AHC Media

Vol. 34, Issue 12, August 2015
AHCMedia.com

Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

GAD Antibody Syndromes: When to Dig Deeper

By Bianca D. Santomasso, MD, PhD

Instructor in Neurology, Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College

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

SYNOPSIS: This retrospective case series identifies the clinical and immunologic features of GAD antibody-positive patients who should be screened for an underlying cancer.

SOURCE: Arino H, et al. Paraneoplastic neurological syndromes and glutamic acid decarboxylase antibodies. *JAMA Neurol* 2015; June 22. doi:10.1001/jamaneurol.2015.0749 [Epub ahead of print].

Autoimmune neurological disorders can be associated with an underlying cancer (in which case they are referred to as paraneoplastic) or they can be idiopathic. High titer antibodies against the intracellular synaptic enzyme glutamic acid decarboxylase (GAD) fall into this latter category and are associated with specific neurologic syndromes including stiff-person syndrome (SPS), cerebellar ataxia, limbic encephalitis, and epilepsy. Rather than a cancer association, GAD antibodies more often occur with organ-specific autoimmune disorders such as diabetes. The clinician faced with a patient with GAD antibodies typically would not embark on a search for an underlying tumor unless the patient also had an additional "onconeural" antibody such as Hu, Yo, Ri, CV2, amphiphysin, or Ma. Nevertheless, there have been case reports of patients with GAD antibodies who have an underlying cancer, suggesting that some cases may be paraneoplastic. This leads to the question: When should we be doing a tumor workup in a patient with GAD-abs and a neurological syndrome?

The authors, who are affiliated with a large center in Barcelona, Spain, for autoimmune neurological disorders, retrospectively examined patients between 1995 and 2013 whose samples were submitted for onconeural antibody analysis. Patients whose samples were sent in for analysis met criteria for definite or

Financial Disclosure: *Neurology Alert*'s editor in chief, Matthew Fink, MD; peer reviewer M. Flint Beal, MD; executive editor Leslie Coplin; and associate managing editor Jonathan Springston report no financial relationships relevant to this field of study.

Neurology
[ALERT]

Neurology Alert,
ISSN 0741-4234, is published monthly by
AHC Media, LLC
One Atlanta Plaza
950 East Paces Ferry NE, Suite 2850
Atlanta, GA 30326.
AHCMedia.com
GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA 30304
and at additional mailing offices.

POSTMASTER: Send address changes to
Neurology Alert,
P.O. Box 550669,
Atlanta, GA 30355.

SUBSCRIBER INFORMATION
1-800-688-2421
customerservice@ahcmedia.com
AHCMedia.com

Editorial Email:
leslie.coplin@ahcmedia.com

Questions & Comments:
Please contact Leslie Coplin, Executive Editor, at leslie.coplin@ahcmedia.com

Subscription Prices
United States:
Print: 1 year with free *AMA PRA Category 1 Credits™*: $369
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $319
Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.
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
AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 2.25 *AMA PRA Category 1 Credits™*. Physicians should only claim 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.

AHC Media

possible paraneoplastic neurologic syndrome. Unexpectedly, they found 15 patients who had no onconeural antibodies but who had high titer GAD-abs and an underlying tumor. The tumors included six lung cancers (four of them SCLC), four neuroendocrine tumors (two pancreas and two thymic carcinoid), two thymoma, two breast cancer, and one non-Hodgkin lymphoma. Interestingly, eight of the 15 GAD patients with tumors presented with classical paraneoplastic neurologic syndromes (limbic encephalitis, encephalomyelitis, cerebellar degeneration, or opsoclonus-myoclonus syndrome) rather than the typical GAD-ab-associated syndromes of SPS, cerebellar ataxia, and epilepsy. In most patients, the neurological syndrome preceded the diagnosis of the cancer. Three tumors were examined for GAD protein by immunohistochemistry and all were found to express it, suggesting triggering of the immune response by the tumor.

The authors then compared the 15 paraneoplastic GAD-ab patients to a cohort of 106 patients with nonparaneoplastic GAD-ab disorders. There was no significant difference in the levels of antibody in the serum and CSF between the groups. They found that patients with paraneoplastic GAD-abs were older (median age 60 vs 48 years; $P = 0.03$), were more frequently male (60% vs 13%; $P < 0.001$), and more often had coexisting neuronal cell-surface autoantibodies (53% vs 11%; $P < 0.001$) such as γ-aminobuteric acid B antibodies, γ-aminobutyric acid A receptors antibodies, and glycine receptor antibodies. Eight of 15 patients with paraneoplastic GAD-abs had one of these or other antibodies to unknown targets on the neuronal cell surface. The patients also presented with more classical paraneoplastic syndromes (limbic encephalitis, paraneoplastic cerebellar degeneration, paraneoplastic encephalomyelitis, or opsoclonus-myoclonus syndrome) than SPS or cerebellar ataxia. The authors contrasted their series with reviewed cases of paraneoplastic GAD from the literature where SPS was the most common neurological syndrome (rather than limbic encephalitis) and thymic tumors (rather than lung) were the most common underlying neoplasm. They conclude that there seem to be distinct subgroups of patients with GAD-abs, some of whom have underlying tumors that are likely triggering their neurologic symptoms.

All study patients received immunotherapy with high-dose corticosteroids, intravenous immunoglobulin, intravenous immunoglobulin plus rituximab, or intravenous immunoglobulin plus cyclophosphamide. In addition, 10 (71%) patients received treatment of their underlying cancer with surgery, chemotherapy, radiotherapy alone, or combined therapy. Compared with their series, the previously reported cases were more likely to have clinical improvement and the probability of clinical improvement was greater in patients with thymic tumors.

[...every patient with a high level of GAD-abs should have screening for an underlying cancer, including mammogram and CT chest or PET scan.]

■ COMMENTARY

Many neurologists have the ability to order comprehensive antigen test batteries, which allow for the detection of neuronal cell surface antibodies in addition to GAD-abs. Although this study found the risk of cancer to be seven-fold higher in patients with concomitant antibodies against neuronal cell surface antigens, almost half of the patients in this study with an underlying tumor had no other antibodies detected. The clinical presentation, while helpful, is also not 100%; in this study, tumors in two SPS patients would have been missed by relying only on the clinical presentation alone as a way to distinguish paraneoplastic from idiopathic GAD-abs. Importantly, limbic encephalitis can be seen as a neurologic syndrome in both paraneoplastic and non-paraneoplastic cases. Therefore, one reasonable conclusion from this study is that every patient with a high-level GAD-abs should have screening for an underlying cancer, including mammogram and CT chest or PET scan. ■

ABSTRACT & COMMENTARY

Scrub Typhus and the Brain

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: Scrub typhus infections involve the nervous system in a majority of cases and should be suspected in patients who live in, or are returning from, endemic regions with a compatible clinical syndrome.

SOURCE: Misra UK, et al. Neurological manifestations of scrub typhus. *J Neurol Neurosurg Psychiatry* 2015;86:761-776.

Rickettsial diseases are bacterial infections transmitted to humans through bites from infected ticks, lice, fleas, or mites. Rickettsial diseases manifest in three forms, including typhus, spotted fever, and scrub fever. The most common rickettsial disease in the United States is Rocky Mountain spotted fever, caused by *Rickettsia rickettsii*. Other rickettsial diseases occur with more frequency in other parts of the world and can cause neurologic manifestations including meningoencephalitis. Scrub typhus is caused by *Orientia tsutsugamushi* and is endemic in northern Japan, northeastern Russia, parts of Australia, Pakistan, and India. Scrub typhus has varied clinical manifestations from a nonspecific febrile illness to severe multi-organ failure, with scattered reports of neurologic involvement as well. The diagnosis is often delayed, leading to poor outcomes including death. Scrub typhus responds well to antibiotic therapy, so it is important to make the proper diagnosis.

In this paper, the authors present a cross-sectional study evaluating the medical and neurologic manifestations of scrub typhus at a tertiary care teaching hospital in North India. Over the course of 2 years, 37 patients were identified. There was no gender predilection. Median age of the patients was 37 years. The median course of illness was 2 weeks. All patients had fever and myalgias. The vast majority of patients had headache, respiratory symptoms, and altered sensorium (> 80%). Typical eschar skin lesion was present in only half of the patients, as was nuchal rigidity. Eight patients (22%) had seizures as part of their disease course. Other clues to the diagnosis included lymphadenopathy (65%), vomiting (73%), hepatomegaly (35%), and focal weakness (38%). Almost all patients were anemic, half demonstrated thrombocytopenia, and half demonstrated leukocytosis. Elevated ALT was present in 89% of the patients.

Twenty-eight of the 31 patients with altered sensorium underwent lumbar puncture. In those patients, the mean cerebrospinal fluid (CSF) white blood cell count was 112 with a predominantly lymphocytic pleocytosis as well as elevated protein. Patients with altered sensorium but normal CSF were classified as experiencing an encephalopathy syndrome as opposed to a meningoencephalitis syndrome. Many of the patients with meningoencephalitis presentation experienced at least 10 days of progressive symptoms, suggesting a subacute meningitis. MRI scan was performed in most patients, and was normal in all but one patient who demonstrated meningeal enhancement. No patients had parenchymal lesions. EEG demonstrated slowing in 25% of encephalitic patients but none demonstrated epileptiform activity.

[U.S. neurologists need to be informed about the various infections that can affect the central nervous system.]

All patients were treated with oral doxycycline and ultimately all patients recovered, although patients with a higher degree of disability on admission were more likely to recover slowly. Most patients improved rapidly within 48 hours of doxycycline therapy.

■ COMMENTARY

This is an important study for a number of reasons. For neurologists who practice in countries where scrub typhus is endemic, this paper provides significant data as to the typical presentation, signs, diagnostic testing, and prognosis of patients. For other neurologists, this paper educates us about this important Rickettsial illness, especially the rapid globalization of the world's population. While it is unlikely that a neurologist in the United States would see this illness, it should be considered in the differential diagnosis of febrile encephalopathy or meningoencephalitis in patients who have travelled to endemic regions. This is especially important, as this disease is rapidly and easily treatable with oral doxycycline but can be fatal without treatment. It is important for U.S. neurologists to stay informed about the various infections that can affect the central nervous system, regardless of the endemic territories. Today, infectious diseases are all global. ■

ABSTRACT & COMMENTARY

A Modern Epidemiologic View of Status Epilepticus in the United States

By Kimberly Pargeon, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: In this retrospective review of mortality and hospitalization related to status epilepticus from 1999 to 2010, the authors found that the overall mortality remained relatively stable, whereas the rate of related hospitalizations significantly increased, particularly in patients who were intubated and in whom status epilepticus was not the primary diagnosis.

SOURCE: Betjemann JP, et al. Trends in status epilepticus-related hospitalizations and mortality: Redefined in U.S. practice over time. *JAMA Neurol* 2015;72:650-655.

Status epilepticus (SE) is a common neurological emergency that can have significant effects on morbidity, mortality, and healthcare costs. Although definitions have changed, SE is presently defined as a prolonged seizure or multiple seizures with incomplete return to baseline function lasting longer than 5 minutes. The incidence in the United States is about 10-41 per 100,000 people with higher rates among some ethnic minorities.[1] The overall reported mortality in adults is about 20%, with worse outcomes seen in older adults. SE can be further categorized as either convulsive or nonconvulsive, although nonconvulsive SE is often not well-defined in the literature. Recent efforts have focused on early seizure termination, typically with pre-hospital benzodiazepines, and early seizure detection, particularly for nonconvulsive events, through the increased use of continuous EEG monitoring.

Betjemann et al sought to examine trends in SE-related hospitalizations and mortality in the United States using retrospective data from large national administrative databases, from January 1999 to December 2010, for 408,304 hospitalized patients. The overall and age-standardized mortality rates were determined using data from the Centers for Disease Control and Prevention, and population-adjusted hospitalization rates were determined using the Nationwide Inpatient Sample. They further categorized hospitalizations as to whether SE was the principal or secondary diagnosis, whether the patient was intubated, and by insurance type. The use of video-EEG monitoring was identified using a specific ICD-9 procedure code.

One of the primary findings was that overall mortality from SE (two deaths per 1,000,000 persons) remained relatively stable from 1999 to 2010, particularly when it was the primary or underlying cause of death, increasing by only 5.6%. However, the rate of related hospitalizations increased by 56.2%, with the most significant increase seen for patients with a secondary diagnosis of SE as compared to a primary diagnosis (102.0% as compared to 33.4%). The use of video-EEG in SE-diagnosed patients also increased from 1.1% in 1999 to 4.3% in 2010, with the largest relative increase among intubated patients with a secondary diagnosis. Hospital discharges were also categorized by diagnosis type (principal vs secondary) and whether the patient was intubated. Although each of the four categories demonstrated an increase, the largest increase (181.8%) was seen again in intubated patients with a secondary diagnosis. The investigators also found that SE hospitalizations increased for all insurance types from 1999 to 2010, but initially remained relatively stable for Medicare until an abrupt 81.1% increase occurred around 2005.

■ COMMENTARY

Much of the previous epidemiology of SE has been based on observational studies with relatively small populations with limited generalizability. The current study, however, used national administrative databases to evaluate trends in diagnosis and mortality over a 12-year span. The authors found overall mortality related to SE was relatively stable, while related hospitalizations significantly increased, particularly after 2005, and most dramatically in intubated patients whose primary diagnosis was not SE. The authors postulate that the findings were likely attributable to the changes in coding practices, particularly after 2007, when coding rules and incentives changed for Medicare and Medicaid, and increased detection through the broader use of video-EEG monitoring. Thus, we are identifying more patients with nonconvulsive seizures and nonconvulsive SE, particularly in critically ill patients. Although overall mortality may not be significantly increased, nonconvulsive SE may be a marker of underlying brain injury leading to increased morbidity.

The authors also note that the related mortality was significantly lower in their study, at about 0.5-2%, as compared to previously reported mortality rates, as high as 20%. This difference highlights a shortcoming in our present coding system. The authors used ICD-9 codes for one of the databases, specifically 345.3 for grand mal status epilepticus and 345.2 for petit mal status epilepticus, the latter technically intended for absence status epilepticus. Many patients with secondary diagnoses in non-neurological ICUs could be alternately coded as seizure NOS (780.39) or altered mental status (780.02), so this study may underestimate the actual incidence of SE.

Although retrospective and possibly underestimating the true incidence of SE-related mortality, this study highlights a shift in our practice to better identify SE, particularly nonconvulsive events, through the increased use of continuous EEG monitoring. However, we know that both convulsive and nonconvulsive SE can lead to extensive physiologic and neuronal damage, so mortality rates alone may paint a limited picture, particularly in critically ill patients. ■

REFERENCE

1. Dham BS, et al. The epidemiology of status epilepticus in the United States. *Neurocrit Care* 2014;20:476-483.

ABSTRACT & COMMENTARY

RYR1-related Myopathies

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Ryanodine receptor gene mutations are among the most common genetic disorders found in a variety of congenital myopathies, both mild and severe.

SOURCE: Snoeck M, et al. RYR1-related myopathies: A wide spectrum of phenotypes throughout life. *Eur J Neurol* 2015;22:1094-1112.

Increased skeletal muscle cytoplasmic calcium, released from its main store in the sarcoplasmic reticulum (SR), is the first trigger initiating muscle contraction. It results from a propagated post-synaptic potential reaching the transverse (T) tubules, which make close contact with the SR at so-called "triads," formed by two SR terminal cisternae on each side of a T tubule. Called excitation-contraction coupling, the transformation of an action potential into calcium release is performed by a macromolecular complex, the calcium release complex (CRC), the main players of which include the dihydropyridine receptor (DHPR) and the ryanodine receptor (RYR1). Opening of the RYR1 receptor, triggered by a conformational change of DHPR, allows massive calcium influx, which interacts with the myofilaments, resulting in contraction. Muscles relax when RYR1 closes and calcium is taken back into the SR. Located on chromosome 19q13.2, the RYR1 gene consists of 5038 amino acids, and both malignant hyperthermia and congenital myopathies are associated with its dysfunction. What is the full range of RYR1-related disorders?

To answer this question, a retrospective, observational, cohort study, with a cross-sectional design, was carried out on all pediatric and adult patients seen between 2008-2012 at Radboud University Medical Center and the Malignant Hyperthermia Investigation Unit, Nijmegen, Netherlands, a national referral center for malignant hyperthermia and congenital myopathies.

Among 272 patients tested, RYR1 mutations were found in 77 non-related patients, 16 of which were of undetermined significance. Clinical history and ancillary investigation results on these patients were obtained through neurologists and geneticists of the national neuromuscular network.

Among the 77 patients, 61 different mutations were detected, of which 24 were novel. Inheritance was autosomal dominance in 64% and recessive in 15%, with the remainder of undetermined pathogenicity and inheritance pattern. Median age of onset and diagnosis were 8 and 29 years, respectively, with onset ranging from birth to late adulthood.

"Induced myopathies" were seen in 51%, including malignant hyperthermia susceptibility in 38%, as determined by a positive halothane-caffeine in vitro contracture test (IVCT) performed on freshly biopsied quadriceps muscle, exercise-induced rhabdomyolysis in 12%, and hyperCKemia in 1%. Permanent weakness was found in the remaining 49%, encompassing central core disease and multicore disease in 30% and 9%, respectively, and facial akinesia, nemaline myopathy, centronuclear myopathy, and King-Denborough syndrome, an autosomal dominant disorder characterized by a triad of dysmorphic features, malignant hyperthermia susceptibility, and myopathy, in 1% each. Axial myopathy, and congenital myopathy not otherwise specified, were each found in 3%.

■ COMMENTARY

Congenital myopathies related to RYR1 mutations are among the most frequent congenital myopathies, most of which are moderate in severity, but 15% of which are associated with severe neonatal disease resulting in respiratory failure and death within weeks, a third of whom demonstrate arthrogryposis at birth. Pathophysiological mechanisms associated with RYR1 mutations include either gain of function of the ryanodine channel, resulting in increased calcium release, generalized muscle contraction, and a hypermetabolic state as seen in malignant hyperthermia, or a loss of function, resulting in uncoupling of the dihydropyridine receptor and the ryanodine receptor, causing congenital myopathies. Some patients, mostly with recessive forms of disease, have a mutation causing a reduction in RYR1 amount. ■

ABSTRACT & COMMENTARY

Migraine and Cognitive Dysfunction

By Dara Jamieson, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is on the stroke adjudication committee for Bayer and is a consultant for Boehringer-Ingelheim.

SYNOPSIS: During an attack of migraine without aura, patients may experience transient cognitive impairment, with predominant involvement of verbal processing speed, learning, and memory, due to reversible cortical dysfunction.

SOURCE: Gil-Gouveia R, et al. Cognitive dysfunction during migraine attacks: A study on migraine without aura. *Cephalalgia* 2015;35:662-674.

Patients often report a sense of confusion and impaired thinking during migraine attacks, including immediately before and after the head pain, but studies designed to validate these observations have produced inconsistent results. The authors used a comprehensive battery of cognitive and behavioral tests to investigate changes in cognitive performance of migraineurs during attacks of migraine without aura. The only allowed daily medications were oral contraceptives and migraine prophylactics, and treatment with acute pain medication was not permitted. This prospective randomized, crossover study compared the within-subject neuropsychological evaluations during a naturally occurring untreated migraine attack and also during a headache-free period. Half the subjects were tested first during the attack, and half were first tested during the headache free-period. There was at least a month between testing during the migraine attack and during a headache-free period to avoid learned testing proficiency. Patients were evaluated with the Headache Impact Test and the Migraine-Specific Quality of Life questionnaires and with the Zung Depression scale and the State-Trait Anxiety Inventory. Pain intensity was scored with a 10-point visual analog scale. Paper and pencil neuropsychological testing was applied by licensed neuropsychologists using a standard battery of tests to test executive functioning, long-term memory, perception, motor control, and language.

Out of 39 patients with episodic migraine without aura (37 females, average age 38 years), 24 completed the study with evaluation at both times. Seven participants (29%) were on preventive medication (two propanolol, two propanolol and amitriptyline, two amitriptyline, and one topiramate and amitriptyline). Migraine impact was moderate to high, with most participants having one to four attacks monthly, with moderate to severe pain intensity. Migraineurs performed worse during the attack of head pain and accompanying symptoms in the majority of cognitive tests, compared to their headache-free period. Testing during the headache periods was impaired in reading and processing speed (word reading speed, $P = 0.013$) as well as verbal memory and learning short-term verbal recall with ($P = 0.01$) and without ($P = 0.013$) semantic cueing and delayed recall with ($P = 0.003$) and without ($P = 0.05$) semantic cues. Differences found in cognitive performance during a migraine attack were unrelated to patient baseline characteristics, including age, gender, literacy, condition order, the interval between the two evaluations, anxiety, pain intensity, or duration of the attack. The authors considered potential mechanisms by which cognitive impairment occurs during an attack of migraine without aura, including a cortical spreading depression — like phenomena, activation of the raphe nuclei and its cortical serotoninergic projections, or activation of the thalamus, with its effect on perception, learning, and cognition.

■ COMMENTARY

Patients' complaints of transient difficulty with verbal and memory processing during a migraine without aura have been validated by this well-designed study. However, the sample size was very small and the patients were mostly female, within a restricted age range, not representing the complete spectrum of migraine sufferers. Confounding conditions, including the effect of pain per se and of the accompanying gastrointestinal symptoms and environmental sensitivities, have not been completely eliminated in this study. The authors point out that the findings could be induced by the cognitive

processes related to the head pain, as opposed to an effect unique to migraine. Neuropsychological changes, with impairment in cognitive function, can be associated with chronic pain with resultant neurochemical and anatomic cerebral changes. Patients in this study had to suffer their migraine attacks without pain relief, as attacks treated with abortive medication in the previous 12 hours were not eligible for investigation in this study. Cognitive functioning needs to be assessed in patients who are taking triptans for acute pain treatment, a real-world environment. Because some daily medications used to decrease the frequency and severity of migraine headaches are well known to have cognitive side effects, further investigation should be restricted to patients who are not on oral preventive medications. The argument could be made that these medications, especially topiramate, could cause decreased memory and verbal fluency equally during the attack and during headache-free periods. However, as side effects vary according to dose escalation, these medications could have a differential effect on cognition over time. Despite the study limitations, the conclusions validate patient experiences. Migraine patients with cognitive complaints during a migraine attack without aura should be advised to avoid bar and board examinations during a headache, and other intellectual challenges, adding to the disability of the attack, as well as to anticipatory anxiety. ■

ABSTRACT &COMMENTARY

Nerve Biopsy for Asymptomatic Vasculitic Neuropathy

By Norman Latov, MD, PhD

Professor of Neurology and Neuroscience, Department of Neurology and the Brain and Mind Research Institute, Weill Cornell Medical College

Dr. Latov reports he is a consultant to Grifols and Baxter Pharmaceugicals; receives grant/research support from Grifols; owns stock in Therapath LLC; and participates in clinical trials for CSL Behring.

SYNOPSIS: Nerve biopsy is a safe and highly sensitive definitive diagnostic test for systemic vasculitis, even without symptoms of peripheral neuropathy, when electrodiagnostic tests indicate an axonal neuropathy.

SOURCE: Kurt S, et al. Asymptomatic vasculitic neuropathy. *Muscle Nerve* 2015;52:34-38.

Kurt and colleagues describe the clinical and electrodiagnostic features, as well as neuropathological findings, in 21 patients with asymptomatic vasculitic neuropathy. These constitute 7.8% of 270 cases of biopsy-proven vasculitic neuropathy seen in their institution over a 42-year period. The presence of vasculitis was suspected by the referring physicians based on the systemic symptoms and laboratory abnormalities, and although the patients did not have symptoms or findings on the neurological examinations that were indicative of neuropathy, screening electrodiagnostic tests showed involvement of the peripheral nerves, with features of axonal neuropathy. Subsequent nerve biopsy revealed the presence of vasculitic neuropathy in all 21 patients.

■ COMMENTARY

The authors report that peripheral nerve involvement is common, but can be subclinical in patients with vasculitis; electrodiagnostic studies can detect the presence of neuropathy in otherwise asymptomatic patients. The diagnosis of vasculitis can be definitively made on nerve and muscle biopsy.

The typical presentation of vasculitic neuropathy is an axonal sensorimotor neuropathy, in a multifocal distribution, with multiple organ involvement, and is associated with collagen vascular disease, hepatitis C infection, or elevated inflammatory serological markers such as erythrocyte sedimentation rate, anti-neutrophil cytoplasmic antibodies, eosinophilia, or cryoglobulinemia. However, patients with vasculitic neuropathy can also present with a distal symmetric polyneuropathy, without systemic involvement, and with normal serological studies. Other investigators have also reported vasculitic neuropathy presenting as sensory ataxic neuropathy,[1] demyelinating polyneuropathy,[2] or small fiber neuropathy with normal electrodiagnostic studies.[3]

Nerve and muscle biopsy is usually considered in the evaluation of neuropathy if the neuropathy is progressive, and no cause can be identified by other tests.[4] Aside from vasculitis, nerve biopsy may reveal the presence of other potentially treatable conditions such as sarcoid, amyloidosis, or sensory chronic inflammatory demyelinating polyneuropathy, that would have otherwise been missed.[5,6,7,8] Although it is an invasive procedure, nerve biopsy is relatively safe, with few adverse effects if performed by an experienced physician, as reflected in the authors' experience. In some cases, the vasculitis can be diagnosed by skin biopsy, obviating the need for the more invasive procedure.[9]

There is debate regarding whether patients with progressive neuropathies of otherwise unknown etiology warrant a trial of therapy with corticosteroids prior to biopsy, or if the biopsy is unrevealing. Given that vasculitis is a multifocal inflammatory disease, the pathology can be missed in a blind biopsy specimen, especially if a sufficiently long segment of nerve is not available or an insufficient number of sections are examined. However, treatment with corticosteroids can mask the pathological changes, so that a later biopsy may be uninformative if more aggressive treatment is being considered. It is hoped that advances in peripheral nerve imaging will make it possible to identify inflammatory lesions, to help distinguish between inflammatory and non-inflammatory neuropathies, and help decide on the site of biopsy. ■

REFERENCES

1. Harada K, et al. Sensory ataxic dominant neuropathy associated with polyarteritis nodosa. *Intern Med* 2000;39:847-851.
2. Mohamed A, et al. Conduction block in vasculitic neuropathy. *Muscle Nerve* 1998;21:1084-1088.
3. Zafrir B, et al. Small fiber neuropathy due to isolated vasculitis of the peripheral nervous system. *Isr Med Assoc J* 2004;6:183-184.
4. Vrancken AF, et al. Progressive idiopathic axonal neuropathy — a comparative clinical and histopathological study with vasculitic neuropathy. *J Neurol* 2004;251:269-278.
5. Chin RL, et al. Sensory CIDP presenting as cryptogenic sensory polyneuropathy. *J Peripher Nerv Syst* 2004;9:132-137.
6. Singhal NS, et al. Sarcoid polyneuropathy masquerading as chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve* 2015; doi:10.1002/mus.24652.
7. Vital A, et al. Sarcoid neuropathy: Clinico-pathological study of 4 new cases and review of the literature. *Clin Neuropathol* 2008;27:96-105.
8. Vital A, Vital C. Clinical neuropathology practice guide 3-2014: Combined nerve and muscle biopsy in the diagnostic workup of neuropathy — the Bordeaux experience. *Clin Neuropathol* 2014;33:172-178.
9. Yamanaka Y, et al. Leucocytoclastic vasculitic neuropathy diagnosed by biopsy of normal appearing skin. *J Neurol Neurosurg Psychiatry* 2006;77:706-707.

CME QUESTIONS

1. Which of the following GAD-ab positive patients is most likely to have an underlying tumor?
a. A 31-year-old woman with diabetes mellitus and cerebellar ataxia
b. A 40-year-old man with stiff person syndrome
c. A 67-year-old man with limbic encephalitis and a y-aminobutyric acidbR antibody
d. A 25-year-old woman with temporal lobe epilepsy

2. Which of the following statements regarding Rickettsial diseases is false?
a. Rickettsial diseases are present throughout the world.
b. The most common Rickettsial disease in the United States is Rocky Mountain spotted fever.
c. Scrub typhus is endemic in Asia and Australia, but can be brought to the United States by travelers.
d. Scrub typhus is invariably fatal.

3. In the current definition, a prolonged seizure meets criteria for status epilepticus if it lasts longer than how many minutes?
a. 5 minutes
b. 15 minutes
c. 30 minutes
d. 60 minutes

4. Ryanodine (RYR1) gene mutations may cause which of the following?
a. Malignant hyperthermia susceptibility
b. HyperCKemia
c. Exercise-induced rhabdomyolysis
d. All of the above

5. Which of the following is associated with an attack of migraine with aura?
a. A decrease in word reading speed
b. An increase in verbal memory
c. A decrease in animal naming
d. A transient increase in depression
e. A transient increase in anxiety

6. Peripheral nerve biopsy is indicated for which of the following disorders?
a. Chronic inflammatory demyelinating polyneuropathy
b. Guillain-Barré syndrome
c. Progressive neuropathy of unknown cause
d. Congenital myopathies

[IN FUTURE ISSUES]

Stroke Update