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Neurology
[ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Autoimmune Antibodies in Patients with Epilepsy of Unknown Etiology

By Peter B. Forgacs, MD

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

SYNOPSIS: In this prospective study of patients with epilepsy of unknown origin (including new-onset and established epilepsy), more than 20% of patients were found to have neurological autoantibodies strongly suggesting autoimmune origin of their epilepsy.

SOURCE: Dubey D, Algallaf A, Hays R, et al. Neurological autoantibody prevalence in epilepsy of unknown etiology. *JAMA Neurol* 2017;74:397-402.

The etiology of more than 30% of all adult epilepsies remains elusive even after the most comprehensive evaluation, based on currently available diagnostic tests. As a result, targeted therapeutic interventions are highly limited and symptomatic treatment with anti-epileptic medications remains the only approach to prevent further seizures in these patients. Many ongoing studies aim to find specific causative processes in these cases, as understanding the underlying pathological mechanisms may open up new avenues in treatment of such epilepsies — or even a possible cure or prevention of progression of epilepsy in some patients. Over the last decades, autoimmunity has been recognized as an etiological factor in many neurological diseases previously thought to have uncertain origins. Specifically, seizures are a well-known symptom of some immune-mediated neurological diseases (such as autoimmune encephalitides). Therefore, it has been long thought that some epilepsies with unknown origin may have immune-mediated etiology. In addition, a number of autoantibodies have been identified that specifically target neuronal cells. The association between presence

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of these antibodies and seizures has been demonstrated in a number of retrospective studies or case series; however, this is the first major study to prospectively examine the prevalence of autoantibodies in new-onset or established epilepsies of unknown etiology.

A total of 112 patients were included in this study over a 12-month period from various inpatient and outpatient settings in a single center, including the epilepsy monitoring unit, neurology clinic, inpatient service, and intensive care units. Thirty-one percent of the patients had new-onset epilepsy; the remaining patients had previously established epilepsy with mean duration of more than 12 years.

The main result of the study is that serum antibodies suggesting a potential autoimmune etiology were detected in 34.8% of these patients. Even after excluding antibodies with unclear roles in the pathogenesis of autoimmune epilepsy (such as TPO-Ab) and antibodies of unknown significance that are prevalent in the general population (such as GAD65-Ab < 20 mmol/L), 20.5% of patients had evidence for at least one neurological antibody (or combination of antibodies) strongly suggestive of an autoimmune cause of epilepsy.

Additional important findings include prospective utilization of a clinical score that successfully predicted antibody prevalence in the observed cohort with sensitivity and specificity of ~80%). In fact, certain clinical characteristics were more commonly present in the group of patients with positive serological findings compared to patients with negative serology. These include a viral prodrome, autonomic dysfunction, neuropsychiatric changes, faciobrachial dystonias or dyskinesias, and, importantly, mesial temporal sclerosis on MRI. Additionally, patients with new-onset epilepsy had higher prevalence of antibodies compared to patients with established epilepsy (37% vs. 13%), and differences also were found in the specific antibody profile between these two groups.

Furthermore, a clinically highly relevant result of the study is that the presence of autoantibodies was associated with better seizure outcome at the time of their first follow-up (defined as 50% or more seizure reduction; $P = 0.002$), including higher proportion of seizure freedom ($P = 0.02$). Furthermore, in seropositive patients who received some form of immune-modulatory therapy (especially intravenous methylprednisolone or plasmapheresis), the treatment was associated with better seizure outcome.

■ COMMENTARY

This study is important as it sheds light on a possible mechanism of epileptogenesis in a potentially large number of patients with currently unknown etiology of their epilepsy. The high prevalence of autoantibodies found in this study population is striking and strongly warrants further follow-up studies.

This study raises many questions and some weaknesses that are worth mentioning. First, there may be additional, currently unidentified autoantibodies that also are associated with the development of epilepsy, raising the possibility that the number of patients with autoimmune epilepsy may be even higher than identified here. In addition, it is important to point out that the prospective design makes this study strong, but it remains a correlative study. The observed association between seropositivity and development of epilepsy does not necessarily prove causation, especially in an individual patient, which can explain why some patients did not respond to immunotherapy. Furthermore, some observed autoantibodies also may be present in the general population without causing any symptoms; therefore, it is also possible that the study overestimates the number of patients for whom immune-mediated mechanisms are responsible for the development of epilepsy.

Importantly, the proposed clinical score used in this study appears to have good sensitivity and specificity to predict immunological origin of epilepsy, but it will need further validation in independent studies before widespread clinical application should be considered. However, such clinical scoring could be very useful in determining which patients with unknown epilepsy should have antibody testing. Lastly, additional studies are needed to further clarify the natural history of autoimmune epilepsies and the best treatment strategies for patients with presence of neurological antibodies, such as selection criteria for patients who most likely will benefit from immunotherapy and the timing of introduction and optimal duration of immunotherapy. Sending a serum

antibody panel in patients with unexplained epilepsy, especially if some clinical symptoms suggest possible immunological origin, should be strongly considered on an individual basis. ■

ABSTRACT & COMMENTARY

Serotonin Transporter Increases in Premotor Parkinson's Disease

By Claire Henchcliffe, MD, PhD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Henchcliffe reports she is a consultant and on the speakers bureau for Acadia, Impax, and Allergan, and is a consultant for US WorldMeds and Gerson Lehrman Group.

SYNOPSIS: In a small cross-sectional study, increased serotonin transporter was detected using 11C-DASB PET in striatum, hypothalamus, and brainstem in LRRK2 carriers who did not have clinical Parkinson's disease. This contrasts with later decreases previously described and implies a likely early compensatory mechanism.

SOURCE: Wile DJ, Agarwal PA, Schulzer M, et al. Serotonin and dopamine transporter PET changes in the premotor phase of LRRK2 parkinsonism: Cross-sectional studies. *Lancet Neurol* 2017;16:351-359.

A battery of positron emission tomography (PET) ligands were applied to two independent patient groups to investigate the dopaminergic and serotonergic systems in genetic and sporadic Parkinson's disease (PD) and in an at-risk cohort with leucine-rich repeat kinase 2 (LRRK2) gene mutations but without PD, assumed to have premotor PD. Multiple ligands for dopamine and serotonin investigations were grouped into two studies. The first study quantitated dopamine transporter (^{11}C-d-threo-methylphenidate) and dopamine synthesis/storage (^{18}F-6-fluoro-L-DOPA:^{18}F-FDOPA) in 138 participants, of whom 15 had LRRK2 mutations leading to PD (LRRK2-PD), 25 had LRRK2 mutations without PD (LRRK2-premotor), 63 had sporadic PD, and 35 were healthy volunteers. Those with PD were mean age 65 ± 11 years (LRRK2-PD) and 63 ± 11 years (sporadic PD), with mean age of PD onset of 58 ± 11 years (LRRK2-PD) and 57 ± 9 years (sporadic PD). LRRK2-premotor participants had a mean age of 50 ± 14 years. As expected, LRRK2-PD subjects had reduced striatal dopamine transporter and ^{18}F-FDOPA uptake, similar to those with sporadic PD. However, LRRK2-premotor participants had comparable ^{18}F-FDOPA uptake to controls, but lower dopamine transporter binding.

In the second study, subjects underwent PET with ligands for serotonin transporter (SERT) (^{11}C-3-amino-4-(2-dimethylaminomethylphenylsulfaryl)-benzonitrile: ^{11}C-DASB), vesicular monoamine transporter (^{11}C-dihydro tetrabenazine), and ^{18}F-FDOPA PET. In this smaller group, seven of the 38 participants had LRRK2-PD, nine were classified as LRRK2-premotor, 13 had sporadic PD, and nine were healthy controls. SERT binding was increased in LRRK2-premotor subjects in the hypothalamus (compared with all other groups), striatum (compared with sporadic PD), and brainstem (compared with LRRK2-PD). As predicted, VMAT density was reduced in the striatum for those with sporadic and LRRK2-PD vs. controls, and was asymmetrically decreased in a single subject classified as LRRK2 premotor.

■ COMMENTARY

The serotonergic system is garnering increasing attention in PD, with evidence drawn from biochemical, postmortem, and in vivo PET imaging studies. However, it remains difficult to piece together how the cellular and neurochemical changes that occur relate over time to clinical symptoms and medication responses. Loss of the dorsal raphe nuclei, with projections to basal ganglia, cortex, and limbic system, has been demonstrated in early PD. However, striatal hyperinnervation has been observed at postmortem, suggested to be a compensatory change. Improving understanding of how serotonin function changes in PD is critical, as it is involved in mood, psychosis, sleep, and other important non-motor symptoms. Moreover, a key role for serotonin neurons has been proposed in levodopa-associated dyskinesia.

Multiple previous studies have demonstrated increased SERT density in various stages of PD, with a single study describing preserved levels in very early PD. Therefore, the strength of the present study is its focus on LRRK2 mutation carriers who do not have PD but are at high risk of developing the disorder. It can be assumed that the majority of the individuals studied by Wile and colleagues actually are in the premotor phase of PD, despite lack of supporting longitudinal data. The finding of serotonergic changes in multiple brain regions in presumed premotor PD is not only novel but has important implications. The authors suggested it occurs as a compensatory change (that also has been suggested to explain decreased dopamine transporter in the context of depleted dopamine in early PD). Confirmation and longitudinal data will be critical.

However, there are some limitations of the study. Numbers of participants who underwent the ^{11}C-DASB scans are very small, thus limiting interpretation. Clinical data are incomplete; for example, the Beck Depression Inventory and Montreal Cognitive Assessment were performed only in the second study, and then only for 5/9 and 4/9 LRRK2 carriers without PD, respectively. Age ranges are quite broad (for example, 35-68 years at onset in sporadic PD). Two participants in the first study with LRRK2 without PD had significant motor dysfunction, although judged not to be PD (one had a history of poliomyelitis). There is little detail on medications or patient status at the time of clinical motor measurements and limited assessment of motor complications. Given the importance of studies on LRRK2 carriers without PD, it also would be interesting to have more data on other potential premotor manifestations.

For now, it is too early to say what this "premotor" SERT increase means and how its measurement might be applied. However, at a time when the importance of premotor and non-motor features in PD are increasingly appreciated, the study is a superb example of how neuroimaging focused on multiple neurochemical systems can help tease apart the complexity of this neurodegenerative disorder. Longitudinal follow-up is now a critical need. ■

ABSTRACT & COMMENTARY

Vascular Risk Factors and Their Role in the Development of Alzheimer's Disease

By Richard S. Isaacson, MD

Associate Professor of Neurology (Education), Weill Cornell Medical College

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

SYNOPSIS: This study has found an association between mid-life, but not late-life, vascular risk factors and brain amyloid deposition as imaged on amyloid-labeled PET.

SOURCE: Gottesman RF, Schneider AL, Zhou Y, et al. Association between midlife vascular risk factors and estimated brain amyloid deposition. *JAMA* 2017;317:1443-1450.

The future of Alzheimer's disease (AD) prevention most likely will rely on a combination of interventions that include pharmacologic as well as non-pharmacologic therapies. Several promising clinical trials are currently underway, with most focused on amyloid-beta lowering; yet, an increasing number of lifestyle-based interventions (e.g., physical exercise, nutrition) also are being studied. Numerous reports have suggested an association between cardiovascular and cerebrovascular risk factors and increased risk for AD, and prevention may be most effective when started as early as possible.

The most recent AD diagnostic criteria (described in 2011) most accurately reflects the current understanding of AD (National Institutes of Aging/Alzheimer's Association criteria). These standards describe a spectrum of AD that starts many years before the first symptoms occur. This new model breaks down AD into three different stages. Before AD starts, patients can be classified in the prodromal stage, meaning the disease has not started, and no symptoms are present. In Stage 1, AD has started in the brain but there are no symptoms (preclinical AD). In Stage 2, patients have mild memory loss, but still can perform all their usual daily activities (mild cognitive impairment due to AD). In Stage 3, the patients have dementia caused by AD. To have the most optimal effect and offer the most clinically relevant neuroprotection, interventions will need to be initiated at a preclinical or prodromal stage.

Along these lines, a new study by Gottesman and colleagues has found an association between mid-life vascular risk factors (including hypertension, diabetes, total cholesterol > 200, body mass index > 30 kg/m^2, and current smoking) and brain amyloid deposition as imaged on amyloid-labeled PET. The Atherosclerosis Risk in Communities — PET Amyloid Imaging Study was a prospective cohort study (n = 322) of subjects without dementia in three states (Maryland, North Carolina, and Mississippi). These subjects have been evaluated longitudinally for more than 30 years, with baseline demographics of a mean age of 52 years, 58% female, and 43% black. In 2011, subjects began receiving amyloid-labeled PET scans with florbetapir when they were between 67 and 88 years of age.

The study found that elevated body mass index in midlife was associated with elevated brain amyloid (odds ratio, 2.06; 95% confidence interval [CI], 1.16-3.65). At baseline, 65 participants had no vascular risk factors, 123 had one risk factor, and 134 had two or more risk factors. In alignment with hypotheses generated based

on several past epidemiologic studies, a higher number of mid-life vascular risk factors were associated with elevated brain amyloid. Compared with no mid-life vascular risk factors, the odds ratio for elevated brain amyloid associated with one vascular risk factor was 1.88 (95% CI, 0.95-3.72) and for two or more vascular risk factors was 2.88 (95% CI, 1.46-5.69). Interestingly, late-life vascular risk factors were *not* associated with late-life brain amyloid deposition.

■ COMMENTARY

Prior studies have demonstrated that vascular risk factors contribute to brain amyloid deposition, particularly in blacks, as well as in the setting of the most common late-onset genetic risk factor for AD, carriage of the APOE4 gene. However, in this study, no relationship was found between race or APOE4 status. Taken together, these findings suggest that there is a role of vascular disease in the pathogenesis of AD across a broad spectrum of patient populations, and offer additional evidence toward the potential utility of cardio and cerebrovascular risk factor modification in mid-life in an effort to reduce risk and/or slow the progression toward dementia due to AD.

At this time, from a practical clinical perspective, vascular risk factor modification in mid-life seems to be a worthwhile approach toward addressing AD risk via possible attenuation of brain amyloid deposition across genotypes. However, more rigorous prospective, randomized studies are warranted to definitively prove that this hypothetical approach truly reduces AD risk over time. ■

ABSTRACT & COMMENTARY

Spinal Manipulative Therapy for Acute Low Back Pain

By Bridget Carey, MD

Assistant Professor of Neurology and Assistant Attending Neurologist at NewYork-Presbyterian/Weill Cornell Medical Center; Assistant Attending Neurologist at the Hospital For Special Surgery

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

SYNOPSIS: Spinal manipulative therapy for acute low back pain may provide some benefit, but carries a significant risk of treatment-associated pain.

SOURCE: Paige NM, Miake-Lye IM, Booth MS, et al. Association of spinal manipulative therapy with clinical benefit and harm for acute low back pain: Systematic review and meta-analysis. *JAMA* 2017;317:1451-1460.

This review and meta-analysis investigated the potential benefits and harms from spinal manipulative therapy (SMT) as a treatment for acute low back pain. The authors performed a meta-analysis of randomized clinical trials (RCTs) extracted from the medical literature between January 2011 and February 2017. In addition, narrative descriptions of studies that did not meet criteria for statistical inclusion in the meta-analysis were included in the review.

Acute low back pain was defined as low back pain of a duration ≤ 6 weeks. The predominant patient population of the included studies had symptoms of axial low back pain, but a subpopulation of patients who also endorsed sciatic (radicular) symptoms were included. In the analysis, however, studies consisting solely of patients with radicular pain were excluded.

SMT refers to manual therapy performed on the back. Per the authors, SMT is "a term that encompasses a large variation in the type of manual therapy." For the purpose of this analysis, the intervention had to be classified as either a "thrust" or "non-thrust" technique; other variants of manipulation were excluded. The intervention could be performed by a physical therapist, chiropractor, osteopathic practitioner, or a physician.

In all studies, SMT was assessed in comparison to an alternative treatment, such as medication, exercises, physical therapy, or sham-SMT. Effectiveness was measured through outcomes of pain and functional status. In addition, the potential for harm was evaluated. Outcomes were assessed at two time-points: 2 weeks or less (immediate term) and 3-6 weeks (short term).

Paige et al included 26 RCTs in the statistical analysis for effectiveness (outcome measures of pain and functional status). The assessment of adverse events included eight articles, including RCTs and observational studies. Pain outcomes were reported using the 100 mm visual analog scale (VAS), 11-point numeric rating scale, or other numerical pain scales. For both immediate and short-term outcome points, a modest but statistically significant benefit was seen for SMT over the alternative treatment (mean effect of -9.95 mm for short term and -9.76 mm for immediate on VAS scale).

Functional status outcomes were reported using the Roland-Morris Low Back Pain and Disability Questionnaire (RMDQ) or the Oswestry Disability Index. A modest but statistically significant benefit was seen for SMT over the alternative treatment at both immediate and short-term outcome points (improvement by 1-2.5 points in the RMDQ score).

The assessment of adverse effects was based on eight studies (N ranging from 68-1,058 patients). Harms were assessed by patient questionnaire, and 50-67% of patients reported "mild transient harms," including but not limited to complaints of transient local discomfort, increase in pain, headaches, and/or muscle stiffness. Serious adverse events, which have been reported in case reports and in other reviews, are acknowledged by the authors, but not included for evaluation in this review.

■ COMMENTARY

This is a thorough review of the medical literature pertaining to the role of SMT in patients with acute low back pain. The data indicate that overall SMT probably is slightly helpful in the management of acute axial back pain in the short term (< 6 weeks), while at the same time associated with frequent transient increases in pain.

Despite a thorough meta-analysis, limitations to the interpretation and implementation of these findings are significant. A main issue is that SMT is not well-defined. Practitioners trained in different fields perform different manipulation procedures, in concert with additional therapeutic modalities. Therefore, it is not possible from the information provided in this review to link a specific method of therapy (or manipulation) to a specific outcome.

Further, it is notable that more than half of the patients who undergo SMT experience transient treatment-associated pain. The severity and duration of this pain was not stratified or described, nor was it factored into the analysis. Therefore, whether this transient pain is "worth" the modest improvements in short-term pain and functional metrics is not at all clear. Prospective or retrospective trials of specific protocols for SMT that are standardized between providers would be more helpful in the determination of beneficial interventions. ■

ABSTRACT & COMMENTARY

Hematopoietic Stem Cell Transplantation for Adult Cerebral X-linked ALD

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: Based on review of data from 14 patients with adult cerebral X-linked adrenoleukodystrophy who were treated with hematopoietic stem cell transplantation, the authors suggested that this might be an intervention that potentially could have long-term benefits and recommended further studies to evaluate this therapy.

SOURCE: Kuhl JS, Suarez F, Gillett GT, et al. Long-term outcomes of allogenic haematopoietic stem cell transplantation for adult cerebral x-linked adrenoleukodystrophy. *Brain* 2017:140;953-966.

X-linked adrenoleukodystrophy (ALD) is a neurodegenerative disease caused by a defect in the ABCD1 gene that results in alterations in the peroxisomal oxidation of long-chain fatty acids. This leads to accumulation of very long-chain fatty acids in tissues. This disease primarily affects the brain and adrenal glands. Several phenotypes of this disease have been described, and they mainly are divided into the following four categories: cerebral inflammatory, adrenomyeloneuropathy (AMN), Addison's disease only, and asymptomatic. The cerebral form is characterized by rapidly progressive neurologic impairment, including cognitive, behavioral, and sensory motor deficits, and is seen mostly in very young children, representing about one-third of the cases of ALD. This presentation is seen less commonly in adults, representing about 5-10%. This also can present as a later development in adults who have had the AMN phenotype for several years.

Allogenic hematopoietic stem cell transplantation (HSCT) is an established treatment for children with cerebral ALD based on several studies that showed benefits to survival and neurologic outcomes from treatment despite the risks associated with transplantation, as there is no alternative effective therapy. However, other than anecdotes, such data are not available for adults with cerebral ALD. But given the poor prognosis in adults with the cerebral form, HSCT has been tried in this patient population as compassionate use. The authors conducted a retrospective analysis of 14 adult patients with cerebral ALD who received HSCT in centers in Germany, France, and the United King-

dom to study the feasibility and long-term outcomes of this treatment.

All patients had detailed neurological/neuropsychological and neurophysiologic and magnetic resonance imaging (MRI) examinations before and at specified time points post-transplantation as well. Assessment tools included Adult X-linked ALD Clinical Symptom Score, Kurtzke Expanded Disability Status Scale (EDSS), modified Rankin scale, and Loes MRI severity score. Post-treatment assessment intervals were six months and about 24 months (at least 12 months). Survival was compared by Kaplan-Meier estimates and comparisons done by log method. Comparison of continuous variables was performed by non-parametric tests.

The patients had a median age of 34 years (range 21-48 years), and eight of 14 patients were alive at a median follow-up of 65 months (range 38-116 months). The estimated overall probability of survival was 57.1 ± 13.2%. Among the 14 patients, two patients who received cord blood transplantation with reduced intensity conditioning and two patients who received peripheral stem cell transplantation after myeloablative conditioning did not survive. Eight out of 10 patients who received myeloablative conditioning followed by bone marrow transplantation survived. There were a total of six deaths in the study. The deaths were attributed to the following causes: one death was due to primary disease progression without complications of HSCT, two deaths were due to secondary disease progression after life-threatening infection, one death was

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Neurology [ALERT]

Stroke Alert

By Matthew E. Fink, MD

Excellent Outcome 2 Years After Endovascular Mechanical Thrombectomy

SOURCE: Van den berg LA, Dijkgraaf MG, Berhkemer OA, et al. Two-year outcome after endovascular treatment for acute ischemic stroke. *N Engl J Med* 2017;376:1341-1349.

In 2015, in the *New England Journal of Medicine*, these authors reported the 90-day outcomes of the Multicenter Randomized Clinical Trial of Endovascular Treatments for Acute Ischemic Stroke in the Netherlands (MR CLEAN), in which standard treatment was compared with endovascular treatment within six hours after onset of ischemic stroke symptoms. The trial showed that functional recovery at 90 days was better than intervention with standard treatment, specifically intravenous thrombolysis. Now the group reports the results of clinical follow-up at two years after randomization among the patients who were enrolled in the MR CLEAN trial.

Of the 500 patients who underwent randomization in the original trial, two-year data were available for 391. The distribution of outcomes on the modified Rankin scale favored endovascular treatments over conventional treatments (odds ratio = 1.68; 95% confidence interval, 1.15-2.45; $P = 0.007$). There were no significant differences between treatment groups in the percentage who had an excellent outcome, which is a Rankin score of 0 to 1. The cumulative two-year mortality was 26% in the intervention group and 31% in the control group, and was not significantly different. The authors concluded that the beneficial effects of endovascular treatments on functional outcome at two years in patients with acute ischemic stroke was similar to those reported at 90 days in the original trial. ■

Consumption of Artificially Sweetened Beverages Increases Stroke Risk

SOURCE: Pase MP, Himali JJ, Beiser AS, et al. Sugar- and artificially sweetened beverages and the risks of incident stroke and dementia: A prospective cohort study. *Stroke* 2017;48:1139-1146.

Sugar-sweetened beverages have been associated with cardiometabolic diseases, including coronary heart disease, stroke, diabetes, and obesity. Artificially sweetened beverages have been heavily advertised as an alternative to reduce the cardiometabolic consequences of high sugar intake. To investigate the possible roles of both sugar-sweetened or artificially sweetened beverage consumption on risks of stroke and dementia, the Framingham Heart Study Offspring cohort was followed for a decade, with a specific focus on the effects of sweetened beverage consumption on the risk of stroke and dementia.

There were 2,888 participants aged > 45 years evaluated for incident stroke and 1,484 patients aged > 60 years evaluated for incident dementia. Beverage intake was quantified from a questionnaire over several time periods from 1991 until 2001, to determine cumulative consumption. Surveillance for events continued for 10 years. During that time, the investigators observed 97 cases of incident stroke and 81 cases of incident dementia. After adjustments for age, sex, education, caloric intake, diet quality, physical activity, and smoking, higher recent and higher cumulative intake of artificially sweetened soft drinks was associated with an increased risk of ischemic stroke (hazard ratio = 2.96) and Alzheimer's disease (hazard ratio = 2.89). In a surprise finding, sugar-sweetened beverage consumption was not associated with stroke or dementia. As an observational study, causation cannot be inferred, and further investigation and further studies will be needed to confirm these findings. ■

Continued from page 79

due to graft rejection, and three early patient deaths were attributed to transplantation-associated infection with non-engraftment or due to immobility due to advanced disease. Among the variables examined, survival was related to extent of baseline motor dysfunction. Limited AMN with EDSS < 6.0 was significantly associated with superior survival compared to advanced AMN with EDSS ≥ 6.0. Significant neurological and/or behavioral deterioration was seen in all but one patient during the transplantation and during early follow-up. This markedly improved or disappeared in all surviving patients between 6-12 months.

■ COMMENTARY

This analysis of 14 adult patients with cerebral ALD shows that HSCT can, at least in a subgroup of patients, prolong survival and preserve neurologic function by arresting inflammatory demyelination. Even though hematopoietic stem cell transplantation was associated with significant risks, including death and disease deterioration in the few months immediately following transplantation, given the devastating prognosis associated with this form of ALD, this is a potentially beneficial option that deserves to be studied further for carefully selected adults with cerebral ALD. ■

CME QUESTIONS

1. **In patients with epilepsy, which of the following clinical features does *not* predict a high likelihood of autoantibody seropositivity?**
   a. Mesial temporal sclerosis on MRI
   b. Viral prodrome
   c. Neuropsychiatric features
   d. Family history of epilepsy
   e. Autonomic dysfunction
2. **In LRRK2 mutation carriers, either with or without Parkinson's disease (PD), which of the following statements is correct?**
   a. Brainstem serotonin transporter density is increased in LRRK2 PD and in sporadic PD.
   b. Striatal serotonin transporter density is increased in LRRK2 PD and in sporadic PD.
   c. Dopamine transporter density inversely correlates with serotonin transporter density in LRRK2 mutation carriers without PD.
   d. Striatal serotonin transporter is increased in LRRK2 mutation carriers without PD but not in LRRK2 PD.
   e. Serotonin transporter is increased in LRRK2 PD but not in sporadic PD.
3. **Recent evidence suggests that mid-life vascular risk factors are associated with brain amyloid deposition later in life. Which of the following factors is not among the risk factors identified?**
   a. Type 2 diabetes mellitus
   b. Total cholesterol > 200
   c. Physical inactivity
   d. Current smoking
4. **Treatment of acute low back pain may include all but which of the following?**
   a. Bed rest
   b. Simple analgesics
   c. Spinal manipulative therapy
   e. Epidural steroid injections
   e. Physical therapy
5. **Adults with adrenoleukodystrophy usually have severe disabilities and shortened lifespan.**
   a. True
   b. False
6. **Endovascular thrombectomy has been shown to have superior results in neurological outcome compared to intravenous thrombolytic therapy in patients with ischemic stroke.**
   a. True
   b. False
7. **Long-term consumption of artificially sweetened beverages appears to be associated with an increased risk of both stroke and all-cause dementia, including Alzheimer's disease.**
   a. True
   b. False

[IN FUTURE ISSUES]

Update on Migraine Management