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INSIDE

Is Vitamin E Useful For the Prevention or Treatment of Amyotrophic Lateral Sclerosis (ALS)?

ABSTRACTS AND COMMENTARY

Synopsis: *Vitamin E had no significant effects in slowing disease progression, and no significant side effects in the patient population were encountered. Patients who regularly take vitamin E have a 60% reduced risk of getting ALS.*

Sources: Ascherio E, et al. Vitamin E Intake and Risk of Amyotrophic Lateral Sclerosis. *Ann Neurol*. 2005;57:104-110; Gerlach M, et al. High Dose Vitamin E Therapy in Amyotrophic Lateral Sclerosis As Add-on Therapy to Riluzole: Results of a Placebo-Controlled Double-Blind Study. *J Neural Transm*. 2004; Miller E, et al. Meta-Analysis: High Dosage Vitamin E Supplementation May Increase All-Cause Mortality. *Ann Intern Med*. 2004;142:1-11.

THERE HAVE BEEN SEVERAL RECENT ARTICLES WHICH HAVE enhanced the controversies overtaking vitamin E supplements. A recent meta-analysis suggested that high dosage vitamin E supplementation may increase all-cause mortality, meaning death from any cause. This was a meta-analysis of 135,967 participants in 19 clinical trials. Of these, 9 tested vitamin E alone and 10 tested vitamin E combined with other vitamins and minerals. Ascherio et al obtained the data by abstracting the study reports. They assert that patients taking high dosage vitamin E, which they defined as 400 international units daily, had an increased risk of all-cause mortality of 39 per 10,000 persons. For low dosage vitamin E trials, the risk difference was -16 per 10,000 persons. Interestingly, only 2 of these studies were in patients with neurologic diseases. In both, the Alzheimer's disease collaborative study of high dose vitamin E in symptomatic patients with Alzheimer's disease, as well as in the DATATOP study in Parkinson's disease, which both used a dose of 2000 units daily, there was actually a reduction in overall mortality, meaning death from any cause. Nevertheless, when Ascherio and colleagues plot a dose response relationship, DATATOP was said to have an all-cause mortality risk difference of 0.02.

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Most of the studies were done in patients with either cardiovascular disease, a history of large bowel adenoma, or early age related cataracts.

More recently, a study examined whether patients who regularly used supplements of the anti-oxidants vitamins E and C have a lower risk of developing ALS than non users. This study was an outgrowth of a large study sponsored by the American Cancer Society. Gerlach et al recruited volunteers in 50 states. A total of 957,740 individuals 30 years of age or older participated. These individuals had information on vitamin use collected at the time of recruitment in 1982. The patients were found, then followed up, for ALS deaths determined from death certificates from 1989-1998. This was done via linkage with a national death index. They documented 525 deaths from ALS. They found that regular use of vitamin E supplements, which was defined as using vitamin E more than 15 times per month, had a markedly reduced incidence of developing ALS. The age and smoking adjusted risk was 0.99 among occasional users, 0.59 in regular users for less than 10 years, and 0.38 for regular users for 10 years or more, as compared with non users of vitamin E. Therefore in users for more than 10 years, there could be roughly a 60% reduction in the risk of dying of ALS. There was no significant association found for use of vitamin C or multi-vitamins. Adjustment for other vitamins such as vitamin A also did not alter the results. Further adjustment for education, level of physical activity, alcohol consumption, servings of fruits and vegetables and high fiber cereals, and use of estrogen replacement therapy did not materially change the result.

A recent controlled, clinical trial examined the effects of vitamin E supplements in patients with diagnosed ALS. One hundred and sixty patients were recruited in 6 German centers that had either probable or definite ALS, and the disease duration of less than 5 years. They were all treated with Riluzole. They were randomly assigned to receive either vitamin E (5000 mg/d) or placebo for 18 months. The primary outcome variable was survival. A number of secondary outcome measurements were also examined. Looking at the primary end point, no significant difference between the placebo and treatment groups could be detected. The functional assessment showed a marginal trend in favor of vitamin E, without reaching significance. Gerlach and colleagues concluded that they had no significant effects in slowing disease progression. However, they did not encounter any significant side effects in the patient population.

COMMENTARY

These 3 studies all address the use of vitamin E both in a general population, as well as in patients who have ALS. The first study is a meta-analysis, which suggested that taking high dosages of more than 400 units of vitamin E per day may increase or cause mortality. The conclusions of this study however are questionable. It was based on a meta-analysis, and these types of studies are known to have significant flaws. The results of subsequent trials have frequently not verified conclusions reached in meta-analysis studies. In particular, the 2 studies examining neurologic patients actually showed a reduced all-cause mortality in patients with both Alzheimer's disease and Parkinson's disease who are taking high doses of vitamin E supplements. We recently re-analyzed the DATATOP data, as well as a continuing follow up, and found that there was no increased all mortality risk in these patients. The results of the meta-analysis above may be confounded by its being a study in largely confined patients with coronary artery disease, cancer, or cataracts. The degree of the overall increase in all-cause mortality was extremely small, being 39 per 10,000 persons or 0.39%. The ability to detect such a small change could very well be largely due to chance. The confidence interval which they found was between 3-74 per 10,000 persons.

The second study is of significant interest. It is carried out by a group at the Harvard School of Public Health,

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which had earlier found that there is an increased incidence of ALS in servicemen participating in a number of different wars, starting with WWII. Gerlach and colleagues now found that patients using regular vitamin E supplementation for more than 10 years have up to a 60% reduction in the incidence of ALS. This finding could be happenstance and merely reflect greater usage of a number of vitamins, improved diet, or improved physical activity. This, however, does not appear to be the case. All of these were controlled, and none of these other factors showed any association with the reduction of risk of ALS.

Interestingly, the findings are similar to those seen with a number of other neurodegenerative diseases. It appears that taking vitamin E may reduce one's risk of developing neurodegenerative diseases associated with oxidative stress such as ALS, Parkinson's disease, and Alzheimer's disease. The evidence, however, that treatment with vitamin E will have any beneficial effect in these illnesses once they've been diagnosed, is much more limited. Vitamin E was unsuccessful in the DATATOP trial in Parkinson's disease. A more recent trial in patients with mild cognitive impairment did not show any efficacy of vitamin E supplements. In the German trial noted above, vitamin E supplementation at high levels also did not show any benefit in symptomatic ALS patients. The overall data is therefore much more consistent with a preventative effect, rather than a therapeutic effect, once patients become symptomatic. — **M. FLINT BEAL**

Acute Stroke Therapy Beyond IV tPA: Clot Removal—Bust It Up or Pull It Out

ABSTRACTS & COMMENTARY

Synopsis: *This phase 1 study shows that cerebral embolectomy with the Merci Retriever was safe and that successful recanalization could benefit a significant number of patients, even when performed in an extended 8-hour time window.*

Sources: Gobin YP, et al. MERCI I: A Phase I Study of Mechanical Embolus Removal in Cerebral Ischemia. *Stroke.* 2004;35:2848; Alexandrov AV, et al. For the CLOTBUST Investigators. Ultrasound Enhanced Systemic Thrombolysis For Acute Ischemic Stroke. *N Engl J Med.* 2004;351:2170.

THE TREATMENT OF ACUTE ISCHEMIC STROKE IS IN ITS most simple terms a matter of plumbing. There is an artery occluded by clot. Blood flow must be restored as quickly as possible to provide the best possible chance of salvaging ischemic brain, and optimizing clinical outcome. While intravenous or intra-arterial thrombolysis may achieve this goal, recanalization rates are incomplete, and there may be the complication of intracerebral hemorrhage. These 2 contemporaneous reports, while very different in methodology, both open the horizon of a different, perhaps more effective, and likely safer method of stroke treatment-mechanical clot disruption or removal.

In the CLOTBUST study, Alexandrov et al applied transcranial doppler (TCD) to patients under treatment with intravenous tPA for acute ischemic stroke. It is believed that ultrasound may enhance thrombolysis by improving drug transport, altering fibrin structure, and improving the binding of tPA to fibrin. The randomized CLOTBUST study was based on compelling pilot data, and is a bridge towards a larger Phase III efficacy study.

Target patients were exposed to continuous therapeutic TCD examination for 2 hours, while control patients had TCD probes applied with only brief diagnostic examinations at 30, 60, 90, and 120 minutes. Patients were eligible for the study if they had abnormal flow in the middle cerebral artery confirmed on initial screening TCD. The predetermined end point of the study was complete arterial recanalization, or dramatic clinical recovery, within 2 hours. This was reached in 31/63 patients in the target group (49%), compared with 19/63 patients in the control group (30%), $P = 0.03$. When purely clinical end points were used, at 2 hours, 24 hours, and 3 months, there was a non-significant trend towards benefit in the target group. Larger studies will be needed to confirm whether these trends are meaningful. There was no difference in rates of bleeding between the 2 groups.

In the MERCI trial, Gobin et al applied a newly developed endovascular device that is capable of snaring blood clots and removing them from intracranial vessels. The device is a coiled wire composed of nitinol (nickel titanium), a material capable of assuming a linear shape while inside a catheter and then a coiled shape upon deployment into a clot.

The MERCI Phase I trial included 28 patients, treated up to 8 hours after stroke onset (mean time 6 hours, 15 minutes). The study required an initial NIH Stroke Scale (NIH-SS) of 10, and for enrolled patients, the median initial NIH-SS was 22. Successful recanalization with embolectomy alone was achieved in 12 (43%) patients and with the addition of intra-arterial tPA in 18 (64%) patients. There was 1 technical complication, in which the tip of the retriever device became detached in the

vessel. Another MERCI retriever was used to capture this, without any clinical consequences. There were no symptomatic hemorrhages. At 1 month, there were 9/18 revascularized patients, and none of the 10 non-revascularized patients had achieved significant recovery. Recovery was defined as a modified Rankin score of 0-2 for patients with initial NIH-SS of 10-20 and 0-3 for patients with an initial NIH-SS of greater than 20.

The MERCI I study is to be followed shortly by the MERCI II data, extending these results to a much larger number of patients. Unfortunately, none of the MERCI data is in any way blinded, randomized or placebo controlled, making it difficult to draw definitive conclusions about its efficacy.

COMMENTARY

The CLOTBUST and MERCI studies share much in terms of their strengths and also in their weaknesses. Unlike IV tPA, which is a drug that can be given quite indiscriminately to stroke patients, only limited by a 3 hour time window and fairly simple clinical and radiographic selection criteria, these technologies raise complex issues in terms of patient selection, operator skill, and overall generalizability. Both CLOTBUST and MERCI apply primarily to large strokes affecting the middle cerebral artery (MCA--M1 or M2 trunks). Patients who have these lesions must therefore be accurately and quickly identified. A vascular diagnosis can be imputed on clinical grounds, but ideally requires confirmation by tests such as CT or MR angiography. For patients with distal MCA disease or penetrator artery lesions, CLOTBUST and MERCI are of limited or no use.

Perhaps more importantly, both of these technologies are extremely user dependent. CLOTBUST requires that TCD be performed by an experienced sonographer who can accurately insonate the MCA, and reliably analyze its waveforms. The TCD technology itself is inexpensive and portable, but there is a significant human element than cannot be underestimated. For MERCI, there must exist a tertiary care center with immediate availability of an endovascular suite and team of specialists who can effectively navigate the embolectomy device into intracranial clots. Clearly, the safety of the MERCI device and the reproducibility of its efficacy will not be easily replicated by novice users.

Despite the many unanswered questions, CLOTBUST and MERCI represent important advances in our ability to treat acute ischemic stroke. Interestingly, although future studies are pending, both TCD (sold commercially by many manufacturers) and the MERCI retriever (recently FDA approved) are at present available for use should any clinician choose to employ them. — **ALAN Z. SEGAL**

Back to Basics: The EEG in CJD

ABSTRACT & COMMENTARY

Synopsis: *These data prove the high diagnostic value of our objective EEG criteria in CJD.*

Source: Steinhoff BJ, et al. Diagnostic Value of Periodic Complexes in Creutzfeldt-Jakob Disease. *Ann Neurol.* 2004; 56:702-708.

SPORADIC CREUTZFELDT-JAKOB DISEASE (SCJD) IS THE most frequent human prion disease, and always has a fatal course. The diagnosis is proved only by brain biopsy or post-mortem examination. Non-invasive diagnostic methods such as the presence in CSF of the 14-3-3 protein,[1] or MRI appearance[2] have been proposed, but lack sufficient sensitivity to replace tissue diagnosis.

In 1996, Steinhoff et al[3] published electroencephalogram (EEG) criteria to define periodic sharp-wave complexes (PSWCs) diagnostic of CJD (*see Table*).

In the present study, Steinhoff and colleagues investigated sensitivity, specificity, and predictive values of these EEG criteria in cases of autopsy that confirmed (n = 150) or excluded (n = 56) CJD.

Clinical symptoms alone were sufficient for the correct diagnosis of CJD in 139 patients (93%). In the non-CJD patients, clinical criteria suggested a false diagnosis of CJD in 34 of 56 (61%). Therefore, clinical criteria alone achieved a sensitivity of 93% and a specificity of 39%. The positive predictive value (PPV) was 80% (139/173), and the negative predictive value (NPV) was 67% (22/33).

In CJD patients, typical EEG findings were apparent in 96 (64%). The first typical EEG was recorded 3.7 ± 3.1 months after the onset of disease. In 54 CJD patients (36%), typical EEG criteria were not satisfied.

In the non-CJD group, an EEG typical for sCJD was found in 5 patients (9%). At autopsy, 4 of them had Alzheimer's disease, and 1 had multiple cerebral infarcts.

TABLE 1

DIAGNOSTIC CRITERIA FOR PSWCS IN SCJD

1. Strictly periodic cerebral potentials, the majority with a duration between 100 and 600 m sec and an intercomplex interval between 500 and 2,000 m sec.
2. Generalized or lateralized complexes.
3. At least 5 repetitive intervals with a duration difference of < 500 m sec to rule out semiperiodic activity.

Therefore, the EEG criteria for CJD used alone had a sensitivity of 64% and a specificity of 91%. The PPV was 95% (966/101) and the NPV was 49% (51/105).

Of the 150 autopsy-proven cases of CJD, 94 had been classified as probable, based on both clinical findings and EEG results. The diagnostic sensitivity of the clinical and EEG criteria when combined was 63%. Only 1 non-CJD patient fulfilled both criteria and was misclassified as probable CJD. Therefore, when both criteria were applied, the specificity was 98%, PPV and NPV were 99% and 49%, respectively.

COMMENTARY

In CJD, PSWCs are a specific diagnostic indicator, and are able to differentiate the sporadic form of CJD from other prion diseases. PSWCs have been recorded only occasionally in familial CJD, but have not been reported to occur in cases of Kuru, Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, or new variant CJD.

In this study the combined specificity of the established clinical and EEG criteria was 97%. Clinicians, especially neurosurgeons and pathologists who must handle infectious tissues, can look forward with hope to the time when clinical and EEG criteria, combined with MRI and other studies, will yield a definitive ante mortem diagnosis of sCJD, without the need for brain biopsy. — **JOHN J. CARONNA**

References

1. World Health Organization Consensus on Criteria for Diagnosis of Sporadic CJD. *Wkly Epidemiml Rec.* 1998;73:361-365.
2. Schroter A, et al. *Arch Neurol.* 2000;57;1751-1757.
3. Steinhoff BJ, et al. Arch Neuruol. 1996;53:162-166.

Challenges in Parkinson's Disease Dementia Treatment

ABSTRACT & COMMENTARY

Synopsis: *In this placebo-controlled study, rivastigmine was associated with moderate improvements in dementia associated with Parkinson's disease but also with higher rates of nausea, vomiting, and tremor.*

Source: Emre M, et al. Rivastigmine For Dementia Associated With Parkinson's Disease. *N Engl J Med.* 2004; 351:2509-2518

This study is a 24-week multicenter, randomized, double blind, placebo-controlled trial of rivastigmine for dementia associated with PD (PD-dementia). 541 patients were enrolled, almost two thirds of whom were men. Subjects had a mean age of 72.7 years, and had a DSMIV diagnosis of dementia due to Parkinson disease. Rivastigmine treatment began at 1.5 mg twice daily, and was slowly adjusted to the highest well-tolerated dose, up to 12 mg/day maximum. The mean dose of rivastigmine was 8.6 mg/day, with 55% taking 9-12 mg/day by 24 weeks. Primary outcome measure was the cognitive subscale of the Alzheimer's Disease Cooperative Study (ADAS-cog), a 0 to 70-point scale. Seventy-three percent of those taking rivastigmine completed the trial, compared to 82% in the placebo arm. Groups were well matched for baseline ADAS-cog scores, with 23.8 ± -10.2 in the rivastigmine group, and 24.3 ± -10.5 in the placebo group. ADAS-cog scores improved by 2.1 ± -8.2 at 24 weeks, compared with worsening by 0.7 ± -7.5 in the placebo group, a significant between-group difference of 2.9, with $P < 0.001$. Significant differences were also demonstrated in secondary efficacy variables, addressing activities of daily living, behavior, attention, verbal fluency, and visuospatial skills. Nausea and vomiting were more frequent in the rivastigmine group (29.0% and 16.6%, respectively), compared to placebo (11.2% and 1.7%, respectively). In the rivastigmine group, 5.5% withdrew because of these adverse effects, as compared to only 1.2% in the placebo arm. Increased tremor (rivastigmine: 10.2%; placebo: 3.9%) only accounted for 1.7% of those withdrawing from the rivastigmine group. Only 4.7% of patients taking rivastigmine reported hallucinations, compared to 9.5% in the placebo group.

COMMENTARY

This is the first large, multicenter, clinical trial comparing the cholinesterase inhibitor rivastigmine to placebo in PD dementia. Dementia in those with PD is common; in cross-sectional studies it occurs in approximately 45%. It contributes to functional decline with reduced quality of life and increased morbidity, yet optimal treatment is not well defined. Phenotypically, dementia with PD is quite different from Alzheimer's disease (AD), with more prominent bradyphrenia and visuospatial deficits, and relatively less memory impairment. Visual hallucinations may occur. Pathology associated with PD-dementia includes widespread Lewy bodies, as well as changes characteristic of Alzheimer disease in some, but a few cases have no such changes, and this heterogeneity presents a challenge. The present study is certainly a step forward in terms of demonstrating benefit of rivastigmine for PD dementia, but unfortunately this benefit proves disappointing in

magnitude. One problem is that the ADAS-cog has been specifically designed for AD, and may not provide a true estimate of changes in PD dementia. It is also important to define whether a specific subgroup of patients exists that may derive greater benefit. In the meantime, in the office setting, rivastigmine and other cholinesterase inhibitors may help some individuals, and their use can be guided by clinical response monitored by patient, caregivers and the physician. — **CLAIRE HENCHCLIFFE**

Diabetic Autonomic Neuropathy

ABSTRACT & COMMENTARY

Synopsis: *These findings indicate that autonomic symptoms and deficits are common in diabetes, but mild in severity, and that the correlation between symptom scores and deficits is overall weak in mild diabetic neuropathy, emphasizing the need to separately evaluate autonomic symptoms.*

Source: Low PA, et al. Autonomic Symptoms and Diabetic Neuropathy: A Population-Based Study. *Diabetes Care*. 2004;27:2942-2947.

Diabetic patients (n = 231) enrolled in the Rochester Diabetic Neuropathy Study at the Mayo Clinic, and healthy controls (n = 245) underwent comprehensive autonomic function evaluation to determine the prevalence of autonomic dysfunction in multiple organ systems in diabetes. Ninety-nine percent of the diabetics were white, approximately half were men, and overall mean age was 59.4. Type 2 diabetics, as a subgroup, were older than type 1 patients, with a mean age of 64.1 vs 50.9 years. Normal controls were of comparable age and sex to the patient group. Evaluations undertaken included an Autonomic Symptom Profile (ASP) and a Composite Autonomic Severity Score (CASS). ASP comprises 169 questions covering 11 domains, including orthostatic intolerance, secretomotor, urinary, diarrhea, constipation, sleep, pupillomotor, male sexual failure, vasomotor, upper gastrointestinal symptoms, and syncope. Self-reported, ASP is designed to provide an indication of the severity of dysautonomia. CASS is a battery of autonomic reflex tests, including sudomotor axon-reflex testing, beat-to-beat blood pressure, and heart rate in response to head-up tilt, and Valsalva maneuver and heart rate response to deep breathing. Data was analyzed using 1-way analysis of variance, Kruskal-Wallis, Mann-Whitney U tests, Bonferroni corrections, and Spearman correlations.

Autonomic dysfunction was found in 54% and 73% of type 1 and 2 diabetics, respectively. However, the degree of dysfunction was mild, with mean CASS 2.3 (maximum 10) and only 14% with a CASS of 5 or more, indicating more severe autonomic involvement. Secretomotor, pupillomotor, and sexual failure in men were the only domains where type 1 patients differed from controls, while type 2 patients differed significantly in 9 domains, with only constipation and syncope showing no difference. Comparing type 1 and 2 patients, the latter demonstrated greater problems with diarrhea and urinary domains on the ASP, and cardiovagal abnormalities on CASS. Peripheral neuropathy and autonomic neuropathy occurred in similar percentages. Autonomic neuropathy is common in diabetes but mild in severity.

COMMENTARY

In a separate study performed by a group in Sweden, Type 1 (n = 43) and type 2 (n = 17) diabetics were examined to determine the frequency of sympathetic and parasympathetic neuropathy in these patients. Laser Doppler perfusion of a heated finger was used to measure the vasoconstriction index (VCI), a sympathetic nerve function, and R-R interval (RRI) during deep breathing provided an index of parasympathetic function. Spearman's correlation coefficient, Wilcoxon's signed rank, t test, and Fisher's test provided statistical analysis.

Sympathetic function (VCI) was abnormal in an equal percentage of type 1 (40%; n = 17) and type 2 (41%; n = 7) patients, but parasympathetic function (RRI) was significantly more prevalent in type 2 (65%; n = 11), compared to type 1 (42%; n = 18) diabetics. Twenty-three percent (n = 10) of type 1 and 29% (n = 5) of type 2 patients had abnormalities of both measurements, but these correlated only in the former (P = 0.0002 vs 0.97, respectively). Sympathetic and parasympathetic dysfunction is frequent among both diabetic groups, but a correlation between the 2 is seen only in type 1. — **MICHAEL RUBIN**

Amyloid Neuropathy

ABSTRACT & COMMENTARY

Synopsis: *If routine staining is negative for amyloid, Congo red and thioflavine S staining need be performed, with ultrastructural examination of Epon-embedded nerve. Anti-light-chain and transthyretin immunostaining of frozen nerve completes the investigation.*

Source: Vital C, et al. Amyloid Neuropathy: A Retrospective Study of 35 Peripheral Nerve Biopsies. *J Peripher Nerv Syst.* 2004;9:232-241.

AMYLOID NEUROPATHY MAY BE FAMILIAL OR ACQUIRED, the former caused by transthyretin (TTR) gene mutation, the latter by kappa or lamda chain transformation into amyloid consequent to monoclonal gammopathy. Forty three cases of amyloid neuropathy, diagnosed from 1974-2003 at Victor Segalan University in Bordeaux, France, were reviewed to determine the clinical and pathological characteristics of amyloid neuropathy. Eight were excluded from analysis due to lack of clinical information (n = 7), or due to the presence of a biclonal gammopathy (n = 1). Twenty two men and 13 women, ages 27-82 years, including 26 French Caucasians, 7 Portuguese, and 1 each Spaniard and Caribbean, comprised the study population (n = 35).

Chronic sensorimotor polyneuropathy of the distal legs was the presenting clinical picture in 32 patients, with chronic inflammatory demyelinating polyneuropathy, pure motor peripheral neuropathy, and impotence with minor sensory disturbances in the feet the presenting picture in 1 patient each. Amyloidosis was previously documented in 13, newly suspected in 6 based on family history or co-existence of multiple myeloma, and unexpectedly discovered on peripheral nerve biopsy in 16. Biopsies were taken from the superficial peroneal nerve and peroneus brevus muscle.

Acidophilic amyloid deposits were easily seen under light microscopy in 22 specimens, and also when stained both with Congo red and thioflavine S. Solitary, small deposits of endoneurial amyloid were seen in 4, but ultrastructural examination was required to reveal amyloid in 6, and Congo red and thioflavine S staining was needed in 3. Striking myelinated fiber loss was evident in 34, affecting predominantly large (n = 15), or both large and small fibers (n = 15), with 4 showing primarily small fiber loss. Unmyelinated fibers were affected in all cases, and segmental demyelination was seen in 10. Amyloid must be included in the differential diagnosis of axonal and demyelinating polyneuropathy and, given the occasional paucity of findings, whole-nerve biopsy with muscle taken from the same incision is recommended. If routine staining is negative for amyloid, Congo red and thioflavine S staining need be performed, with ultrastructural examination of Epon-embedded nerve. Anti-light-chain and transthyretin immunostaining of frozen nerve completes the investigation.

COMMENTARY

Amyloidosis, the result of insoluble fibril deposition in the extracellular space, due to an abnormality of protein folding, is classified according to the fibril precursor protein (*Sem Cell Dev Biol.* 2004;15;39-44). Deposits may occur in multiple organs or be restricted to certain tissues or vessels. Primary (AL) amyloidosis is the most common systemic amyloidosis, and is seen with monoclonal plasma cell dyscrasias, developing consequent to monoclonal immunoglobulin light chain fragments depositing as fibrils in any organ other than the brain. Prognosis is poor. Secondary (AA) amyloidosis, a reactive disease associated with chronic inflammatory diseases, results from the acute phase reactant serum amyloid A protein acting as the fibril precursor. Unlike AL amyloid, it is rare in the heart and peripheral nervous system, most often affecting the kidneys. Long-term hemodialysis is often complicated by 2-microglobulin amyloidosis (A 2M), due to impaired clearance of this HLA class I cell surface molecule. Senile systemic amyloidosis (ATTR), with normal plasma transthyretin serving as the fibril precursor protein, is often asymptomatic or may cause cardiac failure.

Hereditary amyloidoses are more recently recognized. Fibrinogen A-chain, transthyretin, apolipoprotein AI or AII, lysozyme, cytostatin C, and gelsolin are among an increasing number of proteins, mutations of which result in amyloidosis. Familial amyloid peripheral, autonomic neuropathy (genetically variant transthyretin), and cerebral amyloid angiopathy with recurrent lobar hemorrhage (genetically variant cytostatin C) are some of the neurologic diseases identified for which rational therapies may be devised as understanding of these conditions advances.

— MICHAEL RUBIN

CME Questions

4. **All of the following are potential therapies for acute ischemic stroke EXCEPT:**
   a. Transcranial Doppler augmentation for IV tPA
   b. MERCI mechanical embolectomy device (clot retriever)
   c. IV tPA
   d. IV Streptokinase

5. **Periodic sharp-wave complexes have been found in which of the following conditions:**
   a. Sporadic Creutzfeldt-Jakob Disease.
   b. KURU.
   c. Gerstmann-Straussler-Scheinker Syndrome.
   d. Fatal familial insomnia.
   e. New variant CJD.

6. **Which of the following are true?**

IVIG treatment in MS has been beneficial in the following setting(s):
   a. acute relapses
   b. secondary progressive MS
   c. first demyelinating event
   d. A and C

7. **Choose the correct statement**
   a. Autonomic dysfunction is found in 73% of type 1 diabetics.
   b. Autonomic dysfunction was found in 54% of type 2 diabetics.
   c. Comparing type 1 and 2 patients, type 2 patients demonstrate greater problems with diarrhea and urinary domains.
   d. Peripheral neuropathy is much more frequent than autonomic neuropathy in diabetes.
   e. None of the above are true

8. **Amyloidosis:**
   a. May almost always be diagnosed by routine staining and using light microscopy.
   b. Rarely requires full thickness nerve biopsy for diagnosis.
   c. Should not require concomitant nerve and muscle biopsy for diagnosis.
   d. Always requires anti-light-chain and transthyretin immunostaining of frozen nerve for complete diagnosis.
   e. Is untreatable and therefore not cost effective to diagnosis.

Answers: 4. (d); 5. (a); 6. (c); 7. (c); 8. (d)

CME Update Symposium

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Statins and the Incidence of Rhabdomyolysis

The most commonly prescribed statins have a low incidence of rhabdomyolysis, according to the results a new study of more than 250,000 patients. Atorvastatin, pravastatin, and simvastatin were found have very low and virtually indistinguishable rates of rhabdomyolysis of 0.44 per 10,000 person-years (95% CI, 0.20-0.84). The data were obtained from 11 managed care health plans across United States from January 1, 1998, through June 30, 2001. Cerivastatin (Baycol-Bayer), which was withdrawn from the market in 2001, was found have a much of a higher rate of rhabdomyolysis, 5.34 cases per 10,000 person-years (95% CI, 1.46-13.68). The concomitant use of a fibrate with atorvastatin, pravastatin, or simvastatin was found to have increased the rate to 5.98 (95% CI, 0.72-216.0), while use of a fibrate with cerivastatin dramatically increased the rate to 1035 cases per 10,000 person-years of treatment (95% CI, 389-2117), or nearly 1 in 10. Older patients, especially those with diabetes, were found to have higher rates of rhabdomyolysis. The authors conclude that the most commonly prescribed statins have a low incidence of rhabdomyolysis, which is increased with the addition of a fibrate (*JAMA.* 2004;292:2585-2590).

The study confirms the safety of the most commonly used statins, but raises issues regarding the post marketing surveillance of cerivastatin. These concerns were addressed in a review in the same issue of *JAMA* regarding the potential conflict of interest once initial reports of rhabdomyolysis were reported to the company, and the delay in the availability of this information to consumers. The critique is accompanied by Bayer's rebuttal (*JAMA.* 2004;292:2622-2631, 2643-2646, 2655-2657, 2658-2659), which makes fascinating reading given the recent criticisms of the FDA and post marketing surveillance regarding coxibs.

A Crackdown on Importation of Drugs

Officials in both the United States and Canada are taking steps to crack down on the importation of prescription medications across the border. A New York District Court issued an injunction in December against Canada Care Drugs Inc., which gave the FDA authority to inspect the company to assure that they no longer import drugs to American consumers. The FDA had petitioned the court to take this action based on a sting operation run by the agency. FDA investigators purchased Neurontin and Sporanox through Canada

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Care. Instead of Neurontin, investigators received APO-gabapentin and NOVO-gabapentin, formulations of the drug that are not subject to FDA scrutiny in this country. The Sporanox shipment included 84 tablets of the correct drug, but investigators felt that the amount was excessive, determining that patients should not take Sporanox continuously without checking with their physician. The court is scheduling a trial date for Canada Care, an action that is sure to put other Canadian importation companies on alert. Meanwhile, the Canadian government is also cracking down on Internet pharmacies that export drugs to the United States without evaluation by Canadian doctors. The government is considering making it illegal for Canadian doctors to countersign prescriptions from other countries. This move in Canada is prompted by concern over shortages of drugs for Canadian citizens, especially given threats by American drug companies to withhold additional shipments of drugs to Cananda, where they have strict price controls, knowing that many of these drugs may come back to the US market were there are no price controls. These moves are strongly supported by PhRMA, the powerful pharmaceutical advocacy group.

FDA Actions

The FDA has approved a new non-benzodiazepine hypnotic for the treatment of insomnia. Sepracor, a company that specializes in marketing active isomers of currently approved drugs, has received approval to market eszopiclone, the active (S)-isomer of zoplicone, which is available outside the United States. The drug is similar to zopidem (Ambien) and zaleplon (Sonata) in that it has a lower incidence of tolerance, dependence, and withdrawal symptoms than benzodiazepines. Based on a 6-month, double-blind, placebo-controlled safety and efficacy trial, the FDA decided not to limit eszoplicone's indication to short-term use. Eszoplicone will be available in 1mg, 2mg, and 3mg tablets, and will be marketed in United States under the trade name Lunesta. Sepracor is also studying the drug for treatment of insomnia in patients with depression or pain, and in peri-menopausal women.

Novartis has received approval to market darifenacin extended release tablets for the treatment of overactive bladder with symptoms of urging incontinence, urgency, and frequency. The drug is an M3 (muscarinic) receptor blocker that increases urinary capacity and decreases urinary episodes and frequency of incontinence, along with feelings of urgency. Darifenacin, which is already available in Europe, will be marketed in the United States as Enablex.

Drugs approved under the FDAs accelerated approval program are often approved on the basis of surrogate end points, such as tumor markers that would indicate the likelihood of clinical benefit. The FDA, however, requires that cancer drugs in particular, must document clinical benefit in subsequent studies to remain marketable. A recent case-in-point is AstraZeneca's gefitnib (Iressa), which was approved for treatment of non small cell lung cancer in patients who failed other courses of cancer therapy. A recent study of gefitnib involving nearly 1700 patients failed to show a survival benefit better than placebo. The drug, which was initially approved in 2003, now faces a FDA review to determine whether the drug will be removed from the market. In a letter to physicians, AstraZeneca "urges you to consider other treatment options in recurrent non small cell lung cancer patient population." In the meantime, Genentech and Roche's erlotinib (Tarceva), which has shown survival benefit for the same patient population, remains a viable option.

The FDA has issued a Public Health Advisory regarding the use of anti-inflammatories including COX-2 inhibitors because of recent indications that the drugs may increase the risk of cardiovascular disease and stroke. The agency is requiring evaluation of all prevention studies that involve the COX-2 inhibitors celecoxib (Celebrex) and valdecoxib (Bextra) to ensure that adequate precautions are in place. Several prevention studies regarding potential benefit of these drugs on colon polyps and Alzheimer's disease are either in progress or planned in the near future. Meanwhile, the agency is recommending that physicians should prescribed Celebrex or Bextra with caution, particularly in patients at risk for cardiovascular disease, and should weigh the risk vs benefits.

The FDA is also recommending that consumers should use over-the-counter anti-inflammatories in strict accordance with the label directions, taking them for no longer than 10 days without consulting a physician. ■