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Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

# Predicting the Risk of Late-onset Alzheimer's Disease and Dementia Based on Common Genetic Variants

*By Makoto Ishii, MD, PhD*

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

SYNOPSIS: Using a genetic risk score of 23 common genetic variants and *apolipoprotein E* genotype could help stratify individuals into those very likely to those very unlikely to develop late-onset Alzheimer's disease and dementia.

SOURCE: van der Lee SJ, Wolters FJ, Ikram MK, et al. The effect of APOE and other common genetic variants on the onset of Alzheimer's disease and dementia: A community-based cohort study. *Lancet Neurol* 2018;17:434-444.

Despite the recent advances in understanding the determinants of late-onset Alzheimer's disease (AD), accurately predicting an individual's risk for developing AD remains challenging. Large genetic screens have discovered several important genes in sporadic forms of AD, but the individual contribution of each gene, including *apolipoprotein E* (*APOE*), remains relatively small. Therefore, van der Lee et al set out to determine whether combining *APOE* genotype and 23 other common genetic variants could help predict an individual's likelihood of developing AD and dementia.

Study participants were part of the Rotterdam Study, a large prospective community-based cohort study enrolling residents aged 55 years and older in a district of Rotterdam, Netherlands. Dementia was screened at baseline and subsequent visits with the Mini-Mental State Examination and the Geriatric Mental Schedule organic level. Subjects were excluded if there was no follow-up time beyond age 60 years. Additionally, the entire cohort was monitored continuously for dementia through electronic linkage with outpatient medical records. A consensus panel made the final diagnosis of

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AD or dementia according to standardized criteria. DNA for genotyping was obtained from baseline blood samples. The investigators included 23 genetic variants that showed genome-wide significant evidence of association with AD to generate a weighted genetic risk score (GRS) using reported effect estimates as weights. Subjects were categorized into tertiles of the GRS. Mortality was accounted as a competing event.

A total of 12,255 of 14,926 participants met study criteria. Follow-up was completed for 92% of 144,738 potential person-years, with median follow-up of 11.0 years. *APOE* genotype was imputed for 3% of subjects, which had a greater than 98% concordance with direct genotyping. Directly genotyped or imputed *APOE* genotype data were available for 11,375 out of 12,255 subjects.

As expected, *APOE* genotype had a strong effect, with E4/E4 having 48.3% (95% confidence interval [CI], 40.1-57.3) and heterozygous for E4 having 18.4% (95% CI, 16.5-20.4) risk for developing AD by age 85 years. By comparison, the risk was 8.6% (95% CI, 7.7-9.6) for E3/E3 and 5.5% (95% CI, 4.1-7.4) for E2/E2 or E2/E3 genotypes. For all, the risk of dementia was higher than AD but showed similar overall patterns. When stratified by tertiles of GRS, the risk for developing AD by age 85 years was 15.8% (95% CI, 14.1-17.6) for the high-risk, 11.8% (95% CI, 10.3-13.5) for the middle-risk, and 7.7% (95% CI, 6.5-9.1) for the low-risk.

When accounting for both the *APOE* genotype and the GRS, the risk for developing AD or dementia by age 85 years was the lowest in individuals with E2/E2 or E2/E3 genotypes and in the GRS low-risk tertile at 4.1% (95% CI, 2.1-7.7%) for AD and 7.2% (95% CI, 4.5-11.5%) for dementia. By comparison, individuals with E4/E4 genotypes and in the GRS high-risk tertile had the highest risk with 62.7% (95% CI, 47.2-78.2%) for AD and 77.5% (95% CI, 63.1-89.3%) for dementia. Within the same APOE genotype, risks of both AD and dementia were higher in the GRS high-risk tertile than the low-risk tertile.

When examining the percent risk by age, individuals with E4/E4 and GRS high-risk tertile attained 5% risk of AD at age 67 years and 12.5% at age 71 years. By comparison, individuals with E2/E3 or E2/E2 and GRS low-risk tertile had a 5% risk of AD at age 85 years and 12.5% by age 100 years. Furthermore, E4/E4 with GRS high-risk tertile attained a 40% risk of AD 10 years earlier than those in the low-risk tertile. Similar patterns were seen with risk for developing dementia. Finally, when parental history of dementia was considered, the risk for developing dementia was further increased in individuals with a positive parental history of dementia in the highest risk group (*APOE* E4/E4 and GRS high-risk tertile) compared to those in the same risk group who did not have a parental history of dementia.

## ■ COMMENTARY

There are significant strengths to this study, including using a large community-based setting, prospective determination of AD and dementia, high follow-up completion (92%), length of study (up to 25 years), and adjustments made for competing risk of mortality. However, notable limitations exist. All study participants are of native Dutch descent, possibly leading to cohort-specific effects requiring validation in other populations. Additionally, GRS was comprised of genetic data obtained from other studies in different cohorts. Therefore, it is not clear if the reported effect estimates of these genetic variations accurately predict those in this or other populations. Nevertheless, van der Lee et al demonstrated that stratifying an individual's risk for developing AD or dementia could be accomplished using noninvasive genetic screenings that are becoming increasingly more common in clinical practice. Furthermore, accurately predicting an individual's risk for developing AD would be extremely useful in prevention trials, where investigators can recruit subjects with the highest risk of AD without being confounded by those with very low risk. Alternatively, studies on subjects with the lowest risk could yield new insight regarding protective factors against dementia. Finally, since individuals with *APOE* E4/E4 genotype and high-risk tertile for GRS have a risk for developing AD of 62.7% and not 100%, non-genetic determinants, such as environmental and lifestyle factors, likely contribute to an individual's risk despite significant genetic risk factors. Although significant work needs to be done, additional research building on this important study could help move the field from prediction to prevention and ultimately treatment. ■

ABSTRACT & COMMENTARY

# Ufmylation and Brain Development: Effects of Gene Mutations

*By M. Elizabeth Ross, MD, PhD*

*Nathan Cummings Professor and Head, Laboratory of Neurogenetics and Development; Director, Center for Neurogenetics; Chair, Neuroscience Graduate Program; Weill Cornell Medical College*

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

SYNOPSIS: Genetic mutations that can modify post-translational proteins and their interactions may result in serious developmental disorders of the brain. Ufmylation is such a process, and mutations in the genes that regulate this process may have profound effects on the developing brain.

SOURCE: Nahorski MS, Maddirevula S, Ishimura R, et al. Biallelic UFM1 and UFC1 mutations expand the essential role of ufmylation in brain development. *Brain* 2018; Jun 2. doi/10.1093/brain/awy135/5032368. [Epub ahead of print].

Numerous single-gene mutations are known that cause microcephaly, with infantile encephalopathy manifested by severe global developmental delay and epilepsy. The report by Nahorski and colleagues is unusual, as it provides a first functionally verified example of a human brain developmental disorder caused by recessive mutation that affects a still rather esoteric pathway for post-translational modification of proteins called "ufmylation."

The biochemical modification of proteins after they are translated from RNA greatly expands the actions of modified proteins by altering their stability, subcellular localization, and protein-protein interactions. Ufmylation is carried out in a pathway similar to ubiquitination, requiring participation of activating, conjugating, and ligating enzymes that are called ubiquitin-like proteins (UBLs). Ubiquitin-fold modifier 1 (UFM1) is a 9.1 kDa (73 amino acids) protein that resembles ubiquitin and is among the UBL1 proteins like SUMO that get conjugated to their target proteins. The ufmylation pathway produces covalent attachment of UFM1 to its target proteins through the actions of E1-activating enzyme UBA5, followed by E2 conjugation by UFC1, and finally transfer of UFM1 to its target by formation of a thioester bond catalyzed by UFL1 ligase. Diseases previously associated with ufmylation include cancer, diabetes, ischemic heart disease, and alcoholic liver disease.

## ■ COMMENTARY

Several significant insights were obtained in this study. Exome sequencing was used to identify UFM1 missense mutations in four children from two unrelated Sudanese families and UFC1 missense mutations in three Saudi families and one Swiss family with eight affected members. Thus, the connection between mutations in UFM1 and UFC1 and brain development is made on genetic grounds. The investigators take the study further by showing that these variants produce hypomorphic dysfunction of the UFM system by altered UBA5-UFM1 mutant interaction, and reduced thioester formation by the mutant UFC1 versions. In fly, worm, and zebrafish models, ablation of UBA5 causes lethality while a brain-specific, conditional knockout of UBA5 in mice produces microcephaly and evidence of increased neural apoptosis, suggesting that ufmylation is important for neuronal development and survival. Therefore, Nahorski et al tested the possibility of whether the altered ufmylation due to the discovered missense mutations resulted in endoplasmic reticulum stress-mediated apoptotic cell death. The authors concluded that stress-induced apoptosis is not the underlying cause of pathogenesis in these families. Thus, it appears that the partial loss of ufmylation pathway function may disrupt neurodevelopment through effects on brain proteins that interact with UFC1 or other pathway components.

[This report is significant as a striking example of the importance of dysfunctional post-translational processing of proteins as a potential cause of neurological disease. It follows that targeting post-translational modifications beyond phosphorylation may yield exciting new treatments.]

The report is significant as a striking example of the importance of dysfunctional post-translational processing of proteins as a potential cause of neurological disease. It follows that targeting post-translational modifications beyond phosphorylation may yield exciting new treatments for a number of neurological disorders. ■

ABSTRACT & COMMENTARY

# Cannabidiol: Does It Help in Drug-resistant Epileptic Encephalopathies?

*By Padmaja Kandula, MD*

*Assistant Professor of Neurology and Neuroscience, Comprehensive Epilepsy Center, Weill Cornell Medical College*

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

SYNOPSIS: In this double-blind, placebo-controlled trial, the authors investigated the efficacy of adjunctive cannabidiol in a population of severe developmental epileptic encephalopathies and found some efficacy.

SOURCE: Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. *N Engl J Med* 2018;378:1888-1897.

The International League Against Epilepsy recognizes more than 20 different epilepsy syndromes, defined as a distinctive combination of clinical features, signs, electrographic patterns, and age of onset. Lennox-Gastaut syndrome is a severe epileptic encephalopathy defined by multiple seizure types, particularly tonic and atypical absence seizures, but also atonic and myoclonic seizures. The disorder also is characterized by a distinctive diffuse slow (less than 3 Hz) spike-and-wave pattern on electroencephalogram (EEG). Seizures occur generally before age 8 years, and patients are left with severe cognitive impairment. Although six broad-spectrum anticonvulsants are approved for the treatment of the various seizure types, no particular drug has been shown to be highly effective. Despite pharmacologic treatment, most patients remain medication-resistant with poor neurologic outcome. Drop seizures caused by an increase in motor tone (tonic) or loss of tone (atonic) are particularly troublesome because of the risk of injury in these patients. In addition to traditional anticonvulsant therapy, vagus nerve stimulation, ketogenic diet, and corpus callosotomy also have been used with some success. More recently, an open-label trial of cannabidiol in severe, intractable, childhood-onset, treatment-resistant epilepsy was promising for efficacy and relative safety in drug-resistant epilepsy. These same authors have embarked on a double-blind, placebo-controlled trial to assess the effectiveness and safety of adjunctive low and high doses of cannabidiol specifically on drop seizures in Lennox-Gastaut syndrome.

Thirty participating sites recruited patients over a seven-month interval in 2015. The Phase III trial was structured with a baseline four-week period, a 14-week treatment period, and a 10-day tapering period. A four-week follow-up period after cannabidiol or placebo was discontinued also was included. Patients were followed for up to 24 weeks.

Lennox-Gastaut patients were eligible for the trial if they were between 2 and 55 years of age with characteristic slow spike-and-wave discharges on EEG and at least two types of generalized seizures, including drop seizures (tonic, atonic, tonic-clonic) for at least six months. Eligible patients required at least two drop seizures weekly during the baseline period. All pharmacologic and non-pharmacologic treatments (ketogenic diet, vagus nerve stimulator) were stable during the four weeks before screening and during the trial. Concurrent use of recreational or medicinal cannabis in the prior three months, use of corticotropins in the last six months, or felbamate within the last year were excluded.

Eligible patients were assigned to one of four groups: cannabidiol at 20 mg/kg, cannabidiol at 10 mg/kg, or matching placebo for both the 20 mg/kg and 10 mg/kg groups. The active ingredient was a plant-derived pharmaceutical formulation of purified cannabidiol oral solution (100 mg/mL) administered twice daily. Patients and their caregivers recorded number and types of seizures daily as well as adverse events. Office visits occurred at two, four, eight, and 14 weeks after randomization. Follow-up telephone calls at six and 10 weeks post-cannabidiol or placebo taper also were made.

The primary outcome was absolute percentage change from baseline in frequency in drop seizures. Key secondary outcomes were 50% reduction from baseline in drop seizures, percent change from baseline in frequency of all seizure types, and the patient/caregiver global impression of change from baseline. Additional secondary outcomes included 25%, 75%, and 100% reduction from baseline in drop seizures.

Ultimately, 225 patients were included in the study: 76 patients were assigned to the 20 mg/kg cannabidiol group, 73 patients were assigned to the 10 mg/kg cannabidiol group, and 76 were assigned to the placebo group.

The median reductions in drop seizures were 41.9% for the 20 mg/kg group, 37.2% for the 10 mg/kg group, and 17.2% for the placebo group. Thirty-nine percent

in the 20 mg/kg group, 36% in the 10 mg/kg group, and 14% in the placebo group had at least 50% drop seizure reduction from baseline. Although not a key secondary outcome, the median percent reduction in non-drop seizures was 61.1% for the 20 mg/kg group, 54.6 for the 10 mg/kg group, and 34.3% for the placebo group. Caregiver global impression of change was 57% in the 20 mg group, 66% in the 10 mg group, and 44% in the placebo group.

Adverse events were common in all groups. Ninety-four percent of patients in the 20 mg group, 84% in the 10 mg group, and 72% in the placebo group most commonly reported somnolence, decreased appetite, diarrhea, upper respiratory symptoms, pyrexia, and vomiting. The investigators classificed most adverse effects as mild. However, seven patients were withdrawn from the trial for elevated liver transaminase three to 12 times the upper limit of normal. Fourteen patients had elevated liver enzymes at three times the upper limit of normal. Of these 14 patients, 11 were receiving concurrent valproate therapy.

■ COMMENTARY

Cannabidiol represents an interesting adjunctive treatment for severe drug-resistant epileptic encephalopathies. The perceived "naturalistic" effect of the agent also is appealing to both caregivers and patients. However, although the initial results are promising, there are some methodological limitations. All quantification of seizure types was dependent solely on caregiver or patient report without EEG confirmation. There was no statistical difference in global impression of change (slightly improved, much improved, or very much improved) between both cannabidiol and placebo groups, raising the question of large placebo effect. Also, it is difficult to separate individual drug effects. Nearly 40-50% of patients were on polypharmacy with either valproic acid or clobazam treatment. The P450 2C19 effect of cannabidiol is known to inhibit clobazam. Hence, the increase in active metabolite calls into question the enhanced effect from clobazam that may not be attributable entirely to cannabidiol. In previous trials, the 50% responder rates for vagus nerve stimulation and clobazam treatment were similar if not better than both doses of the cannabidiol treatment groups. Additionally, it is unclear whether the liver enzyme elevation was independent of cannabidiol effect or enhanced from valproic acid adjunctive therapy. Although the epileptic encephalopathies represent a challenging population in need of additional therapeutic options, there are still many unresolved questions regarding cannabidiol efficacy and safety. ■

## ABSTRACT & COMMENTARY

# Chemotherapy-induced Neuropathy in Childhood Cancer Survivors


***By Michael Rubin, MD***

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



SYNOPSIS: Long-term symptoms and disability from chemotherapy-induced peripheral neuropathy occur in more than half of childhood survivors of cancer, with vinca alkaloids and platinum agents implicated most often.



SOURCE: Kandula T, Farrar MA, Cohn RJ, et al. Chemotherapy-induced peripheral neuropathy in long-term survivors of childhood cancer: Clinical, neurophysiological, functional, and patient-reported outcomes. *JAMA Neurol* 2018; May 14. doi:10.1001/jamaneurol.2018.0963. [Epub ahead of print].


Survival for five years or more after a diagnosis of childhood cancer is associated with a normal life span and, given an 80% survival rate for many childhood and adolescent cancers, long-term effects of cancer therapy can result in significant long-term morbidity. What is the disease burden and functional effect of surviving childhood cancer but suffering chemotherapy-induced peripheral neuropathy in the long term?

Kandula et al recruited cancer survivors who had received chemotherapy for extracranial malignancy prior to the age of 17 years between April 2015 and December 2016 from the Long-Term Follow-Up Clinic at the Kids Cancer Centre at Sydney Children's Hospital in Australia for this cross-sectional observational study. Exclusionary criteria encompassed other diseases associated with neuropathy, including diabetes, critical illness, and hereditary neuropathic or developmental disorders. Neuropathy assessment comprised nerve conduction studies, the pediatric-modified Total Neuropathy Score, the Movement Assessment Battery, the Pediatric Quality of Life Inventory Generic Core Scales, and the Pediatric Outcomes Data Collection Instrument, which, for participants 17 years or older, included Von Frey monofilaments, grating orientation task, grooved peg board task for functional measures, the European Organization for Research and Treatment of Cancer quality-of-life questionnaire, and the chemotherapy-induced peripheral neuropathy

questionnaire. Statistical analysis involved two-tailed *t* tests and Mann-Whitney U tests for nonparametric subgroup analyses, $\chi 2$ tests for nominal data, one-way analysis of variance for multiple groups, and Pearson or Spearman correlations, with a $P$ value < 0.05 considered significant.

Among 169 patients who met inclusion criteria, 48 declined participation or were unreachable, leaving a cohort of 121 long-term childhood cancer survivors to be studied, of whom 53.7% were male, 46.3% were female, with a median age at diagnosis and chemotherapy of four years, and a median age at evaluation of 16 years, which was a median of 8.5 years after completing chemotherapy. Leukemia comprised the largest group (52.9%), followed by solid tumors (29.8%) and lymphoma (14%). Vinca alkaloids were the most common form of chemotherapy (71.1%), among whom 4.1% received multiple vinca alkaloids. Platinum agents were used in 16.5%, including cisplatin or carboplatin (5.8% each), with 5% who received both. Both platinum agents and vinca alkaloids were given in 10.7%, and radiotherapy was given to 43.8% overall.

Peripheral neuropathy was seen in 50.5% of patients treated with neurotoxic chemotherapy, predominantly associated with sensory axonal neuropathy in the legs, accompanied by impaired manual dexterity, distal sensation, and balance, and by patient-reported reduced global quality of life and physical functioning, with cisplatin more frequently causing long-term neurotoxicity than vinca alkaloids. Peripheral neuropathy is common in long-term childhood cancer survivors.

## ■ COMMENTARY

No effective pharmacologic intervention is available to prevent chemotherapy-induced peripheral neuropathy, and no consensus exists to evaluate its incidence or severity. Whereas very few conventional, neuroprotection, drug-based trials are available that address this problem, there are an increasing number of non-conventional trials that do, using physical treatments including magnetic field therapy, diathermy, photobiomodulation, or electroacupuncture, alone or in combination with physical therapy. None have shown evidence of clinical effectiveness, although subjective relief is reported occasionally. New methodological approaches are necessary. Nitro-oxidative stress resulting from neuronal mitochondrial dysfunction, representing final common pathways in the development of chemotherapy-induced polyneuropathy, may be such an avenue, using drugs such as metformin or interleukin 10. Hopefully, future research will bridge the gap.[1,2] ■

### REFERENCE


1. Ma J, Kavelaars A, Dougherty PM, Heijnen CJ. Beyond symptomatic relief for chemotherapy-induced peripheral neuropathy: Targeting the source. *Cancer* 2018;124:2289-2298.
2. Cavaletti G, Marmiroli P. Pharmacotherapy options for managing chemotherapy-induced peripheral neurotoxicity. *Expert Opin Pharmacother* 2018;19:113-121.


ABSTRACT & COMMENTARY

# Prodromal Symptoms Predict the Onset of α-Synucleinopathies


***By Harini Sarva, MD***

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

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



SYNOPSIS: In this review of the common prodromal symptoms of α-synucleinopathies, such as Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy, the authors provided a potential framework for a timeline of the development of these conditions, starting with these prodromal symptoms.


SOURCE: Savica R, Bradley BF, Mielke MM. When do α-synucleinopathies start? An epidemiological timeline: A review. *JAMA Neurol* 2018;75:503-509.

Alpha-synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), are chronic progressive neurodegenerative conditions that result from abnormal deposition of misfolded α-synuclein into neurons, and in the case of MSA, into oligodendrocytes. Although pathological hallmarks begin many years before their clinical diagnoses, several prodromal features have been described in various studies. Neuropathological and functional imaging studies suggest the development of a premotor stage of at least five years before the clinical diagnosis of PD. Common prodromal symptoms described in the literature include olfactory dysfunction, constipation and dysautonomia, anxiety and depression, and REM-sleep behavior disorder. Two epidemiological studies have shown that anosmia can be predictive of Lewy body pathology and DaTscan positivity. Constipation is among the most commonly reported symptoms

and, on average, can predate the clinical features of PD by at least 10 years. Anxiety and depression are also very common and may predate PD motor symptoms by 20 years. REM-sleep behavior disorder, another very common premotor symptom, may assist in predicting conversion to clinical features of PD. New studies indicate a median conversion of 7.5 years to PD, DLB, or MSA. Because of the lack of concrete predictive

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Neurology [ALERT®]

# Stroke Alert

By Matthew E. Fink, MD

## Dual Antiplatelet Therapy for Minor Ischemic Stroke or TIA

SOURCE: Johnston SC, Easton JD, Farrant M, et al; for the Clinical Research Collaboration, Neurological Treatment Trials Network, and the POINT Investigators. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med* 2018; May 16. doi:10.1056/NEJMoa1800410. [Epub ahead of print].

After a minor ischemic stroke or transient ischemic attack (TIA), the risk of recurrent ischemic stroke in the next 90 days ranges from 3-15%. Use of aspirin reduces the risk of recurrent stroke by approximately 20%. Clopidogrel inhibits platelet aggregation in a mechanism that is synergistic with aspirin when tested in platelet aggregation assays. The combination of these two drugs has been used effectively to reduce the risk of ischemic events in patients with coronary artery events. These investigators undertook this study to evaluate the effect of clopidogrel plus aspirin, vs. aspirin alone, in an international population of patients who had minor ischemic stroke or TIA — Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT).

From 2010 to 2017, the investigators enrolled 4,881 patients at 269 sites in 10 countries in North America, Europe, Australia, and New Zealand, with most patients (82.8%) enrolled in the United States. After an interim analysis, the investigators halted enrollment after 84% of the anticipated number of patients had been enrolled because the combination of clopidogrel and aspirin was associated with both a lower risk of major ischemic events (ischemic stroke, myocardial infarction, or death from an ischemic vascular event) and a higher risk of major hemorrhage from aspirin alone at 90 days. Five percent of patients receiving clopidogrel plus aspirin and 6.5% of patients receiving aspirin plus placebo (hazard ratio, 0.75; $P = 0.02$) experienced major ischemic events, with most occurring during the first week after the initial event. Major hemorrhages occurred in 0.9% receiving clopidogrel plus aspirin and 0.4% receiving aspirin plus placebo (hazard ratio, 2.32; $P = 0.02$). Hemorrhage risk was the same throughout the 90-day follow-up period.

The investigators were unable to compare the disabilities that resulted from ischemic events compared to hemorrhagic events, but mortality was not significantly different between the two groups. Based on this study and the CHANCE trial from China (*N Engl J Med* 2013;369:11-19), a reasonable approach for treatment would be 30 days of treatment with dual antiplatelet therapy following acute ischemic stroke or TIA, and then conversion to a single agent. However, such recommendations are my opinion, and not based on evidence from any study. ■

## Tenecteplase vs. Alteplase for Ischemic Stroke

SOURCE: Campbell BCV, Mitchell PJ, Churilov L, et al; for the EXTEND-IA TNK Investigators. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med* 2018;378:1573-1582.

Intravenous thrombolysis with alteplase is the sole approved treatment for eligible patients with acute ischemic stroke. It also is used to treat patients before endovascular thrombectomy, although this recommendation remains controversial. Alteplase is given as an infusion over one hour after a bolus injection and has been associated with a low incidence of reperfusion for large vessel occlusion before thrombectomy. Tenecteplase is a genetically modified variant of alteplase with greater fibrin specificity and a longer half-life that permits bolus administration, and in trials involving acute myocardial infarction, it had a lower incidence of systemic hemorrhage than alteplase. Tenecteplase is easier to administer and costa less than alteplase.

Campbell et al enrolled 202 patients at 13 centers in Australia and New Zealand who were eligible if they could undergo intravenous thrombolysis within 4.5 hours after onset of ischemic stroke and had a large vessel occlusion on CT angiography of the internal carotid artery, the first or second segments of the middle cerebral artery, or the basilar artery, and treatment could begin to retrieve the intra-arterial clots within six hours after stroke onset. There was no upper age limit and no restriction on clinical severity. Equal numbers of patients were assigned randomly to receive tenecteplase or alteplase. The primary outcome, reperfusion of > 50% of the involved territory or an absence of retrievable thrombus, occurred in 22% of patients treated with tenecteplase vs. 10% of those treated with alteplase (incidence difference = 12 points; $P = 0.002$ for noninferiority; $P = 0.03$ for superiority). Tenecteplase treatment resulted in a better 90-day functional outcome than alteplase, and symptomatic intracerebral hemorrhage occurred in 1% of patients in each group.

Treatment with tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome than alteplase if administered to patients with ischemic stroke within 4.5 hours of symptom onset. ■

*Continued from page 87*

value of any of these prodromal symptoms, Savica et al proposed a three-stage representation: Stage 1 begins with neuropathology and early manifestations such as anosmia; Stage 2 consists of anxiety and RBD; and Stage 3 involves the striatum and presentation of parkinsonian symptoms.

## ■ COMMENTARY

Although various prodromal symptoms have been identified and have expanded our knowledge about the pathology and clinical phenomena of α-synucleinopathies, there is still a gap in predicting the development of specific types of disorders based on these early manifestations. Further complicating the issue is that PD itself is not a single disorder and has multiple subtypes. Thus, while having several prodromal features simultaneously may increase predictability, exactly which subtype of PD will develop is difficult to determine. In addition, exactly how the α-synuclein pathology propagates is unclear despite Braak's work and as shown by the clinical manifestations of DLB. The role of genetic and epigenetic factors in the development of these conditions is not understood entirely. Lastly, much of the work on prodromal features of these conditions has been performed on patients with PD and cannot be generalizable to atypical parkinsonisms, which are rare. The high misdiagnosis rate between PD and parkinsonisms further complicates the predictability of these prodromal symptoms. Thus, large-scale epidemiological studies of at least five years with radiological and biological specimens are needed to aid not only in the development of good biomarkers but also in assisting in better using these prodromal features to predict the diverse forms of these neurodegenerative disorders. ■

## CME QUESTIONS

1. **According to the Rotterdam Study, which of the following is true about individuals with *APOE* E4/E4 genotype and highest genetic risk scores based off 23 common genetic variants?**
   a. Higher risk for developing Alzheimer's disease when compared to individuals with the same APOE genotypes but with lower genetic risk scores
   b. Increased risk for developing Alzheimer's disease at an earlier age when compared to individuals with the same APOE genotype but with lower genetic risk scores
   c. A positive parental family history further increases risk for developing dementia
   d. All of the above
2. **Gene mutations that alter post-translational proteins may cause serious human neurological disorders.**
   a. True
   b. False
3. **Which of the following is *not* a noted adverse effect with cannabidiol treatment?**
   a. Dizziness
   b. Liver enzyme elevation
   c. Decreased appetite
   d. Somnolence
4. **Long-term survivors of childhood cancer with chemotherapy-induced polyneuropathy may complain of which of the following?**
   a. Imbalance
   b. Sensory loss in the legs
   c. Impaired manual dexterity
   d. All of the above
5. **Which of the following is *false* regarding α-synucleinopathies?**
   a. This group of disorders includes Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy.
   b. Anosmia, REM behavior disorder, constipation, and mood disorders are commonly described prodromal symptoms.
   c. Constipation and dysautonomia have been found to predate clinical motor features of Parkinson's disease by 10 years.
   d. Parkinson's disease presents with diverse subtypes complicating the predictability of these prodromal symptoms.
6. **Dual antiplatelet therapy for acute ischemic stroke is associated with a higher risk of severe hemorrhage than use of a single agent.**
   a. True
   b. False
7. **Tenecteplase appears to be more efficacious in reperfusion of the brain following large vessel occlusion, compared to alteplase.**
   a. True
   b. False

## [IN FUTURE ISSUES]

New Developments in Headache Treatment