executive function, episodic memory, and behavioral regulation. Each participant underwent flortaucipir PET (for the detection of tau), florbetapir PET (for the detection of amyloid-beta), and T1-weighted volumetric MRI of the head. Overall demographic characteristics, including mean ages and years of education, were similar between the two groups, except the group of former NFL players included a higher percentage of black participants and lower MMSE scores (former NFL players: 27.23 ± 1.73; controls: 29.06 ± 0.81; $P < 0.001$).

An analysis of the age-adjusted flortaucipir standard uptake value ratios (SUVRs) found significantly higher tau tracer uptake in the former NFL players group compared to the control group, primarily in the bilateral superior frontal, bilateral medial temporal, and left parietal regions. Although mean differences in flortaucipir SUVRs were significantly different between the groups, there was significant overlap on an individual level. There also was no significant difference in flortaucipir SUVRs between self-identified black and white former players. Furthermore, flortaucipir SUVRs were not significantly associated with cognitive or neuropsychological test scores. However, years of playing football did correlate with tau tracer uptake. With respect to amyloid PET, there were no significant differences in the florbetapir SUVRs between former NFL players and control subjects. One former NFL player and two controls had positive amyloid PET scans.

■ COMMENTARY

This important study provides good evidence that non-invasive tau PET imaging can detect tau pathology in vivo in a pattern similar to postmortem neuropathological studies of CTE. However, there are significant concerns and limitations. First, as the authors pointed out, there was significant overlap in tau tracer uptake between the groups. Therefore, it would not be possible to use flortaucipir as is to diagnose individuals with CTE. Second, the overall positive tau uptake was significantly lower than that seen in AD, suggesting that flortaucipir does not bind to the tau aggregates in CTE

as well as it does in AD. This could be because of differences in the molecular structures of tau aggregates between CTE and AD or from the difficulty in imaging tau accumulation in the deep sulci as commonly seen in CTE. Also, flortaucipir is a first-generation tau tracer that may have nonspecific binding and other specificity and sensitivity issues.

Additionally, the tau tracer uptake did not correlate with any cognitive or neuropsychological measure. Although this could be from a low sample number resulting in an underpowered study or from the relatively mild cognitive symptoms, it also is possible that tau aggregates in CTE do not necessarily reflect functional outcomes. Furthermore, since these neuropsychological symptoms are relatively common and may be seen in many other conditions, some of the symptomatic subjects may not have CTE. Finally, there are study design considerations. This study was cross-sectional, with subjects accrued from several other studies across different sites, including a majority of control subjects recruited from non-CTE studies. While the investigators did their best to match the groups, there was likely to be variability within the groups due to the differences in the enrollment sites.

Despite limitations, this study significantly advances the field by showing that it is feasible to detect tau pathology in CTE by PET. Replication studies are needed with larger numbers of well-matched subjects using the newer second-generation tau tracers that may be more specific. It would be ideal to conduct longitudinal studies including clinicopathological correlation with the tau PET. While tau PET is not yet ready for prime time, future studies based on this one are likely to help establish whether tau PET can be used as a diagnostic agent in clinical practice and for the development of prevention and treatment trials. ■

CME QUESTIONS

1. **Which of the following statements regarding eculizumab treatment for neuromyelitis optica spectrum disorder (NMOSD) is correct?**
   a. Eculizumab is FDA-approved for treatment of NMOSD.
   b. NMOSD is not a serious or life-threatening condition.
   c. Eculizumab treatment resulted in significant reduction in relapses in NMOSD patients.
   d. Rituximab and eculizumab may be used together to treat NMOSD.
2. **Which of the following is most commonly seen in systemic lupus erythematosus?**
   a. Peripheral sensorimotor polyneuropathy
   b. Autonomic neuropathy
   c. Cranial neuropathy
   d. Peripheral motor neuropathy
3. **Why are circadian rhythms important?**
   a. Circadian rhythms determine when we wake up and when we go to sleep.
   b. Circadian rhythms regulate vital metabolic and hormonal functions.
   c. Circadian rhythms are tightly linked to times of sunrise and sunset.
   d. Circadian rhythms do not affect brain health.
4. **Which of the following statements regarding progressive multifocal leukoencephalopathy (PML) is true?**
   a. PML can develop in otherwise healthy people who have a normal immune system.
   b. PML does not cause significant disability.
   c. There is no current treatment for PML other than improving immune function.
   d. PML only develops in people who have leukemia or lymphoma.
5. **Based on the recent tau PET study of former NFL players, which of the following is true?**
   a. As a group, former NFL players had increased tau tracer uptake in three brain regions compared to the control group.
   b. As a group, former NFL players had increased amyloid tracer uptake compared to the control group.
   c. Tau tracer uptake was significantly associated with cognitive and neuropsychological measures.
   d. Tau PET can be used to distinguish those with symptoms consistent with chronic traumatic encephalopathy on an individual level.

[IN FUTURE ISSUES]

Treatment of Primary Brain Tumors