Relias Media
From Relias

Vol. 41, Issue 5, January 2022
ReliasMedia.com

Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Thalamic Stroke and Sleep Impairment: An Experiment of Nature

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: In a detailed clinical and electrophysiological study of sleep patterns in 12 patients with thalamic stroke, comparing them with 11 patients who had extrathalamic stroke, the investigators identified a marked decrease in slow wave sleep activity in the group with thalamic stroke. The clinical significance of this finding is uncertain but may have an effect on daytime cognitive performance.

SOURCE: Jaramillo V, Jendoubi J, Maric A, et al. Thalamic influence on slow wave slope renormalization during sleep. *Ann Neurol* 2021;90:821-833.

The thalamus is known to play a key role in arousal and sleep-wake states. With modulation of thalamic activity, direct changes in cortical neurons occur — a process elucidated recently in rodents using a technique known as "optogenetics." By transgenic incorporation of light-sensitive proteins into cell membranes, in vivo nerve circuits can be directly manipulated into states of stimulation or inhibition. Seminal work involving optogenetic manipulation of the thalamus (specifically the centromedial nucleus [CMT]) has shown that, with tonic stimulation of the CMT, there is depolarization of cortical pyramidal neurons and production of spike activity (the so-called UP state).[1] This has been demonstrated most prominently at the transition between non-rapid eye movement (NREM) sleep and the waking state. Conversely, burst stimulation of the CMT produces cortical quiescence (the DOWN state), which promotes sleep. When this burst activity is optimally synchronized, there is production of high amplitude, slow-wave activity (SWA), which is the hallmark of deep NREM sleep.

According to the authors, sleep-wake fluctuations of cortical activity, generated by the thalamus, contribute to plastic changes in the

Financial Disclosure: None of the 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.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

Questions & Comments:
Please contact Jason Schneider at jschneider@relias.com.

Back issues: Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

Relias LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The Relias LLC designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the neurologist. It is in effect for 36 months from the date of the publication.

structure of synapses in the brain — a concept known as "synaptic homeostasis." During wakefulness, there is a potentiation of synaptic activity, producing an increase in synaptic strength. With sleep, particularly with pronounced SWA, there is a reduction in synaptic strength — a process known as "synaptic renormalization." Optimal renormalization theoretically would allow the brain to reboot in preparation for the next day. The study provides various lines of evidence for this process, such as animal studies using two-photon imaging and electron microscopy to show an increase in dendritic spines ("a key marker for synaptic strength") during wakefulness and a decrease during sleep.

In their investigation, Jaramillo and colleagues studied patients who had thalamic strokes and compared them to stroke patients with lesions outside of the thalamus ("extrathalamic"). Recapitulating thalamic lesional studies done in animals, this research takes advantage of stroke as a "natural experiment" to better define these processes in living humans. The study included 23 patients, 12 with thalamic strokes and 11 with extrathalamic strokes. Thalamic lesions were located as follows: five paramedian, five inferolateral, and two tuberothalamic.

The vast majority of these patients (10/12) also had extrathalamic lesions. The 11 extrathalamic patients had lesions (which could be multiple) in the following regions: cortex (n = 8), basal ganglia (n = 5), midbrain cerebral peduncle, and medulla. Representative diffusion-weighted imaging (DWI) of all patients was included in the manuscript.

The extrathalamic subjects underwent 15 days of polysomnography (PSG) and the thalamic subjects underwent 17 days of PSG. Subjects had enhanced electroencephalogram (EEG) analysis during their PSGs, which included high-density lead placement and spectral analysis to compute the power of SWA. Sleep parameters using standard visual scoring did not differ between the two groups. By contrast, power analysis showed pronounced differences between thalamic and extrathalamic groups, with a marked decrease in SWA (defined as EEG power between 1 Hz and 4.5 Hz) among the thalamic stroke patients. This effect was seen in all cortical leads (frontal, central, temporal, parietal, and occipital) but was most striking in the right frontocentral region. Interestingly, this area has been shown to be the most sensitive brain region to the onset of drowsiness.

Subjects were tested daily using subjective sleepiness ratings (such as the Epworth Sleepiness Scale) and 11 cognitive tasks, such as the Corsi block-tapping task, which assesses visuospatial function and short-term working memory. Other tests captured motor/sensory examinations, verbal abilities, and executive function. The only statistically significant difference between the thalamic and extrathalamic patients was in Epworth score (as measured in the morning but not at other times, such as before bed). However, the authors observed that out of 13 total outcome measures, all but one pointed in the negative direction in thalamic subjects, a result well beyond that which could occur by chance ($P = 0.05$ by chi-squared test).

The authors outlined two mechanisms to explain their results, referred to as "wake-centered" and "sleep-centered" models, which, stated differently, can be considered a standard chicken-or-egg quandary. Both models focus on the concepts of synaptic potentiation during the day and synaptic renormalization at night. In the "wake-centered" scenario, lesions of the thalamus result in impairments in attention and "experience-dependent learning," which blunts synaptic growth. This reduction then decreases the need for sleep-associated synaptic renormalization, manifested as decreases in SWA. In the "sleep-centered" version, the authors suggested that decreased SWA among the thalamic subjects creates impairments in renormalization, leading to reductions in daytime alertness and cognitive performance.

■ COMMENTARY

At a minimum, these data show that subjects with thalamic strokes sleep poorly and experience significant daytime cognitive impairments — a relationship that almost certainly is bidirectional. Whether the former contributes more to the latter or vice versa is not known. However, these data fall short of taking the next step of defining SWA generated by the thalamus as evidence of a restorative physiological role of sleep. The authors attempted to use the concept of synaptic renormalization to take limited data from animal experiments and translate them into humans. Synaptic renormalization is an elegant hypothesis, but it involves multiple assumptions and conjecture, and cannot be accepted as the mechanistic underpinning of the homeostatic need for sleep — a phenomenon that largely has eluded modern neuroscience. ■

REFERENCE

1. Gent TC, Bandarabadi M, Gutierrez Herrera C, Adamantidis AR. Thalamic dual control of sleep and wakefulness. *Nat Neurosci* 2018;21:974-984.

ABSTRACT & COMMENTARY

Neuropathological Findings in the Brains of Patients Who Died from COVID-19

By Alexander E. Merkler, MD, MS

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical College, and Assistant Attending Neurologist, New York-Presbyterian Hospital

SYNOPSIS: In an autopsy study of 41 patients who died from COVID-19 in a single medical center in New York City, most of the brain pathology was the result of hypoxic-ischemic injury, infarction, and hemorrhage, with microglial activation and neuronophagia caused by inflammation. Studies for the presence of viral proteins were negative, and very low levels of viral ribonucleic acid were detected.

SOURCE: Thakur KT, Miller EH, Glendinning MD, et al. COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. *Brain* 2021;144:2696-2708.

COVID-19 is the most impactful pandemic of our lifetime and at present has affected more than 247 million people and led to 5 million deaths worldwide.[1] Neurological manifestations of COVID-19 are common and include olfactory and gustatory dysfunction, cerebrovascular disease, encephalopathy, seizures, and neuropathy. Whether these neurological disorders are all a result of systemic medical illness caused by COVID-19 or may be a consequence of direct nervous tissue invasion of SARS-CoV-2 remains uncertain. Furthermore, long-term neuropsychiatric sequelae of COVID-19 are relatively common and yet we continue to lack a clear understanding of its pathophysiology.

In the current study, Thakur et al described the clinical, neuropathological, and molecular findings of 41 consecutive patients with SARS-CoV-2 infection who died and underwent autopsy at a tertiary care academic medical center in New York City during the early surge in Spring 2020. Among these 41 patients, 24 (59%) were admitted to the intensive care unit, eight (20%) had deep vein thrombosis/pulmonary embolism, seven (17%) had acute kidney injury requiring dialysis, and 10 (24%) had positive blood cultures during admission. Eight (20%) died within 24 hours of hospital admission and 11 (27%) died more than four weeks after hospital admission.

[Neurological manifestations of COVID-19 are common and include olfactory and gustatory dysfunction, cerebrovascular disease, encephalopathy, seizures, and neuropathy.]

Evidence of cerebrovascular disease was common. Head computed tomography was performed on 11 (27%) patients and two (5%) also underwent brain magnetic resonance imaging (MRI). Intracerebral hemorrhages were found in three patients and multiple subacute ischemic strokes were found in one patient. Five patients had imaging evidence of diffuse cerebral edema and hypoxic-ischemic injury, three of whom had concurrent prior hemorrhages. Nine brains (22%) were imaged post-mortem; five had evidence of

intracerebral hemorrhage and one had an acute cerebral infarct. At autopsy, all brains had evidence of hypoxic damage; 18 (44%) had evidence of ischemic stroke (acute, subacute, or chronic) and eight (19%) had intracranial hemorrhage, the majority of which seemed to represent hemorrhagic transformation of an ischemic stroke.

[Patients with COVID-19 have evidence of significant neuropathology that likely is a result of systemic medical illness, coagulation disorders, and inflammation and is not related to direct SARS-CoV-2 infection of brain tissue.]

Among 28 patients studied, polymerase chain reaction analysis revealed low to very low detectable levels of SARS-CoV-2 ribonucleic acid (RNA) within brain tissue. In addition, RNAscope and immunocytochemistry failed to detect SARS-CoV-2 messenger RNA or SARS-CoV-2 viral proteins in the brains. Microglial activation with microglial nodules was present in 81% of patients and was most prominent in the brainstem. Perivascular lymphocytic inflammation and infiltration into the brain parenchyma was sparse. Eighteen patients (44%) exhibited pathologies of neurodegenerative diseases — not a surprise, since the mean age of the group was 74 years. Based on these findings, the authors concluded that direct brain tissue invasion of SARS-CoV-2 is an unlikely explanation for the identified neuropathological findings. Instead, the neuropathological findings likely are the result of systemic medical illness, coagulation disorders, and inflammation.

Limitations of this study include the fact that all patients were from New York City at a single academic medical center, many had significant preexisting medical comorbidities, and the majority of patients were of Hispanic ethnicity.

■ COMMENTARY

Overall, this study adds to our growing understanding of the effects of COVID-19 on the central nervous system. Cerebrovascular manifestations of COVID-19 are common and appear to be the result of systemic effects of COVID-19 on the coagulation system rather than direct SARS-CoV-2 invasion of the brain.

The authors also opined that the distribution of microglial activation potentially may help explain the long-term neuropsychiatric effects of survivors of COVID-19. Microglial activation was found throughout the brain, but particularly in the brainstem. Although intriguing, patients with long-term neuropsychiatric effects of COVID-19 do not appear to have symptoms of brainstem pathology, such as cranial nerve dysfunction. Neuroimaging, including MRI, on patients who have recovered has not revealed any pathology other than ischemic stroke.

In conclusion, patients with COVID-19 have evidence of significant neuropathology that likely is a result of systemic medical illness, coagulation disorders, and inflammation and is not related to direct SARS-CoV-2 infection of brain tissue. ■

REFERENCE

1. World Health Organization. WHO coronavirus (COVID-19) dashboard. https://covid19.who.int/

ABSTRACT & COMMENTARY

Intravenous Immunoglobulin for Stable CIDP: Stop or Taper?

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: First-line therapy for chronic inflammatory demyelinating polyneuropathy is intravenous immunoglobulin (IVIG), but the timing and method for withdrawal of this treatment are uncertain. In a retrospective review of stable patients on IVIG, investigators at the National Hospital in London observed that there was no significant difference in the likelihood of deterioration or response to retreatment if IVIG was stopped abruptly or tapered slowly.

SOURCE: Kapoor M, Compton L, Rossor A, et al. An approach to assessing immunoglobulin dependence in chronic inflammatory demyelinating inflammatory polyneuropathy. *J Peripher Nerv Syst* 2021;26:461-468.

Intravenous immunoglobulin (IVIG), which is easy to administer compared to plasma exchange and has a more rapid response compared to glucocorticoids, is effective treatment for chronic inflammatory demyelinating polyneuropathy (CIDP). Improvement within one month is significantly higher with IVIG compared to placebo (44% vs. 26%), the relapse rate is significantly lower (13% IVIG vs. 45% placebo), and IVIG provides a longer time until relapse.

Unfortunately, treatment with IVIG alone usually does not result in remission. Of the 75% of patients who will improve initially, 85% will require maintenance treatment, with only about 15% able to stop IVIG after two to three years. When a patient is doing well on maintenance IVIG, how may one best assess disease activity? In a stabilized patient, should IVIG be stopped abruptly or should gradual dose reduction be pursued?

Using European Federation of Neurological Societies/Peripheral Nervous System guidelines, investigators retrospectively identified all CIDP patients seen between 2008 and 2018 at the National Hospital of Neurology and Neurosurgery, London, in whom IVIG dependence was tested either by gradual dose reduction or immediate treatment cessation.

Data collected included disease duration, clinical and neurophysiological information, and IVIG maintenance regimen. Baseline and follow-up outcome measures were obtained in response to an IVIG dependence challenge, with IVIG restarted if IVIG dependence was determined. IVIG independence (remission) was defined as absence of deterioration for at least two years following discontinuation of IVIG, with patients evaluated at six- to 12-month intervals.

Outcome measures included the Inflammatory Rasch-built Overall Disability Scale (I-RODS) and the Medical Research Council sum score. Statistical analysis comprised Mann-Whitney U tests and Fisher's exact tests, with two-tailed *P* values < 0.05 deemed significant.

Among 33 stable CIDP patients on IVIG maintenance therapy who underwent at least one IVIG dependence challenge between 2008 and 2018, 16 (48.4%) underwent treatment cessation and 17 (51.2%) underwent gradual dose reduction. When evaluating the entire group (33 patients), 21 (63.6%) were deemed to have active disease and were IVIG dependent, and 12 (36.4%) were in remission without the need for further IVIG, with similar proportions from each group.

[When a patient is doing well on maintenance intravenous immunoglobulin (IVIG), how may one best assess disease activity? In a stabilized patient, should IVIG be stopped abruptly or should gradual dose reduction be pursued?]

Among the 21 patients with active disease, no significant difference was appreciated in the deterioration of scores between the two groups who had IVIG withdrawn, with a mean time of five months from baseline to nadir, longer for the gradual reduction group (8.8 months) compared to the cessation group (3.5 months). Time to deterioration was unrelated to IVIG dose or frequency of administration, and re-stabilization was achieved in all patients, more rapidly in the gradual reduction group compared to the cessation group, two weeks vs. 14.1 weeks, respectively.

Overall, one-half of the patients who deteriorated after IVIG withdrawal improved within one week

of retreatment. No statistically significant factor was identified to discern which patients still proved to have active disease and which did not. IVIG cessation, with close clinical monitoring, is a safe and effective manner of determining which CIDP patients require continued maintenance therapy and which are in remission.

■ COMMENTARY

To what degree does demyelination vs. axonal degeneration play a role in the disability of CIDP? Among 95 patients with typical or variant CIDP who underwent electrophysiological studies in a single-center, prospective, observational, cohort study at St. Josef-Hospital, University Hospital Bochum, Germany, nerve conduction study (NCS) evidence of axonal loss strongly correlated with disability, both at initial diagnosis and during the course of active disease.

Upper limb distal compound muscle action potential amplitudes correlated best with overall clinical function. Axonal damage, as opposed to demyelination, is the main determinant of disability in CIDP and, although symptoms usually are more predominant in the legs, upper limb NCS is most predictive of disability.[1] ■

REFERENCE

1. Gruter T, Motte J, Bulut Y, et al. Axonal damage determines clinical disability in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): A prospective cohort study of different CIDP subtypes and disease stages. *Eur J Neurol* 2021; Oct 22. doi: 10.1111/ene.15156. [Online ahead of print].

ABSTRACT & COMMENTARY

Neuropathological Variability of NMDAR-Encephalitis

By Hai H. Hoang, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: The neuropathological features of N-methyl-D-aspartate receptor (NMDAR)-encephalitis are described in an autopsy cohort of four patients — two diagnosed in life with comorbid brain disorders, and two diagnosed at autopsy and never treated. The two untreated patients had inflammatory infiltrates composed of perivascular and parenchymal T cells and B cells/plasma cells in the basal ganglia, amygdala, and hippocampus. The two treated patients had variable pathologies that reflected their underlying neurological disorders (lymphoproliferative disease and multiple sclerosis). Overall, the topographic distribution of inflammation in patients with NMDAR-encephalitis reflects the clinical symptoms of movement disorders, abnormal behavior, and memory dysfunction with inflammation predominantly observed in the basal ganglia, amygdala, and hippocampus. Loss of NMDAR-immunoreactivity correlated with disease severity.

SOURCE: Zrzavy T, Endmayr V, Bauer J, et. al. Neuropathological variability within a spectrum of NMDAR-encephalitis. *Ann Neurol* 2021;90:725-737.

N-methyl-D-aspartate receptor (NMDAR)-encephalitis is associated with a characteristic clinical syndrome presenting with acute psychiatric symptoms, cognitive deficits, epileptic seizures, movement disorders, and autonomic dysregulation. In vivo and in vitro experiments demonstrated that the antibodies bind to an extracellular region of the NMDAR, causing internalization of the receptor and neuronal dysfunction.

The reversibility of neuronal dysfunction is reflected by good response to immunotherapy. Neuropathologic assessments are rare, since most patients recover or reach a diagnosis with biopsy. This study characterized the spectrum of inflammatory changes in different brain areas in patients who have or have not been treated with immunotherapy.

Four patients who underwent autopsies were included in this study. Two patients died before NMDAR-encephalitis was systematically tested and did not receive immunotherapy. NMDAR antibodies were retrospectively tested in archival cerebrospinal fluid (CSF) samples. Two patients were diagnosed with NMDAR-encephalitis during their lifetime and treated with immunotherapy but developed a co-pathology and died. Both patients received immunosuppressants, including steroids and intravenous immunoglobulin (IVIG). One of the patients also received chemotherapy and plasma exchange.

Neuropathologic evaluation of one of the two patients with postmortem diagnosis of NMDAR-encephalitis demonstrated immunohistochemical staining of the hippocampus with a decrease in NMDAR-expression compared to an age-matched

control. In one of the two patients with NMDAR-encephalitis and central nervous system (CNS) comorbidities, brain biopsy showed a monomorphic post-transplant lymphoproliferative disease (PTLD), Epstein-Barr virus (EBV)-associated diffuse large B cell lymphoma (DLBCL). EBV-negative plasma cells were abundant in the medial temporal lobe, including amygdala and hippocampus. In the other patient with NMDAR-encephalitis and CNS comorbidities, whole brain sections showed periventricular demyelinating plaques with perivenous finger-like extensions into the adjacent white matter consistent with multiple sclerosis. Immunohistochemistry for both patients with NMDAR and CNS comorbidities for NMDAR revealed a mild reduction of immunoreactivity in the hippocampus compared to a healthy control.

Significant negative findings in the autopsies of the patients included the absence of detection of complement deposits. Hematoxylin and eosin (H&E) and immunohistochemistry for neurofilament, glial fibrillary acidic protein (GFAP), and human leukocyte antigen-DR isotype (HLA-DR) showed no neuronal loss, reactive scar-forming astrocytes, or microglial nodules in the pyramidal cell layer of the hippocampus, cortical regions, brainstem, or cerebellum.

■ COMMENTARY

This is one of very few studies that evaluated the neuropathologic changes in patients with NMDAR-encephalitis. The investigators were able to compare two untreated NMDAR-encephalitis patients with two treated NMDAR-encephalitis patients, noting that the patients who were treated had other CNS comorbidities. As expected in the two untreated NMDAR-encephalitis patients, the authors found that the amygdala, hippocampus, and basal ganglia were the areas with greatest inflammation, which correlated with the clinical presentation of abnormal behavior, memory dysfunction, and movement disorders. Additionally, overlapping CNS pathologies in patients led to changes in the distribution and composition of inflammatory infiltrates, and the pro-inflammatory microenvironment may have enhanced the intensity of inflammation. Neurons were well preserved but had reduced NMDAR-immunoreactivity, and the extent of decreased immunoreactivity correlated with disease severity.

[Overlapping central nervous system pathologies in patients led to changes in the distribution and composition of inflammatory infiltrates, and the pro-inflammatory microenvironment may have enhanced the intensity of inflammation.]

Clinical implications of this study include the identification of pharmacologic targets for future therapies. Given that no complement depositions were found in any of these autopsies, therapies, such as complement inhibitors used for the treatment of neuromyelitis optica and myasthenia gravis, would not be ideal therapies for patients with NMDAR-encephalitis. ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to ReliasMedia.com and click on My Account. First-time users must register on the site. Tests are taken after each issue.
3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, your browser will be directed automatically to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be emailed to you.

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. **Thalamic stroke may cause which of the following changes in sleep patterns?**
   a. Reduction in rapid eye movement-sleep time and dreaming
   b. Increased daytime sleepiness
   c. Overall reduction in sleep time
   d. Difficulty falling asleep at night

2. **A 79-year-old man with hypertension, diabetes, high cholesterol, and prior stroke develops acute respiratory failure secondary to SARS-CoV-2 pneumonia. During the hospitalization for acute respiratory failure, he develops atrial fibrillation and heart failure and has an acute right middle cerebral artery infarction. Which of the following is the most likely cause of his new stroke?**
   a. The right middle cerebral artery stroke likely is the result of his new atrial fibrillation and heart failure.
   b. The right middle cerebral artery stroke likely is the result of direct SARS-CoV-2 invasion of the brain tissue and cerebral vasculature.
   c. The right middle cerebral artery stroke likely is the result of vasculitis.
   d. The right middle cerebral artery stroke likely is the result of small vessel disease.

3. **Regarding treatment of chronic inflammatory demyelinating polyneuropathy (CIDP), which of the following statements is correct?**
   a. Never modify the frequency or dosage of maintenance intravenous immunoglobulin (IVIG) administration in CIDP patients who have responded to IVIG and are stable.
   b. In CIDP patients who have responded to IVIG and are stable, one may stop the IVIG abruptly and monitor the result.
   c. In CIDP patients who have responded to IVIG and are stable, withdrawal can be done by reducing the dose rather than reducing the frequency of administration of IVIG.
   d. Long-term IVIG maintenance therapy is not an acceptable mode of treatment for CIDP.

4. **Regarding N-methyl-D-aspartate receptor-encephalitis, which one of the following statements is *false*?**
   a. Clinical symptoms include behavior changes, movement disorders, seizures, and cognitive changes.
   b. The neuropathology is perivascular infiltration with T-cells, B-cells, and plasma cells.
   c. Patients present with acute hemiplegia and visual loss.
   d. Inflammation occurs in the basal ganglia, amygdala, and hippocampus.