AHC Media

Vol. 35, Issue 3, November 2015
AHCMedia.com

Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

# Autoimmune Cerebellar Ataxia — Responses to Treatment

*By Ulrike W. Kaunzner, MD, and Jai Perumal, MD*

*Dr. Kaunzner is a Fellow in Neurology, Weill Cornell Medical College, and Dr. Perumal is Assistant Professor of Neurology, Weill Cornell Medical College*

**Dr. Kaunzner reports no financial relationships relevant to this field of study. Dr. Perumal reports she is on the speakers bureau for Biogen Idec, Teva Pharmaceuticals, Genzyme Corp., and Acorda Therapeutics.**

SYNOPSIS: This study analyzed patients diagnosed with antibody-mediated paraneoplastic and non-paraneoplastic cerebellar ataxia, and treatment benefit was seen predominantly in the non-paraneoplastic group.

SOURCE: Jones AL, et al. Responses to and outcomes of treatment of autoimmune cerebellar ataxia in adults. *JAMA Neurol* 2015; Sep 28:1-10. doi: 10.1001/jamaneurol.2015.2378.

Autoimmune cerebellar ataxia belongs to a heterogeneous group of neurological diseases caused by a variety of autoantibodies. It can occur as paraneoplastic syndrome, appearing in association with malignancy, commonly with lung tumors, gynecologic tumors, and lymphoma, especially Hodgkin's lymphoma, and can precede the cancer diagnosis for years.[1] On the other hand, it can develop without any relation to malignancy and is referred to as non-paraneoplastic syndrome. At least 17 autoantibodies have been associated with this entity, and anti-Yo and anti-Tr antibodies exclusively affect the cerebellum.[2] Symptoms may be acute or subacute, and may include classic brain stem findings. The disease has a poor prognosis and often results in severe disability. Treatments have been variable and unpredictable.

This study by Jones et al from the Mayo Clinic investigated the treatment response of patients with paraneoplastic and non-paraneoplastic cerebellar ataxia, and measured the ability to ambulate as a primary outcome. This retrospective cohort study analyzed patients who were included in a database between 1989 and 2013. The 118 selected patients were ≥ 18 years

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.

Weill Cornell Medical College
NewYork-Presbyterian

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.



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of age, positive for at least one antibody, presented with cerebellar ataxia, and were treated with either immunotherapy or chemotherapy. All patients had cerebellar signs, with gait ataxia present in all 118 patients, and other common symptoms including dysmetria, nystagmus, and dysarthria. Extra-cerebellar signs were found in 63 patients (53.4%), with myelopathy and neuropathy the most frequently documented symptoms. Interestingly, 35 patients (29.7%) had neurological diagnoses other than autoimmune cerebellar ataxia prior to evaluation at the Mayo Clinic. All 118 patients had at least one autoantibody detected in serum, and of the 45 patients who underwent lumbar puncture, 25 had CSF autoantibodies. Common antibodies included GAD65, anti-Yo, CRMP-5 and anti-Hu. Out of 118 tested patients, 63 (53.4%) were diagnosed with paraneoplastic syndrome, and in 29 patients malignancy was discovered after antibody detection, with a median range of 3 months until cancer diagnosis. The remaining 55 patients (46.6%) were considered non-paraneoplastic.

Neurological improvement attributed to therapy was reported in 54 out of 118 patients (45.8%) and treatment included either immunotherapy (n = 51) or chemotherapy and radiation therapy (n = 3). While corticosteroids, intravenous immunoglobulin, and plasma exchange appeared efficacious in both groups and showed higher treatment effects in the non-paraneoplastic group, difference in treatment was statistically significant only for steroids. Improvement following steroid treatment was seen in 20.5% of patients with paraneoplastic disorder vs 55.6% of patients with non-paraneoplastic disorder. Cyclophosphamide was only beneficial in the paraneoplastic group, and rituximab did not show any effect in either group.

Overall, 22 patients had a robust response, which was defined as sustained improvement from one ambulation level to the next. Out of these 22 patients, eight required more than one immunotherapy, and 16 patients needed continued immunotherapy, including mycophenolate mofetil or cyclophosphamide. Beneficial outcome was associated with PMP channel or receptor antibodies (e.g., NMDA). In the case of positive GAD65 antibodies, earlier initiation of treatment showed a better outcome. Non-paraneoplastic disorder was the single strongest predictor of positive response to immunotherapy, and 76.4% of patients within this group remained ambulatory.

## ■ COMMENTARY

This study documents a positive response to immunotherapy in a large cohort that previously had been described in anecdotal reports or small series. There were treatment benefits in 45.8% of all patients, with better results in those with a non-paraneoplastic presentation. Limitations of this study are that it was retrospective and did not address therapy of the underlying cancer in the paraneoplastic group and how this affected recovery. The rarity of these disorders and the variability of treatment response, often based on the underlying antibody, make the design of a prospective study difficult, but it would be ideal to compare individual and combined immunotherapies in a prospective trial.

[The study authors emphasized that treatment should be initiated in both non-paraneoplastic and paraneoplastic syndromes as soon as autoimmune cerebellar ataxia is diagnosed.]

In summary, the results from this study are encouraging. The authors emphasized that treatment should be initiated in both non-paraneoplastic and paraneoplastic syndromes as soon as autoimmune cerebellar ataxia is diagnosed, while a search for underlying malignancy is undertaken. Moreover, sequential or maintenance immunotherapy might be required to preserve and maintain a positive treatment effect. ■

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ABSTRACT & COMMENTARY

# Potential Imaging Biomarkers of SUDEP: Can We Predict Sudden Death in Epilepsy?

*By Kimberly Pargeon, MD*

*Assistant Professor of Clinical Neurology, Weill Cornell Medical College*

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

SYNOPSIS: The authors retrospectively conducted a voxel-based analysis of T1 MRI scans to compare gray matter volumes in 12 cases of sudden unexpected death in epilepsy (SUDEP) acquired at a median of 2 years before death with patients at high or low risk for SUDEP and with healthy controls, and demonstrated significant anatomical differences between the groups.

SOURCE: Wandschneider B,et al. Structural imaging biomarkers of sudden unexpected death in epilepsy. *Brain* 2015;138:2907-2919.

Sudden unexpected death in epilepsy (SUDEP) is one of the most common causes of premature, non-accidental death in patients with chronic epilepsy, with an estimated incidence of sudden death in epilepsy patients being 20 times that of the general population. It is typically defined as sudden and unexpected death with no history of trauma or drowning, with or without an associated seizure, and excluding cases of status epilepticus. In cases of "definite" SUDEP, no other identifiable cause is found on post-mortem examination.[1]

The present study was retrospective and conducted at a tertiary care center in the UK. The authors identified 12 patients from a clinical database who died with either definite (n = 2) or probable (n = 10) SUDEP and matched those with 53 living patients with epilepsy. Patients were stratified into "high-" or "low-" risk groups using a risk factor analysis score gleaned from Hersdorffer et al.[1] Increased risk was associated with nocturnal seizures, frequent (≥ 3/year) generalized tonic-clonic seizure, young age at onset, and/or long disease duration. There were 34 "high-" and 19 "low-" risk patients. All patients had to have undergone a high-resolution T1 volume scan using the same 3T MRI scanner. All groups were matched for gender, age, epilepsy syndrome, and disease duration, and those with major brain lesions were excluded. Scans of 15 healthy age- and gender-matched controls were included for comparison. Coronal T1 MRIs were analyzed using voxel-based morphometry with statistical mapping software.

The primary finding was that SUDEP cases and those at high clinical risk showed increased gray matter volume in the right anterior hippocampus and the parahippocampal gyrus relative to those at low risk and controls. Decreased gray matter volume was also seen in the bilateral posterior thalamus for SUDEP cases and on the left for high-risk patients, which for all patient groups seemed to be correlated with disease duration. Several subgroup analyses were performed, which demonstrated no effects related to presence of lesions, seizure frequency, and different sites of ictal onset, although relatively limited information was available for the latter.

## ■ COMMENTARY

Although SUDEP remains a leading cause of death in individuals with chronic epilepsy, the pathophysiology still remains somewhat unclear. The most noteworthy finding was the increased gray matter volumes in the right hippocampus and parahippocampal gyrus in SUDEP cases and in subjects at high risk. The authors postulated that this could represent one of two anatomical changes. One possibility could be microdysgenesis within the hippocampus with dystrophic neurons and diminished gray-white matter demarcation, as seen in many cases of sudden unexpected death in childhood. Another possibility could be gliosis, which would represent a response to injury, altering neuronal activity and increasing susceptibility for SUDEP. The authors further cited a study by Bernhardt et al looking at post-surgery seizure freedom rates and using structural imaging findings for predicting outcomes.[2] Although most groups demonstrated unilateral or bilateral atrophy, a subgroup that was more likely to have unsuccessful surgery showed bilateral increased volumes in the hippocampus and amygdala. Further histopathology confirmed hippocampal gliosis in almost all of these patients.

Another key finding was the right lateralization, which they attributed to characteristics of autonomic regulation. The right limbic system, specifically the right insula, plays a significant role in sympathetic outflow. Complex arrhythmias and even sudden death have been attributed to acute right-sided insular strokes, suggesting a potential mechanism in SUDEP. The secondary finding of decreased volume in the posterior thalamus across all epilepsy groups correlated with increased disease duration. The authors postulated this may be related to repeated hypoxic insults. The posterior thalamus appears to play a significant role in mediating respiratory responses, which may break down with repeated injury.

Thus, the authors concluded that these combined changes may increase potential for SUDEP.

It still remains unclear whether this small subset of SUDEP cases is representative of high-risk patients for sudden death and whether findings are generalizable. For instance, there were two instances of left mesial temporal sclerosis (MTS) among the SUDEP cases, but no instances of right MTS, so this could have been a factor. For instance, a recent meta-analysis of voxel-based morphometry studies on unilateral refractory temporal lobe epilepsy found significantly decreased gray matter volumes in ipsilateral mesiotemporal structures and bilateral thalami in both refractory left and right temporal lobe epilepsy.[3] Regardless, if a replicable imaging biomarker could be demonstrated, this could assist clinicians in identifying those patients at greatest risk for sudden death. ■


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ABSTRACT & COMMENTARY

# Lower Risk of Parkinson's Disease After Vagotomy: Implications for Spread of Pathology


***By Claire Henchcliffe, MD***

*Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College*



**Dr. Henchcliffe reports she is on the speakers bureau and advisory boards for Teva, IMPAX, and ACADIA; and receives grant/research support from Biogen and Kaneka.**



SYNOPSIS: Truncal vagotomy was associated with a reduced risk for Parkinson's disease with a hazard ratio of 0.58 for those with more than 20 years' follow-up. This suggests the vagus nerve as a possible route of entry into the central nervous system for this neurodegenerative process.

SOURCE: Svensson E, et al. Vagotomy and subsequent risk of Parkinson's disease. *Ann Neurol* 2015;78:522-529.


Parkinson's disease (PD) pathology, as demonstrated by abnormal alpha-synuclein deposition, may begin in the enteric nervous system and the olfactory bulb many years prior to appearance of motor symptoms. Therefore, it has been proposed that these structures are "portals of entry" for external triggers of PD pathology. A compelling hypothesis is that spread from the gastrointestinal tract to the central nervous system might then occur via the vagus nerve. Vagotomy is a procedure that has been undertaken for peptic ulcer disease, allowing this hypothesis to be tested. Moreover, in treating peptic ulcers either truncal vagotomy may be performed or superselective vagotomy in which only nerves supplying the fundus and body of the stomach are resected, leaving the route to the brain from other regions relatively intact. Svensson and colleagues compared rates of occurrence of PD in those undergoing the two types of vagotomy procedures, and additionally compared each group with population-based controls.

Patients who had undergone truncal vagotomy or superselective vagotomy between 1977-1995 who had > 5 years' follow-up (truncal vagotomy: n = 5339; superselective vagotomy: n = 5870) were identified and compared with more than 120,000 individuals who had not. This latter group, with 10 individuals matched for age and gender to each vagotomy patient, was randomly selected from the general population. Diagnosis of PD was made on the basis of records from the Danish National Patient Registry. Multiple potential confounders were examined, including rheumatologic disease, cardiovascular disease, diabetes, and others. Median age was 56 years (truncal vagotomy) and 47 years (superselective vagotomy) at the time of index date. Of those with truncal vagotomy, 61% were men vs 69% of those with superselective vagotomy, and those who had undergone truncal vagotomy had a higher prevalence of comorbidities. The investigators found that fewer cases of PD were identified in those undergoing truncal vagotomy (n = 45) vs superselective vagotomy (n = 59) or vs the general population cohort, with hazard ratios (HR) of 0.85 (95% confidence interval [CI], 0.56-1.27) and 0.84 (95% CI, 0.63-1.14), respectively. More robust associations were determined in those with > 20 years follow-up in whom HR was 0.58 (95% CI, 0.28-1.20) for truncal vagotomy vs superselective vagotomy, and

0.53 (95% CI, 0.28-0.99) for truncal vagotomy vs the general population cohort. Smoking had not been measured, but attempts to adjust for this potential confounder still resulted in adjusted risk ratios from 0.61 and 0.66 depending on assumptions for the percentage of the truncal vagotomy cohort who smoked (between 75-85% vs 60% of the general population cohort).

## ■ COMMENTARY

The gastrointestinal tract has been proposed as a "portal of entry" for potential pathogenic agents in PD. This, as well as entry via the olfactory system, is a compelling argument, given data suggesting environmental risk factors such as pesticides. The question is how the pathogenic process, as tracked by alpha-synuclein-based pathology, spreads to the central nervous system where more specific and recognizable effects lead to characteristic motor symptoms of PD such as bradykinesia, tremor, and rigidity. The vagus nerve represents a potential route, and in animal studies spread of alpha-synuclein pathology induced by rotenone has been observed to spread from the enteric nervous system through the vagus nerve to the brainstem. The strength of this study by Svensson and colleagues is in examining long-term follow-up of patients who underwent not only truncal vagotomy, but also superselective vagotomy in which only nerves supplying the fundus and body of the stomach are resected. This population-based, registry-linkage, cohort study takes advantage of a national health registry and civil registration system to facilitate access to substantial numbers of patients and healthy individuals. The major finding that severing the vagus nerve is associated with lower risk of subsequent development of PD indeed supports the hypothesis that spread of PD pathogenesis occurs from the gut and that the vagus nerve plays a critical role in its transmission. However, there are some points that temper excitement. Statistical significance was not reached for most of the group comparisons. Diagnoses and procedure codes may be inaccurate. It is difficult to adequately control for all confounders, including known PD associations such as smoking or caffeine intake. And it does not, of course, address other potential origins and routes of spread. PD was not reduced to zero in those who had undergone truncal vagotomy. Nonetheless, this study has major implications and should quickly prompt efforts to replicate its findings in other populations. ■

ABSTRACT & COMMENTARY

# Botulinum Toxin and Treatment of Spasticity


***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: AbobotulinumtoxinA is effective at reducing spasticity and reducing disability in patients with upper limb spasticity due to stroke or traumatic brain injury.


SOURCE: Gracies JM, et al. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: A double-blind randomized controlled trial. *Lancet Neurol* 2015;14:992-1001.

Assessment of tone is an important part of the neurologic examination. Causes of increased tone include spasticity, rigidity, and paratonia. Spasticity is a common neurologic consequence of upper motor neuron damage, and can occur in the setting of stroke, traumatic brain or spinal cord injury, multiple sclerosis, and other central nervous system conditions. For many patients, spasticity can be quite disabling and may impair functional status more than weakness. Additionally, the care of the patient with spasticity may be difficult due to fixed flexion of upper limb muscles. Upper limb spasticity may impair basic daily activities such as feeding and toileting. Botulinum toxin is an approved therapy for reduction of upper limb spasticity.

These authors report the results of a randomized, controlled trial assessing the effectiveness of abobotulinumtoxinA 500 mg, abobotulinumtoxinA 100 mg, or placebo at reducing muscle tone in patients with upper limb spasticity. The primary endpoint was change in muscle tone using the Modified Ashworth Scale. Secondary endpoints included a Physician Global Assessment score and perceived function using the Disability Assessment Scale in dressing, hygiene, limb position, and pain. Injections were performed into a number of muscles including most hypertonic of the primary target muscle group (flexors of the elbow, wrist, or fingers).

Eighty-one patients were randomized to each of the three groups: 500 units, 1000 units, and placebo. Outcome measures were recorded at weeks 1, 4, 12, 16, and 20 after treatment. Reduction in Modified Ashworth Score was 0.3 in the placebo group, 1.2 in the 500 unit group, and 1.4 in the 1000 unit group at 4 weeks. Of note, benefits were seen as early as 1 week and persisted even at 16-20 weeks. The Physician Global Assessment score was also improved in the treatment group in a dose-

dependent manner as compared to placebo. Disability Assessment Scale scores were better in the treatment group (no difference between low and high dose) compared to placebo. There were two deaths (one in the placebo group) that were not related to treatment effect. The most common adverse events in the treatment groups included muscle weakness and fatigue.

■ COMMENTARY

This study adds to the literature on the use of botulinum toxins in treating upper limb spasticity after stroke or traumatic brain injury. It demonstrates some interesting findings, including evidence of a benefit even 1 week after treatment as well as a sustained benefit from a single treatment even after 12 weeks. This is important to note because if treatment can be spaced out further than every 3 months, there would be less burden on patients and caregivers to return for frequent follow-up treatment visits. Additionally, the study demonstrated not only reduction in passive tone but also improvement in active range of motion of the affected limb. This potentially could lead to significant improvement in the quality of life of the patient and caregivers, as patients can use the affected limb in a more useful way. ■

ABSTRACT & COMMENTARY

# Treatment for Ulnar Neuropathy at the Elbow


***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: In a randomized treatment trial of steroid injection into the cubital tunnel for ulnar neuropathy, there was no difference in outcome compared to placebo.



SOURCE: vanVeen KEB, et al. Corticosteroid injection in patients with ulnar neuropathy at the elbow: A randomized, double-blind, placebo-controlled trial. *Musc Nerve* 2015;52:380-385.


Conservative management for ulnar neuropathy at the elbow (UNE) is preferable to surgical treatment, and includes splinting or padding the elbow, modification of activities, avoiding provocative factors, and nerve gliding exercises. However, none of these conservative treatments are of proven benefit. In a Cochrane review of randomized or quasi-randomized controlled clinical trials, no difference was found between simple decompression and transposition of the ulnar nerve for either clinical or neurophysiological improvement,[1] and in the single trial evaluating conservative treatments, night splinting and nerve gliding exercises added no benefit over simply avoiding prolonged movements or positions. Are glucocorticoid injections, often used for carpal tunnel syndrome, of any benefit for UNE?

In this randomized, double-blind, placebo-controlled trial, patients with UNE seen at the Medical Center Haaglanden, The Hague, between September 2009 and April 2014, were recruited for evaluation. Inclusion criteria comprised motor or sensory symptoms of ulnar neuropathy, coupled with positive electrodiagnostic or ultrasonography findings for UNE, with patients excluded if they were < 18 years of age, had a history of prior ulnar nerve subluxation or UNE, were taking oral corticosteroids or anticoagulants, or had prednisolone allergy. Electrodiagnostic criteria for UNE required either motor nerve conduction velocity (MNCV) across the elbow slower than 43 m/s, slowing of MNCV across the elbow by more than 15 m/s compared to the forearm segment, or motor conduction block across the elbow of greater than 16%, comparing above to below elbow stimulation. Ultrasonography (US) was considered positive for UNE if the cross-sectional area (CSA), examined in perpendicular planes from at least 2 cm proximal to 2 cm distal to the medial epicondyle was > 10 mm. Patients were randomized to receive, by US guided injection, 1 mL containing either NaCL 0.9% or 40 mg depo-medrol (methylprednisolone acetate and 10 mg lidocaine hydrochloride). Subjective improvement at 6 months, as defined by a 6-point scale, was the primary outcome measure, with changes in electrodiagnostic studies and US findings comprising the secondary outcome measures. Statistical analysis included the chi-square test, the Mann-Whitney U-test, and Wilcoxon signed rank test.

Among 63 patients included in the study, which was halted due to slow recruitment, five were lost to follow-up, leaving 27 men and 28 women, with a mean age of 55 years, for analysis. No significant difference was found between the treatment vs placebo groups for either the primary or electrodiagnostic secondary outcome. Nerve CSA decreased significantly in the depo-medrol group, from 11.9 $mm^2$ to 10.9 $mm^2$. Neither symptoms


*Continued on page 24*

Neurology [ALERT]

Stroke Alert

By Matthew E. Fink, MD

## Every 5-minute Delay in Performing Endovascular Reperfusion Results in 1 out of 100 Patients Having a Worse Disability Outcome

SOURCE: Sheth SA, et al. Time to endovascular reperfusion and degree of disability in acute stroke. *Ann Neurol* 2015;78:584-593.

In the past year, multiple clinical trials have reported that intra-arterial endovascular reperfusion with mechanical clot extraction, using the SOLITAIRE stent retriever device and others, results in better neurological outcomes than treating patients with intravenous thrombolysis alone with TPA. There is still uncertainty regarding the maximum time window, and how important early intervention is as related to neurological recovery and long-term outcomes. The investigators used the combined databases of the SWIFT (*Lancet* 2012) and STAR (*Stroke* 2013) trials to identify patients treated with the SOLITAIRE device who achieved substantial reperfusion.

They then ranked the 90-day modified Rankin scale outcomes for "time of onset to recanalization" (OTR) time intervals ranging from 180 min to 480 min.

Analysis of these data showed substantial time-related reductions in disability for the entire range of outcomes. A shorter OTR time was associated with an improved 90-day Rankin Scale outcome in all groups. The mean Rankin scores were 1.4 for the 120-240 min OTR group, 2.40 for the 241-360 min group, and 3.3 for the 361-660 min group ($P < 0.001$). There were no significant differences between the groups in the incidence of intracerebral hemorrhage, mortality, or length of hospitalization. The predicted probability and confidence interval of good neurological outcome (mRS 0-2) at 90 days was a continuous variable inversely related to the time from symptom onset to recanalization. For every 15-min acceleration in the time to reperfusion, 34 per 1000 patients treated will have improved disability outcomes, which translates to 1 out of 100 patients improved, for every 5 minutes of reduced OTR time. ■

*Continued from page 22*

nor neurological findings differed, comparing findings at 3 months to those at study initiation. Four depo-medrol patients reported complications, including hand swelling or pain, swelling, or depigmentation at the injection site, compared to one patient in the placebo group with pain at the injection site. US-guided corticosteroid injection in UNE is no better than placebo.

## ■ COMMENTARY

What causes ulnar neuropathy at the elbow? Among 117 patients with confirmed UNE, prospectively recruited, and seen by four blinded examiners who each performed separate neurologic evaluations and electrodiagnostic and ultrasound studies, 73% and 27% had lesions at the retro-epicondylar groove (REG) or under the humero-ulnar aponeurosis (HUA), respectively. HUA ulnar neuropathy was associated with manual labor, dominant arm involvement, and older age, whereas REG ulnar neuropathy was due to compression, mainly affecting the non-dominant arm of younger administrative personnel. These findings may assist in the prevention of UNE. ■

## REFERENCE

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## CME QUESTIONS

1. **Which of the following statements regarding the treatment of autoimmune cerebellar ataxia is true?**
   a. Patients should be treated with a different immunotherapy in case initial treatment fails.
   b. All patients, regardless of underlying antibody profile, should be treated.
   c. Patients might require sustained immunotherapy.
   d. Patients with paraneoplastic and non-paraneoplastic presentation should be treated.
   e. All of the above

2. **Which of the following is not considered a risk factor for sudden unexpected death in epilepsy patients?**
   a. Frequent generalized tonic-clonic seizures
   b. Diurnal seizures
   c. Young age at onset
   d. Long disease duration
   e. Polytherapy with anti-epileptic drugs

3. **Which of the following best describes how the vagus nerve may be involved in Parkinson's disease?**
   a. Alpha-synuclein pathology in Parkinson's disease is thought to spread from the dorsal motor nucleus of the vagus nerve to the enteric nervous system where it results in specific non-motor symptoms.
   b. Vagotomy performed for peptic ulcer disease is associated with an increased risk of Parkinson's disease.
   c. Superselective but not truncal vagotomy is associated with decreased risk of Parkinson's disease.
   d. Truncal vagotomy is associated with an approximately 50% decrease in Parkinson's disease risk, suggesting the vagus nerve as a route of spread of pathogenesis.

4. **Botulinum toxins are effective and approved for use in treating spasticity associated with all of the following conditions *except*:**
   a. stroke.
   b. traumatic brain injury.
   c. cerebral palsy.
   d. multiple sclerosis.

5. **Which of the following therapies have been shown, by double-blind, placebo-controlled trial, to be beneficial for ulnar neuropathy at the elbow?**
   a. Splinting or padding the elbow
   b. Modification of activities
   c. Nerve gliding exercises
   d. Corticosteroid injection into the elbow
   e. None of the above

6. **When treating acute ischemic stroke patients with endovascular clot extraction, the speed with which recanalization is accomplished is not a significant factor in determining the eventual neurological outcome.**
   a. True
   b. False

## [IN FUTURE ISSUES]

Update on Migraine Research