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Scooped: American Migraine Study II

ABSTRACT & COMMENTARY

Source: National Headache Foundation Expedited Press Release, March 2000.

A new american study (ams ii) by the national headache Foundation (underwritten by a grant from Glaxo Wellcome Inc.) was undertaken to measure the prevalence of migraine and the effect this chronic illness has on the daily lives of patients. The study was designed to replicate the seminal 1989 American Migraine Study I (Stewart WF, et al. *JAMA* 1992;267:64-69) and compare fundamental changes in patient management over the past 10 years in light of significant scientific breakthroughs and the emergence of the triptan class of medications.

A 20-item symptom screening and impact questionnaire following International Headache Society (IHS) guidelines was mailed to 20,000 U.S. households in 1999. Approximately 13,869 completed questionnaires were returned (69.3% response rate) and included data from 29,258 individuals aged 12 and older. The study identified 12.6% (compared to 12.1% in 1989) of the population, or an estimated 28 million Americans (compared to an estimated 24 million in 1989), suffering from migraine.

Other key findings include:

- 48% of respondents who met IHS criteria for migraine still report never having their condition diagnosed by a physician (compared to 65% undiagnosed in 1989).
- 57% of migraine sufferers reported using only over-the-counter medications for treatment, virtually the same as 59% 10 years ago.
- 80% of respondents reported their headaches as severe, including 24% who sought care at an emergency room.
- 51% of sufferers report a 50% or more reduction in work and/or school productivity; 66% report a 50% or more reduction in household work.

COMMENTARY

The AMS II confirms the high prevalence and significant mor-

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bidity associated with migraine. It is striking to note the similarities in findings with the original Stewart et al study (AMS I). Over the past 10 years, diagnosis and treatment of migraine has not progressed despite the revolution in migraine treatment as initially promised by the new triptan class of drugs. Migraine as a legitimate medical condition has not even gained in appreciation despite major scientific breakthroughs in migraine research using positron emission tomography (PET) and fMRI to identify dynamic blood flow changes in the cortex of migraine sufferers, as well as genetic studies localizing the subgroup of autosomal dominant familial hemiplegic migraine patients to chromosomes 1 and 19.

As the current survey reconfirms, migraine patients suffer major disability ranking among the lowest by any number of quality-of-life parameters. The chief problem has been a lack of education and understanding on the part of both patients and physicians. Neurologists must take the lead to ensure progress in overall migraine care and provide relief to this often neglected group of patients. **—jr**

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VICE PRESIDENT/ GROUP PUBLISHER: Donald R. Johnston.
EXECUTIVE EDITOR: Glen Harris.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
ASSOCIATE MANAGING EDITOR: Robin Mason.
ASSISTANT MANAGING EDITOR: Neill Larmore.
COPY EDITOR: Michelle Moran.

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Customer Service E-Mail Address: customerservice@ahcpub.com
Editorial E-Mail Address: michelle.moran@medec.com
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White Matter Cerebral Changes Related to Cognition

ABSTRACTS & COMMENTARY

Sources: de Groot JC, et al. Cerebral white matter lesions and cognitive function: The Rotterdam scan study. *Ann Neurol* 2000;47:145-151; Smith CD, et al. White matter volumes and periventricular white matter hyperintensities in aging and dementia. *Neurology* 2000;54:838-842.

These two reports explore the relationships between cerebral white matter lesions and cognitive dysfunction in two different groups of elderly patients. During a single year, de Groot and colleagues obtained magnetic resonance images (MRIs) to determine the association of white matter lesions (WML) with cognitive scores in 1077 relatively healthy, elderly Dutch persons. The entire group was stratified into five quintiles of declining numbers between the ages of 60 and 90 years. Some severely demented individuals apparently were excluded. Average minimental scores for the seventh, eighth, and ninth decades ranged between 26.8 and 27.8 (perfect = 30). The total 80- to 89-year group, however, included less than half the number of persons of either the 70-79 or the 60-69 year group. Similarly, the group average median age of the 80-89 year patients was 1.5 years younger than the subjects aged 60-69 years. Smith and colleagues took a different approach. They studied the autopsied brains of 52 aged nuns and correlated the application of postmortem MRI brain imaging with direct pathological examinations of the brains at autopsy.

The Dutch study correlated the relationships between periventricular and subcortical (remote from the ventricular borders) WMLs either singularly or together with neurocognitive capability. Particular attention was given to psychomotor speed, memory performance, and global cognition. WMLs were measured by both proton density and T2-weighted MRIs. Periventricular zones of interest included frontal and occipital WML caps, plus similar adjacency to the walls of the lateral ventricles. Subcortical WML volumes were calculated on hard copy by their diameters and termed small (1-3 mm), medium (3-10 mm), or large (> 10 mm). Overall brain atrophy or numbers of cerebral infarctions were not influential. Increased WMLs found in both periventricular and subcortical areas were associated with worsening mental status. Persons in the older quintiles, however, who did not

increase the periventricular WMLs did not change their cognitive index rating. Some of them, however, selectively increased their subcortical WMLs but remained cognitively stable.

The Smith group of 52 nuns all possessed a long history of good health, good nutrition, and an average 15-16 years of education. Their age of death averaged 89.1 ± 4.8 years. Thirty-three of the 52 met the pathological anatomic criteria for Alzheimer's disease (AD), but only 19 of the 33 were clinically identified as demented by standard cognitive testing. Total brain and white matter volumes were lower than was found in the nondemented nuns and their brain weights were lower as well (P = 0.06). Of the remaining 19 nuns, three were clinically demented. Two of the latter showed hippocampal sclerosis and one possessed large infarcts and many lacunes.

The interesting finding is that postmortem studies using T-1- and T-2-weighted MRIs on the nuns' brains failed to correlate periventricular areas with white matter hyperintensity with dementia. Nevertheless, the demented brains, whether with AD, had proportionately lower absolute overall white matter volumes, although total brain weight was reduced even more. De Groot et al conclude that "the cerebral atrophy found on MR imaging is strongly related to the presence of dementia" (despite) "a lack of association with hyperintensities" on MRI films.

COMMENTARY

These two informative reports might at first glance appear to be antithetical. Much neurological literature has emphasized that periventricular white matter hyperintensities, with or without subcortical white patches, associate with cognitive decline. DeGroot et al, who were dealing with five quintiles of age between 60 and 90 years, selectively excluded an increasing population of severe dementia at later ages. Not unexpectedly, the older the quintile, the greater the proportion of brains succumbing to progressive dementia associated with periventricular hyperdensities-WELs. This inference may explain why many fewer subjects older than 78 years could be found to have high mini-mental scores and still retain high amounts of periventricular WELs. Estimates of brain volumes were not performed, but by the third quintile group (age 78 years), periventricular damage appeared far more serious than subcortical lesions.

Now, examine Smith et al's postmortem MRI findings of brain volumes and brain weights on old, old persons with a mean age of 89.1 ± 4.8 years. As presented, 33 of the 52 had pathological evidence of AD, but only 19 of the ADs expressed clinical dementia. Among the other 19 nuns free of AD by pathological criteria, two who were demented had hippocampal sclerosis and one more had multifocal brain infarction. Is it possible that the nuns managed to reach 89 years because none of them had acquired the leucoencephalopathy that deGroot found in younger persons? Is the periventricular leucoencephathy an early elderly illness associated with chronic hypertension, diabetes, hypercholesteremia, alcoholism, or, perhaps, AD? Whatever the answer, further analysis and management may generate some protection for many persons around the world as they move into their late eighth decade. **—fp**

Dizziness: A Geriatric Syndrome

ABSTRACTS & COMMENTARY

Sources: Tinetti ME, et al. Dizziness among older adults: A possible geriatric syndrome. *Ann Intern Med* 2000;132: 337-344; Drachman DA. Occam's razor, geriatric syndromes, and the dizzy patient. *Ann Intern Med* 2000;132:403-404.

Tinetti and colleagues studied 1087 community-living elderly persons to determine the predisposing characteristics and situational factors associated with dizziness. Dizziness was categorized into four groups of symptoms: loss of balance, near-fainting, spinning or movement, and other or multiple sensations. Tinetti et al used an interview and questionnaire to assess medical history and symptoms, standard tests such as the mini-mental state exam, and psychiatric inventories to assess cognition, effect, and anxiety state. Physical examinations were limited to screening tests of blood pressure, balance, and hearing. Of the participants, nearly one-quarter (261; 24%) reported long-term recurrent episodes of dizziness. More than half of dizzy persons (56%) described several sensations and almost three-quarters (74%) reported several positions or activities that were associated with the occurrence of dizziness. Getting up from either lying down or sitting, turning either the head or the entire body, and being upset or anxious were the most frequently reported triggering activities.

Seven characteristics were associated with dizziness: anxiety, depression, impaired balance, previous myocardial infarction (MI), postural hypotension, five or more medications, and impaired hearing. The more of these characteristics that elderly patients had, the more likely

they were to report dizziness. Tinetti et al conclude that dizziness may often be multifactorial in origin and, as such, is similar to other "geriatric syndromes" such as falling, delirium, and urinary incontinence.[1,2]

In an accompanying editorial, Drachman agrees with Tinetti et al that dizziness, especially among the elderly, is often due to multiple disorders involving multiple organ systems. He recalls the "all-too-familiar dizzy patient who has cataracts, hearing loss, peripheral neuropathy, cervical spondylosis, and atrial fibrillation and takes a number of medications for these conditions."

Drachman also points out that the questions asked and screening tests used by Tinetti et al in their epidemiologic study are not the way physicians, especially neurologists, diagnose the cause of dizziness in patients. The physician must sort out the diagnosis by taking a detailed history to identify specific and distinctive symptoms and then perform a physical examination that evaluates cognition, vision, vestibular function, coordination, peripheral sensation, and motor functions.

Finally, Drachman fears that identifying dizziness as a "geriatric syndrome" may suggest not only that multiple problems can produce the symptoms, but also that it is just another undiagnosable and untreatable condition of old age.

COMMENTARY

Equilibrium and stability result from interactions among multiple organ systems. Therefore, it is not surprising that Tinetti et al found an association between multiple predisposing factors and dizziness. In their study, both depressive symptoms and antidepressant drugs were associated with dizziness. Furthermore, the strong relation between numbers of medications and dizziness supports the need to review the possible role of medication side effects in patients who have dizziness.

The study supports a comprehensive approach to the dizzy patient and suggests that clinicians should not only seek to diagnose one discrete cause for dizziness but also try to identify potentially treatable contributing factors. **—jjc**

References

1. Tinetti MC, et al. Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes. *JAMA* 1995; 273:1348-1353.
2. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA* 1996;275:852-857.

Valproate Has a Benign Effect on Cognition and Possibly for Myoclonic Status Epilepticus

ABSTRACTS & COMMENTARY

Sources: Dikmen SS, et al. Neuropsychological effects of valproate in traumatic brain injury: A randomized trial. *Neurology* 2000;54:895-902; Sheth RD, Gidal BE. Intravenous valproic acid for myoclonic status epilepticus. *Neurology* 2000; 54:1201.

Valproate already enjoys a reputation of being an anticonvulsant that has the fewest cognitive effects. It is difficult to obtain hard data that confirms this. Put briefly, anticonvulsants may improve cognitive function in the epileptic by controlling seizures, yet worsen baseline cognitive function as the attacks subside. Indeed, few large studies have specifically examined the cognitive effects of anticonvulsants in the absence of clinically expressed seizures. Dikmen and colleagues report the neuropsychological outcome of 279 nonepileptic patients randomized to receive anticonvulsant treatment vs. placebo following traumatic brain injury. Patients were randomized to three arms of the study: 1) one week of phenytoin; 2) one month of valproate; or 3) six months of valproate. After completing treatment, patients in the first two groups received placebo until six months after injury. Patient outcome and neuropsychological testing after one month and six months constituted the primary measures of treatment effect. As this population experienced few seizures—of 279 patients, there were a total of five seizures in the first month and seven in the subsequent five months distributed randomly across treatments—the cognitive effects of anticonvulsants were not confounded by treatment of frequent seizures.

Dikmen et al found no significant change in cognitive function between treatment groups tested one month and six months after injury. Patients taking valproate for one or six months fared no worse or better than patients taking phenytoin (Dilantin; Parke-Davis) for one week followed by placebo. Valproate produced no additional cognitive impairment. In contrast, there was a trend toward higher mortality in both of the valproate-treated groups ($P = 0.07$) when compared to the phenytoin-treated group. These investigators conclude that valproate neither prevented post-traumatic seizures, nor did it worsen cognitive function.

A series of recent case reports document the first experience with intravenous valproic acid in the treatment of nonconvulsive status epilepticus. The latest of these communications—a letter from Sheth and Gidal—reports the first intravenous use of valproate in two patients with juvenile myoclonic epilepsy. Both patients presented initially with a subacute impairment of mentation accompanied by myoclonic jerks and paroxysmal changes on electroencephalogram (EEG) despite ongoing treatment with appropriate doses of lamotrigine in one patient, and of phenytoin in the other. Both patients received 500 mg valproic acid intravenously over 30 minutes. Almost immediately upon completion of the valproate infusion, both patients returned to their preseizure baseline mental status.

COMMENTARY

More experience with intravenous valproate is necessary before it can be accepted as first-line treatment for nonconvulsive status epilepticus. Primary generalized epilepsies, especially juvenile myoclonic epilepsy, however, often respond well to valproate. In patients whose underlying epilepsy is known to be sensitive to valproate, intravenous valproic acid may provide an effective treatment of myoclonic status epilepticus without risk of sedation. In cases of nonconvulsive status epilepticus in which the underlying seizure disorder is known to respond to valproate, clinicians should consider the risks of sedation or other side effects from first-line anticonvulsants. As a start, one could compare benzodiazepines or phenytoin against the potential benefit and side effects of intravenous valproate. But, a note of caution should appear. As with phenytoin, intramuscular injection of valproate can cause tissue necrosis. Furthermore, since valproate inhibits the metabolism of lamotrigine, physicians should adjust the latter's dosage if valproate is added to the daily regimen. **—fal**

Brain Amyloid Levels Mirror Dementia Severity in Alzheimer's Disease

ABSTRACT & COMMENTARY

Source: Naslund J, et al. Correlation between elevated levels of amyloid beta-peptide in the brain and cognitive decline. *JAMA* 2000;283:1571-1577.

A plethora of evidence from genetic, biochemical, and physiologic studies suggests that amyloid beta protein (a β accumulation is among the earliest steps in a cascade of events that leads to the pathogenesis of Alzheimer's disease [AD]). Nevertheless, several past investigations have failed to find a correlation between amyloid burden in the brain and the severity of dementia in AD. Instead, neurofibrillary tangles and neuronal/synaptic loss have been found to correlate more closely with the degree of cognitive impairment. This issue is potentially important to future treatment strategies. If amyloid accumulation is relevant only to the preclinical stages of the illness, anti-amyloid therapy is less likely to be valuable in treating patients already suffering from dementia. Naslund and colleagues, however, provide evidence that brain amyloid levels are already elevated prior to the clinical onset of AD and continue to rise in direct correlation with the severity of dementia.

This study examined the autopsied brains of 79 nursing home residents whose cognitive and behavioral status was evaluated during the last six months of life using the Clinical Dementia Rating (CDR) scale. The cohort included 16 cognitively normal individuals (CDR = 0), 11 with questionable dementia (CDR = 0.5) and comparable numbers of cases with mild (CDR = 1), moderate (CDR = 2), and severe dementia (CDR = 4 or 5). All subjects with dementia had definite AD by formal neuropathological criteria. The levels of Aβ peptides ending at the 40th or 42nd amino acid position were assayed using a sensitive ELISA technique in tissue homogenates derived from five cortical regions. Immunostaining for the tau protein in frontal cortex was also performed, and the correlation between tau pathology and amyloid burden was examined as a function of CDR stage.

Levels of both the 40 and 42 species of Aβ were found to be elevated at early stages of dementia in the five brain areas examined. Aβ peptide levels increased with progression to higher CDR stages, indicating that the intracerebral amyloid burden increases with progression of cognitive decline. In frontal cortex, increased Aβ levels preceded the appearance of abnormal tau staining in neurons, consistent with amyloid accumulation being one of the initial events in development and subsequent propagation of AD neuropathology throughout the brain.

COMMENTARY

Several past studies that failed to find a correlation between regional amyloid plaque density and the severity of AD-related dementia used conventional histologic immunohistochemical techniques. The Naslund study used well-characterized, highly specific antibodies

against the major Aβ species, and assayed both soluble and fibrillar forms of Aβ in multiple brain regions. Another advantage to the current investigation was the availability of brain tissue from a sizable number of early-stage dementia patients and mildly impaired individuals considered at increased risk for AD. Shortcomings include the absence of immunohistochemical studies of the amyloid pathology (i.e., stereologic plaque counts) and the correlative nature of the analyses performed. Nevertheless, the study provides strong additional evidence in favor of the amyloid hypothesis and suggests that Aβ is important to the progression of AD as well as its initiation. Work is ongoing to develop and test anti-amyloid therapies for AD. The demonstration that levels of Aβ in the brain are elevated in preclinical stages of dementia and continue to rise in association with disease progression provides an important rationale for vigorously pursuing this promising line of therapy. **—nrr**

Alzheimer's Patients Fail to Improve in Estrogen Trial

ABSTRACT & COMMENTARY

Source: Mulnard RA, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: A randomized controlled trial. *JAMA* 2000;283:1007-1015.

The hypothesis that estrogen replacement therapy can be used as a treatment for Alzheimer's disease (AD) was supported by the results of several small, open-label pilot studies over the past decade. No large-scale or well-controlled prospective trials examining estrogen's effects on cognition in AD patients had been carried out until the Alzheimer's Disease Cooperative Study Group initiated a randomized, double-blind trial in hysterectomized AD patients in 1995. This group now reports that estrogen treatment for a period of one year is no better than placebo in maintaining the cognitive status and daily functioning of female AD patients.

One hundred twenty hysterectomized women with mild to moderate AD participated in this trial. The study was restricted to women who had undergone hysterectomies to permit the use of estrogen unopposed by progesterone over a one-year period. Participants ranged in age from 56-91 years and had Minimental State Exam (MMSE) scores between 12 and 28. The three-armed design compared daily use of 0.625 mg and 1.25 mg of conjugated equine estrogen (premarin) to placebo. Women who had been previously treated with estrogen were admitted into the study. The primary outcome measure was the seven-point Clinical Global Impression of Change score. A variety of secondary outcome measures were used to assess changes in cognition, mood, and activities of daily living.

A total of 97 participants completed one year of treatment. At one year, there were no significant positive differences on either the primary or the secondary outcome measures between the estrogen-treated patients and those who received placebo. One secondary measure, the Clinical Dementia Rating Scale, actually indicated a marginally greater decline in the estrogen-treated group. At two and six months of treatment, patients receiving 0.625 of estrogen did score higher on the MMSE, but they did not show comparable performance advantages on any of the other tests used. In supplemental analyses, no significant difference was observed between patients receiving the low- and high-dose estrogen regimes. Mulnard and colleagues conclude that estrogen is not of benefit in the primary treatment of AD, but further studies are needed to examine its potential use in the prevention of AD.

COMMENTARY

This well-designed trial took more than four years to complete. Although fewer patients completed the study than were originally planned, the lack of a trend toward statistical significance on any of the one-year outcome measures argues against the negative results being a function of sample size. There were some possible biases introduced by the study's inclusion criteria. The inclusion of AD patients who had been previously treated with estrogen was pragmatically necessary but could be potentially problematic if it selected out a group of patients who developed AD despite receiving hormonal treatment. Likewise, the inclusion of women with relatively advanced dementia may have adversely affected the results, since estrogen receptors occur in highest concentration in areas of the brain such as the amygdala and hippocampus that are presumably affected much earlier in the course of AD. It is conceivable that other benefits of estrogen accrue early in the disease process, or with longer treatment times, than were used in this study. In the latter part of the study, patients receiving donepezil were permitted to participate, and no detailed analysis of the results stratified by donepezil status was presented in the published manuscript. Nevertheless, it is undeniable that the largest prospective study to date addressing the value of estrogen replacement therapy in treatment of patients with AD has failed to show significant benefits.

Several retrospective epidemiologic studies have indicated that estrogen replacement therapy may

reduce the risk of AD when initiated during the postmenopausal period. There is still considerable reason for optimism that the putative preventative effects of estrogen will be borne out in the prospective studies that are currently ongoing. The lack of apparent benefits of unopposed estrogen therapy in this one-year study does not preclude it possibly being of value as an adjunct treatment for AD. An ongoing study is examining whether estrogen boosts the beneficial effects of cholinesterase therapy, an effect previously observed in retrospective studies and which is mechanistically plausible based on estrogen's known biological effects. **—nrr**

Neurotherapeutic Alerts

Muscle or Nerve Biopsy for Vasculitis

Source: Claussen GC, et al. Diagnostic value of nerve and muscle biopsy in suspected vasculitis cases. *J Clin Neuromusc Dis* 2000;1:117-123.

Based on a retrospective review of 115 nerve and muscle biopsies performed over 20 years to rule out or confirm vasculitis (101 cases) or peripheral neuropathy (14 cases), nerve biopsy appears more sensitive than muscle biopsy for the diagnosis of suspected vasculitis. All 115 patients—58 men and 57 women—underwent both nerve and muscle biopsy, the sural nerve in all, and the tibialis anterior, gastrocnemius, vastus lateralis, deltoid, or biceps as the chosen muscle, depending on clinical involvement. Vasculitis was defined as definite (active or inactive) or probable, and myositis was defined by the presence of muscle necrosis and perivascular or endomysial inflammatory cells.

Muscle never demonstrated vasculitis in the absence of nerve vasculitis, although in three cases the muscle was definite, whereas the nerve was only probable. In 26 cases, nerve but not muscle showed vasculitis. Sixteen (14%) showed myositis without vasculitis and in seven of these, vasculitis was found in nerve. Overall, 45 biopsies (39%) demonstrated vasculitis, significantly more often (P = 0.0001) in nerve (n = 45; 39%) than muscle (n = 19; 17%).

COMMENTARY

The debate continues, with studies reporting either nerve or muscle biopsy as more sensitive for vasculitis. Until the dust settles, if ever, cases of suspected vasculitis require both nerve and muscle biopsy, particularly if electrodiagnostic studies show abnormal sural sensory nerve conduction studies. **—mr**

IVIG, not Pheresis, for GBS with Anti-GM1b Ganglioside

Source: Yuki N, et al. Clinical features and response to treatment in Guillain-Barré syndrome associated with antibodies to GM1b ganglioside. *Ann Neurol* 2000;47;314-321.

Among 132 guillain-barré syndrome (gbs) patients who participated in the Dutch GBS trial and for whom suitable pretreatment serum was available, 25 (19%) demonstrated high anti-GM1b antibody titers of the IgG (n = 15) or IgM (n = 14) isotype, or both (n = 4). Compared to GM1b antibody-negative patients, antibody-positive patients more frequently experienced preceding diarrhea and serologic evidence of recent *C. jejuni* infection, without antecedent evidence of CMV, EBV, or *M. pneumoniae*. Onset was more rapid, limb weakness more severe, distal weakness more prominent, recovery time more prolonged, and response to intravenous immunoglobulin (IVIG), compared to plasmapheresis, was significantly faster in the GM1b antibody-positive cases. Cranial nerve involvement, paresthesiae, and sensory deficits were less frequent, whereas electrodiagnostic findings were not significantly different in the antibody-positive or negative cases. Comparison IgG vs. IgM GM1b antibody-positive patients revealed that IgM positive cases did not differ from antibody-negative patients with respect to cranial and sensory nerve involvement and time to peak severity. GM1 and GM1b antibody-positive patients demonstrate similar clinical features, but identification of the specific anti-GM1b antibody in GBS may have therapeutic ramifications.

COMMENTARY

The precise role of GM1 antibodies in GBS pathogenesis remains unclear. Their presence in sensory ganglia and sensory axons begs the question of why GBS has a predilection for motor involvement. GM1 antibody interference with sodium and potassium currents may result in conduction block (Waxman SG.

Ann Neurol 1995;37:421-423), but their binding to nodes of Ranvier, activating the complement cascade, did not cause such block (Paparounas K. et al. *Brain* 1999;122:807-816). Perhaps axonal destruction ties these observations together, but if that were true, how would one explain rapid improvement in axonal GBS? Conceivably, reversible distal conduction block at the motor nerve terminal might generate the phenomenon (Kaji R. *Brain* 1999;122:797-798). Further study should clarify this present puzzle. **—mr**

Advice for Slap-Happy Electromyographers!

Source: Pohl M, et al. Insertion pain in needle electromyography can be reduced by simultaneous finger slapping. *Neurology* 2000;54:1201-1202.

Finger-slapping the patient's skin adjacent to, and simutaneously with, needle insertion during electromyography (EMG) study significantly ($P < 0.001$) decreases the pain intensity of EMG study. Using a 100-mm visual analog scale among 77 patients, finger-slapping reduced pain from a mean of 13.8 mm to 6.7 mm on first insertion, and from 22 to 7.5 on second needle insertion. Should the patient forget to premedicate with analgesics (LaJoie WJ. *Arch Phys Med Rehabil* 1963;44:42-44), should audio analgesia be not available (Spence WR, et al. *Arch Phys Med Rehabil* 1966;47:771-774), or should monopolar needles simply not do the trick, this manueuver can't hurt! One cautionary note: take care not to prick your slap-happy finger with the needle! **—mr**

CME Questions

15. For the diagnosis of vasculitis:
a. nerve biopsy is definitely more sensitive than muscle for the diagnosis of suspected vasculitis.
b. nerve biopsy is definitely less sensitive than muscle for the diagnosis of suspected vasculitis.
c. neither nerve nor muscle biopsy is warranted.
d. it is most prudent to perform both muscle and nerve biopsy.

16. Which statement is correct?
a. Both deGroot et al and Smith et al found comparative loss of brain white matter in elderly, demented patients.
b. Smith found dementia in 33 nuns, all with pathological Alzheimer's disease.
c. Periventricular and subcortical leucoencephalography were equally associated with dementia in the Dutch study.
d. The Dutch study followed patients for five years, but the Smith study examined only postmortem brains.

17. Dizziness in the elderly is "a geriatric syndrome" because:
a. it is a normal part of aging.
b. it is undiagnosable and untreatable.
c. it often is the product of multiple conditions.
d. None of the above
e. All of the above

18. Following traumatic brain injury, treatment with valproic acid was associated with:
a. increased mortality at six months.
b. increased incidence of myoclonic status epilepticus at six months.
c. improved cognitive function at six months.
d. cognitive impairment in nonepileptic patients.
e. worsened cognitive function at six months.

19. Amyloid levels in the brain:
a. rise before the onset of Alzheimer's, then plateau thereafter.
b. do not rise until late in Alzheimer's disease.
c. are normal at the onset of Alzheimer's, then decline.
d. rise before the onset and throughout the course of AD.

20. The use of estrogen in the treatment of Alzheimer's disease:
a. is warranted based on the results of a recent double-blind treatment trial.
b. is possible in hysterectomized women only.
c. has clear benefits for cognition after one year of high-dose therapy.
d. has comparable effects to placebo irrespective of dosage.

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