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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Cancer in Autoimmune Necrotizing Myositis

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: Immune-mediated necrotizing myopathy is a distinct syndrome that can be differentiated from polymyositis and dermatomyositis, and is commonly associated with underlying malignancy.

SOURCE: Allenbach Y, Keraen J, Bouvier AM, et al. High risk of cancer in autoimmune necrotizing myopathies: Usefulness of myositis specific antibody. *Brain* 2016;139:2131-2135.

Immune-mediated necrotizing myopathy (IMNM) is classified as one the inflammatory myopathies, which include polymyositis, dermatomyositis, and inclusion body myositis. Although immunosuppressive medication may be beneficial for IMNM, supporting an immune-mediated mechanism, inflammatory infiltrates generally are not found and little is known regarding its precise underlying pathogenesis. In 15-20% of patients, dermatomyositis in adults may be associated with malignancy, particularly lung, ovarian, stomach, pancreatic, and colorectal cancer, but polymyositis and inclusion body myositis are not. Is IMNM associated with cancer?

To answer this question, a long-term, French, observational multicenter study was undertaken looking at three groups of IMNM patients diagnosed between 2000-2014: those positive for either of the two myositis-specific antibodies (MSA) strongly associated with IMNM, anti-signal recognition particle (SRP) antibodies or anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies, and those negative for any MSA, including anti-Jo1, anti-PL7, anti-PL12, anti-MI2, anti-melanoma differentiation-associated gene 5, anti-nuclear matrix protein 2, and anti-transcriptional intermediary factor 1γ. Diagnosis of IMNM was based on criteria developed by the 2003 European Neuromuscular Center international workshop held in Naarden, The Netherlands,[1] and was considered cancer-associated if cancer was diagnosed within three years, before or after, the diagnosis of IMNM. Statistical

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analysis included Mann-Whitney, Kruskal-Wallis, and Fisher's exact tests, with a P value < 0.5 considered statistically significant.

Among 115 IMNM patients analyzed, comprising 52 with HMGCR antibodies, 49 with SRP antibodies, and 14 with no MSA antibodies, malignancy was present in 17.3%, 8.1%, and 28.6%, respectively. Mean age of cancer diagnosis was 67, 68, and 73 years, respectively, with no particular form of cancer predominant. Only one patient was diagnosed with cancer before age 50. Mean time between myopathy diagnosis and cancer was 4.2, 6.7, and 1.2 years, respectively. Compared to an age- and sex-matched general population, the incidence of cancer was significantly higher in MSA-negative and HMGCR-positive patients, with survival significantly lower in MSA-negative IMNM. SRP-positive patients demonstrated no increased risk of malignancy. Cancer screening is warranted in MSA-negative and HMGCR-positive IMNM but not in SRP-positive myositis.

■ COMMENTARY

IMNM is more common than polymyositis, occurs in all ages but predominantly in adults, and reaches its zenith within days to weeks, although it may progress subacutely in a progressive decline, resulting in severe weakness with high creatine kinase levels, and occasionally interstitial pneumonitis. Autoimmune and antibody mediated, it also may occur following viral infections or with malignancy. Necrotic myofibers, phagocytosed by macrophages, and regenerating myofibers characterize its pathology and, unlike other idiopathic inflammatory myopathies, there is only mild, if any, myofiber re-expression of major histocompatibility complex class I.

No randomized, controlled trial of immunotherapy has yet been performed for IMNM. Thus, treatment is based on case reports and case series. Patients with prior statin exposure appear more responsive to therapy than statin-naïve patients, but limited experience indicates that overall IMNM patients appear more resistant to corticosteroid monotherapy, and additional intravenous immunoglobulin (IVIG) often is required. Although most respond to a combination of prednisone and a steroid-sparing immunosuppressant, relapse often occurs as the dose is tapered. Triple therapy at initiation of treatment has been recommended, including corticosteroids, immunosuppressants, and IVIG.[2] Other agents, including intravenous cyclophosphamide, azathioprine, cyclosporine, methotrexate, and rituximab, have been used in individual cases with varied success. ■

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ABSTRACT & COMMENTARY

Functional Outcomes in Acute Ischemic Stroke Patients Receiving Prehospital Thrombolysis in Mobile Stroke Units

By Michael P. Lerario, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College; Attending Physician, New York-Presbyterian Queens Hospital; and Medical Director of the New York-Presbyterian Mobile Stroke Unit

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

SYNOPSIS: Deployment of a mobile stroke treatment unit in the field results in a higher percentage of patients treated with intravenous tPA, at a shorter interval from onset of symptoms, and results in better outcomes.

SOURCE: Kunz A, Ebinger M, Geisler F, et al. Functional outcomes of pre-hospital thrombolysis in a mobile stroke treatment unit compared with conventional care: An observational registry study. *Lancet Neurol* 2016;15:1035-1043.

Clinical data have established that the benefit-to-risk ratio of intravenous (IV) thrombolysis for acute ischemic stroke progressively improves when IV tPA is administered closer to the time of stroke onset.[1] The number needed to treat to obtain one favorable outcome of no disability at three months following IV thrombolysis ranges from 4.5 for treatment within 0-90 minutes, to 9.0 for 91-180 minutes, to 14.1 for 181-270 minutes.[1] Even delays as small as 15 minutes have been shown to significantly worsen in-hospital mortality, increase the risk of symptomatic intracranial hemorrhage (ICH), reduce the rate of recovery to independent ambulation, and decrease the likelihood of discharge home from the hospital.[2] Unfortunately, only a minority of patients receive tPA within 90 minutes of stroke onset,[3] or even within 60 minutes of arrival to the emergency department.[4] This has resulted in the development of systematic approaches aimed to reduce in-hospital door-to-needle times.[5] However, such approaches do not address prehospital delays, which have been shown to be the largest contributor to delays in tPA administration.[6]

Recently, a German team of physicians published their experience with prehospital IV thrombolysis for acute stroke patients. They equipped a specialized ambulance with an on-board computed tomography scanner and point-of-care laboratory testing. These mobile stroke units (MSUs) are staffed with a neurologist, a paramedic, and a radiology technician and are dispatched to the scene when a patient's emergency call raises the clinical suspicion for stroke. Such units are capable of bringing standard-of-care stroke diagnostics and treatments directly to the patient's doorstep, effectively removing unnecessary delays associated with transport times and hospital handoffs. In PHANTOM-S, the first randomized MSU trial, Ebinger et al reported a median reduction of 25 minutes in the time to treatment from stroke alarm, when compared to the routine transport of stroke patients.[7] Thrombolysis rates were higher for stroke patients treated on the MSU, and the proportion of patients treated within the first hour following stroke onset (i.e., "the golden hour") was six-fold higher with MSU deployment. Although an effect on the time to treatment was clearly demonstrated in this study, PHANTOM-S was not powered to detect a clinical benefit.

In a recent issue in *Lancet Neurology*, Kunz et al assessed the effect of MSU treatment on three-month disability outcomes using a prospective registry. Patients included in the registry were taken from the PHANTOM-S trial and its pilot phase, as well as an ad-hoc, nonrandomized continuation of the study based on a sample size calculation performed following the completion of the PHANTOM-S trial. The analysis was restricted to patients admitted to hospitals within the MSU catchment area and who were transported either by the MSU or by primary emergency medical services as a control arm. Patients were required to have a known time of stroke onset within 4.5 hours for this study. To better assess disability outcomes, the primary study population was restricted to patients who had lived at home without assistance before the index event. Follow-up for outcome assessment was assessed at three months by a standardized telephone interview, mail-in questionnaire, or via a discharge letter in patients who died in the hospital. The primary outcome was the proportion of patients with a modified Rankin Scale (mRS) score of 0-1 (i.e., no disability) at three months.

The registry included 305 patients in the MSU arm and 353 patients in the standard transport arm who were evaluated in the primary analysis. Except for more women, higher blood pressure, and lower initial blood glucose values in the MSU group, the baseline parameters were well-balanced. In this study, the mean onset-to-treatment time was 33 minutes shorter (96.3 vs. 129.3; $P < 0.0005$) for patients receiving care in the MSU. Significantly more patients in the MSU arm received tPA within 60 minutes (37% vs. 4%; $P < 0.0005$) and 90 minutes (62% vs. 35%; $P < 0.0005$) of onset. In the primary outcome (mRS 0-1 at three months), there was no significant difference between treatment groups (53% in the MSU arm vs. 47% with conventional care; $P = 0.14$). However, multiple secondary outcomes clearly demonstrated the potential for benefit with MSU care. The dichotomized secondary outcomes of mRS score 0-3 (i.e., survival without severe disability; 83% vs. 74%; $P = 0.004$) and mortality (6% vs. 10%; $P = 0.22$) were more favorable for patients treated on the MSU. After adjusting for stroke severity and other covariables, there was a trend for higher rates of survival without disability in patients treated on board the MSU, with an odds ratio of 1.40 (95% confidence interval, 1.00-1.97; $P = 0.052$). Ordinal regression analysis resulted in a significantly better outcome for patients in the MSU cohort over the full range of the mRS. Safety outcomes did not differ between patients in the two arms, for either symptomatic ICH ($P = 0.27$) or seven-day mortality ($P = 0.23$).

■ COMMENTARY

This study further demonstrates the time benefit of a novel prehospital treatment approach for stroke patients, with MSU care allowing tPA administration approximately 30 minutes earlier than compared with standard transport. When taken together, these results describe the potential of MSU care to benefit acute ischemic stroke patients by significantly reducing severe disability and death at three months with similar rates of hemorrhage. This study was mainly limited by its nonrandomized design and by nonblinded outcome assessments, which were performed by different raters in the two study arms. Although studies such as this one are promising, further trials are necessary to prove that MSU care is an effective and cost-saving approach to shortening tPA treatment times and improving disability outcomes in stroke patients. Experience with stroke ambulances in the United States has been increasing as well, and a multisite, randomized trial is currently enrolling to more precisely establish the benefit of prehospital thrombolysis.[8] ■

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ABSTRACT & COMMENTARY

Disease Rebound After Stopping Fingolimod in Patients with Relapsing-Remitting Multiple Sclerosis

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Perumal reports she receives grant/research support from Genzyme Corp., and is on the speakers bureau for Biogen Idec, Genzyme Corp., Acorda Therapeutics, and Teva Pharmaceuticals.

SYNOPSIS: A review of patients with relapsing-remitting multiple sclerosis who discontinued fingolimod therapy showed that five out of 46 (10.9 %) of these patients developed a rebound phenomenon between 4 to 16 weeks, where disease activity returns and often exceeds pre-treatment levels.

SOURCE: Hatcher SE, Waubant E, Nourbakhsh B, et al. Rebound syndrome in patients with multiple sclerosis after cessation of fingolimod treatment. *JAMA Neurol* 2016;73:790-794.

With the increasing number of disease-modifying therapies that are available for the treatment of multiple sclerosis, appropriate patient selection and careful sequencing of these medications is of paramount importance to both ensure optimal disease control and safety, and to prevent any untoward adverse events.

Return of disease activity and rebound, and even an overshoot phenomenon, have been seen after withdrawal of immune-suppressive treatment for multiple sclerosis. Most of these examples have been following discontinuation of natalizumab treatment. More recently there have been a few case reports of similar disease resurgence following discontinuation of fingolimod treatment.

Hatcher et al undertook a study to evaluate this rebound syndrome following fingolimod cessation to better understand the frequency and the potential risk factors associated with a higher risk of rebound, including level of pre-treatment disease activity, dura-

tion of treatment, and age of the patients, among other variables. This was a chart review study of the electronic medical records of patients seen at the Multiple Sclerosis Center at the University of California at San Francisco. All patients who discontinued fingolimod between January 2014 and December 2015 were included in the analysis. Forty-six patients discontinued fingolimod for the following reasons: pregnancy, adverse events, and refractory disease. Of these 46 patients, five (10.9%) experienced a disease rebound phenomenon.

The five patients who experienced rebound syndrome after fingolimod cessation were women at a mean age of 32.2 years (standard deviation, 6.4 years), and they had been on fingolimod for between 10 months and four years, had a disease duration between four and 18 years, and their onset of resurgent disease was four to 16 weeks after discontinuation of fingolimod. These patients had been treatment-naïve or had tried other medications, including interferons, glatiramer acetate, or natalizumab, prior to going on fingolimod. The rebound phenomenon was characterized in all of these patients by severe clinical relapses and flagrant radiologic activity, i.e., median of 9 (range 0-30) gadolinium-enhancing lesions, and new T2 lesions (median 9, range 0-30). The development of new gadolinium-enhancing lesions in these patients continued for three to six months despite treatment with corticosteroids (n = 3) and treatment with B-cell targeted, anti-CD-20 therapy (n = 2). In addition to these patients, the authors conducted a literature review and identified 11 other case reports of patients who experienced a similar rebound phenomenon post-fingolimod treatment.

■ COMMENTARY

The authors reported a disease rebound phenomenon that occurs four to 16 weeks post-fingolimod discontinuation in patients with multiple sclerosis. This was of significant clinical and radiologic severity. In this review, among the 46 multiple sclerosis patients who discontinued fingolimod therapy, five patients (10.9%) experienced rebound disease. The exact mechanism of action of this phenomenon has not been delineated, but it coincides with the recovery of peripheral circulating lymphocytes and potentially is related to the re-entry of these cells into the central nervous system. Such a rebound phenomenon has been reported with other immunosuppressive treatments, most prominently natalizumab treatment for multiple sclerosis. This study, along with other published case reports of this phenomenon, makes it imperative that clinicians who use fingolimod be aware of this phenomenon. Though no specific treatment strategies have been adequately studied or proven to be effective in mitigating this, steroids are usually given to reduce the inflammation. Another proposed strategy is initiation of another disease-modifying therapy in a timely manner to suppress the immune system and prevent the occurrence of this resurgence; however, one would need to take into consideration any potential safety concerns that might arise from adding another immunosuppressive therapy. ■

ABSTRACT & COMMENTARY

Zika Virus Infection and Guillain-Barré Syndrome

By Joseph E. Safdieh, MD

Vice Chair and Associate Professor, Weill Cornell Medical College

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

SYNOPSIS: Guillain-Barré syndrome is a defined complication of Zika virus infection and presents in a typical manner, similar to other post-viral GBS syndromes.

SOURCE: Dirlikov E, Major CG, Mayshack M, et al. Guillain-Barre' syndrome during ongoing Zika virus transmission – Puerto Rico, January 1 – July 31, 2016. *MMWR Morb Mortal Wkly Rep* 2016;65:910-914.

Zika virus is a flavivirus that recently has garnered worldwide attention, as it is associated with microcephaly in children born to mothers infected during pregnancy. Zika virus is transmitted by a mosquito vector, and is unique in that it can be transmitted sexually from an infected human to an uninfected partner. Zika virus outbreaks have occurred in Central and South America as well as the Caribbean, and recently, cases have been transmitted from mosquitoes in parts of Florida. In addition to its well-described effects on a developing fetus, there have been indications that Zika virus is associated with the subsequent development of post-infectious Guillain-Barré syndrome (GBS).

To study the association between Zika and GBS,

the Department of Health in Puerto Rico, with the assistance of the CDC, set up a registry of all cases of GBS to determine the clinical characteristics, as well as recent Zika exposure. Dirlikov et al reviewed the cases of GBS between January and July 2016, when Zika activity in Puerto Rico was high. Physicians were requested to submit all GBS cases to a central registry along with samples of serum, urine, saliva, and cerebrospinal fluid. All specimens were tested with polymerase chain reaction (PCR) as well as immunoglobulin M (IgM) for Zika, Dengue, and Chikungunya. Zika virus infection was confirmed if the PCR was positive and was presumed if the IgM was positive, and flaviviral infection was suspected if both Zika and dengue IgM were positive, as they often cross-react.

Over the six-month period, 56 cases of GBS were reported to the registry. Thirty-four of these patients had suspected or confirmed Zika or flavivirus infection, representing 61% of the GBS cases. Zika was confirmed by PCR in 10 of these cases. Sixteen of these cases had presumptive Zika infection (negative PCR, positive Zika IgM) and eight had presumptive flavivirus infection (positive Zika and Dengue IgM). Twenty patients in the GBS cohort had no evidence of Zika infection.

Of the 34 cases of GBS associated with confirmed or presumptive Zika infection, the median age at diagnosis was 55 years. Fifty-nine percent of the patients were women. Ninety-four percent of the patients recalled an antecedent illness within two months of GBS diagnosis, most commonly rash, fever, or diarrhea. The median time from antecedent illness to GBS diagnosis was only five days. Patients presented in a typical fashion with limb weakness, facial weakness, areflexia, numbness, and dysphagia. All patients demonstrated cerebrospinal fluid cytoalbuminologic dissociation. Only five patients underwent electrophysiologic studies, all of which demonstrated the demyelinating subtype of GBS. All patients were hospitalized and treated with IVIG. Sixty-two percent of patients required ICU care and 35% required mechanical ventilation. Forty-four percent of patients were discharged home, and 38% were discharged to a rehabilitation facility. At the time of publication, 18% remained hospitalized. One patient died of sepsis.

■ COMMENTARY

GBS is often triggered by a viral infection, and it is not surprising that the immune activation caused by viral infection of a previously immune-naïve population would trigger molecular mimicry in some patients leading to autoimmune demyelination. Given the likely continued spread of Zika virus into the United States, it certainly would not be surprising if there were an uptick in GBS cases. The fact that 61% of cases of GBS over a six-month period in Puerto Rico were attributed to confirmed or presumed Zika infection is quite impressive and suggests that the association between Zika and GBS is strong, although the absolute number of GBS cases is low as compared to the presumed number of Zika-infected patients.

There does not appear to be much difference between Zika-associated GBS and the GBS we typically see in routine clinical practice, although longer-term follow-up would certainly be needed to confirm this. Despite earlier reports of axonal-variant GBS being associated with Zika, the current cases studied were demonstrated to be the more typical, and more treatment-responsive, demyelinating form. Treatment of Zika-associated GBS is the same as GBS due to any other cause. Neurologists should consider Zika testing in patients with GBS, especially in areas of the country where Zika is prevalent, or if patients have traveled to Zika-infested areas before developing illness. ■

ABSTRACT & COMMENTARY

Headaches in the Elderly: A Non-specific Marker for Stroke Risk

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a consultant for Bayer and Boehringer-Ingelheim.

SYNOPSIS: Non-migrainous headaches, for which there are many causes, appear to be a risk factor for stroke in an elderly population, but the mechanism is uncertain.

SOURCE: Norton J, Portet F, Gabelle A, et al. Are migraine and non-migrainous headache risk factors for stroke in the elderly? Findings from a 12-year cohort follow-up. *Eur J Neurol* 2016;23:1463-1470.

The authors expanded the proposition that migraine is a risk factor for stroke, examining the incidence of stroke in an elderly population with migraine and with the more common non-migrainous headache (NMH). Invitation letters were sent to randomly selected community-dwelling persons, aged 65 years and over, living in Montpellier, France, between March 1999 and February 2001. These elderly persons were invited to attend a half-day clinical examination to check eligibility for the retrospective study. The 2,259 eligible subjects who responded were interviewed about their medical history and underwent a neuropsychiatric interview and a neurological examination. Among subjects reporting headaches, a diagnosis of NMH was made only after excluding a diagnosis of migraine, as based on the International Headache Society (IHS) criteria. After recruitment, all subjects were to be followed up at 2, 4, 7, 9, and 11 years. The 136 subjects who were lost to follow-up, and thus excluded from the analysis, were older, more disabled, and less educated with lower income, with more vascular risk and cognitive impairment. Despite more medical and social impairment, these excluded participants had no significant differences in current or lifetime NMH and migraine. The 1,919 remaining subjects with no history of stroke at baseline and no missing values for the main covariates were followed for stroke incidence for a median follow-up period of 8.8 years. At each follow-up examination, subjects reported neurological events that occurred since the previous visit. Strokes, either hemorrhagic, ischemic, or unknown, were adjudicated, but brain imaging, mainly computerized tomography, was available for "more than 80% of validated stroke cases." Lifetime migraine by IHS criteria was reported in 17.4% and current migraine was reported in 5.4% of the elderly subjects. The diagnosis of NMH, made during their lifetime, was 11.4% of subjects, and was diagnosed in 8.9% currently. The majority of subjects were said to report only one type of headache. The NMH diagnoses were varied: "tension headaches" 36.5%, "rheumatology-related" 25.1%, "Arnold's neuralgia" (occipital neuralgia) 12.9%, "hypertension-related" 4.5%, "glaucoma-related" 3.3%, "trigeminal neuralgia" 3.3%, "intra-cranial" 3.3%, "ear, nose, and throat-related" 2.8%, "histaminic cephalalgia" 2.2%, and "other aetiologies" 6.1%. In the elderly subjects with a migraine history at study recruitment, 1.9% (2/106) had a stroke during the follow-up period, as compared to 6.2% (10/161) of the baseline NMH sufferers, and 4.3% (11/258) of subjects with a past history of migraine or NMH. Cox proportional hazard models indicated that current migraine history in the elderly population (mean age for migraine and NMH: 72 years) was not a risk factor for stroke; however, NMH sufferers were twice as likely to have a stroke (hazard ratio, 2.00; 95% confidence interval, 1.00-3.93; $P = 0.049$).

■ COMMENTARY

Convincing epidemiological studies have shown that migraine with aura is a risk factor for ischemic stroke in a younger population, most notably in women. Yet stroke is more common in an older population, whose headaches, including migraine, are likely to have dissipated with age. Norton et al evaluated a possible correlation between headaches, both migraine and non-migraine, and stroke in an older population. Unfortunately, a small, selected population of older individuals and a lack of granularity in disease categories, lead to few viable conclusions from these data.

The authors commented on some of the limitations of this retrospective epidemiological study. The small number of strokes detected in follow-up (n = 73), with only two strokes in elderly subjects with migraine, may obscure the correlation that was found in studies with a larger population. Because of the small number of elderly migraineurs in the study, the population was not stratified according to migraine without or with aura or to sex, variables of importance in other epidemiological studies. The authors noted the heterogeneous mix of NMHs, including both primary and secondary headache types. The number of subjects with each headache type was too small to do a sub-group analysis. Likewise, because of the small number of events, there was no sub-analysis according to stroke type. The correlation with migraine is much more robust for ischemic stroke than for intraparenchymal hemorrhage. Given that these details may differentiate between a connection and a coincidence, the study population was too small to make a clear conclusion about a migraine and stroke linkage in the elderly. Another limitation of the study is that the population analyzed was self-selected participants who volunteered for the study, and more disabled individuals were lost to follow-up. The population followed over the long-term were more likely to be the healthy elderly with headache, as opposed to a more representative cross-section of the elderly.

One important inference that can be made from these data is that headache in the elderly deserves investigation and monitoring. The authors suggested that elderly individuals with NMH be followed closely because of an increased stroke risk. In general, headaches are less common in the elderly and, if present, are more likely to be secondary to an underlying systemic disease or identifiable brain lesion. Therefore, secondary headaches in the elderly may be a marker for poor health in general, and may be indicative of greater cerebrovascular risk specifically. Why elderly individuals with multiple headache types should have a somewhat greater stroke risk than those with migraine, the tenuous conclusion from this study, does not have any mechanistic explanation. ■

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CME QUESTIONS

1. **Immune-mediated necrotizing myopathy is:**
   a. associated with cancer in 83% of patients.
   b. untreatable, and care is supportive in nature.
   c. strongly associated with anti-signal recognition particle antibodies, and anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies.
   d. more likely to respond to therapy in statin-naïve patients than in patients who previously took statins.
   e. None of the above

2. **Deployment of a mobile stroke treatment unit (ambulance) in the field resulted in the following statistically significant outcomes, compared to usual ambulance transport, except for one.**
   a. Faster administration of thrombolytics by an average of 33 minutes.
   b. Improved survival without severe disability
   c. Lower mortality
   d. Higher percentage of mRS 0-1 recovery in treated patients
   e. Higher percentage of ischemic stroke patients receiving thrombolysis

3. **Discontinuation of fingolimod in patients with multiple sclerosis may result in all but which of the following?**
   a. No change in disease course
   b. Rebound exacerbation of the disease
   c. Multiple new gadolinium-enhancing MRI lesions
   d. Improvement of the patient's disease

4. **Which of the following features is not associated with GBS-associated with Zika virus?**
   a. Neurologic symptoms develop within five days of infection.
   b. Loss of reflexes and leg weakness are common at presentation.
   c. Respiratory impairment and need for mechanical ventilation are rare.
   d. Standard treatment with IVIG is recommended.

5. **Which statement best describes headache and the elderly?**
   a. Headaches are not indicators of disease risk.
   b. Headache prevalence decreases with age.
   c. Both migraine without and with aura increase stroke risk.
   d. Tension-type headache is a rare cause of headache.

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.

[IN FUTURE ISSUES]

Update on Neuro-oncology