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INSIDE

Neurosarcoidosis: A Review

ABSTRACT & COMMENTARY

Source: Kidd D, Beynon HL. The neurological complications of systemic sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2003;20:85-94.

SARCOIDOSIS IS A MULTISYSTEM GRANULOMATOUS DISEASE MOST often affecting the lungs, eyes, skin, and liver, with neurological involvement in 5-10%. Cranial neuropathy is the most common clinical manifestation, ranging from 60-73%, usually affecting the facial nerve (frequency up to 64%), frequently bilaterally. Sarcoid granulomata may affect the facial nerve in the parotid gland, at the skull base, in the internal auditory canal, or at the brainstem. Other cranial nerves may be affected, including the optic nerve presenting as progressive painless loss of vision or as painful optic neuropathy indistinguishable clinically from demyelinating optic neuritis. Lower cranial nerves IX, X, and XII are involved less frequently.

Cerebral hemisphere involvement occurs either as meningoencephalitis, presenting with altered mental status including psychiatric symptoms, fluctuating focal deficits, or impaired levels of consciousness, or rarely as a focal mass with presentation depending on location of the lesion. Most commonly, intracranial involvement affects the pituitary and hypothalamus and the area around the third ventricle. Diabetes insipidus is most common, but obesity, altered sleep and temperature function, and involvement of the optic chiasm with visual field defects are also seen. Erosion of the sella turcica is rare.

Chronic basal granulomatous leptomeningitis is a common autopsy finding and may be asymptomatic. More often, multiple cranial neuropathies or hydrocephalus due to foraminal obstruction result. Acute meningitis, cerebral infarction, or involvement of the cerebellum or brainstem occur rarely.

Spinal cord involvement most commonly presents as cervical myelopathy or conus medullaris syndrome with severity varying from mild to complete transverse myelitis. Cauda equina involvement, predominantly sensory and painless, also occurs and is associated with elevated protein and cells in the spinal fluid.

Chronic large fiber sensorimotor neuropathy, purely sensory neu-

VOLUME 22 • NUMBER 3 • NOVEMBER 2003 • PAGES 17-24

ropathy, a Guillain-Barré-like syndrome, or mononeuritis multiplex all occur in sarcoidosis. Granulomas may be seen on nerve biopsy but perineural vasculitis is also described. Painful slowly progressive myopathy is seen, as is a nodular, frequently asymptomatic form with palpable lesions in muscle that enhance on magnetic resonance imaging.

Absent any evidence from double-blind, placebo-controlled treatment trials, therapy encompasses steroids and immunosuppressants as steroid-sparing agents including azathioprine, methotrexate, cyclosporine, cyclophosphamide, and chlorambucil. Not all patients respond. Radiotherapy may benefit large, treatment-resistant, mass lesions.

COMMENTARY

Sarcoidosis remains an etiologic enigma. Recently, a thought-provoking article argued cogently that sarcoid might not be the consequence of a specific etiologic agent. Rather, it is the end result of an abnormal immune response to any of a variety of different exposures.[1] Sarcoid granulomas would result from abnormal antigen processing due to an impaired T-cell immune response. Absent the immune system's ability to efficiently clear the invading antigen, granuloma formation would be the "fallback position."

Ample clinical evidence exists in support of this hypothesis. Mortality among steroid-treated sarcoid patients is higher than in nonsteroid treated patients. Perhaps steroids promote such morbidity by impairing an already paretic T-cell system. Conversely, patients with erythema nodosum, implying the presence of a brisk immune response, do better. Those with combined variable immunodeficiency, on the other hand, frequently develop sarcoid, again implicating T lymphocytes. Parenthetically, this hypothesis also explains why no etiologic agent has been identified.

It does not explain all the clinical data, however.[2] Sarcoidosis-like reactions occur in HIV patients but only after the administration of highly active antiretroviral therapy (HAART), making this an example of sarcoid occurring in a relatively privileged situation immunologically rather than underprivileged. Why do sarcoid granulomas develop in allografts following transplantation, given that these tissues are presumably free of inciting antigens? Questions remain, but the theory is intriguing and would preclude our ever finding a cause for sarcoid. Which, ironically, would be the ultimate proof that the theory is on the mark. — **MICHAEL RUBIN**

References

1. Reich JM. *Chest*. 2003;124:367-371.
2. Judson MA. *Chest*. 2003;124:6-8.

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

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

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

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1 year *with* free AMA Category 1 credits: $249
Student/Resident rate: $125
Multiple Copies
2-9 additional copies: $224. 10-20 copies: $199.
Canada
Add 7% GST and $30 shipping.
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Topiramate for Painful Diabetic Neuropathy

ABSTRACT & COMMENTARY

Source: Kline KM, et al. Painful diabetic peripheral neuropathy relieved with use of oral topiramate. *South Med J*. 2003;96:602-605.

TOPIRAMATE MAY SOON LEGITIMATELY BE ADDED TO the list of anticonvulsants useful for the control of painful diabetic peripheral neuropathy. In this case report, a 47-year-old woman, with a 6-year history of diabetes, had a 4-year history of severe peripheral neuropathy, confirmed by electrodiagnostic studies. Gabapentin (1200 mg/d) and ibuprofen (800 mg t.i.d.) failed to control her pain, and she was intolerant to amitriptyline. Topiramate, as her sole analgesic, was then quickly titrated upward from 25 mg b.i.d. to 100 mg b.i.d. but resulted in nervousness, jitteriness, and interference with sleep. Reduction to 25 mg b.i.d. followed by a slower increase, over several months, to 100 b.i.d.

resulted in symptomatic improvement. Hypoglycemic episodes, which developed when topiramate was begun, were controlled by decreasing her oral hypoglycemic medication. Topiramate was consequently well tolerated and effective, blood glucose was better controlled, and the neuropathy did not progress over the ensuing 9 months. Topiramate may prove useful for the treatment of painful neuropathy.

COMMENTARY

Topiramate (2,3:4,5-bis-0-[1-methylethylidene]-ß-D-fructo-pyranose sulphamate) acts on neuronal transmission in several ways.[1] It has a dose-dependent modulatory effect on voltage-gated sodium channels, decreasing the frequency and duration of epileptiform-like bursts of action potential firing. GABA (g-aminobutyric acid) activity at GABAA receptors is enhanced at concentrations of 10-100 µmol/L, with receptor desensitization at higher (> 100 µmol/L) concentrations. L-type voltage-gated calcium channels and kainate/AMPA (amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors are selectively inhibited at low concentrations (10-100 µmol/L). Presynaptically, topiramate impairs glutamate release. Lastly, carbonic anhydrase isozymes II and IV are selectively inhibited, explaining the perioral and digital paresthesiae and nephrolithiasis, which occur as adverse effects.

These mechanisms presage a potential role for topiramate in pain control. Central sensitization, whereby central pain pathways are hypothesized to be altered secondary to peripheral influences, involves kainate/AMPA systems. This, in turn, brings NMDA into play, and topiramate may influence central sensitization by its effect on kainate/AMPA receptors. Descending inhibitory pathways to the dorsal horn also modulate pain input with GABAB receptors likely involved, although the role for GABAA receptors is less clearly defined. ß-endorphins are inhibited by GABAA antagonists, possibly implicating their involvement and supporting a role for topiramate, which potentiates GABAA activity. Carbonic anhydrase inhibition by topiramate may also be relevant at this level. Voltage-gated sodium channels undergo increased expression and translocation following nerve injury, and voltage-gated calcium channels modulate pain and alter opiate tolerance. Both of these effects may be influenced by topiramate, allowing it to be effective in the control of neuropathic pain.

— MICHAEL RUBIN

Reference

1. Chong MS, Libretto SE. *Clin J Pain*. 2003;19:59-68.

Temporal Lobectomy: Emergent Psychopathology

ABSTRACT & COMMENTARY

Source: Carran MA, et al. Mania following temporal lobectomy. *Neurology*. 2003;61:770-774.

Carran and colleagues describe the development of mania and depression in patients undergoing surgery for intractable epilepsy. They compared 16 patients who developed new-onset mania following temporal lobectomy (TLX) with 2 other groups matched for age, gender, and laterality of the epileptic focus. The 2 control groups were patients who developed depression following TLX and those who demonstrated no newly emergent psychopathology following surgery. Two factors appeared to place patients at greater risk of post-TLX mania. First, mania developed more frequently in patients who underwent right-sided resection (12:4) vs no laterality difference (8:8) for those who developed post-TLX depression. In addition, patients who had bilateral epileptiform EEG abnormalities preoperatively had a higher rate of post-TLX mania.

COMMENTARY

The association of epilepsy with psychopathology is well known. Post-ictal psychosis, at times evolving to inter-ictal psychosis, is commonly described. In addition, affective disorders, especially depression, have been associated with epilepsy arising from the right temporal lobe. Less common, and therefore, less well recognized, is the emergence of new psychiatric symptoms in patients following TLX for pharmacologically refractory epilepsy. This is certainly a risk that should be discussed with patients considering surgical treatment. Fortunately, the incidence of this complication seems to be low (8 patients with mania out of an operative database of 415 patients = 2%) and short-lived (all but 1 case remitted within 1 year following onset of mania).

Carran et al describe a number of theories that could account for the de novo development of mood disorders following TLX. One question that remains unanswered is whether there is an increased risk of psychopathology the longer the delay in referral for surgery. As with nearly every surgical treatment study, the mean duration of epilepsy prior to surgery was about 20 years for this group. While there was no significant difference in duration of epilepsy for the mania, depression, and control groups, Carran et al's analysis does not allow us to conclude that duration of epilepsy is not a factor in psychi-

atric co-morbidity, either pre- or postoperatively. With on-going trials of earlier surgery for epilepsy, a more definitive answer to this question may become available and bolster the argument for more timely surgical treatment. — **ANDY DEAN**

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Antifibrinolytics Do Not Improve Outcome After Subarachnoid Hemorrhage

ABSTRACT & COMMENTARY

Source: Roos Y, et al. Antifibrinolytic therapy for aneurysmal subarachnoid hemorrhage. A major update of a cochrane review. *Stroke*. 2003;34:2308-2309.

In current clinical practice, the surgical or endovascular treatment of aneurysmal subarachnoid hemorrhage (SAH) often is delayed for clinical or logistic reasons. Rebleeding is an important cause of death and disability following SAH and probably is caused by dissolution of the thrombus within the aneurysm by activation of the fibrinolytic system. Therefore, antifibrinolytics have been used to reduce the risk of rebleeding. Roos and associates reviewed the effect of antifibrinolytic treatment in patients with aneurysmal SAH. They searched the Cochrane Files Register and the medical literature, and also contacted drug companies in order to find randomized trials comparing oral or intravenous antifibrinolytic drugs (tranexamic acid, epsilon amino-caproic acid, or an equivalent) with control in patients with confirmed SAH. Nine trials involving approximately 1400 patients were included. Three trials involving more than 1000 patients assessed outcome in terms of both case fatality and degree of dependence. In these 3 trials, antifibrinolytic treatment had no beneficial effect on outcome. Death from all causes was not significantly influenced by treatment across all 9 trials. Although antifibrinolytic treatment reduced the risk of rebleeding at the end of follow-up in all trials, treatment increased the risk of cerebral ischemia in 5 trials. Antifibrinolytic treatment had no effect on the reported rate of hydrocephalus in 5 trials. The conclusion of Roos et al was that treatment with antifibrinolytics did not improve overall outcome because the reduction in the rate of rebleeding was offset by an increase in cerebral ischemic events.

COMMENTARY

These findings are important because they do not support the routine use of antifibrinolytic drugs in patients with aneurysmal SAH. Although antifibrinolytic treatment caused a 40% reduction in rebleeding, there was no effect on poor outcome (death, persistent vegetative state, or severe disability), and there was an increased incidence of cerebral ischemia in treated patients compared with controls. The full text of the review is available in the Cochrane Library, issue 2, 2003, or online at www.update-software.com/Cochrane. — **JOHN J. CARONNA**

Risks of Carotid Endarterectomy Reviewed

ABSTRACTS & COMMENTARY

Sources: Bond R, et al. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke*. 2003;34:2290-2301; Crisby M. Editorial comment. Risk stratification by clinical symptoms and timing of carotid endarterectomy: How could it optimize our decision making and benefit patients with carotid stenosis? *Stroke*. 2003;34:2302-2303.

Bond and associates reviewed data from 383 reports on carotid endarterectomy (CEA). The data from 60 of the studies, involving more than 14,000 cases of CEA, demonstrated an operative risk and death for asymptomatic stenosis of 2.8 vs 5.1% for symptomatic stenoses reported in 95 studies. The absolute risk for stroke and death from CEA was less than 3% for patients with only ocular ischemic events but as high as 19.2% for patients with ongoing cerebral symptoms. CEA for patients with either cerebral TIA or stable cerebral stroke was associated with a higher risk than surgery for ocular events only. Unstable patients, defined as those with stroke in evolution and crescendo TIA, presented with the highest operative risk, although only 13 studies, each with a low number of cases, reported the outcome of "urgent" CEA. The results were consistent in all studies: Urgent CEA for evolving symptoms had a much higher risk (19.2%) than CEA for stable symptoms (3.9%). There was no difference between early (less than 3-6 weeks) and late (greater than 3-6 weeks) CEA for stroke and stable TIA patients. Bond et al conclude that their analyses showed that the risk of stroke and death resulting from CEA is highly depen-

dent on the clinical indication, and they suggest that reports of surgical risk should be stratified accordingly. Specifically, they found that patients with only ocular ischemic events were closer in risk to patients with asymptomatic stenoses. As to the timing of surgery, the operative risk of CEA in the acute phase of ongoing cerebral ischemia was too high to justify urgent CEA in routine clinical practice. CEA in the subacute phase in patients with a stable neurologic syndrome was not associated with a higher operative risk than later surgery. As pointed out by Crisby in her editorial comment, progress in therapeutic decision making for CEA is essential for minimizing the risk of stroke and death resulting from CEA.

COMMENTARY

Bond et al have shown by their metaanalysis that the classification of ischemic events into different categories such as ocular TIA, cerebral TIA, and cerebral infarction leads to differences in surgical operative risk and benefit. The ad hoc committees of the American Heart Association Stroke Council have established guidelines on the acceptable operative risk of CEA. The guidelines recommend that the combined risk of stroke and death resulting from CEA should not exceed 3% in asymptomatic patients, 5% in symptomatic patients with TIA, and 7% for those with stroke. Therefore, as the metaanalyses of Bond et al showed, it is important to classify the nature of the ischemic event preoperatively, especially to separate purely ocular from cerebral TIAs and stable patients from unstable patients in order to assure that the patient considered for CEA is an acceptable operative risk, that is, one that is within the American Heart Association Stroke Council's guidelines. **— JOHN J. CARONNA**

Has deCODE Really Decoded a Stroke Gene?

ABSTRACT & COMMENTARY

Source: Gretarsdottir S, et al. The gene encoding phosphodiesterase 4D confers risk of ischemic stroke. *Nat Genet*. 2003; 35:131-138.

THE PUBLICITY GENERATED BY THE HUMAN GENOME project has generated huge expectations. The identification of disease genes was supposed to be just around the corner. Progress in finding these genes, however, has been frustratingly slow. It was one thing to identify the gene defects underlying diseases like cystic fibrosis and Huntington's disease. Not only were these disorders transmitted according to obvious modes of inheritance within families, but the effect of the altered gene was sufficiently strong to cause disease regardless of environmental or other genetic factors. Pedigrees were assembled, the chromosomal location of the gene was identified, and through a careful search of that chromosomal location . . . eureka! The gene was found.

It won't be so easy to find stroke genes, or those for any other complex disease, for that matter. Complex diseases like stroke arise through multiple mechanisms. The genes involved in stroke play a much smaller role than they do in the "single gene disorders" like Huntington's disease. Furthermore, there are likely to be multiple genes with a role in stroke, making them even harder to identify.

The traditional search for disease genes begins with linkage analysis, which identifies the chromosomal location of the gene. Multiple pedigrees with affected individuals are assembled, and an evenly spaced map of DNA sequence variants (known as markers) is determined for each member of the pedigree. This allows researchers to trace the inheritance of each copy of each chromosome. Chromosomal segments that influence the disease of interest are inherited more frequently by affected individuals, and the strength of this inheritance is quantified with a LOD score (log-of-odds ratio). These segments are often quite large, ranging from millions to tens of millions of DNA bases, spanning dozens to hundreds of genes.

The most recent publication of the deCODE investigators from Iceland describes the steps they took to go from a linked chromosomal region to culprit gene. They constructed a map of the roughly 11 million base pair segment of chromosome 5 that they had identified in their previously published linkage analysis as a likely location for a stroke susceptibility gene.[1] They then assembled 864 Icelandic stroke patients and 908 controls and tested to see if any of the DNA variants contained within this segment were found more commonly among cases than controls. Variants in or around the gene encoding phosphodiesterase 4D (PDE4D) were associated with ischemic stroke of cardiogenic and carotid subtypes. The team then turned to transformed cell lines created from randomly selected cases and controls, finding that expression of PDE4D was reduced among stroke and TIA cases.

With no causative mutation definitively identified, however, the team turned to haplotype analysis. Haplotypes are the particular combinations of alleles observed in a population. Whenever new mutations arise, they do

so on a specific segment of DNA with a particular combination of variants. The association between each mutant allele and its ancestral haplotype is disrupted only by mutation and recombination in subsequent generations. Haplotypes can, therefore, be passed on from generation to generation. One particular haplotype was strongly associated with stroke of carotid and cardiogenic origin (P = .0067). It contains a segment of the PDE4D gene that may control the level of its expression, consistent with the results of the cellular expression studies. The deCODE investigators are now, no doubt, carefully examining this haplotype with the hope that it will yield a culprit DNA variant.

COMMENTARY

The role of PDE4D in the development of ischemic stroke remains to be elucidated. The deCODE investigators, relying on the unique features of the Icelandic population, advanced technology, and a large collaborative team, offer the first unbiased identification of a gene that may influence stroke susceptibility. They isolated this gene without any preconceived notions about pathophysiology, which is a huge step forward. Nonetheless, the possibility remains that ultimately these results will never be replicated, an all-too-common fate for genetic studies in complex diseases.[2] One thing, however, does bear notice. deCODE is a for-profit company and, no doubt, has much to gain from the success of its research.

— JONATHAN ROSAND

References

1. Gretarsdottir S, et al. Localization of a susceptibility gene for common forms of stroke to 5q12. *Am J Hum Genet*. 2002;70:593-603.
2. Rosand J, Altshuler D. Human genome sequence variation and the search for genes influencing stroke. *Stroke*. 2003;34:2512-2516.

Jonathan Rosand works in the Stroke Unit at Massachusetts General Hospital and the Whitehead Institute/MIT Center for Genome Research.

Clinical Features of MuSK-Positive Myasthenia Gravis

ABSTRACT & COMMENTARY

Source: Evoli A, et al. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. *Brain*. 2003;126:2304-2311.

Among myasthenia gravis (MG) patients who are seronegative (SNMG) for acetylcholine receptor antibodies (AchR Ab), up to 70% demonstrate positivity for IgG antimuscle-specific kinase (MuSK) antibodies. How do they differ clinically from SNMG patients negative for both AchR Ab and MuSK Ab?

Of 78 SNMG patients with generalized myasthenia, 37 were anti-MuSK positive. Diagnosis of SNMG was based on criteria developed by the MG Foundation of America with repeatedly negative AchR Ab assays and confirmed by a > 11% decrement on repetitive nerve stimulation or increased jitter on single-fiber electromyography. Myopathy and neuropathy were excluded based on normal-needle EMG, nerve conduction studies, and serum creatine kinase in all patients, serum lactate in most, and muscle biopsy in 16. Comparison was made to the remaining 41 MuSK-negative SNMG patients. Students' t tests and X2 tests with Yates correction provided statistical analysis.

MuSK-positive patients were predominantly female (M/F = 0.3) compared to an even gender distribution in MuSK-negative patients. Mean age of onset was similar in the 2 groups, 35 and 39 years, respectively, but younger patients were more frequently MuSK positive, 56.8% presenting before the age of 40. Acute or subacute onset was more frequent in MuSK-positive myasthenics, most often with ptosis and diplopia rapidly progressing to bulbar weakness. All MuSK-positive patients experienced nasal speech and facial weakness, with 35 of 37 noting dysphagia and ocular difficulties. Respiratory crisis was seen in 17 (46%), but limb weakness was clearly evident in only 12 (32%). Only bulbar weakness (100% vs 58.5%) and respiratory crises (46% vs 7.3%) were significantly more common in MuSK-positive compared to MuSK-negative patients. Repetitive nerve stimulation and edrophonium testing were more often positive in MuSK-negative patients, 78% vs 56.8%, and 82.9% vs 70.3%, respectively. Thymectomy did not appear to benefit MuSK-positive patients, and, despite standard high-dose immunosuppressive therapy, 30% experienced periodic deterioration including respiratory crisis requiring, and responding to, plasma exchange. Many developed permanent facial weakness and dysarthria. MuSK-positive patients were, in most instances, clinically indistinguishable from seropositive MG patients and responded well to anticholinesterase and immunosuppressive medication.

COMMENTARY

Compared to adult MG patients, those with childhood and juvenile-onset MG are more likely to be AchR Ab negative. Do they conversely demonstrate a higher degree of MuSK antibody positivity? Among 40 juvenile MG patients, confirmed by pharmacological testing,

27 underwent repeated AchR Ab testing, and 8 (29%) were consistently negative. All had ptosis and extraocular muscle weakness that worsened with fatigue, and 3 had mild generalized weakness. None were positive for MuSK antibodies.[1] Case reports with MuSK positivity in childhood may have correlated with more severe weakness. Previous steroid treatment or thymectomy may also influence positivity. MuSK antibodies appear less frequently in children with ocular or mild generalized disease. **— MICHAEL RUBIN**

Reference

1. Anlar B, Vincent A. *Neuropediatrics*. 2003;34:110-111.

MS and Stress: Role in Exacerbations

ABSTRACT & COMMENTARY

Source: Buljevac D, et al. Self reported stressful life events and exacerbations in multiple sclerosis: Prospective study. *BMJ*. 2003;327:646.

BULJEVAC AND COLLEAGUES ASSESSED WHETHER life events that are perceived as stressful by patients themselves are associated with exacerbations. This prospective study followed 74 ambulatory relapsing-remitting multiple sclerosis patients (EDSS 0-6) who had at least 2 exacerbations in the 24 months before inclusion into the study. Seventy of the 73 patients (96%) reported at least 1 stressful event over an average follow-up time of 1.4 years. Throughout the study, 134 exacerbations occurred in 56 patients, and 136 infections occurred in 57 patients. MS patients who experienced a stressful event had more than a twofold increased risk of having a relapse during the subsequent 4 weeks (relative risk 2.2%, 95% CI, 1.2-4.0; $P = .014$). Infections were associated with a threefold increase in the relative risk of exacerbation, but this effect was found to be independent of experienced stress.

COMMENTARY

Previous studies have defined precipitants for MS exacerbations, most notably infections. The attack rate also increases in the first 3 months postpartum and during menses. Psychological stress has been implicated as a determinant of disease activity in MS since the time of Charcot. While neurologists anecdotally appear to observe a correlation between life stress and worsening disease, prior controlled studies have failed to document such a relationship. While Buljevac et al linked stressful events with a twofold risk of exacerbation, there was no attempt to perform baseline psychological surveys or depression inventories to see if certain patient profiles were more likely to relapse in stressful circumstances. The inciting mechanism behind stress and the induction of inflammatory demyelinating disease is not known but could result from activation of the hypothalamic-pituitary-adrenal axis and cytokine networks. Nonetheless, given the results of the above study, clinicians should recognize that stress may be a negative influence on the disease course. It might be of benefit to provide a variety of stress management strategies to help reduce the potential for exacerbations. **— BRIAN R. APATOFF**

MS and Fatigue: Possible Role of Autonomic Dysfunction

ABSTRACT & COMMENTARY

Source: Flachenecker P, et al. Fatigue in multiple sclerosis is related to sympathetic vasomotor dysfunction. *Neurology*. 2003;61:851-853.

FLACHENECKER AND ASSOCIATES STUDIED 60 PATIENTS with multiple sclerosis (MS) (mean age, 41.5; 72% female; 70% RRMS; mean disease duration, 12.8 years; median EDSS, 3.0) and 36 age- and sex-matched controls. Thirty-two of the MS patients were on immunomodulatory therapy, mainly with interferon-beta (n = 27; 45%). Patients taking beta-blockers, sympathomimetics, tricyclics, or alpha-sympatholytics were excluded.

Patients underwent standard autonomic function EKG and blood pressure tests to measure parasympathetic function (heart-rate responses to Valsalva maneuver, deep breathing, and active change in posture) and sympathetic vasomotor function (blood pressure responses to active change in posture and sustained handgrip). Fatigue was assessed by standardized questionnaires including the Fatigue Severity Scale and the Modified Fatigue Impact Scale with subscores for physical, cognitive, and emotional fatigue.

The median heart rate response to standing was significantly reduced, and blood pressure to handgrip tended to be lower in patients with MS compared to controls. The autonomic dysfunction was more pronounced in MS patients with higher fatigue scores.

COMMENTARY

To the clinician, fatigue in MS appears to be a universal complaint and often the most disabling symptom. The complex neurological substrate(s) underlying fatigue have been debated for years. This study corroborates a few earlier studies indicating that sympathetic vasomotor dysfunction may have a role in MS-related fatigue. Controlled clinical trials of sympathomimetics should be performed to test potential benefits for MS fatigue. The current clinical practice of treating fatigue with psychostimulants such as methylphenidate or modafinil is useful. **— BRIAN R. APATOFF**

CME Questions

16. Which of the following is true? Antifibrinolytic therapy for aneurysmal SAH:

a. reduces rebleeding and improves outcome.
b. reduces rebleeding but does not improve outcome.
c. reduces rebleeding but makes outcome worse.
d. does not reduce rebleeding or affect outcome.
e. increases ischemic events but improves outcome.

17. According to the American Heart Association Stroke Council guidelines, acceptable operative risk of CEA for a patient symptomatic of TIA should not exceed:

a. 1%.
b. 3%.
c. 5%.
d. 7%.
e. 19%.

18. Regarding antimuscle-specific kinase (MuSK) antibodies:

a. they are more frequent in male than female myasthenia gravis patients.
b. elderly patients are more frequently MuSK positive.
c. insidious onset is most frequent in MuSK-positive myasthenics.
d. most MuSK-positive myasthenics patients experience nasal speech and facial weakness.
e. None of the above

19. Which of the following is true? Fatigue in multiple sclerosis:

a. appears to be related mainly to thyroid dysfunction.
b. correlates most precisely with depression scores.
c. significantly corresponds to altered pupillary responses.
d. is related to reduced heart rate and blood pressure responses.

Answers: 16(b); 17(c); 18(d); 19(d)

Annual Statement of Ownership, Management, and Circulation

United States Postal Service
Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
Neurology Alert	0 7 4 1 - 4 2 3 4	10/1/03
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$249.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305 — Contact Person: Robin Salet; Telephone: 404/262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

Publisher *(Name and Complete Mailing Address)*: Brenda Mooney, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and Complete Mailing Address)*: Christine Messina, same as above

Managing Editor *(Name and Complete Mailing Address)*: Glen Harris, same as above

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Thomson American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400 Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Thomson Healthcare, Inc.	Five Paragon Drive Montvale, NJ 07645

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, September 1998 — *See instructions on Reverse)*

13. Publication Name: Neurology Alert — 14. Issue Date for Circulation Data Below: September 2003

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			1944	1804
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	1480	1415
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	7	9
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	92	77
	(4)	Other Classes Mailed Through the USPS	60	53
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2))*			1639	1554
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	10	13
	(2)	In-County as Stated on Form 3541	1	2
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			23	25
f. Total Free Distribution *(Sum of 15d and 15e)*			34	40
g. Total Distribution *(Sum of 15c and 15f)*			1673	1594
h. Copies Not Distributed			271	210
i. Total *(Sum of 15g. and h.*			1944	1804
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			98	97

16. Publication of Statement of Ownership — Publication required. Will be printed in the November 2003 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Brenda Z. Mooney Publisher — Date: 9/30/03

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
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5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

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PS Form **3526**, September 1999 *(Reverse)*

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