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Activated Microglia Imaged in Alzheimer Brain

ABSTRACT & COMMENTARY

Source: Cagnin A, et al. *Lancet.* 2001;358:461-467.

A radio-labelled marker of microglial activation has been found to bind more extensively to the brains of Alzheimer patients than age-matched normals, and could provide a means of monitoring brain inflammation in patients with mild cognitive impairment and dementia. Cagnin and colleagues used positron emission tomography (PET) to quantitate the distribution of carbon-11-labelled PK11195 in the brains of 15 normal patients, 8 Alzheimer's disease (AD) patients, and 1 with mild cognitive impairment (MCI). They used PK11195 for this purpose, a ligand for the peripheral benzodiazepine receptor that binds to brain macrophages and activated microglia. Binding of PK11195 has been shown to increase in the aftermath of stroke and other processes that lead to the activation of microglia and the passage of peripheral macrophages into the brain. Its imagability with PET makes it suitable for measuring active inflammation in the living brain on a regional basis.

Normal subjects, ranging in age from 32-80, showed no significant increases in PK11195 binding, except in the thalamus. Cagnin et al speculate that this constitutive binding could be explained by the proximity of the thalamus to areas in which the blood-brain barrier is leaky. In contrast, Alzheimer patients showed increases in multiple brain areas relative to normals. Significant elevations were found in the entorhinal cortex, temporoparietal area, and cingulated cortex. The AD patients in this investigation were also studied using serial volumetric MRI imaging to quantitate regional brain atrophy. Areas that showed the most significant increases in PK11195 binding were also the regions with the highest rates of brain atrophy. This suggests that the inflammatory markers may reflect active areas of neurodegeneration.

One subject with MCI was examined in this study. This patient showed normal brain glucose metabolism on 18-FDG PET and did not have evidence of significant cognitive decline over a 23-month follow-up period. However, serial MRIs demonstrated atrophy in

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inferior and medial temporal areas that was predicted by the pattern of PK11195 binding when the patient was initially studied. Although this patient was not documented to develop frank AD in the course of the study, the findings suggest that PK11195 binding may increase during the preclinical stages of AD and could be an early marker of neurodegenerative changes.

COMMENTARY

Activated microglia play an important role in the clearance of amyloid deposits in the brain, and may contribute to AD pathology by mediating the conversion of diffuse amyloid deposits into neuritic plaques. A plethora of markers of inflammation have been found in the brains of AD patients postmortem, and inflammatory mechanisms have been targeted in several clinical trials aimed at preventing or slowing the course of AD. The in vivo imaging technique used in this study provides a novel window on the inflammatory component of AD pathology, and could prove extremely useful in the development of anti-inflammatory therapies and preventatives for AD in the future.

The finding that inflammatory changes in the brains of living AD patients correlated with subsequent brain atrophy could be interpreted as evidence that microglial activation is a harbinger of subsequent neural degeneration. However, in direct analogy to stroke, this marker of inflammation could reflect microglia clearance of cellular debris following neuronal death rather than active causation of neuronal pathology. The issues of whether inflammation is part of the problem or part of the solution in AD remains to be resolved.

Epidemiologic evidence suggests that anti-inflammatory medications may decrease the risk of AD, but do not provide evidence that they alter the course of existing dementia. It is currently uncertain whether the concept of treating demented patients with anti-inflammatory medication represents "too little, too late." Recent attempts to use conventional anti-inflammatory treatments in mild-to-moderate AD patients have yielded discouraging results. Low-dose prednisone failed to improve cognition in AD patients, and more recently, the antimalarial anti-inflammatory hydroxychloroquine failed to slow the rate of decline in mild AD (Van Gool WA, et al. *Lancet.* 2001;358:455-460). Preliminary studies of immunotherapy for AD have yet to establish the effectiveness of this approach in humans or establish whether peripheral immunization exerts its effects via the activation of brains microglia. At the present time, the use of anti-inflammatories such as NSAIDs in the treatment of AD patients is not recommended, although further work in this area is clearly justified. **—norman r. relkin**

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Neurologic Testing of Low Yield in Syncope Evaluation

ABSTRACT & COMMENTARY

Source: Pires LA, et al. *Arch Intern Med.* 2001;161: 1889-1895.

It is well appreciated that the diagnosis of acute syncope is best guided by a detailed history and physical examination. The addition of diagnostic tests such as CT scanning, EEG, or cardiac testing may reduce but not eliminate the considerable diagnostic uncertainty involved with syncope evaluations. As Pires and colleagues observe, neurologic tests may be of particularly dubious value unless they are appropriately tailored to the clinical picture.

Pires et al retrospectively reviewed 649 patients admitted to 2 community hospitals with a primary diagnosis of syncope. Patients were studied from 2 time periods: 1994 (451 patients) and 1998 (198 patients). Results did not substantially differ between the 2 hospitals or time periods.

CT or EEG provided a diagnosis in a small subset (11 patients) among whom clinical history was consistent with seizure (n = 14) or stroke (n = 20). CT or EEG was of no use in diagnosis among patients with presentations inconsistent with a CNS event. CT or EEG was performed frequently in almost half the study patients, giving each an overall diagnostic yield of only 2%. Carotid dopplers, performed in 185 patients, and MRI, done in only 10 patients, yielded no significant diagnostic results.

The highest yield test, postural blood pressure testing, was used in a minority of patients, 176 (27%), but successfully explained syncope in 52 of these, a 30% diagnostic yield. Head-up tilt-table testing and electrophysiology studies also had high yields, in the range of about 20%, but were used in even fewer patients.

Other forms of cardiac testing were more widely applied and were not generally successful. Continuous telemetry (performed in all 649 patients), holter monitoring (performed in 193), or echocardiography (performed in 277) explained syncope in only 7, 6, and 3 cases, respectively. These tests thus showed a diagnostic yield in the range of 1-3%, comparable to that of CT/EEG.

Patients undergoing cardiac or neurologic consultation were more likely to have diagnoses falling into these categories than patients seen only by primary care physicians. Thirteen of 92 patients seen by a neurologist were determined to have a neurologic cause for syncope compared with 2/181 seen by a cardiologist or 7/225 seen by primary care providers. Conversely, a cardiac etiology of syncope was identified in 31 patients seen by a cardiologist, compared with 13 or 3 patients seen by a neurologist or primary care physician.

Overall, a diagnosis for syncope was identified in 329 patients. The most common etiologies were a drug reaction or metabolic cause (including orthostatic hypotension, n = 161) or a vasovagal spell (n = 71).

COMMENTARY

Unless stroke or seizure is likely based on clinical grounds, CT and EEG are of little use in syncope evaluation. The most effective "test" proves to be postural blood pressure testing, which is merely an extension of a thorough physical examination. This clearly represents a victory for basic clinical medicine over more expensive modern technologies.

As Pires et al point out, these results may be reinterpreted based on the referral bias. Neurologists may see a subset of the overall population with syncope among whom CNS tests are more justified. On the other hand, only 13 of these patients had a neurological diagnosis, leaving the majority of the 92 cases seen by neurologists in the unknown or cardiac categories.

It is not surprising that carotid doppler ultrasound was of no diagnostic yield in this study, as carotid stenosis, particularly if unilateral, does not typically present in this manner. The study, however, does not address vertebrobasilar disease, which may cause syncope and would warrant either transcranial doppler or MRA evaluation in selected cases. **—alan z. segal**

Spatial Awareness—A Function of the Temporal Lobe

ABSTRACT & COMMENTARY

Source: Karnath HO, Ferber S, Himmelbach M. *Nature.* 2001;411:950-953.

Acute hemi-spatial unawareness in humans, sometimes called "neglect," has long been considered to be the result of acute, severe damage to the right posterior-inferior parietal lobe. Infarcts, hemorrhages, or occasionally, neoplasms, may precipitate such injuries and the functional deficit often fails to recover completely. In some instances, the affected patient cannot recognize the left side of his body or outer space. Indeed, he even may deny the existence of the left half of his own self. Such abrupt, total losses of seemingly instinctive knowledge can appropriately be considered as focal unconsciousness. This clinical report has concentrated on primary damage to the right inferior parietal lobule (IPL), the temporo-parieto-occiptal (TPO) junction, and the superior temporal gyrus (STG).The primary cortical visual system has been avoided but the precortical TPO pathway frequently interrupts parts or all of the subsequent TPO injury.

Karnath and associates, over a 5-year period, have quantified and qualified the correctness of a new concept. They emphasize that most or all past clinical reports or discussions of spatial neglect have focused on parietal lobe dysfunction. Meanwhile, most reports have ignored the concurrent injuries that affected the adjacent geniculo-occipital pathways of the cerebral visual system. Recognizing this potential confusion of 2 dysfunctional perceptive systems, Karnath et al used quantitative CT or MRI scanning measures to identify cerebral functions in 49 patients who suffered from only 'purely' left spatial unawareness. (This indicated that no patient displayed any specific visual dysfunction.) Of the initial 49 patients, 33 had cortical lesions and the remainder suffered only subcortical abnormalities that unclearly

engendered spatial unawareness. Eight of the subcortical group also had unrelated cortical abnormalities and was put aside. This left 25 uncomplicated patients. Each of the 25 patients underwent a careful neurological examination plus pre-programmed CT or MRI brain imaging. Each instrument was preadjusted to provide 8 designated horizontal slices of functional interest.

Imaging results of each of the 25 clinically dysfunctional patients were anatomically and quantitatively similar to the expected changes in every case. Karnath et al state, "In clear contrast to controls, the lesion overlap in the neglect patients centered on the (right) STG (Brodmann areas 22 and 42). Neighboring affected structures consisted of the ventral postcentral gyrus and the operculum." The STG damage amounted to 6.9 times larger in size in neglect patients than at normal baseline ($P < 0.001$). No other predominant involvement in size occurred in the IPL, TPO, the cingulate cortex, or the middle temporal gyrus in patients with pure spatial neglect. Less intense injury affected the ventral post central gyrus and the operculum which functionally joins together the parietal, occipital, and temporal lobes. Unexpectedly, these "pure" patients who lacked visual defects expressed little or no functional involvement that affected the inferior parietal lobule, the temporal-parietal-occipital junction, the cingulate cortex, or the middle temporal gyrus. Furthermore, Karnath et al cite an additional 25 paired patients who suffered cerebral injury in the frontal-parietal areas but spared the STG and avoided any clinical neglect.

Past clinical opinion has often considered that an injured parietal area singularly generated agnosia when compounded with an ipsilateral visual abnormality. Karnath et al of this present report, however, suggest a more likely interpretation of such double-system dysfunctions. To resolve this question, Karnath et al studied 8 patients with acute right-hemispheric strokes. Four of these suffered neglect associated with severe vascular damage to the right parietal lobe plus concurrent injury to the optic radiation as it passes from the posterior horn of the lateral ventricle to reach the occipital cortex. It invoked high dysfunction in the IPL, the TPO junction, and the STG.

Karnath et al conclude that 4 patterns of damage can construct neglect: "1) A clear difference in lesion location between patients with pure neglect and those with both neglect and hemianopia (the latter involving also posterior regions); 2) those areas found as the neural correlate of spatial neglect in patients with pure neglect are affected in the patients suffering from both neglect and hemianopia; 3) the center of lesion overlap in patients with neglect and hemianopia is comparable to that reported in earlier studies (that is, involves the IPL and TPO junction); and 4) the posterior parts of lesion overlap in the patients with neglect and hemianopia also overlap in those patients without neglect but with hemianopia due to a stroke in the territory of the same cerebral artery."

COMMENTARY

In monkeys, damage to STG alone fails to impair accurate, bilateral recognition of spatial objects. Spatial knowledge provides these animals with their very survival. Unlike mankind, however, their small abstract verbal signals prevent intellectual complexity. So-called spatial or object neglect in humans is much more than that. It's focal unconsciousness, known by the quaint early 20th century term of agnosia. Your editor should have recognized a long time ago that a sudden unknown loss of spatial memory cannot by itself be engendered by an injury confined to the parietal lobe. Nor does selective V1-3 damage induce upon persons a state of permanent, unconscious hemianopsia. Temporal lobe damage is required to completely invoke that disability, just as it must do in sustained human spatial unconsciousness. **—fred plum**

Immobilization For the Treatment of Focal Occupational Dystonia

ABSTRACT & COMMENTARY

Source: Priori A, et al. *Neurology*. 2001;57:405-409.

Focal task-specific dystonia (ftsd) is one of the most interesting and mysterious neurologic disorders. Affected patients are otherwise completely well, but are unable to perform a specific skilled manual task. By definition, FTSD affects only 1 part of the body (usually the hand) and is limited to the performance of a specific task. Writer's cramp is the most common FTSD, although the disorder has been described in professional sewers, tailors, engravers, golfers, and virtually all types of musicians (pianists, violinists, guitarists, flutists, clarinetists, drummers, etc).

Until recently, little was known about the mechanisms underlying FTSD. Recent work in patients with FTSD and in primates with focal dystonia of the hand has demonstrated that the cortical sensory representation of the affected hand is markedly abnormal. These findings are similar to the altered cortical sensory maps seen in patients who have undergone limb amputations. Fluo-

ro-deoxyglucose PET scanning and functional magnetic resonance imaging has demonstrated that patients with FTSD inappropriately activate cortical regions (typically supplementary motor cortex) that are not activated during normal performance of manual tasks.

The treatment of FTSD remains challenging. Oral medications commonly used to treat generalized dystonia (such as trihexyphenidyl, baclofen, and clonazepam) are usually not helpful. Injection of botulinum toxin into the affected limb offers substantial functional improvement, particularly in patients with writer's cramp. However, for professional musicians and professionals such as surgeons who rely on accurate and exquisitely controlled complex movements, these treatments remain sufficiently active to prevent them to return to professional life.

The current paper outlines a new technique for the treatment of FTSD—limb immobilization. In this study, Priori and colleagues recruited 7 musicians with FTSD and 1 patient with writer's cramp, all of whom had failed standard therapies for focal dystonia. The arm affected with dystonia was then immobilized for 5 weeks in a rigid splint. Patients were allowed to remove the splint only once per week to attend to hygiene. At the end of the 5-week period, the splint was removed and patients were allowed to use the hand and to resume practicing their instrument. They were assessed over the ensuing 24 weeks with videotaped examinations, and 2 blinded observers used several functional disability scales to rate the patients before and at multiple points after treatment.

Immediately after the splint was removed, all patients reported clumsiness and mild-to-moderate weakness in the limb. Joint edema and pain were common, and nail growth stopped. Four weeks after splint removal, voluntary control and strength in the hand had returned to normal. Three patients had a moderate improvement in focal dystonia, and 4 had a marked improvement, sufficiently good enough to allow public performance. The patients with the most severe dystonia enjoyed the greatest improvement, and 1-year follow-up benefits have been maintained.

COMMENTARY

This report is of considerable interest to movement disorder neurologists and also to those in the neurologic community interested in cortical plasticity. In the last decade, there has been increasing evidence that the adult brain is capable of remarkable plasticity. While Priori et al did not perform functional imaging on their patients, the simplest and most logical explanation for their success is that the 5-week immobilization period reversed or obliterated the aberrant cortical representation of dystonia. In a sense, Priori et al succeeded in resetting the sensory-motor cortex by subjecting patients to a period of profound sensory and motor deafferentation.

This report is preliminary and further studies are warranted. Immobilizing a limb entails the risk of nerve entrapment, muscle atrophy, or, in the worst-case scenario, development of reflex sympathetic dystrophy. However, compared to virtually all other available treatments for FTSD, limb immobilization offers the potential to dramatically improve or even cure focal dystonia. For this reason, this paper offers hope to a frustrated population of professionals whose careers and livelihoods are threatened by this unusual condition. **—steven frucht**

Midlife Vascular Risk Factors and Late-Life Mild Cognitive Impairment

ABSTRACT & COMMENTARY

Source: Kivipelto M, et al. *Neurology.* 2001;56:1683-1689.

Age-related cognitive decline or mild cognitive impairment (MCI) has attracted medical attention because of its relationship to Alzheimer disease (AD). Petersen and associates noted an annual conversion to AD in 10-12% of MCI subjects compared to a conversion rate of only 1-2% in the normal elderly population (Petersen RC, et al. *Arch Neurol.* 1999;56:303-308). There also is evidence that a relationship exists between hypertension and hypercholesterolemia and late-life cognitive decline (Launer LJ, et al. *JAMA.* 1995;274:1846-1851; Kilander L, et al. *Hypertension.* 1998;31:780-786; Carmelli D, et al. *Neurology.* 1998;50:1580-1585).

Kivipelto and colleagues evaluated the effect of midlife elevated serum cholesterol levels and blood pressure on the subsequent development of MCI in a Finnish population. Subjects were derived from random population-based samples from surveys carried out from 1972 to 1987. After an average follow-up of 21 years, more than 1400 subjects aged 65-79 were reexamined in 1998. Subjects scoring ≤ 24 on the MMSE (n = 280) were invited to participate in further testing that included thorough medical and neurological examinations and detailed neuropsychological evaluation. MCI was diagnosed according to criteria devised by the Mayo Clinic Alzheimer Disease Research Center (Petersen RC, et al. *JAMA.* 1995;273:1274-1278). By

applying these criteria the prevalence of MCI in this population was 6.1% (n = 82), after excluding subjects with other health problems that may have had a direct impact on cognitive, the prevalence was 4.8% (n = 64). In these subjects, a high serum cholesterol level (≥ 6.5 mmol/L) at midlife was a significant risk factor for MCI (odds ratio 1.9; 95%; CI, 1.2-3.0). Subjects with MCI tended to have higher systolic blood pressure (SBP) at midlife than controls, and the distribution of SBP values was wider among MCI than control subjects. High midlife SBP approached, but did not reach, significance as a risk for MCI. Sixty-one percent of subjects with MCI had either elevated serum cholesterol or high SBP at midlife. There was no significant difference in the prevalence of cardiovascular or cerebrovascular disease between MCI and control subjects.

Kivipelto et al found a dose-response relationship between elevated cholesterol and SBP at midlife and severity of cognitive decline in late life. At midlife, subjects with MCI had cholesterol and SBP levels that were higher than those of control subjects but lower than those who developed dementia. This graded association may indicate a causal relationship between midlife hypercholesterolemia and systolic hypertension and the severity of late-life cognitive impairment.

COMMENTARY

As the proportion of the elderly increases in the population, so must the number of patients with AD. In the absence of a cure for the condition, any interventions that might delay its onset would have huge public health benefits.

Kivipelto et al have highlighted the relationship between vascular factors, especially hypercholesterolemia and cognitive impairment. These factors may simply increase the risk of dementia by inducing cerebrovascular atherosclerosis and impairing cerebral blood flow. Recently, however, the possible biologic mechanisms whereby elevated serum cholesterol could cause cognitive decline have been studied. Cholesterol modulates the metabolism of amyloid precursor protein in cell cultures, (Bodovitz S, Klein WL. *J Biol Chem.* 1996; 271:4436-4440) and depletion of intraneuronal cholesterol inhibits the production of ß-amyloid in vitro (Simons M, et al. *Proc Natl Acad Sci USA.* 1998;95: 6460-6464). Therefore, it is possible in patients with hypercholesterolemia that increased levels of CNS cholesterol could accelerate the accumulation of ß-amyloid plaques and the development of AD. If this is so, then the benefits of treatment of hypercholesterolemia with statins may be more far-reaching and important than previously appreciated. **—john j. caronna**

Antistriatal Antibodies in Tourette Syndrome: Not a Simple Story

ABSTRACT & COMMENTARY

Source: Wendlandt JT, et al. *J Neuroimmunol.* 2001;119: 106-113.

Tourette syndrome (ts), the most common movement disorder in childhood, is a complex neuropsychiatric disorder. Recent suggestive evidence suggests the potential role of autoimmune mechanisms in TS (for review, see Trifiletti R, Packard AM. *Child Adolesc Psychiatr Clin N Am.* 1999;8:767). A prominent suggestive piece of data is the identification of a subset of patients with TS who appear to have symptoms triggered or at least temporally correlated to Group A beta-hemolytic streptococcal infection (the so-called PANDAS subgroup), similar to Sydenham's chorea. Evidence has also included the finding of serum antibodies against human basal ganglia in patients with TS (Singer HS, et al. *Neurology.* 1998;50:1618-1624; Trifiletti R, et al. *Ann Neurol.* 1998;561), analogous to Sydenham's chorea.

Wendlandt and colleagues extend these observations using powerful statistical techniques to assess the "difference" between serum antibodies directed against human brain and muscle antigens. They compared 20 children with long-standing TS (mean age at onset 6.6 years, mean age in study 10.7 years) to 21 children without such diagnosis, a diagnosis of obsessive-compulsive disorder, or attention deficit disorder with hyperactivity. The TS patients were not specifically selected or assessed with respect to potential streptococcal trigger, but patients with a prior diagnosis of Sydenham chorea were excluded. Wendlandt et al found that the "repertoire" of serum antibodies against human striatal antigens showed prominent and statistically significant differences between TS and controls. The "repertoire" involved many antigens, but was highly reproducible within a given patient. The antibody repertoire against human globus pallidus and human muscle did not show such differences. The technique did not identify "specific" bands which seem to be associated with TS, in contrast to prior studies that used simple visual analysis. (Singer HS, et al. *Neurology.* 1998;50:1618-1624; Trifiletti R, et al. *Ann Neurol.* 1998;561). This suggested that 83-, 60-, and 67-kilodalton targets may be prominent candidate autoantigens.

COMMENTARY

This report is significant because it uses a rigorous and highly objective analysis of gel immunoblot data to demonstrate a consistent pattern of serum autoantibodies against human striatum in patients with TS. This adds further evidence that suggests the striatum is the target of a putative autoimmune response. It was disappointing that no one protein in a complex immunoblot pattern emerged as a dominant autoantigen that provides a clue to the pathophysiology of this condition. The likelihood of a simple serum-based immunological "test" for TS seems remote. **—rosario trifiletti**

Febrile Seizures Following Childhood Vaccinations: A Risk Worth Taking

ABSTRACT & COMMENTARY

Source: Barlow WE, et al. *N Engl J Med*. 2001;345:656-661.

Most children in the world are exposed to pertussis vaccine and measles, mumps, and rubella vaccine during the first 2 years of life, as a part of a routine immunization schedule. No other exposure to a biological agent is as widespread. Therefore, special attention must be paid to whether immunization is a significant cause for seizure cases, even if the risk is small.

Current vaccine consists of diptheria, tetanus, and pertussis as an acellular combined vaccine at 2, 4, 6, and 18 months of age. Measles, mumps, and rubella (MMR) vaccines are typically coadminstered at 12 months of age. Early studies suggested an elevated risk of seizures and encephalopathy with the DTP vaccine, but more recent analyses suggest that the risk extends only to febrile seizures, and lasts for a few days after the administration of vaccine. MMR vaccine administration has also been linked to an increased risk of febrile seizures, with the increased risk typically peaking at 7-14 days after administration of vaccine, coinciding with post-vaccination fever.

The outcome of children who develop febrile seizures following these vaccinations are unknown. Barlow et al are one of the first groups to address these issues.

Barlow and colleagues examined the medical records of 679,942 children from the western United States who received health care through the Kaiser-Permanente system. The relative risk of febrile seizures following administration of DTP and MMR vaccines was calculated and determined to be approximately 6-fold for DTP, with the risk significant only on the day of vaccination. The additional risk of febrile seizures was approximately 3-fold higher during the 8th-14th day following vaccination. Barlow et al could attribute only 6-9 febrile seizure events/100,000 vaccinated to DTP vaccination and 25-34 febrile seizure events/100,000 vaccinated to MMR vaccination. No increased risk of afebrile seizures could be attributed to either vaccination.

Follow-up identified 41 children as having febrile seizures temporarily correlated to vaccination; 521 children had febrile seizures not temporarily correlated to vaccination. No significant difference separated vaccine- and nonvaccine-associated seizures with respect to risk of future epilepsy or developmental delay.

COMMENTARY

This paper highlights that both the DTP and MMR vaccines are associated with a transient increased risk of febrile seizures for 1 and 8-14 days following vaccination. No evidence shows that the long-term significance of these seizures differs no more than standard febrile seizures. The number of febrile seizures attributable to vaccine must be interpreted in light of the overall risk of childhood febrile seizures at ± 5%. Among 100,000 children, about 5000 would be vulnerable to febrile seizure. No parents could plausibly attribute this seizure to either the DTP or MMR vaccines. Considering the well-established health benefits of these vaccines, the tiny increase in febrile seizures seems a risk well taken. **—rosario trifiletti**

Brief Alerts

Modify the Ischemic Forearm Test

Source: Lindner A, et al. *Neurology*. 2001;56:1779-1780.

Serum lactate elevation normally occurs with exercise and absence of such elevation is the basis for the ischemic forearm test in the diagnosis of glycogen storage myopathies. Rarely, serious complications may result.

A 22-year-old woman with exertional cramps, weakness, and fatigue underwent the ischemic forearm test on the left forearm. Following 50 seconds of ischemic exercise with the left hand, she developed transient contracture followed by left forearm swelling, ulnar region hypesthesia, and elevated creatine kinase (3482 U/L, initially 815 u/L). Acute compartment syndrome was diagnosed and after fasciotomy she improved dramatically. Muscle biopsy subsequently revealed McArdle's disease.

COMMENTARY

Nonischemic forearm testing is a safe and reasonable alternative for detecting glycogen storage myopathy (Hogrel JY, et al. *Neurology.* 2001;56:1733-1738). Among 7 patients with myophosphorylase (n = 6) or debrancher (n =1) deficiency, no lactate elevation was seen, compared to 26 healthy controls where 4-fold elevation was produced. Nonischemic testing should replace the ischemic forearm testing if needed. Muscle biopsy or white blood cell enzyme assay remains the necessary and definitive diagnostic procedure in either case. **—michael rubin**

Sjogren's Syndrome and the Peripheral Nervous System

Source: Barendregt PJ, et al. *Ann Rheum Dis.* 2001;60: 876-881.

Among 39 patients with primary sjogren's syndrome (SS) diagnosed by positive serology (at least 1 positive test among antinuclear, rheumatoid factor, SS-A, or SS-B antibodies) and positive salivary gland biopsy or sialography, evidence for peripheral nervous system (PNS) involvement was sought using clinical and electrodiagnostic means. Concomitant diseases affecting the PNS were excluded, including diabetes and renal failure, as were a history of drug use known to cause neuropathy. All patients underwent neurological examination with particular attention to the PNS. Electrodiagnostic studies included routine nerve conduction studies and quantitative sensory testing encompassing vibration detection threshold, and warm and cold sensitivity (temperature discrimination threshold). Autonomic studies comprised cardiovascular function tests using tilt-table testing with blood pressure and heart rate measurements, beat-to-beat variability on Valsalva maneuver, and pupillography. Wilcoxon testing and Pearson's correlation coefficient provided statistical analysis.

COMMENTARY

Although no patients had spontaneous neurological complaints, 8 (one fifth) answered positively on detailed questioning for neuropathic symptoms. Of these, 6 demonstrated abnormalities on examination, 5 on vibration detection threshold, 4 on nerve conduction studies, 3 on cold sensitivity, and 2 on warm sensitivity. Seven (18%) patients had an abnormal neurological examination, 3 showing vibration detection threshold abnormalities, and 3 and 2 cold and warm sensitivity abnormalities, respectively. Overall, 58% (22/38) had abnormal vibration detection threshold, 20% (7/35) and 14% (5/35) had warm and cold sensitivity abnormalities, and 23% (9/39) had nerve conduction studies consistent with polyneuropathy, either motor, sensory, or mixed. Vibration detection abnormalities did not correlate with temperature discrimination threshold abnormalities, nor did autonomic abnormalities correlate with each other or with other electrodiagnostic studies. Subclinical involvement of the PNS is common in asymptomatic patients with primary SS. **—michael rubin**

CME Questions

14. In Alzheimer's disease, evidence of microglia activation can be found:
a. in regions of subsequent brain atrophy.
b. exclusively in the thalamus.
c. using serial volumetric MRI.
d. only by postmortem studies.

15. All of the following statements are true of syncope evaluation *except*:
a. The most useful test is postural blood pressure measurement.
b. CT and EEG are of low yield generally.
c. Neurologic testing is of no use unless clinical history is consistent with a CNS event.
d. Cardiac tests such as continuous telemetry, ECHO, and Holter are of uniformly high yield.

16. The annual conversion rate of patients with MCI to AD is approximately:
a. 1%.
b. 2%.
c. 5%.
d. 10%.
e. 25%.

17. Regarding seizures following DTP and MMR vaccinations in children:
a. studies have consistently documented an increased risk of febrile seizures following these vaccinations.
b. studies have consistently documented an increased risk of afebrile seizures following these vaccinations.
c. the risk of future epilepsy is higher among children who develop a febrile seizure following vaccination, as compared to those who develop it at some other time.
d. most febrile seizures are temporally correlated to vaccinations.

In Future Issues:

Current Knowledge of Science and Management of Major Degenerative Disorders