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INSIDE

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Oscillopsia of Dandy Revisited

ABSTRACT & COMMENTARY

By John J. Caronna, MD

Vice-Chairman, Department of Neurology, Cornell University Medical Center, Professor of Clinical Neurology, NewYork-Presbyterian Hospital

Dr. Caronna reports no financial relationship relevant to this field of study.

Synopsis: The most common cause of bilateral vestibulopathy remains ototoxicity from antibiotics, such as gentamicin.

Source: Zingler VC, et al. Causative Factors and Epidemiology of Bilateral Vestibulopathy in 255 Patients. *Ann Neurol.* 2007; 61: 524-532.

Walter Dandy (1886-1946), who bilaterally sectioned the vestibular nerve to treat Meniere's syndrome, was the first to recognize that total loss of labyrinthine function caused vision to become blurred when the head moves rapidly.[1] Today, impairment or loss of function of both peripheral labyrinths or of both eighth nerves is rare.

Zingler and associates sought to determine the causes and epidemiology of bilateral vestibulopathy (BV). The diagnosis was suspected clinically in patients with the following symptoms:

1. Unsteadiness of gait, particularly in the dark or on uneven ground.
2. Apparent motion of the visual scene during head movements and locomotion (oscillopsia), and
3. Impaired spatial memory and navigation associated with hippocampal atrophy due to chronic loss of vestibular input.[2]

BV was confirmed by the head-thrust test[3] and caloric irrigation of the external auditory canal with oculographic recordings. All patients underwent a standardized neuro-ophthalmological and neuro-otological examination, MRI or CT scans and laboratory tests. In a retrospective review, they found 255 patients (mean age 62 ± 16 years) diagnosed with BV between 1988 and 2005.

Of all patients, 27% (n = 70) suffered from complete BV. The remaining patients (n = 185) exhibited incomplete BV.

The definite cause of BV was defined in 24% and the probable cause in 25%.

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Table: Patients with BV of Definite or Probable Cause (n = 125)*

Cause of BV		Definitive or Probable Cause
	n	%
Antibiotics		
Meniere's Disease	32	13
Meningitis/encephalitis	17	7
Multiple causes	13	5
Spinocerebellar ataxia, MSA	12	5
Autoimmune disease	9	4
B12/folate deficiency	8	3
Creutzfeld-Jakob disease	4	2
Cogan's syndrome	3	1
Familial inner ear disease	3	1
Miscellaneous**	21	8

*after Zingler, et al.

**Neurofibromatosis type 2, aspirin or furosemide toxicity, head trauma,otosclerosis, hemosiderosis, and alcoholism

Episodes of vertigo preceded the manifestations of BV in 36% of patients (n = 91). BV developed slowly in 64% (n = 164). In the 51% of patients who suffered from idiopathic BV of unknown cause, symptoms more often were slowly progressive rather than sequentially progressive. Oscillopsia occurred in 44% and was more frequent in younger patients with an episodic or sequential course and with complete loss of peripheral vestibular function. Hypoacusis occurred bilaterally in only 25% and unilaterally in only 6% of all patients. Hearing loss appeared most often in patients with Cogan's syndrome (inflammatory eye disease, hearing loss, and vestibulopathy), meningitis, or Meniere's disease. In patients without hearing loss, BV generally developed progressively and often in combination with a cerebellar syndrome or a peripheral neuropathy, or both.

Cerebellar signs were present in 25% of patients. Cerebellar dysfunction was associated with peripheral neuropathy in 32% compared with 18% in BV patients without cerebellar signs.

COMMENTARY

Physicians who practiced in the days when streptomycin was a first-line antibiotic for treating bacterial infections such as endocarditis will remember patients who developed BV due to the ototoxicity of that drug. Sadly, ototoxic BV caused by antibiotic treatment with gentamicin alone or in combination with other ototoxic agents such as diuretics was still the most frequent cause of BV in this series. Zingler et al have pointed out that BV may develop insidiously without hearing loss but in association with other neurological findings. BV may be a feature of several spinocerebellar ataxias (SCAs) and of multisystem atrophy. Some patients showed signs of an axonal peripheral neuropathy. Therefore, as pointed out by Leigh and Thurbell in their editorial accompanying this report[4] BV is a condition that neurologists need to be aware of and able to diagnose in patients presenting with problems with balance. ■

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Does the Natural History of Childhood Onset MS Differ from Adult Onset?

ABSTRACT & COMMENTARY

By Susan Gauthier, DO

Assistant Professor of Neurology, Weill Medical College of Cornell University

Dr. Gauthier reports no financial relationships relevant to this field of study.

Synopsis: The time to secondary progression and irreversible disability in childhood-onset MS is slower as compared to adult-onset disease. However, it occurs at a younger age.

Source: Renoux C, et al. Natural history of multiple sclerosis with childhood onset. *N Engl J Med* 2007;356:2603-2613.

The natural history of adult-onset multiple sclerosis (MS) has been well described in a number of large cohort studies, where in the average time for a patient to reach irreversible disability as measured on the Kurtzke Disability Status Scale (DSS) as well as time to secondary progression has been established. Short-term disease progression in adult-onset MS was recently evaluated using a Markov transitional model, which incorporates both clinical and MRI prognostic factors to create short-term predictive curves for various patient profiles.[1] How our understanding of adult-onset MS can be applied to childhood-onset disease has yet to be fully established.

Renoux et al identified a cohort of 394 patients from the European Database for Multiple Sclerosis (EDMUS) with an onset of multiple sclerosis before the age of 16 and compared disability endpoints to the Lyon Natural History Multiple Sclerosis Cohort, an adult-onset MS cohort. In addition to secondary progression, endpoints of irreversible disability were studied and included a DSS score that could be easily assigned retrospectively - DSS of 4 (walking limited to 500 meters), a score of 6 (walking that requires unilateral support), and a score of 7 (the ability to walk no more than 10 meters with an aid). Information regarding the disease course was obtained retrospectively at the time of initial visit and was collected prospectively thereafter.

The mean age of MS onset within the childhood-onset cohort was 13.7 years and the patients were followed for a mean of 17 years. The female to male ratio was higher and more often had a relapsing-remitting onset (98% vs. 84%) as compared to the adult cohort. At disease onset, isolated optic neuritis or brain-stem symptoms occurred more frequently in childhood-onset MS as compared to adult-onset, whereas long-tract symptoms, although the most common initial presentation in both cohorts, occurred less frequently in children as compared to adults. In addition, encephalitic symptoms were present in 7% of childhood-onset patients and essentially absent in adult-onset disease. Secondary progression occurred in 28.6% of the childhood-onset patients after 28 years and at a median age of 41; progression in this cohort was 10 years slower than the adult cohort; however, the childhood-onset patients were 10 years younger when they reached this stage. The times to reach DSS of 4, 6 and 7 for childhood-onset MS were 34.6, 42.2, and 50.5 years, respectively, and were approximately 10 years longer as compared to adult-onset MS; however, once these patients reached an EDSS of 4, the time to an EDSS of 6 or 7 was similar to that of the adult cohort. As in secondary progression, childhood-onset patients were at least 10 years younger at these disability milestones. Prognostic factors associated with higher rates of disease progression included a progressive onset of disease or a higher relapse rate within the first 2 years.

COMMENTARY

This is the largest study to describe a cohort of childhood-onset MS patients and revealed distinct features of childhood-onset MS as compared to adult-onset MS; specifically, there is a higher female to male ratio, the initial course is more often relapsing-remitting and the development of irreversible disability follows a different course. In a separate study of the Lyon Natural History Multiple Sclerosis Cohort, disability was felt to be age dependent wherein regardless of the initial course, either relapsing-remitting or primary progressive, patients reached levels of irreversible disability at similar ages.[2] However, in the Lyon cohort, as in the current study, the younger onset patients (< 19 years of age) were at risk for having irreversible disability at younger age although the time to the disability milestones was longer. Based upon the results of these studies, the age of onset of MS appears to influence the clinical phenotype of the disease.

Lastly, children with MS are typically treated with immunomodulatory drugs approved for the treatment of adult-onset disease and approximately one half of the patients had received therapy within this cohort. How phenotypic differences in MS influence the response to

treatment is presently unknown. Therefore, an effort to further delineate the phenotype of childhood-onset MS and to study therapeutic options specific for this subgroup of MS is warranted. ■

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1. Gauthier SA, et al. Prediction of short-term disability in multiple sclerosis. *Neurology.* 2007; 68: 2059-2065.
2. Confavreux C, Vukusic S. Age at disability milestones in multiple sclerosis. *Brain.* 2006 Mar; 129 (Pt 3):595-605.

How Accurate is Non-Invasive Testing to Diagnose Intracranial Arterial Stenosis?

ABSTRACT & COMMENTARY

By Matthew E. Fink, MD

Synopsis: TCD and MRA have a low positive predictive value in diagnosing clinically significant intracranial stenosis, but are useful as screening tests to rule-out significant lesions.

Source: Feldmann E and the SONIA Investigators. The Stroke Outcome and Neuroimaging of Intracranial Atherosclerosis (SONIA) Trial. *Neurology.* 2007; 68: 2099-2106.

INTRACRANIAL STENOSIS (ICS) CAUSES ABOUT 70,000 ischemic strokes each year in the United States, and is more common in Hispanics, African-Americans, Japanese and Chinese compared to the U.S white population. The WASID study (Chimowitz, et al, Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med.* 2005;352:1305-1316.) documented a one-year recurrent stroke risk of 22% in patients with high-grade intracranial stenosis, based on catheter angiography. Proven therapy for intracranial stenosis is currently limited to antiplatelet drugs, but the development of successful intracranial angioplasty and stenting mandates that we investigate the intracranial circulation as part of every stroke evaluation. The SONIA investigators, starting with the WASID patients, attempted to assess the accuracy of transcranial Doppler ultrasound (TCD) and magnetic resonance angiography (MRA) in diagnosing significant stenosis of the major intracranial arteries (proximal middle cerebral, carotid siphon, intracranial vertebral arteries and basilar), compared to the diagnostic gold standard, catheter angiography.

The SONIA Trial was a parallel study to the WASID trial that enrolled patients who were symptomatic from TIA or ischemic stroke and had positive TCD and/or intracranial non-contrast MRA studies before they underwent cerebral angiography. The investigators also included other patients, outside of WASID, with symptomatic ICS, if they met the same criteria. Significant stenosis of the major intracranial arteries was defined as >50% stenosis by direct caliper measurement of the MRA and angiography films by a blinded neuroradiologist at a central reading site. Stenosis on TCD was defined by measuring the time-averaged mean of the maximum velocity. A positive test was a mean velocity >100 cm/sec in the middle cerebral artery (MCA), >90 cm/sec in the internal carotid artery (ICA), or >80 cm/sec in the basilar artery (BA) or vertebral arteries (VAs).

The primary aim of SONIA was to define velocity values on TCD and anatomic abnormalities on MRA that could identify 50-99% intracranial stenosis of the MCA, ICA, BA or VA, compared to catheter angiography, with a positive predictive value (PPV) of 80%. The secondary aim was to demonstrate that TCD and/or MRA could exclude significant intracranial stenosis with a negative predictive value (NPV) of 90%. A true determination of sensitivity and specificity could not be achieved because only patients with positive TCD/MRA underwent cerebral angiography. For each patient, both normal and diseased vessels were studied and included in the analysis.

Over a 4-year period, 407 patients were enrolled, and there was corresponding TCD data for 451 vessels, and MRA data for 1310 vessels. The ethnic distribution of patients was 54% white, 33% African-American, 6% Hispanic, and 4% Asian. Mean age was 65 years, and 40% of patients were female. Angiography revealed normal studies in 1105 vessels (69%), < 50% stenosis in 141 vessels (9%), 50%-99% stenosis in 315 vessels (20%) and occlusion in 35 vessels (2%). TCD analysis revealed a PPV of 36% (CI = 27-46) and a NPV of 86% (CI = 81-89). MRA analysis showed a PPV of 59% (CI = 54-65) and a NPV of 91% (CI=89-93). If the "cut-point" for TCD velocity was increased (from 100 cm/sec to 240 cm/sec for the MCA) and the "cut-point" for MRA stenosis was increased (from 50% to 80%), the PPV was shown to increase as well, but at a cost of a decrease in the NPV. The investigators made no attempt to compare TCD to MRA, because there were too few patients who had both studies performed.

■ COMMENTARY

The evaluation of patients with TIA or ischemic stroke and suspected intracranial arterial stenosis is difficult, and any help that we can obtain from non-invasive testing is valuable. Few patients will undergo catheter angiography, since it is hard to justify the dis-

comfort, cost, and risk of such studies, without a definitive treatment of proven value other than general therapies such as antiplatelet medications, statins, antihypertensives, and life style modifications. Intracranial stenting, while holding great promise for the future, is an investigational procedure that has been reserved for those patients who have recurrent symptoms after maximal medical therapy. And, intracranial stenting should only be performed in the context of a well designed clinical trial, or else we will never learn if it is a truly effective and beneficial therapy.

MRA is the most widely used non-invasive technique for assessing intracranial vascular anatomy. TCD has fallen out of favor because of variable technical results that are very much operator dependent, as well as difficulty in using an indirect physiological measurement (blood flow velocity) to assess vascular anatomy. The SONIA trial also noted that TCD was requested much less than MRA and this trend has continued. However, as the SONIA trial has so carefully reported, the PPV of MRA is only 59% in diagnosing >50% stenosis of an intracranial artery. This low predictive value is largely due to false positive studies, which is something we all grapple with on a daily basis. However, a normal MRA study carries a NPV of 91%, which may give us and our patients some comfort. The bottom line of the SONIA trial is that TCD and MRA should always be viewed as screening tests that require a confirmatory test when an abnormality is found, as long as there is an available treatment for the underlying pathology that is suspected. ■

Gene Therapy for Parkinson's Disease: The Next Generation of Therapy?

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, DPhil

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Dr. Henchcliffe reports no financial relationship to this field of study.

Synopsis: This is the first ever published phase I clinical trial testing gene therapy in Parkinson's disease(PD). Unilateral introduction of AAV-GAD into the subthalamic nucleus of advanced PD patients was safe and well tolerated up to ≥1 year.

Source: Kaplitt MG, et al. *Lancet*. 2007;369:2097-2105.

THIS PHASE I OPEN LABEL SAFETY AND TOLERABILITY trial enrolled 12 patients with idiopathic Parkinson's disease (PD), for infusion of the human glutamic acid decarboxylase gene (GAD), in an adeno-associated virus (AAV) vector, into the subthalamic nucleus (STN). All subjects had disease of at least 5 years' duration, with motor complications of levodopa therapy. Inclusion criteria were Unified Parkinson Disease Rating Scale (UPDRS) motor score of ≥ 30, and Hoehn and Yahr score ≥ 3 (ie, bilateral symptoms with postural instability) off medication, and absence of significant medical or psychiatric illness. Eleven men and 1 woman aged 51-63 years (mean 58.2 ± 5.7 years) entered the study. Disease duration ranged from 6-13 years, and baseline levodopa equivalents ranged from 250-2300 mg daily. Subjects underwent surgical infusion of low, medium, or high dose AAV-GAD into the STN contralateral to the most impaired side of the body. All patients were discharged home after 2 days, and post-operative MRI revealed no hemorrhage or edema at the infusion site. By 12 months, no adverse events were recorded that were judged related to the gene therapy. There were no deaths, no new neurological deficits, and neuropsychological test results did not change significantly. In the absence of significant changes in daily levodopa equivalents, motor UPDRS scores improved significantly both on and off medications, although there was no relationship to AAV-GAD dose. Improvements were sustained in 10/12 at 12 months (4/12 improved ≥40%). FDG-PET scans at 12 months demonstrated reduced thalamic metabolism in the operated hemisphere, and increased activity in the supplementary motor cortex of the implanted hemisphere, compared to baseline, and compared to the non-operated hemisphere. Titers of anti-AAV2 antibodies did not change significantly from baseline to 12 months, and presence of baseline high titers in 2 subjects did not predict lack of motor improvement.

COMMENTARY

This ground-breaking trial addresses one of many barriers to bringing gene therapy into the arena of human disease treatment, after promising animal studies. Concerns about potential and actual adverse effects have been well described, including the possibility of immune reaction, cell transformation, and infection. Although preliminary, this careful study convincingly demonstrates safety and tolerability of subthalamic AAV-GAD infusion in a small group of advanced PD patients followed for at least one year. Obviously, longer term data are needed, and Kaplitt and colleagues note at the time of publication that safety and tolerability is sustained in 3 subjects followed ≥ 3 years, and 4 subjects followed for 2-3 years. The rationale behind their innovative choice of gene and tissue target,

although oversimplified, is to modulate aberrant excitatory glutamatergic output in PD (that ultimately reduces motor output signaling), by introducing the GAD enzyme to allow production of GABA. The net effect is to convert STN output to an inhibitory signal. Indeed, in a rodent model of PD, AAV-GAD therapy improved motor performance, with increased GABA levels measured in the substantia nigra pars reticulata, a site of STN projection. It is difficult to know how to interpret improvements in motor function observed, and this study, like others in PD, is hampered by lack of established surrogate disease markers. The authors are appropriately cautious, given large placebo effects in prior surgical PD studies. Improvements in bilateral UPDRS scores, as well as improved "best on" scores require further explanation. However, it is encouraging that FDG-PET scans demonstrate region-specific alterations in thalamocortical motor pathway metabolism, as reported after DBS surgery. Other gene therapy trials are currently in progress, investigating the use of neurotrophic factor neurturin (CERE-120) and aromatic amino acid decarboxylase genes in PD. The present study provides an important basis upon which to build experience and further testing of this innovative therapeutic approach. ■

EMG for Sacral Plexopathy

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, NewYork-Presbyterian Hospital, Weill Cornell Medical Center

Dr. Rubin is on the speaker's bureau for Athena Diagnostics, and does research for Pfizer and Merck.

Synopsis: EMG studies are helpful in a minority of patients with suspected sacral plexopathy. Clinical examination and imaging provide more useful information.

Source: Tavee J, et al. Pitfalls in the electrodiagnostic studies of sacral plexopathies. *Muscle Nerve*. 2007;35;725-729.

Are electrodiagnostic studies useful in the diagnosis of sacral plexopathy, allowing one to differentiate the former from sciatic neuropathy or radiculopathy? Retrospective review of 171 cases of suspected sacral plexopathy, seen at the Cleveland Clinic Foundation between 1975-2005, was undertaken to address this question. Each patient had been evaluated clinically, and electrodiagnostically by nerve conduction studies and needle electromyography (EMG). All patients experienced leg weakness, usually manifested as foot drop, hip, leg, or back pain, and occasionally distal sensory loss. Electrodiagnosis of sacral plexopathy was confirmed by EMG if patients demonstrated: (a) absent or reduced sural or superficial peroneal sensory amplitudes, (b) denervation potentials in muscles innervated by the sacral plexus but not by the sciatic nerve, and (c) normal paraspinal muscle EMG.

Using the above EMG guidelines, 60 patients (35%) had abnormalities localizing to the sacral plexus, most often due to cancer, usually gynecologic, colorectal, or prostatic, and including direct tumor invasion, radiation, or chemotherapy associated injury. Trauma, including motorcycle or motor vehicle accidents, gunshot wounds, and falls, was the 2nd most common cause of plexopathy, followed by idiopathic (n = 10, 17%) and iatrogenic (n = 8, 14%) etiologies. Vasculitis, viral, and autoimmune disorders were suspected to underlie the former, while the latter were seen following lumbar laminectomy, and aortic or cardiac surgery. Intrapartum injury (n = 4, 8%), diabetes (n = 2, 3%), herpes zoster (n = 1, 2%), or unknown (n = 4, 5%) was seen in the remainder.

Among the remaining 111 cases, lumbosacral radiculopathy or sciatic neuropathy could not be excluded based on electrodiagnostic studies, and no firm sacral plexus localization was possible. Plexus could not be differentiated from root disease in 52 (30%), most often due to the bilateral absence of sensory responses, either sural (69%) or superficial peroneal (63%). Paraspinal muscle fibrillation potentials (50%) and normal gluteal muscle EMG (67%) also prevented precise localization. Plexus could not be differentiated from high sciatic nerve in 32 (19%) due to normal gluteal muscle EMG in 79%. In 27 (16%), root vs. plexus vs. sciatic neuropathy were equal possibilities due to the variable combination of abnormalities on EMG. Definitive localization of sacral plexopathy is often impossible using EMG.

COMMENTARY

Truth be told, if a single test were warranted for the investigation of all cases of suspected lumbosacral radiculopathy, magnetic resonance imaging would be that test. Needle electromyography (EMG) records the physiologic extent of nerve injury, but usually does not affect decision making, as clinical evaluation suffices. Even in radiographic or surgically documented lumbar disc herniation, needle EMG shows no paraspinal abnormalities in approximately 50%, although estimates vary from 26% to 86%. It is not surprising that EMG often cannot localize sacral plexopathy, or separate it from radiculopathy or high sciatic neuropathy. ■

Biomarkers in the CSF and Blood as Predictors of Alzheimer's Dementia — Are They Ready for Clinical Use?

ABSTRACT & COMMENTARY

By Matthew E. Fink, MD

Synopsis: A variety of peptide markers in the blood and CSF have been identified by proteomic techniques and should increase our ability to identify, at an early stage, those patients at risk for developing Alzheimer's dementia (AD).

Sources: Finehout EJ, et al. Cerebrospinal Fluid Proteomic Biomarkers for Alzheimer's Disease. *Ann Neurol.* 2007; 61:120-129.

Fagan AM, et al. Cerebrospinal Fluid tau/ -Amyloid42 Ratio as a Prediction of Cognitive Decline in Non demented Older Adults. *Arch Neurol* 2007; 64:343-349.

Graff-Radford NR, et al. Association of Low Plasma A 42/A 40 Ratios With Increased Imminent Risk for Mild Cognitive Impairment and Alzheimer Disease. *Arch Neurol*. 2007;64:354-362.

Simonsen AH, et al. Novel Panel of Cerebrospinal Fluid Biomarkers for the Prediction of Progression to Alzheimer Dementia in Patients With Mild Cognitive Impairment. *Arch Neurol.* 2007;64:366-370.

In recent months, a series of studies using advanced techniques of proteomics have shed further light on potential biomarkers that will help us identify patients at risk for AD. Since AD is the most common cause of dementia, and its prevalence doubles every 5 years from the age of 65, it will be extremely important to be able to identify such patients before they are symptomatic or at a very early stage in order to intervene with new therapies that prevent progression. Minimal cognitive impairment (MCI) has a conversion rate of 8% to 15% per year, but we are currently unable to identify which of those patients will be in the progressive group. Previous biomarker studies have documented the high sensitivity of CSF measurements of β-Amyloid$_{42}$, total tau, and phosphorylated tau in patients with MCI and AD, but these tests do not discriminate between MCI, early AD, or patients who will progress. Therefore, the recent studies that I will briefly review are a welcome addition to our current diagnostic capabilities.

The work by Finehour et al studied an antemortem cohort of CSF proteins from 34 AD and 34 non-AD patients and separated the samples using 2-dimensional gel electrophoresis. The protein patterns were analyzed with a multivariate statistical analysis. The gels revealed an average of 1,188 spots, and a Student's t-test analysis comparing spots from AD and non-AD gels identified 252 spots with a significant change in expression level. Further analysis identified 23 spots that could be used to differentiate AD and non-AD gels with a sensitivity of 94%, and a specificity of 94%, and a predicted classification error rate of only 5.9%. The proteins in the 23 spots were identified and fell into 4 classes of compounds related to (1) transport of β-amyloid, (2) the inflammatory response, (3) proteolytic inhibition, and (4) the neuronal membrane proteins.

The work by Fagan et al looked at CSF β-amyloid$_{40}$, Aβ$_{42}$, tau, and phospholylated tau, as well as plasma Aβ$_{40}$ and Aβ$_{42}$, with longitudinal follow-up studies from 1 to 8 years. They studied a group of 139 community-dwelling volunteers aged 60-91 who were judged as cognitively normal, or having very mild AD, and showed that the very mild AD patients had reduced levels of CSF Aβ$_{42}$ and increased levels of CSF tau and phosphorylated tau. The levels of Aβ$_{42}$ corresponded with the presence or absence of brain amyloid (imaged with Pittsburgh Compound B) in both demented and non-demented individuals. The ratio of CSF tau/Aβ42 (hazard ratio = 5.21; 95% CI, 1.58-17.22) predicted the conversion from normal, to demented over the follow-up period. The investigators concluded that even the very mildest degree of cognitive impairment exhibits the same CSF biomarker phenotype as more advanced AD and this corresponds to PET imaging. In addition, the ratio of tau/Aβ shows promise as a marker to identify normal older adults who will go on to develop dementia.

The third study by Graff-Radford et al looked at plasma measurements and ratios of Aβ$_{40}$ and Aβ$_{42}$ to see if they could identify elderly adults at increased risk for mild cognitive impairment and AD. They measured plasma Aβ$_{40}$ and Aβ$_{42}$ in 563 cognitively normal volunteers (median age, 78; 62% female) and followed them for 2 to 12 years (median, 3.7 years) to detect the incident cases of MCI and AD. During follow-up, 53 subjects developed MCI or AD. Subjects with Aβ$_{42}$/Aβ$_{40}$ ratios in the lower quartiles showed a significantly greater risk of developing MCI or AD. Comparing those patients with plasma ratios from the lowest to highest quartile gave a relative risk of 3.1(95% CI, 1.1-8.3) for the development of MCI or AD. The authors concluded that measurements of Aβ$_{40}$ and Aβ$_{42}$ ratios may be useful as a predictor of future development of dementia.

And finally, the study authored by Simonsen et al ana-

lyzed CSF proteins and peptides with a novel technique known as surface-enhanced laser desorption/ionization time-of-flight mass spectroscopy (SEL-TOF-MS) in 113 patients with MCI, 56 who remained stable and 57 who progressed to AD over a 4 to 6 year follow-up period. They also studied 28 healthy controls. The investigators identified 17 potential biomarkers that could distinguish between patients with stable MCI and patients with MCI that progressed to AD. Five of the biomarkers are relevant to the pathogenesis of AD and are involved in the metabolic pathways of Aβ and tau proteins.

COMMENTARY

At a time when we are developing clinical trials for prevention or slowing of progression of AD, it is critical that we have biomarkers that can identify high-risk groups of elderly normals or patients with MCI who will go on to develop AD. The above investigations have gone a long way to accomplish this goal, by demonstrating the ability to use proteomic techniques to identify an array of proteins in the CSF that can distinguish progressive AD from stable MCI syndromes. In addition, reliable measurements of Aβ in the plasma may also provide supportive evidence for high-risk disease, along with CSF studies.

However, these analyses are still in the realm of investigative tests that are difficult to perform outside of research laboratories, and they are not currently applicable for routine clinical testing. Until we have a proven treatment for AD that slows or halts progression, there is no clinical utility for these tests outside of research studies. To facilitate the completion of clinical trials of new therapeutic agents, we would recommend that all neurologists refer appropriate patients to centers where they can be enrolled in clinical trials, thereby speeding up the time it takes to get answers regarding possible treatments of this epidemic disease. ■

CME Questions

31. Which of the following is a true statement?
a. Intracranial stenosis is more common in the white population compared to the Hispanic population
b. TCD and MRA have a high positive predictive value for intracranial stenosis
c. Cerebral angiography should be ordered in all patients with suspected intracranial stenosis
d. TCD and MRA have a high negative predictive value for intracranial stenosis
e. Intracranial stenting is an evidence-based proven therapy for intracranial stenosis

32. What is the proposed neurophysiological basis for use of AAV-GAD gene therapy in Parkinson's disease?
a. recombination of the AAV moiety into the GAD gene disrupts its function in the STN
b. GAD introduction results in reducing an excitatory glutamate output by conversion to GABA
c. GAD results in increased synthesis of glutamate thereby increasing STN excitatory output
d. AAV-GAD inhibits dopamine breakdown
e. AAV-GAD introduction into the thalamus reduces thalamic metabolism as measured by PET scan

33. What is the most common presentation of childhood-onset MS?
a. Optic neuritis
b. Encephalopathy
c. Brain-stem symptoms
d. Long-tract symptoms
e. Partial transverse myelitis

34. Bilateral vestibulopathy may present without all of the following except
a. Hearing loss
b. Cerebellar ataxia and neuropathy
c. Preceding episodes of vertigo
d. Oscillopsia
e. Unsteady gait in the dark

35. Is the following statement True or False? Measurement of CSF β-amyloid$_{40}$, Aβ$_{42}$, tau, and phospholylated tau can reliably predict which patients with mild cognitive impairment will go on to develop Alzheimer's disease.
a. True
b. False

36. Needle electromyography
a. is an integral part of the evaluation of every patient with suspected radiculopathy
b. often cannot definitively localize sacral plexopathy from radiculopathy or high sciatic neuropathy
c. can differentiate sacral plexopathy from high sciatic neuropathy in over 90% of patients
d. can differentiate sacral plexopathy from root disease in approximately 75% of cases
e. none of the above are correct

Answers: 31. (d) 32.(b) 33. (d) 34. (e) 35.(b) 36.(b)

CME Objectives

The objectives of *Neurology Alert* are:

• To present the current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;

• To discuss the pathogenesis and treatment of pain;

• To present basic science lessons in brain function;

• To discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs;

• To discuss nonclinical issues of importance to neurologist, such as the right to die and the physician's legal obligation to patients with terminal illness. ■

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

SSRIs Associated With Low Rate of Birth Defects, Studies Show

In this issue: *SSRIs are safer in pregnancy than previously thought; Estrogen therapy in younger women may be of benefit in preventing cardiovascular disease; Warfarin is substantially better than antiplatelet therapy in preventing stroke in patients with atrial fibrillation; The FDA tightens regulations regarding dietary supplements, Lyrica is approved for treatment of fibromyalgia.*

SSRIs are associated with a low rate of birth defects according to 2 new studies in the *New England Journal of Medicine*. SSRIs are often taken by women in their childbearing years, but the risk of birth defects has been unclear. Paroxetine (Paxil) specifically has been associated with omphalocele and heart defects, but there is little data on the risk of other SSRIs. In the first study from Boston University and Harvard, researchers assessed the association between first-trimester maternal use of SSRI and birth defects among nearly 10,000 infants with and over 5,800 infants without birth defects who participated in the Sloan Epidemiology Center Birth Defects Study. Use of SSRIs was not associated with significantly increased risk of craniosynostosis (odds ratio 0.8), omphalocele (odds ratio 1.4), or heart defects overall (odds ratio 1.2). Analysis of specific SSRIs and specific deficits showed significant associations between use of sertraline (Zoloft) and omphalocele (odds ratio 5.7) and septal defects (odds ratio 2.0) and between use of paroxetine and right ventricular outflow tract obstruction defects (odds ratio 3.3). There were no significant associations with other defects with other SSRIs or non-SSRI antidepressants. In the other study, researchers from the CDC and University of British Columbia looked at data obtained on 9,622 infants with major birth defects and 4,092 control infants born between 1997 and 2002. Records were obtained from birth defects surveillance systems in 8 U.S. states and controls were selected randomly from the same geographic areas. Mothers were interviewed regarding exposure to potential risk factors including medications before and during pregnancy. No significant associations were found between maternal use of SSRIs overall during early pregnancy and congenital heart defects or most other categories or subcategories categories of birth defects. Maternal SSRI use was associated with amencephaly (odds ratio 2.4), craniosynostosis (odds ratio 2.5) and omphalocele (odds ratio 2.8). Their conclusion was that maternal use of SSRIs during early pregnancy was not associated with significantly increased risk of congenital heart defects or most other categories or birth defects. There was an association with SSRI use and 3 types of birth defects, but the absolute risk was small and further studies are warranted (*N Engl J Med* 2007; 356:2675- 2683, 2684-2692). An accompanying editorial points out that 2 previous stud-

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ies had suggested a relationship between paroxetine and cardiac malformations including ventricular septal defects, an association that was not found in these current studies. Although a small rate of congenital heart malformations, including right ventricular outflow tract lesions, were found the rate was still low, less than 1%. The editorialists, Dr. Michael Green from Massachusetts General states, "The 2 reports in this issue of the Journal, together with other available information, do suggest that any increased risks of these malformations in association with the use of SSRIs are likely to be small in terms of absolute risks." (*N Engl J Med* 2007; 356:2732-2733). ■

Estrogen for Younger Postmenopausal Women

Another follow-up study from the Women's Health Initiative suggests that estrogen therapy in younger postmenopausal women may be of benefit in preventing cardiovascular disease. Analysis was done on the "estrogen-only" wing of WHI in women who had undergone hysterectomy prior to enrolling in the study and were not treated with progesterone. Women age 50 to 59 were treated with 0.625 mg per day of conjugated equine estrogens or placebo. CT heart scanning was done at entry to the study and after a mean of 7.4 years of treatment and 1.3 years after the trial was completed. The endpoint of mean coronary-artery calcium scores was lower among women receiving estrogen (83.1) than those receiving placebo (123.1) (P = 0.02 by rank test). After adjusting for coronary risk factors, the odds ratios for coronary-artery calcium scores of more than 0, 10 or more, and 100 or more in the group receiving estrogen as compared to placebo were respectively 0.78, 0.74, and 0.69. The corresponding odds ratios among women with at least 80% adherence to the study estrogen or placebo were 0.64 (P = 0.01), 0.55 (P < 0.001), and 0.46 (P = 0.001). For women who had calcium scores greater than 300 the multivariate odds ratio was 0.58 (P = 0.03) in an intention-to-treat analysis and 0.39 (P = 0.004) among women with at least 80% adherence. The authors conclude that in women age 50 to 59 years old at enrollment, estrogen treatment resulted in a lower calcified plaque burden in the coronary arteries compared to placebo. They also point out that estrogen has complex biological effects and may influence the risk of cardiovascular events and other outcomes through multiple pathways (*N Engl J Med* 2007; 356:2591-2602). An accompanying editorial points out that not only did women in this analysis who were treated with estrogen have lower calcium scores, women in whom hormone replacement therapy was initiated at a younger age also had a 30% reduction in total mortality and did not have significant increases in any adverse outcomes examined. This supports the "timing hypothesis" for hormone replacement therapy that suggests that the cardiovascular benefits of hormone replacement are only evident if treatment is started before atherosclerosis develops. (*N Engl J Med* 2007;356:2639-2641). ■

Warfarin Better for Atrial Fibrillation Patients

Recent meta-analysis has confirmed the value of warfarin in preventing stroke in patients with nonvalvular atrial fibrillation. Twenty-nine trials involving more than 28,000 patients were reviewed. Compared with control, warfarin and antiplatelet agents reduce stroke by 64% (95% CI, 49% to 74%) and 22% (CI, 6% to 35%) respectively. Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy, and increases in extracranial hemorrhage assisted with warfarin were small. The authors conclude that warfarin is substantially more efficacious at preventing stroke in patients with a fibrillation than is antiplatelet therapy (by approximately 40%). (*Ann Int Med* 2007; 146: 857-867). ■

FDA Actions

The FDA has strengthened its regulations regarding dietary supplements, issuing a "final rule" requiring current good manufacturing practices for dietary supplements. The rule ensures the supplements are produced in a quality manner, do not contain contaminants or impurities, and are accurately labeled. Manufacturers will also be required to report all serious dietary supplement-related adverse events to the FDA by the end of the year.

Pregabalin (Lyrica-Pfizer) has been approved for the treatment of fibromyalgia, the first drug approved for this indication. Fibromyalgia, which is characterized by pain, fatigue, and sleep problems, affects up to 6 million people in United States. Approval was based on 2 double-blind, controlled trials involving 1,800 patients that showed improvement in pain symptoms at doses of 300 mg or 450 mg per day. The drug has already been approved for partial seizures, postherpetic neuralgia, and diabetic neuropathy. ■