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Unlocking the Mysteries of Idiopathic Intracranial Hypertension

ABSTRACTS & COMMENTARY

Sources: King JO, et al. Manometry combined with cervical puncture in idiopathic intracranial hypertension. *Neurology.* 2002;58:26-30; Higgins JN, et al. Venous sinus stenting for refractory benign intracranial hypertension. *Lancet.* 2002;359:228-230.

IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH) TYPICALLY occurs in young obese women and involves a constellation of headache, papilledema, raised intracranial pressure, and normal CNS imaging. IIH, more classically termed pseudotumor cerebri, is also known as benign intracranial hypertension (BIH). This variability in nomenclature in part reflects an overall lack of understanding of the pathophysiology of this disorder. Initial theories postulated an imbalance between excess CSF production and inadequate or impaired CSF resorption. With the advent of imaging techniques such as MR venography (MRV) showing venous sinus thrombosis in some previously idiopathic cases, some have argued that venous hypertension is the unifying cause in all cases of IIH. This hemodynamic explanation is particularly compelling for individuals who are pathologically obese and develop IIH as abdominal or intrathoracic venous pressures are transmitted to the CNS. Such theories are less applicable to patients who are slim or who have no evidence of right-sided heart failure.

Using venous manometric catheters passed intracranially into the tranverse sinus (TVS), torcula, and superior sagittal sinus (SSS), several investigators have demonstrated elevated central venous pressures in patients with IIH. Measured pressures have reached as high as 40 mm Hg, 8-fold greater than normal levels. These may occur due to obstruction in the TVS or in some cases, more uniformly throughout the SSS, torcula, and TVS. At the same time, CSF opening pressures are elevated, perhaps reflecting transmitted pressure from the venous system. CSF volumes may increase as the function of arachnoid granulations is impaired by an inappropriate pressure gradient into the venous outflow system.

The data presented by King and colleagues significantly debunk

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these "venous" theories. They suggest that elevated venous pressure may exacerbate CSF hypertension, but that it initially occurs only as an epiphenomenon of a primary increase in intracranial pressure (ICP). King et al's data indicate that when ICP is reduced by CSF drainage, venous pressures drop. King et al studied 21 patients, the majority of whom were postulated to have TVS stenosis, with manometric data showing a significant pressure drop between the proximal and distal TVS. King et al treated a subset of 11 patients with C1-2 puncture and drainage of 20-25 mL of CSF. Somewhat surprisingly, this drainage produced a pressure drop in the proximal transverse sinus by as much as 41 mm Hg, with the most dramatic venous pressure decreases occurring in those patients with the highest initial venous pressures prior to C1-2 puncture. A minority of patients had less striking results, such as Patient 4 whose TVS pressure was only 9 mm Hg prior to CSF drainage, dropping to 5 mm Hg after therapy.

In previous work, King et al demonstrated a pressure drop across the transverse sinus, and postulated that this was due to incomplete recanalization of a thrombosed vein. As noted by King et al, these new data suggest that such a pressure drop may rather be caused by a reversible compression of the transverse sinus in the setting of high ICP. The easily distensible walls of the TVS collapse under pressure, but flow is re-established when ICP is reduced with CSF drainage. King suggests that there may be an asymptomatic phase of the illness during which ICP rises and the TVS remains patent. Once the TVS collapses, the SSS pressure rises rapidly, further impeding CSF absorption and producing a rapid rise in ICP with the acute onset of symptoms. The TVS is thus not the initial culprit in IIH but rather acts as a secondary and multiplicative phenomenon.

In a contrasting report, Higgins and colleagues present a case in which venous sinus stenting dramatically improved a patient with IIH. An obese 30-year-old woman presented with a 2-year history of headache, bilateral papilledema, and normal brain MRI as well as MRV. Therapies such as weight loss and acetazolamide were unhelpful. CSF opening pressure was 35 cm H_20. Venography revealed bilateral stenotic lesions in the TVS with pressures of 27 mm Hg at the torcula and 9 mm Hg at the jugular (gradient = 18 mm Hg). A self-expanding stent was deployed across the stenosis in the right TVS, with the torcula-jugular gradient dropping to 3 mm Hg and immediate improvement of headache.

On the basis of this case, Higgins et al argue that CSF diversion procedures (such as serial LPs, VP shunting, or optic nerve sheath fenestration) often fail to treat IIH, because they do not address the fundamental problem: TVS stenosis. Higgins et al suggest that the TVS pathology was not thrombosis (as previously postulated by King) but rather an idiopathic narrowing of the TVS bilaterally.

COMMENTARY

These 2 reports, published almost simultaneously, provide a fascinating juxtaposition. King et al's work indicates that indeed it is CSF pressure rather than venous disease that may be the true pathophysiology in IIH. Conversely, Higgins et al treated the narrowed TVS, and produced dramatic improvement.

Where do these data leave us in our understanding of this mysterious disorder and how should these findings effect clinical strategies? Most importantly, if increased CSF pressure is the initiating event in IIH, what is the cause of this? How do the arachnoid granulations function and what specific pathology might they develop? With its strong gender predilection, what hormonal influences affect IIH and how does obesity factor in?

Therapeutically, given that IIH is likely a multifactorial process, a combination approach is prudent. Patients failing acetazolamide or other diuretic therapy should be considered for shunt procedures. Venous sinus stenting may be performed in selected cases. Although this may

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

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GST Registration Number: R128870672.
Periodical postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Neurology Alert,*** P.O. Box 740059, Atlanta, GA 30374.

Back issues: $38. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

United States
$279 per year.
Multiple Copies
2-9 additional copies: $206. 10-20 copies: $183.
Canada
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not be treating the primary problem, it may nevertheless be effective. It is possible that ICP-induced TVS compression maintains or even significantly accelerates a process set in motion by excess CSF. **—ALAN Z. SEGAL**

Does Alcohol Prevent Dementia?

ABSTRACT & COMMENTARY

Source: Ruitenberg A, et al. Alcohol consumption and risk of dementia: The Rotterdam Study. *Lancet.* 2002;359:281-286.

LIGHT-TO-MODERATE ALCOHOL CONSUMPTION MAY lower the risk of dementia, according to a recent report from the Rotterdam Study. As part of this prospective, population-based cohort study from the Netherlands, participants were asked to complete a food frequency questionnaire that included self-report of alcohol intake. Patients were subsequently examined over a 6-9 year period to determine the incidence and type of dementia they developed. Ruitenberg and colleagues compared individuals who never drank alcoholic beverages to those who consumed light amounts (> 1 drink per week but < 1 drink per day), moderate amounts (1-3 drinks per day), and heavy amounts (> 3 drinks per day) of spirits. The type of alcoholic beverage was taken into account, as well as a number of possible confounders such as age, gender, diabetes, hypertension, educational attainment, smoking, and body mass index. Great care was taken to exclude individuals from the analysis who were already suffering from dementia or who had other factors that might render their self-report unreliable.

A remarkable 99.7% success rate was achieved in follow-up of 5395 cases. Most participants in the study were older than 55 years of age. As a group, men in the study consumed more alcohol than women. As the amount of alcohol consumption increased, so did the percentage of subjects who smoked and who completed greater amounts of education. Among the more than 5000 participants in the study, a total of 197 developed dementia, representing an incidence rate of 6.1 cases per 1000 persons per year. A total of 146 patients developed Alzheimer's disease (74%). Of these, less than 10% were thought to have a mixture of Alzheimer's disease and vascular dementia. An additional 29 patients (15%) were thought to have a purely vascular dementia, and 11% were diagnosed with other forms of dementia.

For the population as a whole, alcohol consumption of 1-3 drinks per day was found to lower the risk of dementia by 42% (95% CI, 10-62%). This effect appeared to be more prominent in men than women, but was evident in both genders. The effect of alcohol appeared to be most significant in lowering the risk of dementia secondary to cerebrovascular disease. The risk of vascular dementia was reduced by 70% among those who drank 1-3 glasses of alcohol per day. There was no evidence that the type of alcohol consumed (wine, beer, hard liquor, or fortified wine) influenced the risk of dementia. Drinking more than 3 glasses of alcoholic beverages per day was not associated with protection against dementia, nor was there an increased risk documented in this study.

COMMENTARY

This is a well-executed epidemiologic study that provides support for the hypothesis that moderate alcohol consumption can reduce the risk of dementia. Consistent with these newly reported findings, at least one previous study from the Bordeaux region in France found that wine consumption could reduce the risk of dementia (*Rev Neurol.* 1997;153:185-192). One limitation of these studies is their reliance on self reports of alcohol consumption obtained through food intake questionnaires. While this approach can lead to reliable estimates of nutritional intake under many circumstances, self-reports of alcohol consumption are often subject to underestimation. The frequency and extent of alcohol consumption is likely to be correlated with other aspects of lifestyle, which may have an effect on the risk of dementia, falsely imparting the appearance that alcohol is the responsible agent.

Nevertheless, Ruitenberg et al took care to exclude many potential confounders and present some of the strongest evidence to date that alcohol can reduce the risk of dementia. Since the most robust effect was seen on incidence of vascular dementia, they suggest that alcohol's risk-reducing capacity could be related to effects on vascular risk factors, as is postulated to be the case in terms of alcohol's effects on risk of stroke and heart disease. It should be noted that binge drinkers and those with alcohol abuse problems were excluded from this analysis. Apart from documenting a lack of protection from consuming more than 3 drinks a day, this study does not address the issue of the harmful effects of excessive alcohol intake on the brain. The harmful neurologic effects of alcohol abuse are well documented, and its dangers need to be reinforced to patients who may misinterpret the results of the Rotterdam Study or use it to justify alcoholism. **—NORMAN R. RELKIN**

Recurrent Cerebrovascular Events

ABSTRACTS & COMMENTARY

Sources: Mas JL, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med.* 2001;345:1740-1746; Meier B. Patent foramen ovale—beauty spot or health threat? *Cardiology Rounds.* 2001;5:1-8 (www.cardiology-rounds.org).

RESULTS OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY (TEE) during recent years have identified a high prevalence of cardiac abnormalities in the general population. In one study of randomly selected subjects aged 45 years or older, TEE detected patent foramen ovale (PFO) in 26% and atrial septal aneurysm (ASA) in 2%. In patients with a cryptogenic stroke, associated rates of detection of PFO range from 31-77% and for ASA from 4-25% (*Neurology.* 2000;55:1865-1867).

In a prospective multicenter study, Mas and colleagues enrolled 581 patients, aged 18-55 years, who had suffered a cryptogenic ischemic stroke within the preceding 3 months. All received aspirin 300 mg daily for secondary stroke prevention. All patients underwent transthoracic echo cardiography and TEE. Patients were assessed for PFO and ASA at rest and during valsalva maneuver and coughing.

After 4 years, the risk of recurrent stroke was 2% among patients with PFO alone, 15% among patients with both PFO and ASA, 8%, and 4% among patients who had neither of these cardiac abnormalities. No recurrences affected the patients with ASA alone. The presence of both PFO and ASA was a significant predictor of an increased risk of recurrent stroke (hazard ratio, 4.17; 95% confidence interval, 1.47-11.84). The presence of isolated PFO, whether small or large, was not a significant risk factor for recurrence.

In an encyclopedic review, Bernhard Meier has summarized the etiology of PFO, diagnostic methods for PFO and the relationship between PFO and stroke, as well as methods of closure, emphasizing percutaneous transcatheter closure.

COMMENTARY

An ASA is 10 times less common than a PFO. It previously has been identified in the Stroke Prevention Assessment of Risk in a Community (SPARC) Study (*Mayo Clin Proc.* 1999;74:862-869) as a risk enhancer in the presence of PFO, rather than an independent source of embolism. Mas et al have confirmed that finding.

Mas et al did not confirm that the size of the PFO or the degree of shunting was a significant predictor of the risk of recurrent TIA or stroke. In a previous study, Homma and colleagues reported that the size of a PFO and the number of bubbles passing through were significant risk factors for stroke (*Stroke.* 1994;25:582-586).

In view of the low risk of recurrent stroke in PFO patients treated medically with aspirin or warfarin, the role of surgical or percutaneous transcatheter closure of a PFO remains uncertain. Nevertheless, percutaneous close of a PFO seems promising and should be considered in patients with recurrent emboli on medical treatment, with an ASA, or a tendency for venous thrombosis. —**JOHN J. CARONNA**

PARK6-Linked Parkinsonism

ABSTRACT & COMMENTARY

Source: Valente EM, et al. Park6-linked parkinsonism occurs in several European families. *Ann Neurol.* 2002;51:14-18.

THERE HAVE BEEN SEVERAL MAJOR ADVANCES IN the last 5 years in the quest to unravel the genetics of Parkinson's disease (PD). Three genes have been identified to cause dopa-responsive adult-onset familial parkinsonism: alpha-synuclein, the parkin gene, and ubiquitin C terminal hydrolase L1. Mutations in alpha-synuclein (chromosome 4q) produce a syndrome of autosomal dominant dopa-responsive parkinsonism with early age of onset (average age, 46 years). At autopsy, Lewy bodies are abundant in the substantia nigra, and they are indistinguishable from Lewy bodies that occur in sporadic PD. Aside from the original description in one Italian family (the "Contursi" kindred) and one other German family, mutations in alpha-synuclein have not been found to be responsible for sporadic or familial PD.

The gene called parkin (chromosome 6q) was originally discovered in several Japanese families with autosomal recessive parkinsonism. In the last several years, mutations in the parkin gene have been reported in many other families with early-onset PD throughout the world. The disease usually begins in the third decade, and is characterized by an excellent response to levodopa and early development of dopa-induced dyskinesias. Pathologically there is severe neuronal loss in the substantia nigra pars compacta, without Lewy bodies or inclusions. The third gene causing parkinsonism is ubiquitin C ter-

minal hydrolase L1 (chromosome 4p); a mutation in this gene has been reported in 2 siblings of 1 family with typical adult-onset PD. No autopsies are available, and it is unknown if patients with sporadic PD also carry mutations in this gene.

At least 4 other genetic loci have been reported in familial PD: PARK3 (chromosome 2p, autosomal dominant), PARK4 (chromosome 4p, autosomal dominant), PARK 6 (chromosome 1p, autosomal recessive), and PARK 7 (chromosome 1p, autosomal recessive). In the current report, Valente and colleagues report their progress in the search for the gene encoding PARK6 in 8 European families. Of these families, 3 were Dutch, 2 German, 2 Italian, and 1 English. Mean age of onset was 42 years, however, 4 patients developed symptoms after age 45 and 1 patient presented at age 68! Clinical features were indistinguishable from patients with mutations in the parkin gene, with an excellent response to levodopa, and development of levodopa-induced dyskinesias in half of the patients. Using linkage analysis in these 8 families, Valente et al mapped the PARK6 gene to a 9 centiMorgan region of chromosome 1p35-36. There was no evidence of a founder effect, suggesting that distinct mutations in the gene arose spontaneously.

COMMENTARY

It is not known whether mutations in the PARK6 gene are responsible for sporadic adult-onset PD. However, this is a distinct possibility, particularly since PARK6 mutations have been identified in multiple European kindreds and the clinical phenotype is similar to adult-onset sporadic PD. Even if PARK6 mutations are not found to be responsible for sporadic PD, identifying the PARK6 gene and understanding its function will assist in identifying the pathways that lead to selective dopaminergic neuronal demise. **—STEVEN FRUCHT**

Electrodiagnostic Localization of Severe Carpal Tunnel Syndrome

ABSTRACT & COMMENTARY

Source: Boonyapisit K, et al. Lumbrical and interossei recording in severe carpal tunnel syndrome. *Muscle Nerve.* 2002;25:102-105.

Carpal tunnel syndrome is the most frequent motive for patient referrals to EMG laboratories in the United States. In 2-10% of cases, using standard techniques, a measurable response is unobtainable following both median motor and sensory nerve stimulation. These record from the thenar eminence (abductor pollicis brevis) and fingers 1 to 4 digital nerves, respectively. How might one localize the lesion to the wrist in this situation?

Twenty-eight hands were tested in 23 patients with absent, routine, median motor, and sensory nerve responses. Median distal motor latency to the second lumbrical was directly compared to the ulnar distal motor latency to the first palmar/second dorsal interosseous muscle over the same 8-10 cm distance. Active (recording) electrode placement was just lateral to the midpoint of the third metacarpal. Additionally, 92.8% (26 of 28 hands) demonstrated significant prolongation (normal < 0.4 ms) of the lumbrical-interosseous latency difference (range, 3.9-16.7 ms). The 2 remaining hands demonstrated no response. When routine recordings reveal no median response, this measurement can be valuable in localizing median neuropathy to the carpal tunnel.

COMMENTARY

Obesity doubles the risk of developing carpal tunnel syndrome (*Am J Epidemiol.* 1990;132:1102-1110) but, based on body mass indices (weight in kg/height^2 in meters), it does not correlate with severity. Conversely, wrist index (wrist depth/wrist width in mm) and older age do have a correlation with severity (*Muscle Nerve.* 2002;25:3-7). Interestingly, and for unclear reasons, patients with carpal tunnel syndrome are more likely to have shorter but wider palms, and shorter third digits than controls (*Muscle Nerve.* 2001;24:1607-1611). Presumably, this adversely alters the relationship of the median nerve to the carpal ligament and structures in the tunnel and may lead to compression injury.

Tinel's sign, Phalen's test, the reverse Phalen's test, and the carpal compression test are the techniques most familiar to neurologists searching for carpal tunnel syndrome. However, hand elevation appears to be a simpler and yet more provocative and sensitive test (*Ann Plast Surg.* 2001;46:120-124). One hundred eighteen patients possessing 200 hands with carpal tunnel syndrome had hand elevation tests which were more sensitive and specific (75.5% and 98.5%, respectively) than Phalen's test or Tinel's sign. Results for Phalen's test were 67.5% and 91.0%, respectively, and for Tinel's sign 67.5% and 90.0%, respectively. All those in favor of the hand elevation test, raise your hand! **—MICHAEL RUBIN**

Anti-Hu Polyneuropathies

ABSTRACT & COMMENTARY

Source: Camdessanche JP, et al. Paraneoplastic peripheral neuropathy associated with anti-Hu antibodies: A clinical and electrophysiological study of 20 patients. *Brain.* 2002; 125:166-175.

Among 50 anti-Hu positive patients retrospectively reviewed, 27 exhibited a paraneoplastic neurological syndrome, 7 (25.9%) with encephalomyelitis, and 20 (74.1%) demonstrating symptoms and signs of polyneuropathy. Other causes for neuropathy were excluded, including diabetes, renal failure, paraproteinemia, drug toxicity, vitamin deficiency, and cachexia. Data reviewed from the 20 patients included cerebrospinal fluid analysis, nerve conduction studies, and immunohistochemistry for detection of anti-Hu, anti-amphiphysin, and anti-CV2 antibodies. Fisher's exact test and chi-square tests provided statistical analysis.

Among the 17 men and 3 women, polyneuropathy was the presenting symptom in 19 (95%) and the sole manifestation in 6 (30%). Pain was a frequent accompaniment (80%) but atrophy or fasciculations were not. Onset was acute in 1 (5%), subacute in 11 (55%), and progressive in 8 (40%). Cancer was diagnosed in 17 (85%) within a mean of 7.7 months, and in 13 (76.5%) it was small cell lung cancer. Clinically, pure sensory neuropathy was present in 14 (70%), pure motor in 1 (5%), and mixed sensorimotor in 5 (25%). Electrophysiologic study, however, demonstrated motor involvement in 10 of the 14 "clinically pure" sensory neuropathies, with an axonal/neuronal pattern of abnormality in 46.9% of nerves studied, a demyelinating pattern in 4.9%, a mixed axonal-demyelinating pattern in 18.3%, and no abnormality in 29.9%. Anti-CV2 antibody positivity did not correlate with neuropathy in this patient population. Motor involvement is much more common than suspected in anti-Hu sensory neuronopathy, indicating that, although pathology beyond the dorsal root ganglion is present, it does not preclude the diagnosis.

COMMENTARY

Patients with anti-CV2 antibodies may demonstrate a mixed axonal-demyelinating sensorimotor polyneuropathy which, in the presence of co-existent anti-Hu antibodies, may be superimposed over an underlying subacute sensory ganglionitis (*Ann Neurol.* 2001;49: 214-221). Anti-CV2 antibody, likely identical to recently described CRMP-5 antibody, reacts with adult rodent brain oligodendrocytes and recognizes a 66-kd protein of the Ulip/CRMP protein family (*Ann Neurol.* 2001;49:141-142). CRMP-5 antibodies recognize collapsin response mediator protein-5 (CRMP-5, also known as CRAM), which is important for nervous system development as a mediator of axonal guidance. It also appears to be a marker for lung cancer, usually small cell, which was found in 77% of 116 CRMP-5 antibody positive patients (*Ann Neurol.* 2001;49:146-154). **—MICHAEL RUBIN**

Pain Mechanisms in Tension Headache

ABSTRACT & COMMENTARY

Source: Rollnik JD, et al. Botulinum toxin type A and EMG: A key to the understanding of chronic tension-type headaches? *Headache.* 2002;41:985-989.

Excessive pericranial muscle contraction has been speculated as a mechanism for pain generation in chronic tension headache (CTH). However, using surface EMG recordings, excessive contraction has never been demonstrated. Further evidence that muscle contraction plays no role in CTH is offered in this small (n = 8) randomized, placebo-controlled trial comparing pericranial injection of 500 MU botulinum toxin (Botox A) to isotonic saline. Patients satisfied International Headache Society criteria for CTH, had normal brain imaging, and were excluded if there was evidence of analgesic abuse, psychiatric disease, psychosocial factors (eg, workman's compensation), or symptoms of nontension headaches. Examinations were performed at baseline, 6, and 12 weeks and included surface EMG recording of frontal and anterior temporal muscles bilaterally. Headache pain intensity and duration was the primary outcome target, measured as "area under the headache curve." T tests and chi-square tests supplied statistical analysis.

Despite a significant decrease at 12 weeks of temporalis muscle EMG activity in Botox treated patients, neither of the 2 groups at 6 or 12 weeks showed any change of intensity, duration, frequency, or use of analgesics. One must conclude that muscle contraction plays little or no role in pain generation in CTH.

COMMENTARY

Inhibiting nitric oxide (NO) synthesis reduces headache and, conversely, glycerol trinitrate, an NO donor, increases headache in CTH sufferers moreso than in healthy controls. This suggests that NO central sensitization may play a role in the pathogenesis of CTH (*Lancet.* 1999;353:287-289; *Brain.* 2000;123: 1830-1837). Other evidence points to decreased peripheral sympathetic activity in CTH (*Headache.* 2001;41:157-163). Among 28 patients with CTH, transcranial Doppler ultrasonography of the middle cerebral artery demonstrated a lower Mayer wave coefficient of variation than normal controls. Mayer waves, spontaneous cerebral blood flow velocity oscillations at 4-7 cycles/minute, have no central generator but reflect arterial blood pressure. Decreased Mayer wave variability thus supports peripheral sympathetic autonomic dysfunction in CTH. Conversely, B waves that reflect cerebral blood flow velocity oscillations at 0.5-3 cycles/minute and generated by brain stem nuclei, varied more in 30 migraine patients compared to either 28 CTH patients or 30 normal controls. This observation suggests dysfunction of central monoaminergic/serotonergic systems in migraine. **—MICHAEL RUBIN**

Colchicine Myopathy Pathophysiology

ABSTRACT & COMMENTARY

Source: Fernandez C, et al. Colchicine myopathy: A vacuolar myopathy with selective type 1 muscle fiber involvement. An immunohistochemical and electron microscopic study of two cases. *Acta Neuropathol.* 2002;103:100-106.

Colchicine blocks mitosis at metaphase and, rarely, produces a vacuolar myopathy by interfering with microtubular polymerization. Either acute overdose or long-term therapeutic usage may be responsible. It is often associated with polyneuropathy, and is more common in elderly patients with mild renal failure. Proximal weakness and areflexia, moderate creatine kinase elevation, and resolution of symptoms after withdrawal of the inciting agent fulfill the clinical picture. Pathophysiology remains unclear.

Two patients with muscle biopsy proven muscle colchicine myopathy demonstrated selective type 1 muscle fiber vacuolar change and microtubular disarray. Dystrophin and alpha-sarcoglycan, but not merosin, were expressed on the vacuolar membranes but not internally, the contents of which reacted with anti-alphaB-crystallin antibody. Membrane attack complex was observed on the surface of several muscle fibers, possibly due to complement activation resulting from vacuolar exocytosis. Calcium accumulation was not significant, in contrast to X-linked vacuolar myopathy, despite the presence of C5b-9 antibodies on the myofiber cell membrane. Colchicine myopathy is a treatable antimicrotubular myopathy, (by discontinuing the offending agent) selective for type 1 fibers, possibly due to the abundance of alpha tubulin in type 1 more than type 2 muscle cells. Overexpression of alphaB-crystallin in the vacuoles may be a cell protective effort, given that alphaB-crystallin is a heat shock protein shown to protect microtubules during simulated ischemia. Disruption of the microtubules may thus induce alphaB-crystallin synthesis.

COMMENTARY

Microtubules (25 nm diameter), heterodimers of alpha and beta tubulin, comprise the skeletal muscle cytoskeleton, together with intermediate filaments (10 nm diameter) and microfilaments (4-8 nm diameter). Extending between myofibrils, the contractile element of muscle composed of an orderly array of actin and myosin filaments, microtubules run along the long axis of the myofiber, and are associated with MAPs (microtubule-associated proteins), including MAP-1, MAP-2, and tau which modify microtubular function. No known primary disease affects microtubular structure or function. **—MICHAEL RUBIN**

Brief Alerts

MS on the Rise in the US

Source: Noonan CW, et al. Prevalence estimates for MS in the United States and evidence of an increasing trend for women. *Neurology.* 2002;58:136-138.

Investigators at the National Center for Health Statistics in Atlanta, Ga, analyzed data from 1982-1996 in the National Health Interview Survey (NHIS) which is conducted annually among a probability sample of the US population. Overall prevalence data and analyses for geographic, sex, age, and race/ethnicity distributions were performed. The overall prevalence estimate was 85/100,000, or approximately 211,000 (± 20,000). A 50% increase was observed in

the number of women reporting MS for 1991-1994 vs. 1982-1986. The observed trend in higher numbers of self-reported MS among women is consistent with recent observations of higher prevalence and incidence. The trend was strongest in women aged 40-59 years, and women reporting MS as a cause for limitation of activity. The variation in race was consistent (54% white, 25% black, 19% other) with prior reports, as was the estimates of geographic distribution, with the lowest prevalence in the South. Noonan and colleagues note limitations in the self-reported or family reported data that is not case confirmed with medical reports. Some of the increased prevalence trends may reflect greater patient awareness and more active physician diagnoses given the introduction of immunomodulatory therapies since 1993. Physicians may be more inclined to make a diagnosis, and at an earlier stage, as treatment options have increased. By previous surveys, however, as many as 14% of participants would be unaware of their diagnosis and unlikely to report their disease in a health interview. **—BRIAN R. APATOFF**

HSV and Risk of MS—No Benefit of Antiviral Therapy for MS

Source: Bech E, et al. A randomized, double-blind, placebo-controlled MRI study of anti-herpes virus therapy in MS. *Neurology*. 2002;58:31-36.

In a controlled clinical trial by Bech and colleagues, 70 relapsing MS patients were randomized to either valacyclovir (1 gm po tid) or placebo. Monthly MRIs and clinical scoring were performed for 8 months (2 months baseline, 6 months treatment). There were no significant differences between the treated and placebo groups either in the primary outcome measure of new MRI lesions or in the number of clinical relapses. In a small subset analysis of patients with high baseline MRI activity, however, there appeared to be fewer new active MRI lesions in the valacyclovir arm. However, simple antiherpes viral agents that are currently available to treat HSV-1, 2, and 3 do not seem to be of benefit. **—BRIAN R. APATOFF**

CME Questions

10. Factor(s) relevant to the development of carpal tunnel syndrome include:
a. wrist index (wrist depth/wrist width in mm).
b. shorter wider palms, and shorter third digit length.
c. older age.
d. obesity.
e. All of the above

11. The prevalence of PFO is:
a. about 25% in the general population.
b. about 50% in young patients with cryptogenic stroke.
c. ten times that of atrial septal aneurysm.
d. All of the above are correct

12. Consumption of alcohol has been found to lower the risk of dementia:
a. independent of the type of alcohol (wine, beer, hard liquor) consumed.
b. independent of the amount of alcohol consumed.
c. independent of the frequency of alcohol consumed.
d. in men only.

13. Elevated transverse sinus pressures in idiopathic intracranial hypertension most likely occur due to:
a. venous sinus thrombosis.
b. transmitted intrathoracic pressures.
c. sinus compression related to elevations in ICP.
d. hypoplastic venous sinus anatomy.

14. Which one of the following statements is correct?
a. Anti-Hu antibodies are associated with clinically pure sensory neuropathy.
b. Anti-Hu antibodies are associated with clinically pure motor neuropathy.
c. Anti-Hu antibodies are associated with a mixed sensorimotor neuropathy.
d. All of the above

15. Pain in chronic tension may be due to:
a. muscle contraction.
b. dysfunction of central monoaminergic/serotonergic systems in the brainstem.
c. nitric oxide peripheral sensitization.
d. peripheral sympathetic autonomic dysfunction.
e. None of the above

16. Colchicine results in myopathy by affecting:
a. intermediate filaments.
b. microfilaments.
c. microtubule-associated proteins (MAPs).
d. microtubules.
e. tau proteins.

In Future Issues: **Refractory Status Epilepticus Migraine Expresses Its Element**