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INSIDE

Financial Disclosure:

Neurology Alert's physician editor, Fred Plum, MD, reports no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study.
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Natalizumab in Relapsing Multiple Sclerosis—FDA Panel Recommends Use of Drug with Restrictions

ABSTRACTS & COMMENTARY

By Brian R. Apatoff, MD, PhD

Director, Multiple Sclerosis Clinical Care and Research Center, Department of Neurology and Neuroscience, NewYork-Presbyterian Hospital, Cornell Campus

Dr. Apatoff is on the speaker's bureau for Biogen and Teva.

Synopsis: *In 2 studies involving more than 2000 relapsing MS patients followed for 2 years, monthly infusions of natalizumab (Tysabri) were shown to be highly effective in reducing the clinical and MRI measures of disease activity. Although voluntarily suspended from the market for more than one year because of 2 cases of Progressive Multifocal Leukoencephalopathy, the FDA advisory panel said the drug should return with certain restrictions, including a mandatory patient registry.*

Sources: Polman CH, et al. A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. *N Engl J Med*. 2006;354:899-910; Rudick RA, et al. Natalizumab Plus Interferon Beta-1a for Relapsing Multiple Sclerosis. *N Engl J Med*. 2006;354:911-923; Yousry TA, et al. Evaluation of Patients Treated with Natalizumab for Progressive Multifocal Leukoencephalopathy. *N Engl J Med*. 2006;354:924-933.

IN THE STUDY REPORTED BY POLMAN AND COLLEAGUES, OF 942 relapsing multiple sclerosis (MS) patients, 627 were randomized to a monthly infusion of natalizumab, 300mg, while 315 patients received a placebo infusion, for over 2 years. The primary end points were the rate of clinical relapse at one year and the rate of sustained progression of disability, as measured by the Expanded Disability Status Scale (EDSS) at 2 years. Natalizumab reduced the risk of disability progression by 42%. Seventeen percent of patients became disabled in the natalizumab group vs 29% in the placebo group ($P < 0.001$). Natalizumab reduced the rate of relapse at one year by 68% ($P < 0.001$), and led to an 83% reduction in new or enlarging brain lesions on MRI (mean number of lesions, 1.9 with natalizumab, 11.0 with placebo; $P < 0.001$). Hypersensitivity allergic reactions occurred in 4% of patients, and 9% developed detectable anti-

VOLUME 24 • NUMBER 8 • APRIL 2006 • PAGES 57-64

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bodies against natalizumab, some of whom lost efficacy from the drug.

In a second study by Rudick and colleagues, 1171 patients on interferon beta-1a, 30mcg IM weekly, who had experienced at least 1 breakthrough attack in the preceding year, were randomized to monthly natalizumab (589 patients) or placebo (582 patients). The combination therapy resulted in a 24% reduction in the relative risk of sustained disability ($P = 0.02$). Combination therapy was associated with a lower annualized relapse rate than interferon beta-1a alone (0.34 vs 0.75, $P < 0.001$), and with fewer new or enlarging brain lesions on MRI (0.9 vs 5.4, $P < 0.001$). Two cases of progressive multifocal leukoencephalopathy (PML), one of whom died, were discovered in natalizumab patients treated for longer than 2 years (*Neurol Alert*. 2005). Thirty-eight patients (6%) developed persisting antibodies to natalizumab, resulting in a loss of efficacy and an increase in allergic infusion-related adverse events.

Following the reported cases of PML in natalizumab-treated patients, an independent expert panel reviewed the data from 3116 patients who were exposed to a mean of 17.9 monthly doses of natalizumab (including MS, Crohn's disease, or rheumatoid arthritis). Yousry and colleagues reported additional MRI data from all patients, and cerebrospinal fluid (CSF) testing for JC virus DNA in 396 patients. No additional cases of PML were detected, suggesting a risk of PML of roughly one in 1000 patients treated with natalizumab for a mean of 17.9 months.

Neurology Alert, ISSN 0741-4234, is published monthly by Thomson American Health Consultants, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/
GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Lee Landenberger.
MANAGING EDITOR: Robert Kimball.
ASSOCIATE MANAGING EDITOR: Leslie Hamlin.
GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to *Neurology Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Questions & Comments

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

COMMENTARY

Natalizumab is a recombinant monoclonal antibody against alpha-4 integrins that blocks the adhesion of activated T cells to the vascular endothelium, and reduces the trafficking of inflammatory lymphocytes into the central nervous system. The premature release of natalizumab by the FDA on incomplete one-year safety-efficacy data from the above 2-year clinical trials was reasonable, given the superior benefits of drug to currently available drugs (interferon-beta and glatiramer acetate), and adverse events similar to other humanized monoclonal antibodies, in terms of allergic hypersensitivity reactions. While natalizumab was heralded as a selective immunomodulating drug for MS and possibly other autoimmune disorders, there was scrutiny toward the possibility of increased infection and neoplasm in treated patients, given that this important function of immune surveillance would be impaired. While there was no obvious increase in conventional infections such as urinary tract infections or sinusitis, the medical community was stunned when the drug was suspended in February 2005, shortly after its release, when 3 cases of PML were reported. Those cases of PML in MS appeared in 2 patients in the combination trial where natalizumab was used in conjunction with interferon beta-1a, for over 24 months. While there is no clear explanation why a natural anti-viral agent such as interferon-beta should increase this risk, it is possible that interferon-beta further reduced lymphocyte entry into the CNS and contributed to a subtle level of lymphopenia, to increase the relative risk of PML. In the case of Crohn's disease, the patient had only been treated for several months with natalizumab, but was on additional immunosuppressants such as azathioprine and corticosteroids.

Given that natalizumab provides a therapeutic advance in the treatment of MS, by reducing relapses, clinical disability, and brain MRI lesions, it is not surprising that the FDA advisory panel recently recommended that sales of the drug should resume with a black box warning if Biogen creates a mandatory patient registry to track adverse events and imposes other controls on its use. The panel was mixed in its view whether natalizumab should be used as a first-line agent for MS, or whether it should just be applied in patients with more refractory disease who had failed other therapies. The panel indicated that natalizumab should not be used in combination with interferon-beta or other immunomodulatory drugs, other than periodic corticosteroid treatment for relapses, and be used only for relapsing forms of MS at centers experienced in the use of natalizumab and its potential complications. Despite these safeguards and its use as a monotherapy, it

is likely, however, that additional cases of PML will emerge at some low frequency as patients are treated natalizumab over longer periods of time. Hopefully future cases of PML, if recognized early enough, can be treated by abrupt cessation of the drug. The prescribing neurologist will need to have a complex discussion with prospective patients regarding the risks and benefit of this effective drug, with the unfortunate side-effect of a possible fatal brain infection. ■

Myelopathy in Copper Deficiency

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, DPhil

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

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

Synopsis: *Spinal cord magnetic resonance imaging (MRI) in patients with copper deficiency myelopathy may show increased T2 signal, most commonly in the dorsal midline cervical and thoracic cord.*

Source: Kumar N, et al. Imaging Features of Copper Deficiency Myelopathy: A Study of 25 Cases. *Neuroradiology*. 2006:48:78-83.

KUMAR AND COLLEAGUES RETROSPECTIVELY ANALYZED clinical and imaging findings in 25 patients (age range 36-78 years; 20 women, 5 men) with laboratory-confirmed copper deficiency myelopathy at the Mayo Clinic, Rochester, MN. Patients developed symptoms between 2 months and 10 years prior to examination. Serum copper levels ranged from undetectable to 0.45 g/mL (normal range, 0.75-1.45 g/mL). Hypocupremia was due to gastric surgery (n = 10), malabsorption (n = 4), large doses of iron or zinc ingestion (n = 2), or etiology was unknown (n = 9). Twenty of the 25 had leukopenia or anemia, either at presentation or by history. Somatosensory evoked potentials demonstrated impaired conduction in central pathways, and there existed varying degrees of peripheral neuropathy in those 20 examined.

Although all patients had normal vitamin B_{12} levels at the time of examination, 9 had a history of vitamin B_{12} deficiency (7 of these had undergone gastric surgery). In these, clinical worsening was recorded despite vitamin B_{12} administration that had resulted in normal vitamin B_{12} serum levels. Two of the 9 had increased methylmalonic acid levels, but 6 had normal levels (levels not determined in one case). MRI of the spine was normal in 14 patients. However, in the remaining 11, MRI revealed segmental T2 hyperintensity in the cervical or thoracic cord, or both; 5 of these 11 had no prior vitamin B12 deficiency. Of note, radiographic findings were subtle in some cases, and had originally been interpreted as normal in 2 MRI scans. Signal abnormality involved the central and dorsal midline cord, and involved the posterior columns. There was no signal enhancement after gadolinium administration. Follow-up imaging was available in one patient, and demonstrated T2 signal normalization after correction of hypocupremia.

COMMENTARY

The present study, along with the Kumar et al's previous clinical case series,[1] provide an excellent clinical description of hypocupremic myelopathy. This recently recognized disorder is rare, but important to consider in the differential of myelopathy, as clinical symptoms may reverse with oral or intravenous copper supplementation. This study verifies posterior column involvement as the underlying structural abnormality in hypocupremic myelopathy in humans, and for the first time demonstrates resolution of MRI signal abnormalities in one case treated with copper supplementation. The human neurologic syndrome seems to be characterized by sensory ataxia, lower limb spasticity, and acral paresthesias, similar to clinical features of subacute combined degeneration (SCD) in vitamin B_{12} deficiency. In fact, in malabsorption states, vitamin B_{12} and copper deficiency may co-exist. Although some clinical features associated with hypocupremia suggest similarity to vitamin B_{12} deficiency, there do appear to be differences between the 2 disorders. Vitamin B_{12} has been associated with cognitive impairment and macrocytic anemia, while hypocupremia is associated with normocytic anemia and, as yet, there are no reports of cognitive impairment. Rarely, hypocupremia is due to genetic disorders, like Menkes disease, an X-linked genetic disorder characterized by progressive demyelination and death in early childhood. However, copper deficiency is increasingly seen in patients with malabsorption secondary to gastric or intestinal surgery, chronic diarrhea, peritoneal dialysis, excessive zinc ingestion, or entero-jejunal feeding. Myelopathy secondary to hypocupremia should be considered in patients with an unexplained myelopathy, and copper levels should be determined in those with presumed SCD who fail to respond to vitamin B12 supplementation. ■

Reference

1. Kumar N, et al. Copper Deficiency Myelopathy Produces a Clinical Picture Like Subacute Combined Degeneration. *Neurology*. 2004;63:33-39.

Does Your Cell Phone Give You Headaches? Not Likely

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD

Associate Professor, Clinical Neurology, Weill Medical College of 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: *No evidence was found to indicate that people with self-reported sensitivity to mobile phone signals are able to detect such signals or that they react to them with increased symptom severity.*

Source: Rubin GJ, et al. Are Some People Sensitive to Mobile Phone Signals? Within Participants Double Blind Randomized Provocation Study. *BMJ*. 2006. Epub ahead of print.

THE LABEL OF ELECTROMAGNETIC HYPERSENSITIVITY (EHS) is given to individuals who report non-specific symptoms that are perceived to be related to electrical devices, including cell phones, visual display units, and power lines. Surveys of susceptible individuals with EHS ascribe a multitude of complaints to electromagnetic field (EMF) exposure, including headaches, sleep disorders, dizziness, fatigue, and tension. (Al-Khlaiwi T, Meo SA. *Saudi Med J*. 2004:25:732-736. Roosli M, et al. *Int J Hyg Environ Health*. 2004;207:141-150). A review of the literature published between 2000 and 2004 evaluated 13 observational or experimental studies of exposure to EMF (Seitz H, et al. *Sci Total Environ*. 2005;349:45-55). Results of randomized cross-over studies were contradictory. No causal relationship was noted in a provocation study of purportedly sensitive individuals. Results of studies of the association between EMF exposure and headache were mixed. Further investigation was suggested.

Rubin and colleagues performed a double-blind, randomized, within-participants provocation study in London to test whether people who reported sensitivity to mobile phone signals had more symptoms when exposed to a pulsing mobile signal than when exposed to a sham signal or non-pulsing signal. Sixty sensitive people who reported headache-like symptoms within 20 minutes of using a 9000 MHz global system for mobile communication (GSM) mobile phone were compared to 60 control participants who denied any symptoms related to mobile phone use. Conditions for 3 exposures, GSM signal, an unpulsed continuous wave signal, and sham without signal, were exactly the same for 50 minutes with an antenna mounted above and behind the left ear. Each participant was randomly administered the exposure in a blinded fashion in 3 separate sessions. Questionnaires about subsequent symptoms, with visual analogue scale measures, were administered at the end of the exposure and 24 hours later. The participants were also asked to state their degree of confidence that a particular exposure had taken place. Statistical calculations including 2-way analysis of variance and generalized estimating equations found no evidence that self-reported sensitivity to the mobile phone signals was correlated to reported symptoms. Headache severity increased during exposure and decreased immediately afterwards without correlation between exposure conditions and symptom severity. The proportion of sensitive participants who believed a signal was present during GSM exposure (60%) was similar to the proportion that believed one was present during sham exposure (63%). Rubin et al note that as sham exposure was sufficient to trigger severe symptoms in sensitive participants, psychological factors may have an important role in purported sensitivity to mobile phones.

COMMENTARY

The psychological factors linked to headaches are notable by the high rate of placebo effects from multiple types of interventions. This scientifically rigorous study debunks the notion that use of a mobile phone might trigger headaches due to EHS exposure. It also illustrates the importance of the nocebo effect on headaches, and requires that epidemiological studies of headache causation be carefully designed to take this factor into consideration. Patients who report sensitivity to mobile telephone use should be encouraged to seek alternative explanations for their headache symptoms.

Tailoring Treatment for Glioblastoma Multiforme

ABSTRACT & COMMENTARY

By Adilia Hormiga, MD, PhD

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical Center at Memorial Sloan-Kettering Cancer Center

Dr. Hormiga reports no financial relationship related to this field of study.

Synopsis: *Coexpression of EGFRvIII and PTEN by glioblastoma cells is associated with responsiveness to EGFR kinase inhibitors.*

Source: Mellinghoff IK, et al. Molecular Determinants of the Response of Glioblastomas to EGFR Kinase Inhibitors. *N Engl J Med*. 2005;353:2012-2024. Erratum in: *N Engl J Med*. 2006;354:884.

In recent years, new biologic agents such as inhibitors of the kinase domain of epidermal growth factor receptor (EGFR) have been used in phase I and phase II clinical trials for patients with recurrent glioblastoma multiforme (GBM). Erlotinib and Gefitinib belong to this class of agents. In GBM tumors EGFR can be overexpressed, amplified, or mutated to be independent of ligand for activation. When the epidermal growth factor ligand binds the EGFR, it initiates signal transduction through PI3K/AKT pathway. A normal inhibitor of this pathway is the tumor suppressor protein, PTEN. In some GBM, PTEN can be lost. In tumor cells, the loss of PTEN together with constitutive activation of the receptor promotes deregulation of the PI3K/AKT signaling pathway, leading to proliferation and inhibition of cell death.

Mellinghoff and colleagues sequenced the kinase domain of EGFR and EGFR type 2 (Her 2/neu) and analyzed the expression of EGFR, EGFRvIII (constitutively active genomic deletion variant of EGFR), and PTEN protein in tumor tissue of high-grade glioma patients who were treated either with Erlotinib or Gefitinib. They did not find mutations of the kinase domain of the receptors in tumor specimens from 26 patients. EGFR was amplified in 12 of 25 GBMs but no association was found between amplification and response to treatment with EGFR kinase inhibitors. EGFRvIII was detected in 12 of the 26 patients, and 6 of those 12 patients had a response to EGFR inhibitors. In 7 of 13 patients, PTEN protein was present in their tumors and correlated with response to treatment, while all tumors with PTEN loss did not respond to EGFR inhibitors. They verified their data by analyzing tissue from 33 other patients from a different institution. Eight of the 33 patients had a clinical response associated with the coexpression of EGFRvIII and PTEN. They supported their findings from tumor tissue analysis with in vitro studies showing that coexpression of EGFRvIII and PTEN in U87MG glioblastoma cells in tissue culture sensitized the tumor cells to Erlotinib.

COMMENTARY

GBM is the most frequent brain tumor in adults and is almost invariably fatal in about one year. Although chemotherapy with alkylating agents has been used to treat GBM in the United States, only recently was shown definitely that temozolomide chemotherapy during the course of radiation followed by adjuvant temozolomide improved survival of patients when compared to those who received radiotherapy alone.[1] Patients receiving temozolomide in that study responded to treatment and had a longer survival when methylation of promoter for MGMT (O6-methylguanine-DNA methyltransferase DNA-repair gene) was found in their tumor tissue.[2] Their work showed that response to treatment and prognosis could be correlated to an epigenetic variation.

What Mellinghoff et al's paper taught us was that GBM response to EGFR inhibitors was associated with coexpression of both EGFRvIII and PTEN. Although their results will need further validation, and upfront treatment is not yet based on the molecular features of a particular tumor. Last year's publications, listed below, may establish a new era for GBM management. Identification of molecular events may allow a more rational treatment approach in the future by using a single or combination of agents the target that specific molecular event(s) or pathways that drive tumor maintenance in an individual patient.

References

1. Stupp R, et al. Radiotherapy Plus Concomitant and Adjuvant Temozolomide for Glioblastoma. *N Engl J Med*. 2005;352:987-996.
2. Hegi ME, et al. MGMT Gene Silencing and Benefit From Temozolomide in Glioblastoma. *N Engl J Med*. 2005;352:997-1003.

Stroke vs Stroke Mimics: Diagnosis at the Bedside

ABSTRACT & COMMENTARY

By Dana Leifer, MD

Associate Professor, Neurology, Weill Medical College of Cornell University

Dr. Leifer reports no financial relationship related to this field of study.

Synopsis: *This prospective study demonstrates that clinical features such as focal deficits, a clear time of onset, and absence of non-neurological signs distinguish a stroke diagnosis from other diagnoses at the bedside.*

Source: Hand PJ, et al. Distinguishing Between Stroke and Mimic at the Bedside: The Brain Attack Study. *Stroke*. 2006;37;769-775.

THE AVAILABILITY OF A GROWING NUMBER OF THERAPEUTIC options for acute stroke patients makes rapid and reliable diagnosis of stroke at the bedside more important than ever. Modern technology, such as CT and MRI, can often diagnose stroke and rule out other conditions, but to avoid wasting time and resources, accurate diagnosis must be made efficiently by emergency medical personnel in the field and by physicians and nurses in the emergency room.

Hand and colleagues prospectively studied 336 consecutive patients with suspected stroke. Patients were identified by emergency room personnel as soon as possible after arrival and by review of admission registers from the emergency room, stroke unit, and neurology ward. Clinical evaluations were performed by neurology or internal medicine residents, and final diagnoses were determined by the consensus opinion of a panel of experts.

With 350 acute events in 336 patients, the final diagnosis was stroke in 241 cases and stroke mimic in 109, which included 44 episodes that were considered possible stroke or transient ischemic attack. Sixty-two of the stroke mimics were seen within 6 hours. This is an important group because it includes most patients eligible for intravenous thrombolysis or intra-arterial interventions. In this group, seizures accounted for 29% of the diagnoses, syncope in 14.5%, sepsis in 9.7%, toxic/metabolic changes in 9.7%, acute mononeuropathy in 6.5%, space-occupying lesions in 4.8%, acute confusion in 4.8%, vestibular dysfunction in 4.8%, dementia in 3.2%, and migraine in 3.2%. In patients presenting after 6 hours, seizures and syncope were less common and accounted for only 10.6% and 2.1% respectively, but sepsis and space-occupying lesions were more frequent, accounting for 17.0% and 14.9% respectively.

Univariate analysis demonstrated that patients with an uncertain time of onset, seizure at onset, loss of consciousness, non-neurologic symptoms, prior cognitive impairment, no lateralizing symptoms or signs, or signs not consistent with symptoms, were less likely to have a stroke. In contrast, an exact time of onset and any focal neurologic sign or symptom (speech difficulty, visual loss, focal weakness or numbness, upper limb ataxia, extensor plantar) predicted a diagnosis of stroke, as did presence of coronary or peripheral vascular disease and hypertension (SBP > 150, DBP > 90). More severe deficits as measured by the NIH stroke scale (NIHSS) were more likely to be associated with a stroke, as were patients whose syndrome could be classified as a total or partial anterior circulation stroke by the Oxfordshire classification system. Vertigo and leg ataxia were not significant predictors because they occurred frequently in vestibular dysfunction.

Multivariate analysis identified presence of non-neurologic abnormalities and prior cognitive impairment as factors independently predicting that a patient did not have a stroke. Exact time of onset, definite history of focal neurologic symptoms, any abnormal vascular findings (SBP > 150, atrial fibrillation, valvular disease, or absent peripheral pulses), any lateralizing signs, and definite classification by the Oxfordshire system all predicted that a patient had a stroke. The multivariate analysis also confirmed that chance of stroke increased as the NIHSS score increased. The most powerful predictors were definite history of focal neurologic symptoms and NIHSS greater than 10.

COMMENTARY

These results are important because they demonstrate that a few key features make the diagnosis of stroke likely. The results of the study suggest that initial evaluation of potential stroke patients should determine if there is an exact time of symptom onset, any definite history of focal neurologic symptoms, and any lateralizing signs. The key symptoms and signs are straightforward—speech difficulty, visual loss, focal weakness or numbness, arm ataxia. If such symptoms or signs are identified, this study suggests that it is appropriate to activate a rapid protocol for more thorough evaluation by imaging and more detailed clinical evaluation focused on reaching a definite diagnosis and starting treatment.

On the other hand, if focal signs and symptoms are absent or non-neurologic problems are present, diagnoses other than stroke should be considered, and these include potentially serious non-neurologic conditions such as sepsis, syncope, and toxic-metabolic disorders. Although these conclusions may seem obvious to neurologists who have experience with stroke, the study makes a significant contribution because it provides guidelines for non-specialists who may see a stroke patient first, and must recognize that a patient may be having a stroke. ■

Hashimoto's Encephalopathy—Steroid Responsive Syndrome

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: *Subacute encephalopathy associated with thyroid antibodies and a history of autoimmune thyroid disease may respond dramatically to high-dose corticosteroid therapy.*

Source: Castillo P, et al. Steroid-Responsive Encephalopathy Associated with Autoimmune Thyroiditis. *Arch Neurol*. 2006;63:197-202.

Acute and subacute encephalopathy is a common reason for neurological consultation in the hospital, but often, a specific etiology is not forthcoming. A family of autoimmune encephalopathy syndromes, some associated with underlying malignancies, have been described in recent years, and some have had specific anti-neuronal antibodies identified to aid in diagnosis. The existence of the syndrome first described by Lord Brain in 1966 (Brain L, et al. *Lancet*. 1966;2:512-514) and termed Hashimoto's encephalopathy, has been debated in the literature and has not been well characterized. Castillo and colleagues, at the Mayo Clinic, have done an admirable job of characterizing a recognizable syndrome, and have further defined it by a dramatic response to corticosteroids.

In a review of 20 patients followed at the Mayo Clinic, a diagnosis of SREAT (steroid-responsive encephalopathy associated with auto-immune thyroiditis) was based on the following criteria—encephalopathy with cognitive impairment and neuropsychiatric features, presence of serum thyroid antibodies, euthyroid or mildly hypothyroid state, no evidence of other infectious, toxic, metabolic, neoplastic, or vascular process, no serologic evidence of paraneoplastic autoantibodies, and complete or near-complete return of baseline neurological status after treatment with corticosteroids.

All but one patient required acute hospitalization because of the severity of the illness. The median age at onset was 56 years (range, 27-84) and 70% were female. The most common clinical features at presentation were behavioral-cognitive abnormalities (100%), tremor (80%), transient aphasia (80%), myoclonus (65%), gait ataxia (65%), seizures (60%), and sleep abnormalities (55%). Misdiagnoses were common, with the most frequent being Creutzfeldt-Jakob disease, viral encephalitis, and degenerative dementias. A history of hypothyroidism or euthyroid goiter was present in 11 patients, and 5 additional patients were diagnosed with hypothyroidism after resolution of the encephalopathy. Eight patients were diagnosed with other autoimmune disorders in addition to thyroid disease. Serologic studies revealed that 13/13 patients tested positive for thyroperoxidase antibodies, 7/7 patients tested positive for thyroid microsomal antibodies, and 6/10 were positive for thyroglobulin antibodies. Liver AST/ALT levels were elevated in 11/20 patients but other autoantibodies (ANA, ENA, RF, Gliadin) were present in less than half of the patients. CSF had elevated protein in 17/20 and elevated white count in 5/20, but only 2 patients had increases of IgG or oligoclonal bands. EEG testing in 19/20 patients showed generalized slowing that resolved after treatment in the 17 patients who had follow-up studies. Cerebral angiography in 5 patients, and meningeal and brain biopsy in 2 patients did not reveal any significant abnormalities. Brain MRI in 4 patients revealed diffuse increased signal on T2-weighted and FLAIR images in the cerebral white matter that normalized after treatment with corticosteroids.

The SREAT syndrome is defined by its response to therapy, and all of the reported patients received high-dose corticosteroid therapy, 1 gm/day of intravenous methylprednisolone for 5 days, followed by oral prednisone 60-100 mg/day for 10-30 days. Fifteen patients returned to their normal neurological baseline status and 5 had residual symptoms.

COMMENTARY

Castillo et al have done an admirable job of further defining and characterizing the syndrome of Hashimoto's encephalopathy, with particular emphasis on a therapeutic response to high-dose corticosteroids. In a clinically similar group of 12 patients who did not respond to corticosteroids, there was progression of disease in all cases, and 4 autopsy examinations revealed Creutzfeldt-Jakob disease in 2, Lewy body disease in one, and neurofilament inclusion body disease in one. It is likely that the others had a progressive neurodegenerative or prion disease. Therefore, the importance of a therapeutic trial of high-dose corticosteroids cannot be overemphasized, since the alternative diagnoses are progressive, fatal conditions that have no effective treatment. In an appropriate clinical setting, corticosteroid therapy is warranted. However, we do not know what the natural history of SREAT would be in the absence of therapy. It is plausible that there might be spontaneous remission of this encephalopathy, as occurs in other autoimmune conditions. So, there is still much to learn. In order to more clearly define and understand this syndrome, we hope that further studies of Hashimoto's encephalopathy, as well as the broader group of non-vasculitic autoimmune meningoencephalitis (Caselli RJ, et al. *Neurology*.1999;53:1579-1581) will be investigated for evidence of biologically-active, anti-neuronal antibodies that might lead us to the pathophysiology of these mysterious disorders. ■

CME Questions

7. Which of the following is *false*?

a. Natalizumab is a monoclonal antibody that blocks adhesion proteins on activated T-cells.
b. In a 2-year trial, natalizumab had significant reductions in relapse rate, reduction of disability, and brain MRI lesions.
c. Natalizumab is given by infusion on a monthly basis.
d. There was no additional benefit with natalizumab combined with interferon-beta compared to its use as a monotherapy.
e. The FDA advisory panel recommendation for the resumed marketing of natalizumab as a monotherapy indicates that any safety concerns for its use have been overcome.

8. Which of the following is true?

a. Erlotinib and gefitinib are EGFR phosphatase inhibitors.
b. GBM that responds to Erlotinib may have PTEN loss.
c. PTEN inhibits PI3K/AKT signaling pathway.
d. Erlotinib and gefitinib have been used as a first line agent for GBM.
e. PI3K/AKT pathway is not activated in GBM.

9. Which of these diagnoses are among the ones that frequently mimic stroke?

a. Seizure.
b. Vestibular dysfunction.
c. Acute mononeuropathy.
d. Sepsis
e. All of the above.

10. Which of the following make it likely that a potential stroke patient actually is having a stroke?

a. No definite time of onset.
b. Focal neurologic symptoms and lateralizing signs.
c. Vertigo.

Answers: 7. (c); 8. (c); 9. (e); 10. (b)

CME Objectives

The objectives of Neurology Alert are:

• To present 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. ■

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Can Calcium and Vitamin D Prevent Hip Fractures?

It has been a tough few months for marketers of vitamins and herbal products. Calcium plus vitamin D, saw palmetto, and glucosamine/chondroitin have all been the subject of studies that have questioned their efficacy. The calcium plus vitamin D results are possibly the most disappointing. In further data from the Women's Health Initiative study, 36,282 postmenopausal women ages 50 to 79 were randomly assigned to receive 1000 milligrams of elemental calcium with 400 IU of vitamin D3 or placebo, with the end point being prevention of hip and other fractures. After 7 years of follow-up, bone density was slightly higher, but there was no reduction in hip fractures in women who took calcium plus vitamin D (hazard ratio, 0.88 for hip fracture [95% CI, 0.72 to 1.08]). There was also no reduction in clinical spine fractures (HR, 0.90 [0.74 to 1.10]) or total fractures (HR, 0.96 [0.91 to 1.02]). Calcium plus vitamin D did result in a higher risk of kidney stones (HR, 1.17 [1.02 to 1.34]).

The authors conclude that among healthy postmenopausal women, calcium plus vitamin D supplementation did not significantly reduce hip fractures or reduce risks of kidney stones (*N Engl J Med*. 2006;354:669-683). In an accompanying editorial, Joel Finkelstein, MD, points out that many women who take calcium plus vitamin D "believe that they are completely protected against the development of osteoporosis. This study should help correct this important misconception and allow more women to receive optimal therapy for bone health." He also points out that women should not abandon calcium and vitamin D, neither should they rely on it alone as prevention against osteoporotic fractures (*N Engl J Med*. 2006;354:750-752 [correction published *N Engl J Med*. 2006;354:1102]).

Treatment of Benign Prostatic Hyperplasia

Saw palmetto is used by over 2 million men to treat symptoms of benign prostatic hyperplasia (BPH). Now, a new study suggests that it is ineffective. The study, funded by the National Institutes of Health and the National Center for Complementary and Alternative Medicine, looked at 225 men over the age of 49 with moderate-to-severe symptoms of BPH who were randomized to one year of saw palmetto extract 160 mg twice a day or placebo. The primary outcomes were changes in American Urological Association Symptom Index and maximal urinary flow rates. Prostate size, the residual urinary volume after voiding, quality of life, laboratory values, and adverse effects were also measured. After one year, there were no significant differences between patients treated with saw palmetto or placebo in any of the outcomes. There was also no difference in adverse effects. The authors conclude that saw palmetto does not improve symptoms or objective measures of BPH (*N Engl J Med*. 2006;354:557-566). An accompanying editorial welcomes the scientific rigor of placebo-controlled trials applied to dietary supplements, which are generally not held to standards of safety and efficacy. The authors call for similar studies for other

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments? Please call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

commonly used herbal products (*N Engl J Med*. 2006;354:632-634).

Treatment of Osteoarthritis of the Knee

Glucosamine and chondroitin sulfate is used by millions to treat osteoarthritis. In another study supported by the NCCAM, along with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1583 patients with osteoarthritis of the knee were randomized to 1500 mg of glucosamine daily, 1200 mg of chondroitin sulfate daily, combination of glucosamine and chondroitin sulfate, 200 mg of celecoxib daily, or placebo for 24 weeks. Acetaminophen was allowed as rescue analgesia. The primary outcome was a 20% decrease in the pain from baseline at week 24. Glucosamine and conference sulfate were no better than placebo in reducing the pain by 20%, except for combined therapy (glucosamine plus chondroitin) in patients with moderate-to-severe pain at baseline (79.2% response vs 54.3% response placebo, $P = 0.002$). Adverse events were no different in all groups. The authors conclude that overall glucosamine chondroitin did not reduce pain effectively in patients with osteoarthritis of the knee, except in the subgroup of patients with moderate-to-severe knee pain (*N Engl J Med*. 2006;354:795-808). An accompanying editorial recommends telling patients that neither glucosamine nor chondroid alone has been shown to be more effective than placebo in treating knee pain. They suggest that glucosamine sulfate plus chondroitin sulfate may be tried in patients with moderate-to-severe knee pain, but should be discontinued after 3 months if there is no benefit (*N Engl J Med*. 2006;354:858-860).

Refractory Asthma and TNF—Connection?

Refractory asthma is a condition with a high mortality rate and limited treatment options. A new study suggests that the tumor necrosis factor (TNF) axis is up-regulated in refractory asthma, creating the possibility of treating refractory asthma with TNF inhibitors. Researchers from the United Kingdom measured markers of TNF alpha activity in 10 patients with refractory asthma, 10 patients with mild/moderate asthma, and 10 controls subjects. Patients with refractory asthma increased expression of TNF alpha markers compared to those with mild-to-moderate asthma and controls. Study subjects with refractory asthma were subsequently randomized to receive the TNF alpha receptor etanercept 25 mg twice weekly in a placebo-controlled, double-blind, crossover pilot study. Ten weeks of treatment with etanercept was associated with a significant increase in concentration of methacholine required to provoke a 20% decrease in FEV1 ($P = 0.05$), an improvement in asthma related quality-of-life score ($P = 0$ .02), and a 0.32 liter increase in post bronchodilator FEV1 ($P = 0.01$) compared to placebo. The authors suggest that the TNF alpha axis is upregulated in refractory asthma, and that etanercept may be beneficial in these patients (*N Engl J Med*. 2006; 354:697-708). An accompanying editorial reports that several studies of TNF inhibitors in patients with refractory asthma are ongoing, suggesting that we soon should have an answer as to whether these agents are effective for treating this difficult clinical entity (*N Engl J Med*. 2006;354:754-758).

FDA Actions

The FDA has approved anidulafungin, Pfizer's new anti-fungal for the treatment of candidemia. The drug is a new molecular entity that is given intravenously. It is approved for a variety of Candida infections including esophagitis, sepsis, abdominal abscesses, and peritonitis. It will be marketed by Pfizer as Eraxis.

The FDA has approved lubiprostone for the treatment of chronic idiopathic constipation in adults. The drug is a selective chloride channel activator that increases intestinal fluid secretion and motility. The drug will be marketed by Sucampo Pharmaceuticals as Amitiza.

CV Therapeutics has received approval to market ranolazine, the first of a new class of agents for the treatment of chronic angina. The drug is an orally available extended-release anti-anginal drug that acts without reducing heart rate or blood pressure. The drug's mechanism of action has not been fully characterized, but it is felt that it works by affecting changes in cardiac metabolism. Because ranolazine prolongs QT interval, it should be reserved for patients who have not achieved adequate response with other anti-anginal drugs, and should be used in combinations with amlodipine, beta-blockers, or nitrates. CV Therapeutics will market ranolazine as Ranexa.

The FDA has approved an oral vaccine for the prevention of rotavirus gastroenteritis in infants and children. The oral vaccine should be initiated in infants 6 to 12 weeks old, with 2 subsequent doses of 4 to 10 week intervals. The vaccine should be completed before the child reaches 32 weeks of age. Based on clinical trials, the vaccine appears to be 98% effective for preventing gastritis caused by targeted rotavirus serotypes, and 74% effective at preventing gastroenteritis of any severity. Rotavirus vaccine will be marketed by Merck as RotaTeq. ■