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INSIDE

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Pregnancy and Ischemic Stroke: Is Thrombolysis an Option?

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD

Associate Professor, Clinical Neurology, Weill Medical College, Cornell University

Dr. Jamieson is a consultant for Boehringer Ingelheim and Merck, and is on the speaker's bureau for Boehringer Ingelheim, Merck, Ortho-McNeil, and Pfizer.

Synopsis: *rtPA thrombolysis may be used safely in pregnant women.*

Source: Murugappan A, et al. Thrombolytic Therapy of Acute Stroke During Pregnancy. *Neurology*. 2006;66:768-770.

Pregnancy is a prothrombotic state which is rarely associated with ischemic arterial stroke. However, when a stroke occurs, especially in later pregnancy, the options for therapy may be limited. The additional consideration of fetal outcome complicates therapy of the mother, and pregnancy has generally been considered a contraindication for thrombolysis. The confidence and experience in the use of thrombolysis in acute ischemic stroke has increased in the past decade. Although the 3-hour window has remained the standard for intravenous (IV) delivery of recombinant tissue plasminogen activator (rtPA), intra-arterial (IA) delivery has expanded the treatment time and population. The drug is pregnancy category C (unknown safety), with concerns about fetal and maternal hemorrhage risk and teratogenicity. However, animal data have not indicated associated fetal anomalies, and the large molecule does not cross the placenta. Several papers published in 2006 have illustrated that women at different stages of pregnancy can be treated with thrombolysis, either IV or IA, without excess risk to the patient, and with the potential of a viable pregnancy.

Earlier in the year in *Neurology*,[1] a series of 8 patients who underwent IV or IA thrombolytic treatment of ischemic stroke was reported. Half of the patients were treated with urokinase, as opposed to rtPA, and 2 patients had venous, rather than arterial, thrombosis.

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There was one fatal complication from angioplasty (with death of the fetus), and 3 pregnancies were medically terminated. Two healthy babies were delivered. There was one spontaneous first trimester abortion, as well as a fetal demise due to lethal chromosome abnormalities. Murugappan and colleagues reviewed the medical literature and noted that in the mainly non-stroke related cases of thrombolysis during pregnancy, the premature delivery rate was not increased. There was no indication of teratogenicity.

Case reports note success with the treatment. A woman, 13 weeks pregnant, on subcutaneous heparin because of a mechanical mitral valve, was given standard protocol IV rtPA for a left middle cerebral artery infarct.[2] She was restarted on warfarin for the rest of her uncomplicated pregnancy, and she delivered a healthy baby at 37 weeks.

In a review article of 28 published cases of treatment with rtPA in pregnancy,[3] 10 women with stroke were identified. Six of the cases were from an abstract of the recently published paper noted above.[1] One woman with cerebral sinus thrombosis was treated successfully with thrombolysis, and had an uneventful delivery. In the remaining 3 cases (2 IV, one IA), there was good neurological recovery in 2 of the women, and 3 healthy babies were delivered. In the remaining cases where rtPA was given for thrombosed prosthetic cardiac valves, pulmonary embolism, or deep vein thrombosis, fetal complications were rare, and felt to be related to the underlying maternal condition, not the thrombolytic therapy. An addendum to the review article reported a woman with a left middle cerebral artery stroke at 23 weeks, treated with IV rtPA, with variable neurological recovery. She delivered successfully at 33 weeks.

Arterial and venous infarcts can be neurologically devastating during pregnancy, with concern about the outcome of both the patient and fetus. While experience with the use of rtPA during pregnancy is still limited, these reported successes encourage the consideration of rtPA in pregnant women with ischemic stroke. As experience with thrombolysis in acute stroke increases, pregnancy does not appear to be an absolute contraindication, especially in the absence of other effective alternatives. Without specific guidelines for its use in pregnancy, the guidelines for rtPA use in general should apply to the woman who suffers an acute ischemic stroke during pregnancy. ■

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Questions & Comments

Please call **Leslie Hamlin**, Associate Managing Editor, at (404) 262-5416.

Do Sleeping Pills Work?

ABSTRACT & COMMENTARY

By Charles P. Pollak, MD

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Dr. Pollak is a stockholder for Merck, and is on the speaker's bureau for Merck.

Synopsis: *Behavioral therapy is effective in improving sleep efficiency, but the sleeping pill zopiclone is no better than placebo.*

Source: Sivertsen B, et al. Cognitive Behavioral Therapy vs Zopiclone for Treatment of Chronic Primary Insomnia in Older Adults: A Randomized Controlled Trial. *JAMA*. 2006; 295:2851-2858.

When patients complain that they have difficulty getting to sleep or returning to sleep when they awaken during the night, the usual response is a prescription for a sleep aide. A prescription for a hypnotic agent is also the expectation of most patients when they seek help. Both doctor and patient are confident that the prescription is for an FDA-approved hypnotic of proven efficacy, and reasonably free of adverse effects,

including the risk of developing dependency on the drug. If the provider is conscientious, he or she instructs the patient not to take the medication for more than a few weeks and not to increase the dose, if its effect should diminish with time. Alternatives to hypnotic medications are perhaps most often provided if depression or other affective disorder is present.

Now *JAMA* presents us with a well-designed, controlled trial from Norway comparing 7.5mg zopiclone, a modern, non-benzodiazepine hypnotic with a suite of nonpharmacological treatment modules termed cognitive behavioral therapy (CBT) with placebo medication. CBT comprises sleep hygiene education (effect on sleep due to exercise, alcohol, etc), sleep restriction (strict schedule of bedtimes and rising times), stimulus control (limiting the bed and bedroom for sleep), cognitive therapy (correct mistaken beliefs regarding sleep and sleep loss), and progressive relaxation technique (controlling muscle tension). The study subjects were 46 men and women aged 55 or older, with difficulty initiating and maintaining sleep for at least 3 months, along with impaired daytime functioning. Excluded were those with dementia, major depression, sleep apnea, night-shift work, and hypnotic medication use. Subjects were divided into 3 roughly equal groups, and randomly assigned to one of the 3 treatments. Sleep was assessed polysomnographically (PSG) in the subjects' own homes, as well as with sleep diaries.

Sleep was assessed before treatment, after 6 weeks of treatment, and after 6 months. In the CBT group, mean sleep efficiency (proportion of time in bed spent sleeping) improved from 81.4% to 88.9%, and was more than maintained at 6 months (90.1%). Wake time decreased from 107.8 minutes before treatment to 51.4 minutes post-treatment and 47.1 min at 6 months. These dramatic differences were seen in both the objective (PSG) and sleep-diary data. Though total sleep time did not increase in response to CBT, time spent in slow-wave sleep sharply increased at post treatment and at 6 months.

In the zopiclone group, by contrast, the only improvements were in subjective (sleep diary) measures of sleep efficiency, total wake time, and total sleep time. For most outcomes, zopiclone did not differ from placebo.

COMMENTARY

These are not the first experimental findings demonstrating the efficacy of CBT. In my opinion, it is the restriction and regularization of time spent in bed that account for most of the benefit of CBT. In line with this, it was total wake time that most improved, not total sleep time. By instructing a patient to get out of bed when awake, the experience of insomnia—of lying in bed awake—is sharply and promptly reduced. Likewise, this is not the first demonstration of the lack of efficacy for hypnotic drugs, especially for treatment of chronic insomnia. Sivertsen and colleagues speculate that tolerance may have developed to the beneficial, short-term effects of zopiclone.

Zopiclone is not available in the United States, but is the most commonly prescribed hypnotic in Norway. It is a racemic mixture of 2 stereoisomers, one of which is eszopiclone, which is marketed and heavily advertised in the United States under the brand name Lunesta. The 7.5 mg dose used in this study is equivalent to 3.75 of eszopiclone—somewhat larger than the largest 3 mg dose form of Lunesta. Both zopiclone and eszopiclone are promoted as nonbenzodiazepines. They are, however, active at the benzodiazepine/GABA receptor. Reports of drug misuse and dependence on zopiclone have recently been reported after as little as 2 weeks of use. It is listed by the DEA under Schedule IV.

It is timely to remind practitioners who encounter insomniac patients that even the new, nonbenzodiazepine hypnotics have a limited duration of efficacy and a finite risk of drug misuse and dependence. Behavioral methods appear to be more lastingly effective and certainly safer. ■

The Clinical Spectrum of Mitochondrial POLG Mutations

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, DPhil

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Dr. Henchcliffe is on the speaker's bureau for GlaxoSmithKline, Teva/Eisai, and Boehringer Ingelheim

Synopsis: *POLG mutations result in an expanding array of phenotypes, from childhood encephalopathy to milder, later-onset of combinations of ataxia, epilepsy, myopathy, and progressive external ophthalmoplegia.*

Sources: Horvath R, et al. Phenotypic Spectrum Associated with Mutations of the Mitochondrial Polymerase Gamma Gene. *Brain*. 2006;129:1674-1684; Tzoulis C, et al. The Spectrum of Clinical Disease Caused by the A467T and W748S POLG Mutations: A Study of 26 Cases. *Brain*. 2006;129:1685-1692.

THE CLINICAL HETEROGENEITY OF MOST MITOCHONdrial disorders presents a diagnostic challenge to clini-

cians and geneticists. Two European studies have now identified the largest cohorts, to date, of individuals with mutations in the mitochondrial DNA polymerase gamma gene (POLG). Horvath and colleagues selected a large patient collection for genetic testing from several diagnostic centers based upon clinical findings of progressive external ophthalmoplegia (PEO), ataxia, or Alpers syndrome (children with developmental delay, refractory seizures, and liver failure), in the context of biochemical evidence of compromised mitochondrial function. They then carefully characterized those individuals who tested positive for POLG mutations. Age of symptom onset ranged from 6 months to 63 years. Despite overlap in presentations, 3 clinical groups were identified: a) childhood onset of fluctuating encephalopathy hepatopathy (n = 14, 90% male); b) PEO with limb myopathy, often in association with ataxia and sensorimotor neuropathy, usually with adult onset (n = 19, 53% male); and c) adult onset myopathy or ataxia without PEO (n = 5). Of those with childhood onset encephalopathy, 10/14 developed liver failure. Importantly, abnormal liver function followed sodium valproate treatment for seizures in 5 of these children, and mortality was high. No relevant family history could be elicited in 66% of those identified with POLG mutations.

Overall, a total of 89 different mutations were found in 38 patients. The A467T mutation was found in 12/19 cases presenting in childhood. In a complementary study focusing on specific POLG mutations (A467T and W748S), Tzoulis and colleagues describe clinical features in 26 patients belonging to 20 families, mostly from Norway. Age of symptom onset was more restricted (2-36 years). However, phenotypes overlapped with the prior study. Initial manifestations were epilepsy (n = 13), headaches (n = 7), and progressive gait unsteadiness (n = 6). Most developed a combination of epilepsy (n = 22) with status epilepticus, resulting in death in 9. They also developed headaches (n = 23), ataxia (n = 23), sensorimotor neuropathy (n = 25), and ptosis or progressive external ophthalmoplegia (n = 12). Liver failure was a cause of death in 2 and, as in the prior study, was associated in some with administration of sodium valproate. Brain MRI was abnormal in the majority, with high signal lesions on T2, or FLAIR sequences present variably in the occipital lobes, deep cerebellar nuclei, thalamus, and basal ganglia.

COMMENTARY

The POLG mutations described lead to a broad clinical picture ranging from a severe and rapidly progressive hepatocerebral syndrome with high early childhood mortality, to more slowly progressive and milder adult syndromes, such as isolated neuropathy. Although we have yet to understand the full spectrum of this disorder, both papers provide important new descriptive information and, impressively, discern patterns of symptoms that provide diagnostic clues. In addition, Horvath et al suggest a diagnostic algorithm to aid clinicians in navigating their way to a referral for molecular diagnosis. In this algorithm, it is suggested that children with classical Alpers syndrome be screened specifically for the A467T mutation, reserving more extensive sequencing for those who test negative in at least one POLG allele. In the absence of liver failure, or in more complex multi-system disorders, Horvath et al suggest muscle biopsy to quantify mitochondrial DNA prior to considering genetic testing. In adults, the algorithm is less helpful, with suggested muscle biopsy for those with "PEO/unexplained multi-system neurological disorder or isolated neurological disorder with a relevant family history," an unfortunately broad array of disorders. However, in adults, any combination of ataxia, PEO, myopathy, or sensorimotor neuropathy without other explanation should raise clinical suspicion of mitochondrial disease, such as an underlying POLG mutation. Brain MRI abnormalities may provide a tip off, and then following up, as Horvath et al suggest, with muscle biopsy, regardless of MRI results, may be indicated. Ultimately, diagnosis will depend upon an appropriate level of clinical suspicion, making detailed clinical descriptions, such as those presented in these papers, invaluable. ■

Oral Anticoagulation for Stroke Prevention in Patients with Atrial Fibrillation

ABSTRACT & COMMENTARY

By Matthew E. Fink, MD

Vice Chairman, Professor of Clinical Neurology, Weill Cornell Medical College; Chief, Division of Stroke and Critical Care Neurology, NewYork-Presbyterian Hospital

Dr. Fink reports no financial relationship relevant to this field of study.

Synopsis: *Warfarin remains superior to antiplatelet agents for stroke prevention in patients with atrial fibrillation.*

Source: Connolly S, et al. Clopidogrel Plus Aspirin versus Oral Anticoagulation for Atrial Fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W): A Randomized Controlled Trial. *Lancet*. 2006;367:1903-1912.

In the 1980s, primarily from the Framingham Study, atrial fibrillation (AF) was a clearly established

major risk factor for stroke and other cardioembolic vascular events. In the 1990s, several randomized clinical trials established the efficacy of vitamin K-dependent oral anticoagulants (warfarin and other coumarins) in preventing stroke from AF, and also demonstrated its superiority over aspirin. However, because of the difficulty in managing patients who are taking oral anticoagulants (OA), and the reluctance of many patients to undergo frequent blood tests and physician visits, there is a continuing desire to find a simple and safe regimen as an alternative to OA.

Connolly and colleagues compared the effectiveness of aspirin (75-100 mg per day) plus clopidogrel (75 mg per day) versus OA with a coumarin agent. Patients were enrolled if they had AF plus one or more risk factors for stroke—age 75 years or older, treatment for hypertension, previous stroke, TIA, non-CNS embolus, decreased left ventricular ejection fraction, peripheral arterial disease, diabetes mellitus, or coronary artery disease. They were randomly allocated to receive OA (target INR, 2.0-3.0; n = 3371) or clopidogrel plus aspirin (n = 3335). Primary outcome was the first occurrence of stroke, non-CNS systemic embolism, myocardial infarction, or vascular death.

The study was stopped early because of clear evidence for superiority of OA over combined antiplatelet therapy. There were 165 primary events in the OA group (annual risk = 3.93%) and 234 in the aspirin/clopidogrel group (annual risk = 5.6%), with an increased relative risk of 1.44 (1.18-1.76; $P = 0.0003$). In addition, there was no significant difference in overall bleeding complication rates between the 2 groups. Patients who were already on OA therapy, and were maintained on OA, had the best overall therapeutic response, with the lowest rate of primary events, and the lowest rate of bleeding complications.

COMMENTARY

In the quest for a safer and better oral antithrombotic treatment to prevent stroke in patients with AF, warfarin and its relatives still come out on top when compared to combination therapy with aspirin and clopidogrel. It is projected that the number of people with AF will double by the year 2050 and, therefore, neurologists will be treating more patients who have stroke and TIA with some form of OA. The good news from the ACTIVE study is that the annual rate of stroke in the aspirin/clopidogrel group was 2.4%; much lower than in other studies that looked at aspirin alone. It is likely that better management of all risk factors has resulted in an overall reduction in stroke rates in patients with AF, and this finding should give us hope and optimism for the future.

Idiopathic HyperCKemia

ABSTRACT & COMMENTARY

By Michael Rubin, MD

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Dr. Rubin is on the speaker's bureau for Athena Diagnostics, and does research for Pfizer and Merck.

Synopsis: Persistent elevation of serum CK without symptoms should be aggressively investigated, including a muscle biopsy, since half will have HyperCKemia, and half will have a specific pathology.

Source: Capasso M, et al. Familial Idiopathic HyperCKemia: An Underrecognized Condition. *Muscle Nerve*. 2006; 33:760-765.

Persistently elevated serum creatine kinase (CK) raises the specter of myopathy, although idiopathic hyperCKemia (IH) may ultimately be the final diagnosis. Not as well recognized is a familial variant that may be more frequent than previously appreciated. Among 1100 neuromuscular patients seen over an 11-year period, 42 were felt to have probable IH based on persistent serum CK elevation, normal neurological examination, no history of myotoxic drug intake, no exercise-induced muscle cramps or myoglobinuria, no family history of myopathy or malignant hyperthermia, normal basic blood chemistry and thyroid function, normal electrodiagnostic studies, normal or nonspecific muscle biopsy changes, and normal dystrophin immunohistochemistry. Of these 42, 4 each were excluded because their muscle tissue was no longer available for further analysis, or because reduced calpain-3 was found on Western blot, leaving 34 subjects with the possibility of IH. Laboratory information was available on relatives for 28 of these 34, with 13 families demonstrating designated hyperCKemia (FIH) in at least one member, thus constituting the substance of this report.

Mean age among FIH cases was 37 ± 3.4 years. Men were found to have hyperCKemia more often than women. Few subjects complained of muscle pain or fatigue (n = 5; 12%). Neurological examination was reportedly normal in all. Maximum CK ranged from 1.2-7.7 times the upper limit of normal. Among 12 patients seen 2-8 years after initial biopsy, examination and needle electromyography remained normal, and CK was unchanged. Calveolin-3 mutations were not found in 5 families studied. FIH is benign and, in 60% of patients, is autosomal dominant with a high male penetrance.

COMMENTARY

Aggressive evaluation of what otherwise appears clinically to be benign hyperCKemia will yield a probable or definitive diagnosis in the majority. Among 104 asymptomatic (n = 50) or minimally symptomatic (n = 54, muscle pain, cramps, fatigue) patients with elevated creatine kinase (> 500 UI/L) and no muscle weakness, muscle biopsy revealed a diagnosis in 55% (*Neurology*. 2006;66:1585-1587). Glycogen storage diseases, muscular dystrophies, and inflammatory myopathy were the most frequent diagnoses, and diagnosis was more likely in children with higher CK levels. When in doubt, don't give up!

Can Non-Invasive Imaging Differentiate Benign from Malignant Brain Tumors?

ABSTRACT & COMMENTARY

By Andrew B. Lassman, MD

Assistant Attending, Department of Neurology, Memorial Hospital for Cancer and Allied Diseases

Dr. Lassman reports no financial relationship relevant to this field of study.

Synopsis: *When biopsy of a brain tumor is not possible due to high surgical risk, perfusion MRI can help distinguish tumor types with high sensitivity and specificity.*

Source: Weber MA, et al. Diagnostic Performance of Spectroscopic and Perfusion MRI for Distinction of Brain Tumors. *Neurology*. 2006;66:1899-1906.

THE AVAILABILITY OF AN ACCURATE, NON-INVASIVE test for diagnosing tumors of the brain is a holy grail of neuro-oncology. Two tests currently in use or development include magnetic resonance spectroscopy (MRS) and magnetic resonance perfusion (MRP). MRS analyzes metabolic signatures to differentiate necrosis, tumor, or demyelination from normal brain and each other. Various subsets of MRP imaging analyze relative cerebral blood flow, based on the premise that high-grade tumors will exhibit increased cerebral perfusion relative to low-grade tumors, normal brain, and necrosis.

Weber and colleagues performed MRS and MRP on 79 consecutive patients with newly diagnosed primary or metastatic brain tumors, and correlated findings with histology. MRP was superior to MRS, possibly because of false spectroscopic signals resulting from analysis of necrotic areas within high grade gliomas. The sensitivity of MRP for differentiating various lesions from each other was well over 90% in several instances, such as glioblastomas vs CNS lymphomas and glioblastomas vs metastases. However, the specificity in these comparisons did not exceed 80%. While the sensitivity is impressively high, the sensitivity remains too low for routine replacement of biopsy in diagnostic evaluations. Similar results were obtained when attempting to differentiate high grade from medium- and low-grade gliomas.

COMMENTARY

Histological confirmation by a trained neuropathologist remains the gold standard for diagnosis of mass lesions in the brain. However, for patients with surgically inaccessible tumors or with significant comorbidities that increase the risks of surgical intervention, MRP is an important advance that may allow therapeutic planning in the absence of histology in the context of a high false negative rate. An additional question, not addressed in this study, is the utility of MRP (and MRS) in evaluating response of brain tumors to novel anticancer drugs. Several ongoing studies are using MRP to assess the molecular effects of pathway inhibitors on brain tumors, when obtaining tissue during therapy is difficult or impossible for both practical and ethical reasons.

β-Amyloid Plaque Load Correlates with Brain Atrophy in Alzheimer's Disease

ABSTRACT & COMMENTARY

By Gunnar Gouras, MD

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Dr. Gouras reports no financial relationship relevant to this field of study.

Synopsis: *This study on patients with a diagnosis of mild-to-moderate Alzheimer's disease demonstrated a positive correlation of brain β-amyloid load using 11C-PIB positron emission tomography with the rate of brain atrophy using serial volumetric MRI.*

Source: Archer HA, et al. Amyloid Load and Cerebral Atrophy in Alzheimer's Disease: An (11)C-PIB Positron Emission Tomography Study. *Ann Neurol*. 2006;60:145-147.

ALZHEIMER'S DISEASE (AD) IS THE LEADING CAUSE OF dementia, and increases in life expectancy are

placing an ever greater burden on our health care system. β-amyloid peptides, the principle components of the characteristic amyloid plaques that accumulate in the brain with AD, have been increasingly linked to the pathogenesis of the disease. The relative contribution of β-amyloid in AD has been an area of controversy. Rare autosomal dominant familial forms have been found, with mutations that directly elevate β-amyloid, but the relevance of β-amyloid in the more-typical late onset form of the disease has been less certain. This report on a small number of patients with a diagnosis of mild-to-moderate AD provides important new support for the relationship of β-amyloid accumulation and more typical late-onset AD. Brain atrophy is a well established component of the disease that is thought to occur from the progressive destruction of nerve cells. Archer and colleagues demonstrated a positive correlation between the rate of brain atrophy, assessed by 2 MRI scans taken at a mean interval of 12.8 months apart, to the regional uptake on PET of 11C-PIB, a thioflavin-based radioligand that has been shown to detect amyloid plaques in patients with AD (Klunk WE, et al. Imaging Brain Amyloid in Alzheimer's Disease with Pittsburgh Compound-B. *Ann Neurol*. 2004;55:306-319).

COMMENTARY

The emergence of a PET imaging method to detect AD pathology in patients has been an exciting development, with implications both for diagnosis and as a non-invasive method to visualize amyloid plaques in vivo in therapeutic clinical trials. The seminal work by Alzheimer a century ago had correlated dementia with the accumulation of plaques and neurofibrillary tangles, composed of paired helical filaments of the microtubule protein, tau. Although AD is diagnosed at autopsy by the pathological presence of a sufficient number of plaques and tangles, plaque load has been a poor correlate of cognitive impairment. Moreover, the abundance of cerebral plaques in some individuals, without a known history of dementia, has led some to doubt whether β-amyloid can be used as a measure of disease progression. At the same time, transgenic mouse models of β-amyloidosis have reproduced many of the pathological and behavioral features of the human disease and, increasingly, reduction of β-amyloid has become a leading target of emerging experimental therapies for AD.

This combined 11C-PIB PET and serial volumetric MRI brain study strengthens the feasibility of amyloid imaging as a measure of disease progression and, secondarily, supports the validity of PET amyloid imaging for therapeutic clinical trials in AD. Amyloid load correlated with rate of brain atrophy, reflecting neurodegeneration. But several weaknesses of this study should be noted. First, only 9 patients with a diagnosis of mild-to-moderate AD were studied, and 2 with mild dementia had normal 11C-PIB uptake; these 2 individuals also had no decline on follow-up cognitive testing and were eventually thought not to have AD. Second, the timing of the PET scan was not optimal, ranging from before the first MRI to after the last MRI, with a mean of 7.6 months from the midpoint between MRI scans. Nevertheless, this is an important study that strengthens both the amyloid cascade hypothesis and PET amyloid imaging as a measure of disease progression in AD.

How Long is the Incubation Period for Prion Diseases?

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Medical College, Cornell University

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

Synopsis: *The incubation period for the prion disease Kuru can be very long in some cases and suggests that the risk for development of new cases of variant Creutzfeldt-Jakob disease will continue for quite some time.*

Source: Collinge J, et al. Kuru in the 21st Century—An Acquired Human Prion Disease with Very Long Incubation Periods. *Lancet*. 2006;367:2068-2074.

Prion diseases are caused by the accumulation in the brain of an abnormally configured isoform of an intrinsic protein, termed prion protein (PrP). Much attention has been devoted to the variant form of Creutzfeldt-Jakob disease (vCJD), which is caused by dietary exposure to meat from cattle infected with bovine spongiform encephalopathy (BSE), known to the general public as Mad Cow Disease. The first human prion disease to be described was Kuru, an epidemic which occurred in a defined population from Papua, New Guinea, who contracted the disease via human-to-human transmission through ritual cannibalism. Kuru is a progressive cerebellar syndrome that is invariably fatal. Collinge and colleagues attempted to characterize the incubation period of Kuru by

studying cases identified between 1996 and 2004. They argue that the ritual of cannibalism was virtually eliminated by 1960, so that cases appearing in the study period would have a prolonged minimum incubation period. Eleven cases were identified in the study period, all born well before 1960. The minimum incubation period for these cases ranged from 34-41 years, with a likely incubation period of 39-55 years. Of the 10 cases tested, 8 were heterozygous at polymorphic codon 129 of the PrP gene. Heterozygosity at this codon is known to protect against development of Kuru and prolong the incubation period in cases that eventually occur. All documented cases of vCJD in humans are homozygous for methionine at this codon, which is known to increase susceptibility to Kuru as well. Collinge et al conclude that the incubation period of Kuru is very long in some cases, and is partially explained by genetics. They suggest that the incubation period of human BSE infection may also be quite prolonged in some cases, especially due to the less efficient cross-species transmission of BSE compared to the intra-species transmission of Kuru.

COMMENTARY

vCJD was first identified in the United Kingdom in 1996, raising serious public concerns about the safety of the cattle supply. Cattle most certainly acquired BSE through dietary consumption of infected tissue and, in response to the BSE and vCJD epidemic, this practice was stopped. This is analogous to the history of Kuru, where the ritual cannibalism was stopped over a brief, defined period of time. Despite the fact that the cannibalism was stopped, cases of Kuru continued to appear many decades later. The majority of these cases were heterozygous at codon 129 of the PrP gene, which is protective against prion disease. Considering that all cases of vCJD up to this time are homozygous for methionine at this codon, there may be a later peak of cases of vCJD in the heterozygous population. Fifty-one percent of Europeans are heterozygous at this codon. Although the source of human BSE infection has been almost completely eliminated, the burden of vCJD will likely persist for decades, as new cases present with a prolonged incubation period. Neurologists should, therefore, continue to be trained to recognize the presenting signs of vCJD, and realize that the demographics of the disease onset may shift to an older population.

CME Questions

6. Recombinant tissue plasminogen activator treatment during pregnancy:
a. crosses the placenta, explaining its teratogenic effect.
b. has been shown to increase risk of fetal intraventricular hemorrhage.
c. has been delivered intravenously without increased fetal risk.
d. should only be considered for intra-arterial therapy in acute ischemic stroke.
e. has been linked to increased risk of placental hemorrhage.

7. All of the following are common in adults with POLG mutations *except*:
a. Ataxia
b. Progressive external ophthalmoplegia
c. Myopathy
d. Encephalopathy
e. Neuropathy

8. 11C-PIB positron emission tomography (PET) imaging correlated with rate of brain atrophy by serial volumetric MRI in patients with Alzheimer's disease. In the brain, (11)C-PIB binds to:
a. neurofibrillary tangles.
b. amyloid plaques.
c. synapses.
d. blood vessels.

9. Which of the following best characterizes a prion?
a. A small virus
b. A bacterial pathogen
c. A parasitic organism
d. An abnormally configured protein
e. A hyperphosphorylated molecule

Answers: 6. (c); 7. (d); 8. (b); 9. (d)

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; and

• 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.

In Future Issues:

Status Epilepticus in Children

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

CUMULATIVE INDEX

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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.

The Safety of Long-Acting Beta Agonist Inhalers

Do long-acting beta agonist inhalers increase the severity of asthma? Yes, according to the results from a large meta-analysis recently published in the *Annals of Internal Medicine*. Pooled data from 19 trials with nearly 34,000 participants found that the long-acting beta agonists salmeterol, formoterol, and eformoterol were associated with higher rates of asthma exacerbations, requiring hospitalization, (odds ratio 2.6 [95% CI, 1.6-4.3]) and life-threatening exacerbations (odds ratio 1.8 [CI, 1.1-2.9]), compared to placebo. In subgroup analyses, the odds ratio for hospitalizations was 1.7 for salmeterol and 3.2 for formoterol. The risk of hospitalization was especially high in children on long-acting beta agonists (odds ratio 3.5 [CI, 1.3-9.3]). The odds ratio for adults was 2.0 (CI 1.1-3.9). Although the rate of death was low, the odds ratio for asthma-related death was 3.5 (CI, 1.3-9.3).

In the largest of the studies included in the meta-analysis, the Salmeterol Multicenter Asthma Research Trial (SMART), in which 26,000 patients were followed for 6 months on salmeterol or placebo, there was a 2-fold increase in life-threatening asthma exacerbations and a 4-fold increase in asthma related deaths. The authors conclude that long-acting beta agonist use increases the risk of hospitalizations due to asthma, life-threatening asthma exacerbations, and asthma-related deaths. The authors also conclude that inhaled corticosteroids cannot adequately protect against the adverse effects of these drugs (*Ann Int Med*. 2006;144:904-912).

An accompanying editorial suggests that physicians should follow current guidelines which emphasize use of inhaled corticosteroids as the first-line treatment for patients with mild-to-moderate persistent asthma. Only after maximal corticosteroid doses have been reached should long-acting beta agonist be considered (*Ann Int Med*. 2006;144:936-937).

The FDA met one year ago to discuss long-acting beta agonist and required black box warnings on the labeling for these drugs; however, there usage has changed very little in the ensuing year.

Treating Chronic Primary Insomnia

Cognitive behavioral therapy is more effective than zopiclone for the treatment of chronic primary insomnia in older adults, according to a new study from Norway. In a randomized, double-blind, placebo-controlled trial, 46 adults (mean age, 60.8; 22 women) with chronic primary insomnia were randomized to cognitive behavioral therapy, sleep medication with zopiclone 7.5 mg each night, or placebo for 6 weeks. The cognitive behavioral therapy consisted of 6 weekly sessions lasting 50 minutes that covered sleep hygiene education, sleep restriction, stimulus control, cognitive therapy, and progressive relaxation techniques. The main outcome was

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polysomnographic data and sleep diaries, which were used to determine total wake time, total sleep time, sleep efficiency, and slow-wave sleep.

Cognitive behavioral therapy (CBT) resulted in improved short-term and long-term outcomes compared with zopiclone on 3 of 4 outcome measures. CBT improved sleep efficiency from 81.4% to 90.1% at 6-month follow-up compared to a decrease from 82.3% to 81.9% with zopiclone. CBT resulted in better sleep architecture and less time awake during the night. Total sleep time was similar in all 3 treatment groups but, at 6 months, patients receiving CBT had better sleep efficiency than those taking zopiclone. The authors conclude that cognitive behavioral therapy is superior to zopiclone for management of insomnia, both in the short term and long-term. For most outcomes, zopiclone did not differ from placebo (*JAMA*. 2006;295:2851-2858).

Zopiclone is a new generation sleep medication available in Europe. The active isomer of zopiclone has been available in the United States since April 2005 (eszopiclone - Lunesta).

New Breakthrough in Smoking Cessation?

Varenicline, Pfizer's new smoking cessation drug, is the subject of 3 articles in the July 5 issue of *JAMA*. The drug, which is a partial agonist of the 4 2 nicotinic receptor, blocks the action of nicotine but provides a lower level of stimulation of dopamine release to reduce craving and withdrawal symptoms. Two of the 3 articles compared varenicline to bupropion and placebo in combination with behavioral counseling over 12 weeks of treatment. In both studies, varenicline was significantly more effective than placebo or bupropion (*JAMA*. 2006;296:47-55, 56-63). In the third study, 12 more weeks of varenicline was found to be significantly more effective than placebo in maintaining abstinence. This study also found that after 24 weeks of treatment, the benefit of the drug was maintained up to one year (*JAMA*. 2006;296:64-71). An accompanying editorial points out that while the studies of varenicline are promising and the drug represents a new agent with a different mechanism of action, it is not a panacea for smoking cessation, with quit rates still under 50% in these studies (*JAMA*. 2006;296:94-95). These studies could not come at a better time for Pfizer, as the company plans to market the drug within the next few months under the trade name Chantix.

FDA Actions

The FDA has given Biogen-Idec approval to resume marketing natalizumab (Tysabri) for the treatment of relapsing forms of multiple sclerosis. The monoclonal antibody was initially marketed in November 2004, but was withdrawn four months later, after three patients developed progressive multifocal leukoencephalopathy (PML) in clinical trials. Subsequent trials have not shown any additional cases of PML, but the drug is limited to use in patients who have failed or have not tolerated alternative therapies for multiple sclerosis. The re-approval is a restricted distribution program which includes registration of patients, prescribers, infusion centers, and pharmacies and includes patient education materials. Patients are also required to have a brain MRI prior to initiation of therapy. More information is available at: www.fda.gov/cder/drug/infopage/natalizumab/default.htm.

Duramed Pharmaceuticals have received approval to market a new 91 day birth control regimen consisting of 84 days of levonorgestrel 0.15 mg with ethinyl estradiol 0.03 mg, and seven days of ethinyl estradiol 0.01 mg (Seasonique). This product differs from the company's other 91 day birth control regimen (Seasonale) in that it incorporates estradiol rather than placebo for the last seven days in order to reduce bloating and breakthrough bleeding. Both products result in four menstrual periods per year.

The FDA has approved Genentech's ranibizumab (Lucentis) for the treatment of neovascular (wet) age-related macular degeneration (AMD). The drug, which is injected intraocularly, inhibits vascular endothelial growth factor A which is thought to contribute to proliferation, vascular leakage, and angiogenesis. Many ophthalmologists have been using Genentech's other anti-angiogenesis drug bevacizumab (Avastin) for the treatment of AMD, although it is not approved for this indication. Compounded bevacizumab injected intraocularly is approximately $17 per dose. Ranibizumab marketed as Lucentis is projected to cost approximately $2000 per dose.

Two former blockbuster drugs are making the switch to generics. Sertraline (Zoloft- Pfizer) will be available later this year in both generic pill and liquid form. In 2005, Zoloft was the most popular antidepressant in the US. The FDA has also approved a generic form of simvastatin (Zocor) Merck & Co.'s enormously popular statin for the treatment of hypercholesterolemia. Generic simvastatin is currently available 5, 10, 20, 40, and 80 mg strengths. ■