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Relief for Postherpetic Neuralgia

ABSTRACT & COMMENTARY

Source: Kotani N, et al. Intrathecal methylprednisolone for intractable postherpetic neuralgia. *N Engl J Med* 2000;343:1514-1519.

Methylprednisolone was administered intrathecally, once-a-week for up to four weeks, in this randomized, blinded, controlled, clinical trial of 277 patients, to determine its efficacy for postherpetic neuralgia (PHN) involving spinal dermatomes. All patients had intractable PHN, defined as at least one year of burning, lancinating pain with allodynia in the originally affected dermatome. Exclusionary criteria included trigeminal area pain, prior neurolytic nerve blocks, polyneuropathy, or an immunocompromised state. On study entry, all patients received conventional systemic treatment (tricyclic antidepressants, anticonvulsants, topical creams, physiotherapy) for four to six weeks, if not previously tried, followed by oral diclofenac for four weeks. Those with persistent pain were then randomized to intrathecal methylprednisolone (60 mg) plus 3% lidocaine (3 mL), or intrathecal lidocaine alone, or no treatment (control, no lumbar puncture). Only oral diclofenac, up to 200 mg/d, was permitted during the treatment and follow-up period. Patients were followed for two years. Primary end points included 10-cm visual-analogue scale assessments of pain, allodynia, and global pain relief, measurement of the maximally affected surface area as traced by an ink marker, and measurement of interleukin-8 cerebrospinal fluid concentration, elevation of which is associated with painful inflammatory conditions. Statistical analysis included one-way factorial analysis of variance, Scheffe's test, and chi-square analysis.

Astonishingly, 91% (81/89) of the methylprednisolone plus lidocaine group experienced good (50-75%) to excellent (> 75%) global pain relief. This compared to 15% (14/91) and 4% (4/90) at treatment-end in the lidocaine only and control groups, respectively, and 7% (6/91) and 3% (3/90) at four weeks post-treatment and beyond. Allodynia, burning pain, lancinating pain, and diclofenac usage were reduced by 70%, and interleukin-8 cerebrospinal fluid concentration by 50% in the methylprednisolone plus lidocaine group. This was compared to significantly less or no improvement in the other groups. No adverse effects or recurrent pain were

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recorded over two years in the methylprednisolone plus lidocaine group. Intrathecal methylprednisolone plus lidocaine appears safe and effective for intractable non-cranial postherpetic neuralgia, but longer follow-up of larger numbers of patients will be necessary to ensure that worrisome adverse effects, including adhesive arachnoiditis, have not occurred.

COMMENTARY

A milliliter of prevention is worth a kilogram of cure. Can PHN be prevented? In a randomized, prospective trial, 600 acute herpes zoster patients older than age 55 received either intravenous acyclovir (10 mg/kg thrice daily for 9 days) plus prednisolone (60 mg daily with tapering over 3 weeks), or epidural bupivicaine (0.25%, 6-12 mL q 6-8 or 12 h) plus methylprednisolone (40 mg every 3-4 days) for 1-3 weeks, as needed (*Acta Anaesthesiol Scand* 2000;44:910-918). Evaluations were performed four times over the following year and included measurements of pain using a 10-cm visual analog scale, paresthesiae using a 4-point verbal rating scale, or complete recovery. Statistical analyses were performed using two-tailed Z tests and X2 tests, the Mann-Whitney U-test, and Fisher's exact test.

Of 485 patients who completed the study, only 1.6% (4/255) of the epidural treated group complained of pain, compared to 22.2% of the intravenous group. Paresthesiae were noted in 4.3% (n = 11) and 12.2% (n = 28), respectively. Adverse effects in the intravenous group were predominantly gastrointestinal in nature. Episodic sweating or fainting (n = 2), neck pain or leg paresis (n = 1 each), and catheter dislodgment (n = 9) were reported in the epidural group. All adverse effects were reversible. Epidural bupivicaine and methylprednisolone appear significantly more effective than intravenous acyclovir plus prednisolone in preventing PHN and, pending confirmatory studies demonstrating its safety and efficacy, should be considered early on in patients at high risk of developing this disabling condition.

Once PHN develops, what therapeutic options exist? The Table below summarizes the scientific literature. **—michael rubin**

Table

Choices for PHN Treatment

Drug	Effectiveness
Topical capsaicin	conflicting evidence as to benefit
Nonsteroidal creams	of questionable value
Aspirin suspended in chloroform, ether, or acetone	of questionable value
EMLA cream	of questionable value
Lidocaine patch (LidodermTM) (*Pain* 1999;80:533-538.)	approved by FDA for PHN
Tricyclics	most widely used AD for chronic pain
SSRIs (*Pain* 1990;42:135-144; *Clin Pharmacol Ther* 1992; 52:547-552.)	may be efficacious
SNRIs (venlafaxine [Effexor]) (*West J Med* 1996;165:147-148.)	may be efficacious
Gabapentin (*JAMA* 1998;280:1837-1842.)	of proven advantage
Oxycodone (*Neurology* 1998;50:1837-1841.)	of proven advantage
Tramadol (*Clin Drug Invest* 1995;10:208-214.)	may be beneficial
Ketamine (NMDA receptor antagonist) (*Clin J Pain* 1994;10:240-242; *Clin J Pain* 1995;11:336-338)	may be beneficial, but hepatotoxic
Dextromethorphan (*Neurology* 1997;48:1212-1218.)	of no benefit

Food and Drug Administration (FDA); post herpetic neuralgia (PHN); antidepressant (AD); selective serotonin reuptake inhibitors (SSRIs); serotonin-norepinephrine reuptake inhibitor (SNRIs); N-methyl-D-aspartate (NMDA)

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Hemicraniectomy for Severe Ischemia Stroke

ABSTRACTS & COMMENTARY

Sources: Auer RN. Hemicraniectomy of ischemic stroke: Temerity or death cure? *Can J Neurol Sci* 2000;27:269; Wijdicks EF. Hemicraniotomy in massive hemispheric stroke: A stark perspective on a radical procedure. *Can J Neurol Sci* 2000;27:271-273; Demchuk AM. Hemicraniectomy is a promising treatment in ischemic stroke. *Can J Neurol Sci* 2000;27:274-277.

These three articles address the possible value of surgically removing the lateral-coronal skull (hemicraniectomy) so as to relieve compression from acute, grossly expanding, cerebral hemispheric strokes. Such circumstances usually have reflected a sudden occlusion at either the take-off of the middle cerebral artery (MCA) or the intracranial internal carotid artery to the MCA. Even more dangerous would be an additional major threat if the adjacent anterior cerebral artery also became occluded. The pathogenesis of the tissue lesions consists of progressive, expanding edema-necrosis tissues that usually reach a potentially lethal volume between 2-4 days. The process reflects the presence of ever increasing tissue osmols as cells die from anoxia; the ensuing swelling progressively compresses capillary flow and larger vessels in the enlarging penumbra of the primary lesion. The process, if not curtailed, leads to thalamic and possibly fatal brain stem compression. Wijdicks, however, notes that in his hospital-based stroke patients, mortality was 70% in those with large MCA lesions only if clinical deterioration has occurred beyond drowsiness and/or showed signs of diencephalic herniation.

Demchuk carries the flag to perform hemicraniectomy in large MCA strokes, citing several previous reports of the procedure. The first example he gives includes a study in which Rengachary and colleagues studied three persons with large, acute left hemisphere infarctions (*Neurosurgery* 1981;8:321-328). Ages were 51, 27, and 15 years; CT in all showed large areas of potential cerebral infarction. All became unconscious and had a dilated pupil ipsilateral to the side of the lesion. Craniectomy was conducted on each patient. Patients 1 and 2 became aware of self within 12 hours following surgery, but both permanently suffered "severe fixed neurological deficits." Patient 3, the boy, was alert and "seemed normal" two years afterwards.

In the second example, Carter and associates described hemicraniectomy in 14 patients suffering from acute, large infarcts affecting their nondominant hemispheres (*Neurosurg* 1997;40:1168-1176). One-year outcomes depended upon degree of regained function and were as followed: three died a cardiac death, two said "never again," and three said "maybe." Three became able to walk independently, five could walk with assistance, and nine could be at home. None regained self independence.

Demchuk's final example is a study from Schwab and associates (*Stroke* 1998;29:1888-1893) directed at applying hemicraniectomy following severe brain swelling caused by acute MCA stroke (*Neurology Alert* 1998;17:17-19). An earlier report from Schwab et al (*Cerebrovasc Dis* 1996;6:325-329) had indicated that if surgery was applied at an average of 39 hours after progressive symptoms, signs, and brain images all worsened. Of 32 patients, 11 (34%) died; but the survivors averaged a Bartle Index of 62.6. Schwab et al's more recent *Stroke* article from 1998 described 31 additional new patients who suffered from similarly large, dynamically evolving MCA strokes. They differed from the previous group and received hemicraniectomy only at an average of 21 hours following large stroke onset. Only five patients in this last group died (16%) and the Bartle Index climbed to 68.8. The meaning of this change in time is unclear, but it implies that previous decisions to pursue hemicraniectomy later in time and after onset of stroke have less vigorous healing ability.

Demchuk, a neurosurgeon on the faculty of the University of Calgary, contributes a well-described history of the use of hemicraniectomy for decompressing brain swelling in patients suffering lobar-distributed, severe MCA strokes. As he emphasizes, the procedure unquestioningly can save the lives of patients of many ages. Nevertheless, most neurologists have found that almost no patients older than about 45 years of age can recapture a normal working life after such a devastating injury. Even in younger ages a certain fraction can be permanently disabled after decompression. Nevertheless, your editor's guess is that it's far more difficult to kill young nerve and vascular tissues than old ones. The younger the brain, the more it can overcome injury and effectively change its circuitry. Nevertheless, Demchuk removes age as a factor in trying the advantages of hemicraniectomy and seems to pay little attention to what life will be like in those patients.

Wijdicks sensibly clears the problem and reasons the functional neurological processes that can potentially stave off serious injuries to the brain. Furthermore, he possesses the understanding of which age-related physiological steps might have the capacity to preserve or

protect certain injured neural systems that otherwise leave patients with life-long total invalidism.

Auer, a neuropathologist also at Calgary, wisely comments on the advantages of the hemicraniectomy trial. He points out that no functionally oxygenated capillaries lie at the deepest region of the infarct. Indeed, that's where anoxic-injured and dying cells first increase their intracellular osmols, then explode. As these molecules and cells break down, they draw water into cellular and intercellular compartments. They are first generated for defense, but it also dangerously provides the source of progressive swelling. Swelling and breaking cells enlarge the critical penumbra that expands like a water ripple to continue the anoxogenic cellular breakdown. Ultimately, normally protected capillaries become destroyed from adjacent normal arterial beds. Removing the appropriate skull could take away approximately half the pathological pressure on the tissue, thereby decompressing a large part of the compressed infarct. Common sense says that the best time to protect the tissue by skull decompressions would be done shortly after the first serious symptoms, bodily signs, and major MRI diffusion signs appear. Unfortunately, this point cannot accurately be predicted until it has passed.

As Auer puts it, "Still, the concern that supercedes all others here is that we not convert the dead into the severely impaired living." **—fred plum**

Statins May Decrease Dementia Risk

ABSTRACT & COMMENTARY

Source: Jick H, et al. Statins and the risk of dementia. *Lancet* 2000;356:1627-1631.

Jick and colleagues studying the records of thousands of patients in Great Britain found preliminary evidence that lipid-lowering statin medications may decrease the risk of developing dementia. The study was motivated by emerging evidence that the processing of certain lipids may play a role in the pathogenesis of Alzheimer's Disease (AD), as well as vascular dementia.

The study involved a case-control analysis of dementia cases and matched controls in the UK-based General Practice Research Database. This registry is derived from the medical practices of 368 general physicians who have contributed data for more than 3 million patients since 1987. Jick et al selected 284 cases of newly-diagnosed dementia, and 1080 nondemented controls that were most suitable to the purposes of their study.

Factors found to be associated with an increased risk of dementia in this patient cohort included smoking, history of coronary artery bypass surgery, and a low body mass index. Dementia was documented in only 13 patients currently using statins. Adjusting for age, gender, smoking history, vascular risks, and other possible contributing factors, the relative risk of developing dementia among current statin users was 0.29 (0.13-63%), representing a statistically significant 71% risk reduction. In contrast, the risk of dementia in patients with untreated hypertension and in patients taking other, non-statin lipid-lowering medications was not significantly different from controls. There was no significant difference in the effects of statins on men vs. women, or as a function of age.

Jick et al acknowledge that there are certain limitations to their analyses, including the lack of formal confirmation of the dementia diagnoses and the lack of available information on the nature of the hyperlipidemia or the response to medication. Nevertheless, they state that the data are compelling enough to warrant studies of the possible protective effects of statins against dementia be carried out urgently.

COMMENTARY

This report of a possible effect of statins (HMGCoA reductase inhibitors) on reducing the risk of dementia is certainly noteworthy. Statins are widely available, generally well-tolerated and effective as lipid-lowering agents, traits that would seem desirable in a potential dementia preventative intervention. However, one must be cautious about drawing far-reaching conclusions from this single observational epidemiological study. Although the case-control design reduces the likelihood of spurious associations, other explanations of the data are conceivable that would not necessarily support a protective effect of statins. For example, similar odds ratios might result if the physicians who prescribe statins happen to be less prone to diagnose dementia, or more prone to take other steps that reduce the risk of dementia. The accuracy of the dementia diagnosis in this study must also be questioned because the data set derives from busy physicians in general medical practice, a context in which dementia has been shown to be under-recognized and inaccurately diagnosed.

Past studies have failed to show a convincing correlation between cholesterol levels and risk of AD, and the present study leaves open the question of whether statins might mediate protective effects through actions

on systemic lipids or other biological effects. The use of statins in patients with hyperlipidemia may be justified irrespective of whether there is definitive evidence of dementia protective effects. However, prospective studies must be carried out before statins could be recommended for the specific indication of affording protection against dementia. **—norman r. relkin**

Restless Leg Syndrome

ABSTRACT & COMMENTARY

Source: Ondo WG, et al. Restless leg syndrome in monozygotic twins: Clinical correlates. *Neurology* 2000;55:1404-1406.

Restless leg syndrome (rls), one of the most common neurologic disorders, is a highly prevalent disorder, affecting as many as 5% of the population. RLS patients are best classified into two groups: primary and secondary RLS. Patients with primary RLS often have a family member similarly affected, while patients with secondary RLS develop the condition in the setting of reduced iron stores, peripheral neuropathy, renal failure, or pregnancy. Distinguishing primary from secondary RLS can be difficult, as the two conditions are clinically indistinguishable.

To date, little is known about the pathologic mechanisms responsible for the symptoms of RLS. Several researchers have shown that the dopaminergic innervation of the striatum is reduced in RLS patients. RLS symptoms also respond best to treatment with dopaminergic agonists or levodopa. These two pieces of evidence suggest that the dopamine system is critically involved in RLS. However, genetic linkage studies of large families with RLS have failed to identify a locus with adequate lod score. These studies have been hampered by the phenotypic variability of the disorder, and by the fact that the disorder is frequent enough that often, family members on both sides of a family tree are affected.

In this paper, Ondo and colleagues report their studies of 12 monozygotic twins where at least one twin was initially known to be affected with RLS. They identified three twin pairs from their clinic, and obtained the other nine by advertising in the RLS newsletter. Clinical phenotypes and details of family history were established for both members of each twin group.

COMMENTARY

The results of this study were striking. In 10 of 12 monozygotic twin pairs, RLS symptoms were present in both members of the twin pair. An affected parent was identified in all 10 of these cases. Although the twin pairs were highly concordant for the disease, the phenotypic expression varied markedly between the monozygotic pairs. Reported symptoms and severity of symptoms were not tightly correlated. More remarkable, the age of onset of symptoms was not concordant, varying by as much as 42 years between two monozygotic twins. The inheritance pattern was most consistent with an autosomal dominant disorder with high penetrance. Ondo et al also compared these 12 monozygotic twins to their clinic population, affected with sporadic RLS. The mean age of onset of symptoms in familial RLS was approximately 28, while the mean age of onset was 47 in sporadic RLS.

These observations are important for several reasons. The finding of near-complete concordance of monozygotic twins for RLS symptoms confirms prior studies suggesting that familial RLS is a genetic disorder. However, even among monozygotic twins, there is marked phenotypic variability in the disorder, both in age at symptom onset and in the clinical phenotype.

How do these results affect neurologists treating patients with RLS? Ondo et al's work suggests that RLS is best viewed as an amalgam of two conditions: secondary RLS, occurring later in life in the setting of iron deficiency or peripheral neuropathy, and familial RLS, occurring earlier. While both conditions respond to treatment, establishing a patient's age of symptom onset and determination of a family history of RLS should enable the neurologist to separate primary from secondary RLS. **—steven frucht**

Mobility and Survival in Minimally Conscious Children

ABSTRACT & COMMENTARY

Source: Strauss DJ, et al. Life expectancy of children in vegetative and minimally conscious states. *Pediatr Neurol* 2000; 23:312-319.

It has been known for a number of years that children in a vegetative state (VS) have reduced life expectancies than do normal children (*Pediatr Neurol* 1994;10:27-33). What accounts for this? Could the presence of consciousness, even if minimal, play a role in improving survival?

In order to to approach this question, this study from Ashwal and associates compared cohorts of children (3 years old at time of study entry) initially in

PVS, immobile minimally conscious state (iMCS) and mobile minimally conscious state (mMCS) with respect to survival over a 10-year period. Ashwal et al's group used detailed database information collected by the California Department of Developmental Services (CDDS) over the 10-year period from January 1988 to December 1997. The CDDS maintains Client Development Evaluation Reports (CDERs) which provide information regarding 261 variables. By using selected variables in the CDER reflecting mobility, level of independence, perception and language, Ashwal et al were able to develop a 15-item consciousness index (see Strauss et al's article for details). Patients are operationally defined to be in VS if they scored the lowest grade on all items in the index, but in MCS if they scored better than the lowest score on any of the 15 items. Finally, patients in MCS were termed "mMCS" if they were minimally conscious but had either hand use, arm use, or ability to roll and sit. Otherwise they were termed "iMCS."

Strauss and associates found that patients in VS had extremely similar long-term survival rates to iMCS. Mobile MCS patients had improved long-term survival compared to either VS or iMCS patients. Among patients with VS and MCS, there was variability in mortality rate according to etiology, with mortality risk increasing in the order acquired (including traumatic) brain injury < perinatal/genetic < non-specified < degenerative. Strauss et al provide odds ratio calcuations. Using these, one can, for example, compute that a patient with degenerative disease in VS has approximately a four-fold higher mortality rate than a patient with traumatic brain injury in a mobile MCS.

COMMENTARY

This paper highlights several factors that may be important in determining mortality rates of children with severe impairment of consciousness. Etiology of impaired consciousness is clearly important. The level of impairment of consciousness (i.e., complete vs incomplete) appears to be less important than the presence of some degree of mobility. As Strauss et al point out, the reasons for improved survival in mobile patients are unknown. They also point out that mobile patients are more likely to have intact swallowing mechanisms, gag reflex, and improved pulmonary toilet, all of which are associated with improved survival. It might be interesting to compare survival of mobile and immobile MCS patients to fully alert patients with quadriplegia in order to test this idea.

One potential clinical implication of this study is that efforts should be made to improve spontaneous mobility in patients in MCS, as this seems to be associated with improved long-term survival. **—rosario trifiletti**

More Functional Imaging of Headache

ABSTRACT & COMMENTARY

Source: May A, et al. PET and MRA findings in cluster headache and MRA in experimental pain. *Neurology* 2000; 55:1328-1335.

In a previous study, may and colleagues reviewed the early positron emission tomography (PET) findings of hypothalamic activation in patients with cluster headache (CH) (*Neurology Alert* 1998;17:19-20). The current paper by May et al builds on their important ongoing work. In this study, nine patients with active CH and eight patients with inactive CH were investigated with PET. Nitroglycerin (NTG) was used to induce CH in the nine during active periods. NTG will not activate a CH during a period of remission. PET findings fell into three broad categories: 1) activation in the ipsilateral posterior hypothalamic gray, an area specific to CH but not to other primary headache disorders; 2) activation in areas known to be involved in pain processing such as the cingulate cortex, insula, prefrontal cortex and contralateral thalamus; and 3) activation of extracerebral areas such as large intracranial blood vessels.

In addition, a single patient with spontaneous CH was studied with MRA. During this attack, a significant increase in blood flow in the ipsilateral carotid artery was demonstrated. In fact, ipsilateral carotid vasodilatation also was observed in this case when normal volunteers without CH were studied after local injection of capsaicin injection into the forehead. It appears that the pain, rather than a generator of the pain, drove the vascular changes. By contrast, in CH the primary disorder appears neuronal and instigated in the posterior hypothalamus. This region is most likely given the clinical circadian features of CH.

COMMENTARY

Functional imaging and the dynamic blood flow changes in the brain that are associated with the primary headache disorders such as CH and migraine are helping to evolve the concept of the vascular headache into something better thought of as the neurovascular headache. Such a concept better explains the fact that neuronal activation occurs prior to the pain and observed

vasodilatation. In other words, contrary to previous and widely held dogma, the vascular changes may indeed be epiphenomenon. **—jeffrey reich**

Sural Nerve Biopsy

ABSTRACT & COMMENTARY

Source: Gabriel CM, et al. Prospective study of the usefulness of sural nerve biopsy. *J Neurol Neurosurg Psychiatry* 2000;69:442-446.

Fifty consecutive patients underwent sural nerve biopsy to prospectively evaluate its use in the diagnosis and management of polyneuropathy. Thirty men and 20 women, 10-82 years of age, were included, with symptom duration ranging from one week to 40 years. Prebiopsy diagnoses were based on clinical examination and electrodiagnostic studies, and were classified as mononeuropathy multiplex, axonal polyneuropathy, or demyelinating polyneuropathy. Biopsy was performed only where the neuropathy was severe, pathogenesis was uncertain, and biopsy results could alter management. Biopsy specimens were processed for light and electron microscopy, and histochemistry. Teased fiber and morphometric studies were performed only in doubtful cases.

Clinical diagnosis was confirmed by biopsy in 35, and did not contribute to the diagnosis in eight. In seven cases, diagnosis was altered following biopsy, including three whose biopsy demonstrated vasculitis instead of the expected axonal diabetic neuropathy, paraneoplastic neuropathy, or idiopathic sensory neuropathy. Two patients with IgM paraproteinemia, demyelinating neuropathy, and anti-myelin associated glycoprotein (MAG) antibodies demonstrated lymphomatous neuropathy in one and chronic inflammatory demyelinating polyneuropathy (CIDP) in the other. Conversely, a third patient with IgM paraproteinemia and axonal neuropathy showed findings characteristic of IgM paraproteinemic demyelinating neuropathy. Lastly, a teenager with acute motor and sensory axonal neuropathy with inexcitable nerves was shown to have acute inflammatory demyelinating polyneuropathy (AIDP, Guillain-Barre syndrome).

Overall, management was altered or benefited from biopsy in 60%, more often in demyelinating neuropathy (11/15, 73%), and mononeuropathy multiplex (5/9, 56%) than in axonal neuropathy (14/26, 54%). Significantly, at six weeks, 67% (n = 21) of responders to follow-up questionnaires reported increased pain, and 15% (n = 6) reported infection. At six months, 33% (n = 10) and 10% (n = 7), respectively, reported increased pain and infection. Full thickness and fascicular nerve biopsies had equal incidences of pain. Patient satisfaction was 79% and 63% at six weeks and six months, respectively.

COMMENTARY

Among 54 patients in another series who underwent sural nerve biopsy for the investigation of peripheral neuropathy, sensory deficits were reported in 93%, dysesthesia in 19%, and mild persistent pain in 33% at 5-32 months post-biopsy (*J Neurol* 1999;246:93-96). Dysesthesia declined and persistent pain completely resolved over time, supporting a relatively benign outcome following sural biopsy.

Diabetics appear to be at greater risk for complications following nerve biopsy (*Diab Med* 1997;14:353-356). Biopsy site pain was reported by four of 10 diabetics but in none of 21 nondiabetics, up to 44 months following biopsy. Cold intolerance was present in five of 10 diabetics compared to one of 21 nondiabetics. Sural nerve biopsy can result in persistent problems, particularly in the diabetic population.

Consideration of a diagnosis of chronic inflammatory demyelinating polyneuropathy does not require sural biopsy. Of 64 patients where this diagnosis was raised, sural nerve biopsy did not add significantly to the conclusions drawn from clinical examination, electrodiagnostic studies, and cerebrospinal fluid protein levels (*J Neurol Neurosurg Psychiatry* 1998;64:84-89). **—michael rubin**

Brief Alert

Interferon-beta Therapy in MS: Development of Neutralizing Antibodies

Source: Ross C, et al. Immunogenicity of interferon-beta in multiple sclerosis patients: Influence of preparation, dosage, dose frequency and route of administration. *Ann Neurol* 2000;48:706-712.

In this study from denmark, 754 patients starting on different preparations of interferon-beta (IFNb) were prospectively followed in a national protocol in which serum were collected at 0, 3, 6, 12, 18, and 24 months. These samples were then assayed for ability

to bind IFN-b and neutralize the biological activity of IFNb in an antiviral neutralization assay. The IFNb preparations were Betaseron (IFNb-1b, 300 mg SC injection QOD), Avonex (IFNb-1a, 30 mcg IM injection Q weekly), or Rebif (IFNb-1a, 22 mcg SC injection 1-3 times weekly).

Ross and associates found that IFNb-1b preparations had a higher occurrence of binding and neutralizing antibodies by 12 months, compared to IFNb-1a. In addition, IFNb-1a was more likely to be immunogenic when given by subcutaneous vs. intramuscular injection, or when administered three times vs. one time weekly. Antibodies induced against one preparation also seemed to cross-react with other preparations.

COMMENTARY

This study helps to define a potential concern with patients receiving long-term administration of recombinant human cytokines. Previous reports have indicated widely variable frequencies in neutralizing antibodies for patients on IFNb therapy. This study demonstrated that the frequencies are highly dependent on the type and specific conditions in the assays, so that it is helpful that all samples were tested under uniform conditions. In the United States, neutralizing assays are performed by Athena Diagnostics (800-394-4493), or as a service from Berlex Laboratories through IDX Labs.

As IFNb therapy will only provide a moderate reduction in the frequency and severity of relapses, the clinician must decide when "breakthrough" disease activity might indicate the development of neutralizing antibodies. Severe attacks in patients on the drug for a few years, especially those accompanied by gadolinium-enhancing activity on brain MRI, might be related to reduction in drug efficacy. If a patient had a persistently high antibody titer on two separate specimens drawn months apart, then alternative drug therapy might need to be considered. **—brian apatoff**

CME Questions

1. **Treatment for postherpetic neuralgia (PHN) may include:**
   a. oxycodone.
   b. ketamine.
   c. intrathecal methylprednisolone plus lidocaine.
   d. venlafaxine (Effexor), a serotonin-norepinephrine reuptake inhibitor.
   e. All of the above

2. **Which one of these is supported by recent study data?**
   a. Non-statin lipid-lowering drugs do not affect risk of dementia.
   b. Cigarette smoking increases risk of dementia.
   c. Statin drugs decrease risk of dementia.
   d. All of the above

3. **Which of the following is *not* true regarding children in vegetative state (VS) or minimally conscious states (MCS)?**
   a. Children in VS have lower long-term survival rates than normal children.
   b. Children in VS have similar long-term survival as children in MCS who are immobile.
   c. The etiology of VS or MCS has no bearing on long-term survival; only mobility is relevant.
   d. Children in VS or MCS due to degenerative diseases (e.g., Tay-Sachs disease) have a higher mortality rate than those with VS or MCS following traumatic brain injury.
   e. Children in VS or immobile MCS from degenerative disease have the highest mortality rates.

4. **Sural nerve biopsy:**
   a. is useful in the diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP).
   b. carries no greater risk of persistent pain in diabetics than in nondiabetics.
   c. is more often useful in the diagnosis of demyelinating neuropathy and mononeuropathy multiplex than in axonal neuropathy.
   d. leaves most patients unhappy that the procedure was performed.
   e. All of the above

5. **Hemicraniectomy for severe brain swelling associated with middle cerebral artery infarction and swelling enables best survival for which of the following?**
   a. Patients 50 years old and older with severe swelling of the right frontal-parietal lobes and are becoming drowsy by 48 hours after the swelling starts.
   b. Patients 35-40 years old with severe MCI stroke swelling and becoming increasingly drowsy should best be decompressed at 40 hours after onset.
   c. Patients 35-40 years old with functionally severe cerebrally-induced left hemiplegia, but have little somnolenceor herniation signs, should be compressed anyway.
   d. Patients 50 years old and younger should receive craniectomy if their frontal temporal lobes begin to swell and sleepiness increases for about 15-20 hours after swelling begins.

Attention CME Subscribers

In the December 2000 issue of *Neurology Alert*, there was a mistake in CME question no. 31. Answer d. reads as follows: "Loss of hypocretin neurons in the lateral hippocampus." Answer d. should read: "Loss of hypocretin neurons in the lateral hypothalamus." We regret any confusion this may have caused. ❖

In Future Issues:

Spontaneous CSF Hypovolemia: A Syndrome Characterized