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INSIDE

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Peer reviewer M. Flint Beal, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company having ties to this field of study.

Metabolomic Profiling: A Diagnostic Blood Test for Parkinson Disease?

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, DPhil

Assistant Professor, Department of Neurology and Neuroscience, Weill Medical College, Cornell University

Dr. Henchcliffe reports that she is on the speaker's bureau for the following companies: GlaxoSmithKline, Teva, Boehringer Ingelheim, Schwarz Pharma, and Allergan.

Synopsis: *Metabolomic profiling is a technique that measures and analyzes a large array of low molecular weight species in any chosen sample. Metabolomic analysis of plasma accurately distinguishes between subjects with Parkinson disease and healthy controls, thus providing a potential disease biomarker.*

Source: Bogdanov M, et al. Metabolomic profiling to develop biomarkers for Parkinson's disease. *Brain* 2008;131(Pt 2):389-396.

THE PRESENT STUDY USED METABOLOMIC PROFILING TO ANALYZE plasma samples obtained from patients with Parkinson disease (PD) (n=66) and control subjects (n=25). High performance liquid chromatography with electrochemical coulometric array detection (LCECA) was chosen as the metabolomic platform to provide quantitative measurements of approximately 2000 small (<1000 daltons) compounds or analytes that comprised the "metabolome" for each subject. Resulting data were then organized into a format for multivariate analysis. Mean age of the PD subjects was 66.0 +/-11.1 years (vs. 61.5 +/- 12.2 years for controls), and they were 59% male (vs. 33% male for controls). Mean disease duration was 7.1 +/- 4.9 years. Of the 66 PD subjects, 15 took no medications, 20 took carbidopa-levodopa alone, 7 took dopamine agonists, and 24 took a combination of carbidopa-levodopa and dopamine agonists. Using a partial least squares discriminant analysis (PLS-DA) of metabolomic profiles demonstrated complete differentiation between unmedicated PD samples (n=15) and control samples (n=25) ($p<0.01$). From these data, a subset of variables within the metabolomic profile was chosen according to "variable influence on projection" (VIP) (i.e., those analytes with the most significant contribution to differences in metabolomes of PD vs. control subjects). Using this subset of

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variables, metabolomic analysis completely distinguished PD subjects taking carbidopa-levodopa vs. controls, as well as PD subjects taking carbidopa-levodopa plus dopamine agonists vs. controls ($p<0.01$). Of note, urate levels were found to be decreased in PD vs. control samples, as expected based on epidemiological studies demonstrating an association of low urate levels with PD risk in large populations. Moreover, targeted testing for markers of oxidative stress demonstrated an increase in mean plasma concentrations of 8-hydroxy-2-deoxyguanosine (8-OHdG).

COMMENTARY

The "omics" approach has been investigated as a means to develop disease biomarkers in neurodegenerative diseases, including Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and now PD. It allows analysis of any chosen sample (such as plasma or CSF) based on patterns of transcripts (transcriptomics), proteins (proteomics), or small molecules as in this study (metabolomics). Although some of the analytes measured are identified, in this study it is the pattern of analytes (i.e., identified and unidentified) that is useful as a biomarker, rather than a single known compound. The authors convincingly demonstrate that metabolomic analysis of plasma samples can reliably and completely distinguish between subjects with PD vs. controls, and that this is independent of PD medication effects. As such, this holds great promise as a potential diagnostic marker for PD. At present, PD remains a clinical diagnosis. Despite recent advances in PD research, clinical accuracy (even using the most stringent criteria) may be no more than 93%, and underdiagnosis (particularly in early cases) is common. Another important application of this technology will be to identify which metabolites are responsible for contributing to separation of PD vs. control metabolomic profiles. This will not only improve our understanding of PD pathogenesis, but also help identify targets for therapeutic intervention. There is now a critical need to develop biomarkers for PD to improve diagnostic accuracy, to diagnose earlier, to monitor disease progression, and possibly to define "endophenotypes" in this heterogeneous disease. Metabolomic profiling certainly provides promise, and this study is a first step toward developing a diagnostic PD biomarker. ■

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Alcohol Intake and Stroke Risk: Can We Optimize Our Consumption?

ABSTRACT & COMMENTARY

By Alan Z. Segal, MD
Associate Professor of Clinical Neurology, Weill Cornell Medical College, Attending Neurologist, NewYork-Presbyterian Hospital.
Dr. Segal reports no financial relationships relevant to this field of study.

Synopsis: *Heavy alcohol consumption increases the risk of both ischemic and hemorrhagic stroke.*

Source: Bazzano LA et al. Alcohol consumption and risk for stroke among Chinese men. *Ann Neurol* 2007;62:569-578.

LARGE QUANTITIES OF ALCOHOL INTAKE ARE THOUGHT to increase the risk of both hemorrhagic and ischemic stroke. Mild to moderate alcohol intake may prevent ischemic stroke. Red wine may offer a particularly unique benefit. Alcohol in any dose has not been shown to decrease the risk of cerebral hemorrhage. Geographic and ethnic differences may further exist. In an important addition to prior epidemiological studies, Bazzano et al correlate alcohol intake with stroke risk in a large cohort of Chinese men.

In this study, among 64,338 men studied over 493,351 person years of follow-up, there were 3434 strokes (825 [24%] hemorrhagic, 1724 [50%] ischemic, and 852 [25%] unknown). The relative risk (RR) of stroke was elevated for men drinking more than 21 drinks per week (RR = 1.22) compared to 1-6 or 7-20 drinks. A more pronounced increase (RR = 1.30) was found for stroke mor-

tality among men in the highest intake category (more than 35 drinks per week). There was a suggestion from the data that moderate alcohol intake (<20 drinks per week) was protective for ischemic stroke and that heavy alcohol intake (>35 drinks per week) posed a particularly higher risk of hemorrhagic stroke, but none of these findings reached statistical significance. All of the study's findings were attenuated when a history of hypertension was factored into the multi-variate model, indicating the central role of this risk factor in both ischemic and hemorrhagic stroke.

The Chinese study is of interest, in part due to the increasing incidence of alcoholism in China as that country undergoes explosive economic development. Chinese men are disproportionately affected by this problem, as the authors observe, with a more than 30-fold increased frequency compared to women. Asian populations are of further interest due to an increased prevalence of hemorrhagic stroke compared to Western populations. Also, there are important inherited genetic polymorphisms among Asians, such as the alcohol intolerance conferred by allelic variations in the alcohol dehydrogenase enzyme. This may significantly affect alcohol intake patterns and may confound epidemiological studies due to other unknown genetic co-variants.

COMMENTARY

Should a "therapeutic window" for alcohol intake truly exist, it is a narrow one indeed. While light alcohol intake (1-2 drinks per day) may be protective, once daily consumption reaches three drinks, deleterious effects, in particular hemorrhagic stroke, may begin to accrue. Given that alcohol is an addictive substance, "heavy" use (5 drinks per day) always is a danger; it has well-known ill effects, not only in terms of stroke risk, but also on the brain and multiple other organ systems.

Phrenic Nerve Conduction Study: Not New but Improved

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College, New York, NY

Dr. Rubin reports that he is involved with grant/research support for Pfizer, and that he is on the speaker's bureau for Athena.

Synopsis: *Phrenic nerve conduction studies are technically difficult, but are useful in the evaluation of patients with diaphragmatic paralysis.*

Source: Resman-Gaspersc A, Podnar S. Phrenic nerve conduction studies: technical aspects and normative data. *Muscle Nerve* 2008;37:36-41.

ALL TOO OFTEN, DIAPHRAGMATIC MOTOR RESPONSES recorded following phrenic nerve stimulation are unobtainable, poorly reproducible, corrupted by concomitant brachial plexus stimulation, or demonstrate a compound muscle action potential of reversed polarity, with a positive rather than a negative peak. Can these difficulties be overcome or eliminated? Among 29 normal volunteers, 15 men and 14 women, ages 21 to 65 years, bilateral phrenic motor nerve conduction studies were performed using various stimulation sites, adjacent to the sternocleidomastoid (SCM) muscle and along the supraclavicular fossa, to determine which position resulted in a maximal, most reproducible result, at minimum stimulation strength. Motor responses were recorded using a fixed site, with the active, G1 electrode 5 cm above the xiphoid process, and the reference, G2 electrode 16 cm from G1, along the lower costal margin, ipsilateral to the side of stimulation. Measurements were obtained separately during inspiration and expiration. Supramaximal stimulation strength, motor response amplitude, onset latency, duration, and area of the negative phase were measured. Statistical analyzes included both parametric and non-parametric methods, using the paired t-test, Pearson's correlation coefficient, and mathematical transformations. Upper and lower limits were set at the mean +/- 2 standard deviations.

Bipolar surface stimulation, using firm pressure in the supraclavicular fossa between the 2 heads of the SCM muscle, yielded reproducible results using the lowest stimulation strength and without brachial plexus contamination. Momentary neck flexion facilitated observation of these two SCM heads, permitting better localization of the optimal stimulation site between the heads. Occasionally, stimulation at the posterior border of the SCM yielded a better response. Compound muscle action potential amplitude and duration, but not latency or area, varied with respiration, with 8 ms the upper normal limit for latency and 4.4 mVms the lower normal limit for area. The lower normal limits were 0.46 and 0.33 mV for amplitude on inspiration and expiration, respectively. Future phrenic nerve studies may benefit by recording motor response latency and area, rather than amplitude, as the former do not vary with respiration. Meanwhile, modification of stimulation and recording sites will improve routine amplitude measurements as presently performed.

COMMENTARY

Phrenic neuropathy may improve with topiramate. Diaphragmatic paralysis developed in a 57-year-old type

2 diabetic, who presented with a year-long history of stable orthopnea. When peripheral neuropathy was subsequently diagnosed and treated with topiramate, orthopnea and neuropathic symptoms improved within 26 weeks. Regrowth of intraepidermal nerve fibers was demonstrable on skin biopsy. Topiramate may be effective for the treatment of phrenic neuropathy and diaphragmatic paralysis.[1]

Reference

1. Rice AL, et al. Reversal of phrenic nerve palsy with topiramate. *J Diabetes Complications* 2007;21:63-67.

Disruptive Behaviors in Alzheimer's Disease

ABSTRACT & COMMENTARY

by Michael Lin, MD

Assistant Professor of Neurology and Neuroscience, Weill Medical College of Cornell University

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

Synopsis: *Disruptive behaviors are a poor prognostic sign in patients with Alzheimer's disease.*

Source: Scarmeas N, et al. Disruptive behavior as a predictor in Alzheimer disease. *Arch Neurol* 2007;64:1755-1761.

DISRUPTIVE BEHAVIORAL SYMPTOMS (DBSs) SUCH AS wandering, outbursts, threats/violence, agitation/restlessness, and sundowning are well known to occur in Alzheimer's disease (AD), particularly as the disease advances. Somewhat surprising, however, is that the relationship between DBSs and disease outcomes has not been consistent in the literature, possibly due to variability in symptom ascertainment, disease stage, and consideration of neuroleptics.

To address the relationship between DBSs and disease outcomes in AD, Scarmeas and colleagues analyzed 497 patients with moderate AD (average MMSE [Mini Mental State Examination] 20.4, range 5-30), recruited from 5 university-based memory disorders clinics in North America and Europe. Subjects were examined every 6 months for an average of 4.4 years, and the presence of DBSs was assessed using the Columbia University Scale for Psychopathology in AD. Use of cholinesterase inhibitors and neuroleptics was also recorded.

The primary endpoints of the study were: 1) cognitive outcome (Folstein MMSE $\leq$ 10/30); 2) functional outcome (Blessed Dementia Rating Scale Parts I and II score $\geq$ 10/17); 3) institutionalization (as determined by actual institutionalization or an equivalent institutional care dependency scale); and 4) mortality.

DBSs were extremely common. Although only 48% of subjects exhibited a DBS at baseline, this rose to 83% at some point during follow-up. Throughout followup, subjects had on average 2.3 +/- 1.5 DBSs, which increased over time. Agitation/restlessness was present in ~3 of every 4 patients, outbursts and sundowning in ~1 of every 2 patients, and wandering and threats/violence in ~1 of every 3 patients.

DBSs also were predictive of disease outcomes, increasing the risks of cognitive decline, functional decline, and institutionalization each by a factor of approximately 1.5. There was no effect on mortality. Specific DBSs appeared to be more strongly predictive of certain outcomes than others. Neuroleptic use was associated with a higher risk of functional decline (hazard ratio [HR] 1.57) and institutionalization (HR 1.57), but not with cognitive outcome or mortality. Cholinesterase inhibitors were associated with a lower risk of institutionalization (HR 0.47) and mortality (HR 0.36), but not with cognitive or functional outcomes.

Finally, autopsy data were available for 96 patients. Ninety-three percent of cases had AD-type pathology, 21% of which also had Lewy body pathology. Exclusion of subjects with Lewy body pathology did not change the prevalence of DBSs or their association with the disease outcomes.

COMMENTARY

This is a strong study, one of the largest to examine DBSs in AD. It was conducted at university centers by experts in memory disorders, had extensive and nearly complete follow-up (94%), and assessed all the variables of interest over multiple visits in a time-dependent fashion. On the other hand, the population was limited to highly specialized referral centers and was predominantly Caucasian with few comorbidities; this potentially limited the ability to generalize the results. Assessment of predictors and outcomes was conducted by the same examiners, a potential source of bias. The neuropathology underlying DBSs and their association with disease outcomes remain to be explored.

The take home points of this article include the very high prevalence of DBSs in AD, and their predictive value for disease outcomes. Additionally, the study provides further evidence for use of cholinesterase inhibitors in improving disease outcome, and for minimizing the use of neuroleptics.

Prevention of Thromboembolism: Is There Hope?

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD

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Dr. Jamieson reports that she is a retained consultant for Boehringer Ingelheim, Merck, and Ortho-McNeil; and that she is on the speaker's bureau for Boehringer Ingelheim and Merck.

Synopsis: *Anticoagulation for the prevention of venous thromboembolization is underutilized worldwide. Risk of short-term interruption of warfarin therapy appears small. Treatment with idraparinux increases hemorrhage risk, as compared with vitamin K antagonists.*

Sources: Cohen AT, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE) study: a multinational cross-sectional study. *Lancet* 2008;371:387-394; The Amadeus Investigators. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomized, open-label, non-inferiority trial. *Lancet* 2008;371:315-321; Garcia DA, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. *Arch Intern Med* 2008;168:63-69.

Prevention of clotting in persons at risk of arterial or venous thromboembolism is imperfect and fraught with the hazard of hemorrhage. These three recently published articles evaluate the prevalence of thrombotic risk in the acute hospital setting, the risk of interruption of chronic anticoagulation, and the efficacy and safety of a new agent for chronic anticoagulation. The articles demonstrate the difficulty of implementing and maintaining appropriate anticoagulation without risk of either a breakthrough ischemic event or a hemorrhagic complication.

Even transient causes of immobility, such as the middle seat on a transatlantic red-eye flight or bed rest after orthopedic surgery, may result in venous thrombosis with risk of embolization to the lungs or brain. Venous thromboembolism (VTE) during hospitalization for acute medical or surgical illness is the most common preventable cause of in-hospital death. Despite the clear risk, guidelines for VTE prophylaxis often are not observed.

The investigators for the multinational, observational, cross-sectional "Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting" (ENDORSE) study did a chart audit of medical and surgical patients in 358 hospitals in 32 countries. The investigators evaluated the various countries' adherence to the American College of Chest Physicians (ACCP) guidelines for anticoagulant prophylaxis that were published in *Chest* in 2004 for the 35,329 patients found to be at risk for VTE. While about 10% of at-risk patients were not treated because of justifiable contraindications, only about 50% of all patients at risk for VTE received ACCP-recommended prophylaxis. Orthopedic surgery patients were more likely than medical patients to be given appropriate prophylaxis. Only 37% of patients with active malignancy or ischemic stroke received proper prophylaxis. Adherence to ACCP guidelines ranged widely by country, with high percentages (approximately 60-90%) of medical and surgical patients appropriately treated in Germany and Switzerland and very low percentages (less than 5%) treated in Bangladesh and Thailand. The percentage of compliance often varied widely between medical and surgical patients. In the United States, 48% of at-risk medical and 71% of at-risk surgical patients received ACCP-recommended prophylaxis. Globally, including in the United States, a large proportion of hospitalized patients are at risk for VTE and recommended prophylaxis is underutilized.

Non-valvular atrial fibrillation (AF) is the leading cause of cardioembolic ischemic stroke. Most patients with AF are chronically treated with the vitamin K antagonist warfarin to decrease the risk of ischemic stroke. However the necessary dose adjustments and frequent monitoring, along with the not-insignificant risk of hemorrhagic complications, limits the use of warfarin, especially in the elderly or infirm. The Amadeus Investigators compared the efficacy and safety of idraparinux, a synthetic inhibitor of activated factor X, in a randomized, open-label, non-inferiority trial in patients with AF. Patients were randomized to receive either subcutaneous idraparinux (2.5 mg weekly) or vitamin K antagonists (warfarin or acenocoumarol), with a target INR of 2-3. With a mean follow-up period of less than a year, after approximately 2300 patients were randomized into each arm, the study was prematurely terminated because of an excess of clinically relevant bleeding in the subcutaneous idraparinux group. Treatment with subcuta-

neous idraparinux satisfied the non-inferiority criteria for efficacy as compared to vitamin K antagonists; however, treatment also was associated with a statistically significant increased risk of intracranial bleeding. Renal insufficiency and advanced age were associated with an elevated risk of hemorrhage with idraparinux.

Although warfarin remains the standard therapy for chronic anticoagulation, its use poses risk for patients who need an elective procedure or minor surgery. Continuing anticoagulation through the procedure risks bleeding, but interruption of therapy may result in thrombosis. If the possibility of thromboembolism is low, warfarin therapy may be withheld up to a week with minimal danger. However, ischemic stroke occurring after an anticoagulation hiatus is not uncommon. Bridging the interruption of warfarin with a short-acting anticoagulant, such as unfractionated heparin or low-molecular-weight heparin, may decrease the ischemic stroke risk, but adds to the cost and complexity of the procedure.

Garcia and colleagues performed a prospective, observational cohort study of patients whose warfarin therapy was temporarily withheld for an outpatient invasive procedure. In the 1024 individuals, generally at low to intermediate thromboembolic risk, from 101 sites in the United States, the most common indications for anticoagulation therapy were AF, VTE, or mechanical heart valve. The most common reasons for interruption of therapy were colonoscopy and oral and ophthalmic surgeries. Periprocedural bridging therapy was only used in around 8% of cases overall, and was more often associated with prosthetic valves than with AF. Seven patients, none with bridging, sustained 4 arterial and 3 venous thromboembolic events in the 30-day post procedural period. While 85% of the interruptions of therapy were for $\leq$ 5 days, a longer interval was associated with an increased thromboembolic risk. Bleeding, both major (6 patients) and non-major (17 patients), occurred in the 30-day post-procedural period; 14 of these 23 patients received periprocedural heparin or low-molecular-weight heparin. With interruption of therapy in patients at low to intermediate thromboembolic risk, the risk of periprocedural bleeding from bridging therapy must be weighed against the likelihood of thromboembolism.

COMMENTARY

Patients who are at risk of arterial or venous thromboembolism present challenges to physicians of multiple specialties. While high-dose anticoagulation may be temporarily suspended prior to surgery, low-dose prophylaxis against VTE should be standard for most immobilized post-operative patients, as well as for immobilized medical patients. The ACCP recommends that prophylactic low-dose subcutaneous heparin or low-molecular-weight heparins or heparinoids be used for the prevention of deep vein thrombosis and pulmonary emboli in patients with restricted mobility. Unfortunately, observance of these guidelines in the United States lags behind other countries. Unintentional oversight and unwarranted fear of bleeding decreases compliance with the recommendations and increases the risk of hospitalization of bed-bound patients. Stricter adherence to these guidelines should reduce the mortality and morbidity due to thromboembolism in hospitalized patients.

Temporary interruption of anticoagulation portends a period of peril for patients who are at risk of thromboembolism; however, with bridging therapy, risk may cross from an ischemic event to a hemorrhagic event. Discontinuation of anticoagulation for up to 5 days seems to confer minimal risk; however, unexpected periprocedural complications that prolong the break in therapy may increase thromboembolic risk.

As baby boomers age, their risk of AF and resultant arterial thromboembolism is increasing and cardioembolic stroke is becoming more prevalent. Options for chronic anticoagulation are currently limited and fraught with hazard. The chronic use of idraparinux as a substitute for warfarin is unlikely because of excess bleeding. The disappointing results with antagonists of activated factor X increases the interest in other alternatives to vitamin K antagonists including oral direct thrombin inhibitors, currently under investigation. The ongoing Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) trial comparing the efficacy and safety of two blinded doses of dabigatran with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular AF may offer an alternative to customary treatment of these patients.

For now however, no tenable alternative to long-term warfarin anticoagulation has shown equivalent efficacy and safety. More assiduous observance of VTE prophylaxis guidelines and the continuing search for alternatives to warfarin should decrease the major morbidity and mortality associated with arterial and venous thromboembolism. While the results of current investigation may be disappointing, there is hope for improved prevention of thromboembolism in the future.

Why Doesn't "Genetic" Epilepsy Seem to Run in Families?

ABSTRACT & COMMENTARY

By Cynthia L. Harden, MD

Professor of Neurology, Weill Medical College of Cornell University

Dr. Harden reports that she is involved with grant/research support for UCB and Eisai; is a retained consultant for GlaxoSmithKline; and is on the speaker's bureau for UCB, GlaxoSmithKline, and Pfizer.

Synopsis: *Genetic susceptibility to epilepsy is a complex, polygenetic matrix that is heavily influenced by environmental factors.*

Source: Heron SE, et al. Extended spectrum of idiopathic generalized epilepsies associated with CACNA1H functional variants. *Ann Neurol* 2007;62:560-568.

GENETIC VARIATIONS IN THE T-TYPE CALCIUM CHANNEL gene CACNA1H are known to be associated with childhood absence epilepsy. T-type channel gene CACNA1H variations may be associated with a broad range of epilepsy types, not as genes that impart epilepsy in a dominant Mendelian fashion, but clearly as permissive or susceptibility genes. This concept is supported by the observation that autosomal dominant epilepsies are extremely rare and have varied phenotypes even within families, and that some families with recurrent epilepsy have inheritance patterns that are difficult to sort out. Therefore, the genetic component of a familial epilepsy syndrome appears to be polygenic or complex, and the phenotype may be influenced by environmental factors.

Heron et al sought to explore the range of epilepsy syndromes associated with variations within this gene in a mixed group of epilepsy patients, and to determine what types of electrophysiological abnormalities were associated with the genetic variations. The investigators searched for variations in the gene CACNA1H among a group of 240 epilepsy patients (and 95 controls) with a broad mix of seizure types and epilepsy syndromes, including: generalized epilepsies such as juvenile myoclonic epilepsy, myoclonic/astatic epilepsy, focal epilepsies including temporal lobe epilepsy, febrile seizures, and generalized epilepsy with febrile seizures. Some patients were inter-related both within a generation and across generations; control subjects were anonymous blood donors. By direct gene sequencing, more than 100 amino acid variations were found, including 19 novel variants. The investigators determined that a subset of 11 of these variants could possibly result in a clinical effect. If the altered amino acid was a highly conserved site, this variation was thought to be an important genetic variation. Further, if the variation was partially co-segregated with an affected family member, absent in all control subjects, or in a region of known functional significance, it was chosen for further study. These 11 genetic variants were transfected into human embryo kidneys cells and the neurophysiologic characteristics of these cells were evaluated. Nine of the 11 genetic variants altered channel properties in a manner that would increase channel current; therefore, they elevated neuronal excitability and potentially permitted seizures. A range of phenotypes was associated with the same gene variant within a single family, with a trend toward more severe epilepsy in the presence of more than one variant within an individual.

The authors conclude that CACNA1H variations contribute to the manifestations of epilepsy, but are not sufficient to cause it. These susceptibility genetic variants, therefore, are an important influence on epilepsy occurrence; however, they would not be identified readily in a standard genome-wide case control study.

COMMENTARY

The investigators in this study embarked on a well-guided fishing expedition for CACNA1H variations among persons with epilepsy, some of whom were members of large families that had multiple members with epilepsy. Variations in CACNA1H are intriguing candidates for epilepsy susceptibility since they can cause channelopathies, the most promising and validated avenue for the pathogenesis of genetic epilepsy. In cells in which the gene variation was present, the majority of the candidate variations were associated with alterations in calcium currents.

The investigators performed a remarkable experiment that goes "from the clinic to the lab" and discovered that CACNA1H variations present in epilepsy patients may cause calcium current alterations that could be associated with epilepsy. One problem with this report is that the epilepsy population studied appears to be enriched for the occurrence of candidate epilepsy genes, in that there are multiple families with multiple phenotypes who previously have been studied for other epilepsy genes. Therefore, the study population is not representative of a general epilepsy population. One could not extrapolate from this investigation and deduce that so many candidate CACNA1H variations would be found in a population of consecutive epilepsy clinic patients.

What do these findings mean for the practitioner? This complicated and open-ended report raises more ques-

tions than it answers about the genetics of epilepsy. It points out, first of all, that epilepsy is not a simple disease imparted by one errant gene. There are many susceptibility genes, many of which relate to channelopathies, that influence the occurrence of epilepsy. These genes are not sufficient to cause epilepsy, but may be necessary to permit epilepsy in some individuals. This explains why some epilepsies can be "genetic" but not familial. Parents may carry the susceptibility genes, but this is not enough to cause epilepsy in them, while the combination (or further mutation) in the offspring may permit epilepsy.

Patients often ask "why" about their epilepsy, because in more than 50% of incident cases there is no known environmental risk factor or cause. For generalized epilepsies such as juvenile myoclonic epilepsy, the neurologist may reply that the epilepsy is likely to have a genetic component; this evidence has been emerging for the past two decades. But it is conceptually incongruous to the lay person that an illness could be both "genetic" and not "familial." Information from investigations such as this report demonstrate the complexity of epilepsy genetics, and the variability and ubiquity of epilepsy-influencing genes. This polygenic plus environmental matrix fits with the phenotype of variability of epilepsy even within families, and the broad range of susceptibility to seizures within families that in most cases appears sporadic.

Practitioners should accept and understand this complexity and share it with patients when they ask "why?" Such a conversation could start with the lack of known causes for epilepsy in an individual, and proceed to the likely presence of genetic influences that are complex and require multiple gene variations. Evidence suggests that this complexity applies to both generalized and partial epilepsies. Finally, the occurrence of epilepsy requires that multiple genes be present within an individual; therefore, the illness may not manifest in any other family members, although some may be carriers for susceptibility genes in subsequent generations. ■

CME Objectives

The objectives of *Neurology Alert* are:

• To present the current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;

• To discuss the pathogenesis and treatment of pain;

• To present basic science lessons in brain function;

• To discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs;

• To discuss nonclinical issues of importance to neurologists, such as the right to die and the physician's legal obligation to patients with terminal illness. ■

CME Questions

12. A study of metabolomic analysis as a potential biomarker for Parkinson disease (PD) found which of the following?

a. Decreased markers of oxidative stress in plasma from PD vs. control subjects
b. Increased plasma levels of urate in PD vs. control subjects
c. Separation of Parkinson disease metabolomic profiles from controls
d. Levodopa-specific changes in the metabolome

13. Moderate to heavy alcohol intake (>3 drinks per day) is associated with which of the following?

a. Increased risk of all stroke
b. Increased risk of hemorrhagic stroke
c. Both a and b
d. None of the above

14. Phrenic neuropathy:

a. may respond to topiramate.
b. cannot be documented by nerve conduction studies.
c. is almost always asymptomatic.
d. is usually bilateral.
e. None of the above

15. Disruptive behaviors in patients with Alzheimer's disease (AD):

a. predict a slow progression of disease.
b. respond well to neuroleptics.
c. often results in institutionalization.
d. are rare at the time of diagnosis.

16. Most forms of epilepsy are familial.

a. True
b. False

17. Genetic susceptibility to epilepsy can be determined by a whole genome scan.

a. True
b. False

18. Which of the following statements is correct?

a. Subcutaneous idraparinux is a safe and effective alternative to warfarin.
b. The appropriate use of prophylaxis against venous thromboembolism is more common in the United States than in European countries.
c. Antagonism of activated factor X appears to confer less risk of hemorrhage than antagonism of vitamin K.
d. The risk of thromboembolism increases with the length of time that anticoagulation is interrupted.
e. Bridging therapy is generally indicated in patients on chronic anticoagulation who undergo colonoscopy.

Answers: 12. c; 13. c; 14. a; 15. c; 16. b; 17. b; 18. d

In Future Issues: **Treatment of Traumatic Brain Injury**

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

FDA Heightens Warnings on Chantix

In this issue: *Stop smoking drug Chantix rates stronger warning from FDA; Type 2 diabetes surgery on the way?; Vytorin study inconclusive; Influenza A virus found resistant to Tamiflu; FDA actions.*

The FDA has strengthened its warning on the stop smoking drug varenicline (Chantix). Last November the agency issued an Early Communication regarding reports of changes in behavior, agitation, depressed mood, suicidal ideation, and suicidal behavior in patients taking the drug. After review of recent reports, the agency now says that it appears increasingly likely that there may be an association between varenicline and neuropsychiatric symptoms. The FDA has asked Pfizer, the manufacturer of the drug, to elevate the prominence of these warnings on the package label, and the company along with the FDA is working on a Medication Guide for patients. The FDA is recommending that patients should tell their health-care providers about any history of psychiatric illness prior to starting varenicline. There is evidence that the drug may cause worsening of current psychiatric illness, and cause old psychiatric illness to reoccur. Moreover health-care professionals, patients, patients' families, and caregivers should be alert to monitor for changes in mood and behavior in patients treated with varenicline. The FDA warning also states that vivid, unusual, or strange dreams may occur while taking the drug and that patients may experience impairment of the ability to drive or operate heavy machinery. Varenicline was approved in May 2006 under the trade name Chantix by Pfizer Pharmaceuticals to ease withdrawal symptoms associated with smoking cessation.

Weight-loss Surgery Answer for Type 2 Diabetics?

Could surgery be the answer for type 2 diabetes? In a new study from Australia, 60 patients with type 2 diabetes and a BMI of 30-40 were randomized to adjustable gastric banding surgery or conventional therapy. Conventional therapy focused on weight loss by lifestyle changes. The main outcome measure was remission of type 2 diabetes and secondary measures included weight and components of the metabolic syndrome. Remission of type 2 diabetes was achieved by 22 patients in the surgical group (73%) vs 4 patients in the conventional therapy group (13%). Relative risk for remission in the surgical group was 5.5 (95% CI, 2.2-14.0). Surgical patients lost more weight, mean (SD) 20.7% (8.6%) vs 1.7% (5.2%) for the nonsurgical group at two years (P <.001). There were no serious complications in either group. The average weight loss to achieve remission of type 2 diabetes was 10%, which was achieved in 86% of the surgical patients and only 1% of the medical therapy patients. The authors conclude that for patients with type 2 diabetes, surgical therapy was more likely to achieve remission through greater weight loss. These results should be confirmed through larger, more diverse population and have long-term efficacy assessed (*JAMA* 2008;299:316-323). An accompanying editorial suggests that gastrointestinal tract surgery may offer a new goal in diabetes management—remission rather than just treatment. The editorialists also suggest that the cost and risks of such surgery must be balanced

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with the costs and risks of long-term diabetes management (*JAMA* 2008; 299:341-343).

Vytorin Needs More Study

Vytorin has been in the news recently after Merck/Schering-Plough released the preliminary results of the Effect of Combined Ezetimibe and High-Dose Simvastatin vs Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) study. Vytorin is a combination of the statin simvastatin (Zocor) and ezetimibe (Zetia), a medication that blocks cholesterol absorption through the gut. The combination drug is better at lowering LDL than either drug alone, and it was hoped that this would translate to improved cardiovascular outcomes. ENHANCE randomized 720 patients with heterozygous familial hypercholesterolemia to treatment with either simvastatin 80 mg daily or Vytorin (simvastatin 80 mg plus ezetimibe 10 mg). Mean LDL cholesterol levels at baseline were 320 mg/dl. Simvastatin alone lowered LDL by 41% while Vytorin lowered LDL by 58%. The primary endpoint was change in mean carotid intima media thickness after two years of treatment. There was no difference in this primary endpoint or in the incidence of any adverse effects between the two treatment arms. ENHANCE was widely reported as a failure for Vytorin, and there were even reports that Vytorin increased the rate of plaque production, which was not the case. The study has been criticized because of its small size, atypical patient population, and primary outcome (carotid intimal media thickness) which is not a clinical outcome. The American College of Cardiology issued a statement on January 15 suggesting that "major clinical decisions not be made on the basis of the ENHANCE study alone." The FDA issued a statement on January 25 stating that it will conduct a review of Merck and Schering-Plough's trial once the final results of the study are available. Data from the ENHANCE study is due to be presented at the American College of Cardiology meeting in March.

Virus Resistant to Tamiflu Causing Concern

A small percentage of the influenza A virus causing illness worldwide this winter is resistant to oseltamivir (Tamiflu), according to the World Health Organization. Tamiflu-resistant forms have been found in European countries, Canada, and the US. Generally mutations of this sort attenuate the virus, making it less infectious; however this is not found be the case with the resistant strain of A/N1H1 known as A(H1N1 H274Y). The highest rate of resistance was found in Norway with 75% of isolated viruses showing resistance. The rate of resistance in the US was 3.8%. There are currently no plans to change recommendations for use of Tamiflu; however, WHO officials are "troubled by the discovery" according to the *New York Times*.

Choice of Antivirals for Flu

In other flu-related news, the CDC reports that primary care physicians frequently used inappropriate flu drugs during last year's flu season. A survey published in *MMWR* found that of 730 respondents, 54% prescribed anti-viral agents and of those, one quarter prescribed amantadine or rimantadine. These drugs are no longer recommended because of a high rate of viral resistance (MMWR 1/25/08:57(03); 61-65). Finally, the FDA has approved a real-time test for influenza A and B and RSV. The test, called ProFlu+ Assay produces results within about three hours, and has a 98% sensitivity, and 83% specificity. The assay is marketed by Prodesse Inc.

FDA Actions:

The FDA has strengthened its warning on the contraceptive patch Ortho Evra regarding the risk of venous thromboembolism. The warning is based on a study conducted by the Boston Collaborative Drug Surveillance Program that showed that the patch was associated with a higher risk of venous thromboembolism than oral contraceptive pills.

The FDA has taken the strongest stance yet against the use of over-the-counter cough and cold products for children younger than two years of age. On January 17 the agency issued a Public Health Advisory for parents and caregivers recommending that the products should not be used to treat infants and children because of reports of serious adverse events including death, convulsions, rapid heart rates, and decreased levels of consciousness. The agency continues to review use of these medications on children aged two to 11.

The FDA has warned seven pharmacy operations that produce "bio-identical hormone replacement therapy" that claims of their products' effectiveness may be false and misleading because they are not supported by medical evidence. These products are frequently compounded by large pharmacy operations and contain estrogen, progesterone, and estriol. Claims range from reduced risk of stroke, cancer, and lower rates of Alzheimer's disease associated with products. Compounded drugs are not reviewed by the FDA for safety and effectiveness however misleading claims violate federal laws. The FDA considers the term "bio-identical" a marketing term which implies benefit for which there's no medical or scientific basis. Compounding pharmacy that do not address these violations are subject to further enforcement according to the FDA press release. ■