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INSIDE

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Primary Progressive Apraxia of Speech: A Distinct Disorder

ABSTRACT & COMMENTARY

By Michael Lin, MD, PhD

Associate Professor of Neurology and Neurosciences, Weill Cornell Medical College

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

Synopsis: *Primary progressive apraxia of speech has been well characterized as a distinct neurodegenerative disease, but underlying pathology and prognosis are uncertain in most cases.*

Source: Josephs KA, et al. Characterizing a neurodegenerative syndrome: Primary progressive apraxia of speech. *Brain* 2012;135:1522-1536.

APRAXIA OF SPEECH (AOS) IS A DISORDER OF PLANNING OR SEQUENCING MOVEments required for speech. Characteristics include trial and error articulatory groping (in which the mouth searches for the correct positions to create sounds, causing sounds to be repeated or distorted, or pauses to be inserted) and inconsistent articulation when asked to repeat the same phrase, particularly with utterances of increasing length or articulatory complexity. Patients are frequently aware of errors and correct themselves. AOS may co-occur with and be difficult to distinguish from aphasia and dysarthria, but isolated AOS is not associated with the errors in comprehension, grammar, or syntax seen in aphasia, and other dysarthrias are not characterized by trial and error articulatory groping or dependence on length of utterance. AOS is most frequently seen with left hemisphere stroke, but also has been described in neurodegenerative disorders, particularly frontotemporal degenerations. In their recent *Brain* article, Josephs and colleagues characterize primary progressive AOS as a neurodegenerative syndrome.

Over 1 year, 37 subjects with a neurodegenerative speech/language disorder were recruited at the Mayo Clinic. All subjects underwent detailed speech and language examination, neurologic evaluation, neuropsychologic testing, volumetric MRI, tensor-diffusion imaging, FDG PET, and Pittsburgh compound B (PiB) imaging. Dysarthria was permitted, but sub-

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jects with any evidence of aphasia were excluded, as were subjects with concurrent illnesses that could account for the speech deficit, including those meeting criteria for any neurodegenerative disease (Alzheimer's disease, Lewy body disease, frontotemporal degeneration, progressive supranuclear palsy, corticobasal degeneration, multisystem atrophy, or motor neuron disease).

Twelve subjects met their criteria for primary progressive AOS. The median age of onset was 73, and eight of the 12 were women. All subjects scored normally on tests for aphasia. There were no consistent neurologic or neuropsychologic findings, though five subjects had executive dysfunction, four had mild limb apraxia, and three had mild parkinsonism. Volumetric MRI showed focal atrophy of superior lateral premotor cortex and supplementary motor area. There was white matter loss underlying the same areas, extending to the inferior premotor cortex and corpus callosum. Tensor diffusion analysis also showed abnormalities in these white matter tracts, plus the premotor components of the superior longitudinal fasciculus. FDG-PET showed focal hypometabolism of the superior lateral premotor cortex and supplementary motor area. Amyloid burden assessed by PiB retention was increased in only one subject.

■ COMMENTARY

This work defines primary progressive AOS as a clinically distinct neurodegenerative syndrome, different from primary progressive aphasia. The neuroanatomic substrate is focal atrophy and hypoactivity in superior lateral premotor cortex and supplementary motor cortex, consistent with their known function in planning and sequencing motor activity. There was no involvement of the insula, an area sometimes associated with AOS in stroke.

Clinical evolution and ultimate pathologic diagnoses remain to be determined. It is likely that different neurodegenerative diseases may present initially with primary progressive AOS. For example, several of their patients had features of frontotemporal degeneration, corticobasal degeneration, or progressive supranuclear palsy. Only one had PiB retention suggestive of Alzheimer's disease. The long-term clinical and pathologic follow-up of this cohort will be of interest. ■

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New Therapies for Tinnitus

ABSTRACT & COMMENTARY

By Douglas Labar, MD, PhD

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

Synopsis: *It is recognized that most cases of chronic tinnitus are generated by central brain mechanisms that may be amenable to treatment with cognitive therapies and magnetic stimulation protocols of the temporal and frontal lobes.*

Sources: Cima RF, et al. Specialized treatment based on cognitive behaviour therapy versus usual care for tinnitus: A randomized controlled trial. *Lancet* 2012;379:1951-1959. Plewnia C, et al. Treatment of chronic tinnitus with theta burst stimulation: A randomized controlled trial. *Neurology* 2012;78:1628-1634.

IT IS A SURE SIGN THAT EXISTING THERAPIES ARE FALLING SHORT when multiple new therapies are reported in close succession. Such is the case with tinnitus. Recent investigations have studied approaches such as combined sound-based and cognitive behavioral-based therapy, repetitive transcranial magnetic stimulation, transcranial direct current electrical stimulation, and electrical vagus nerve stimulation. Each has shown merit, and no clearly superior treatment has yet to emerge.

The principal approaches for tinnitus have been sound-based and cognitive behavioral-based therapies. Tinnitus retraining (sound-based) therapy involves a masking neutral sound and counseling sessions to reduce tinnitus annoyance. Cognitive behavioral therapy involves psychoeducation and relaxation sessions, and is geared toward minimizing distress. Cima et al combined these approach-

es into a step-wise specialized treatment program, and compared that with less intense usual care.[1]

Randomization to specialized or usual care was carried out for 492 patients with tinnitus. Usual care, carried out by an audiology assistant, a clinical physicist in audiology, and a social worker, consisted of audiological diagnostics, audiological rehabilitation, and social work intake and follow-up interviews. Specialized care was similar, but added tinnitus education, psychology, and individual and group treatments, administered by a psychology assistant, clinical psychologist, movement therapist, physical therapist, and speech therapist. Patients were unaware of which of two treatments for tinnitus they were receiving, as were investigators assessing outcomes (which were measured up to 4 months after the last treatment).

At all follow-up time intervals, there were significant improvements in favor of specialized care on all outcome measures, such as health-related quality of life, emotional state, and tinnitus severity, impairments, catastrophising, and fear. It should be noted that these effects persisted long after the last therapy session. The results were similar in mild and severe tinnitus cases. However, older patients were more likely to be non-responders.

Perhaps not surprising is the result that aggressive, substantive, combined modality therapy for tinnitus is better than basic therapy. Nonetheless, this had not been demonstrated previously in a systematic way in a large population. Perhaps what is surprising is that these effects lasted so long after therapy was completed. Also to be mentioned is the likely high cost of the highly labor-intensive specialized care, as we consider other treatments.

Although repetitive transcranial magnetic stimulation (TMS) of the auditory cortex likely helps tinnitus, questions about this remain, particularly about stimulation settings. For example, Plewnia et al recently reported 4 weeks of daily bilateral theta burst TMS was no better than sham stimulation in 48 patients with chronic tinnitus, with outcomes being measured on the tinnitus questionnaire.[2] Stimulation was delivered each working day, as a 3-pulse burst at 50 Hz cycling every 200 msec (5 Hz cycling) for 600 stimuli (total 2 minutes), which was then repeated 15 minutes later. However, previously this group reported a single 3-second burst of rTMS at 10 Hz over temporal and temporo-parietal cortex immediately reduced or eliminated subjective tinnitus in eight of 14 patients treated.[3] Furthermore, they also previously reported a 2-week course of daily 1 Hz rTMS (30 minutes total duration) yielded improvement on the tinnitus questionnaire in five of six treated patients, with one patient remaining improved 2 weeks later.[4]

As just noted, in the work of Plewnia et al, tinnitus improvement did not even last for 2 weeks in five of their six treated patients.[4] This should be contrasted with the beneficial results of the combined sound-based and cognitive behavioral-based therapies reviewed above,[1] in which improvement seemed to persist for 4 months. However, other authors have reported long-lasing effects of rTMS of auditory cortex. Khedr et al found, in 62 patients treated with daily with 2000 pulses at 1 or 25 Hz, significant improvements remained as long as 10 months after therapy.[5]

■ COMMENTARY

Perhaps evolving from the TMS results, research on transcranial direct current cortical stimulation (tDCS) for tinnitus recently has been undertaken. For example, 20 minutes of anodal stimulation targeting the left temporoparietal area significantly reduced tinnitus intensity and discomfort, immediately and at 1 hour follow-up, in a placebo-controlled study on 20 patients.[6] Among 448 treated patients, 20 minutes of anodal right dorsolateral frontal cortex tDCS significantly reduced tinnitus-related distress and intensity.[7]

Finally, animal model work suggests vagus nerve stimulation (VNS) enhances auditory cortex plasticity in a way that may make it useful in tinnitus therapy.[8] In rats, pairing VNS with repeated exposures to a high-pitched tone abnormally increased the proportion of auditory cortex neurons tuned to the frequency of that specific tone. Then, subsequent pairing of VNS with multiple other tones with slightly different frequencies reversed the abnormal excess tuning to the initial tone. Since tinnitus is thought in part to be due to abnormal auditory cortex neuronal hyperactivity, modifying this pathological process by administering VNS and different tones to patients with tinnitus may ameliorate their symptoms. This led MicroTransponder Inc. to conduct a proof-of-concept clinical trial in Belgium attempting to take advantage of the seeming plasticity-enhancing effects of VNS by pairing it with tones, as a new severe tinnitus therapy. Results were presented at the International Conference on Tinnitus in Bruges, Belgium, in June 2012.[9] Among 10 patients treated for 4 weeks in this open-label pilot study, 40% were responders judged by the Tinnitus Handicap Index, and 70% were responders judged by the Iowa Tinnitus Handicap Questionnaire.

We now have evolving a number of new treatment approaches for tinnitus, a condition for which we had few treatment approaches previously. Hopefully, future research will help practitioners decide which treatment has the best efficacy and least adverse effects; what clinical patient features or diagnostic test findings predict the best results; with stimulation, what parameters and treatment schedule should be used; and what is the most effective use of our health care dollars. ■

Stroke Alert: A Review of Current Clinical Stroke Literature

By Matthew E. Fink, *MD, Interim Chair and Neurologist-in-Chief, Department of Neurology and Neuroscience, Weill Cornell Medical College*

Warfarin vs Aspirin in Patients with Heart Failure Showed No Difference in Mortality

Source: Homma S, et al, for the WARCEF Investigators. Warfarin and aspirin in patients with heart failure and sinus rhythm. *New Engl J Med* 2012;366:1859-1869; on-line 10.1056/NEJMoa1202299.

OVER A 6-YEAR PERIOD, 2305 PATIENTS WITH REDUCED left ventricular ejection fraction and normal sinus rhythm were randomized to warfarin treatment (target INR of 2.0 to 3.5) or aspirin (325 mg per day) and followed to determine the rate of a composite endpoint of ischemic stroke, intracerebral hemorrhage, or death from any cause.

The rates of the primary outcome were 7.47 events per 100 patient-years in the warfarin group and 7.93 in the aspirin group (hazard ratio with warfarin, 0.93; 95% confidence interval [CI], 0.79 to 1.10; $P = 0.40$). Therefore, there was no significant difference in the primary outcome between the groups. Warfarin, compared with aspirin, was associated with a significant reduction in ischemic stroke throughout the follow-up period (0.72 events per 100 patient-years vs 1.36 per 100 patient-years; hazard ratio, 0.52; 95% CI, 0.33 to 0.82; $P = 0.005$). But there was a higher rate of major hemorrhage in the warfarin group compared to aspirin. The rates of intracranial hemorrhage did not differ significantly between the groups. Even though the primary composite outcomes did not differ between the warfarin and aspirin groups, there may be individual patients who would benefit from warfarin, rather than aspirin, and therapy should be individualized. ■

Use of the ABCD² Score Helps Predict True Ischemic Stroke in Dizzy Patients

Source: Navi BB, et al. Application of the ABCD^2 score to identify cerebrovascular causes of dizziness in the emergency department. *Stroke* 2012;43:1484-1489.

THE ABCD^2 SCORE REFERS TO A NUMERICAL SCALE, 0 TO 7, based on a series of clinical features (age > 60, blood pressure > 140/90, clinical features such as weakness or speech disturbance, duration of symptoms > 10 minutes, presence of diabetes) that predicts with a high degree of

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Predicting Response to IVIG or Plasmapheresis in Myasthenia Gravis

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Clinical examination severity appears to be the best predictor of response to immunotherapy in patients with myasthenia gravis.*

Source: Katzberg HD, et al. Predictors of response to immunomodulation in patients with myasthenia gravis. *Muscle Nerve* 2012;45;648-652.

validity a true ischemic TIA/stroke and helps to distinguish this from other disorders that may mimic a stroke (*Lancet* 2007;369:283-292). The authors reviewed the charts of 907 dizzy patients who presented to the emergency department at UCSF. Thirty-seven (4.1%) had a cerebrovascular cause, of which 24 were ischemic strokes. The median ABCD^2 score was 3, and the score predicted the ultimate diagnosis of a cerebrovascular event (c statistic, 0.79; 95% confidence interval, 0.73-0.85). Only 5 of 512 patients (1%) with a score of ≤ 3 had a cerebrovascular event, compared to 25 of 369 patients (6.8%) with a score of 4 or 5, and 7 of 26 patients (27%) who had a score of 6 or 7. Use of this score in the emergency department may help to stratify low-risk vs high-risk patients and result in more rational and efficient use of scarce resources. ■

Thrombotic Stroke Risk is Increased by the Use of Estradiol-Containing Oral Contraceptives

Source: Lidegaard O, et. al. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012;366:2257-2266.

In this 15-year Danish historical cohort study, a total of 1,626,158 women, without any history of cardiovascular disease, contributed 14,251,063 person-years of observation, during which 3311 thrombotic strokes (21.4 per 100,000 person-years) and 1725 myocardial infarctions (10.1 per 100,000 person-years) occurred. Use of combination oral contraceptives that included ethinyl estradiol at a dose of 30 to 40 µg and various progestins was associated with relative risks (and 95% confidence intervals) for thrombotic stroke and myocardial infarction, ranging from 1.6 to 2.2 compared to non-users of oral contraceptives. The specific type of progestin had little effect on the risk of stroke or myocardial infarction. With ethinyl estradiol at a dose of 20 µg, the corresponding relative risks ranged from 0.9 to 1.7, again, with little influence from the progestin. For transdermal patches, the corresponding relative risk was 3.2 (0.8 to 12.6) and for a vaginal ring, 2.1 to 2.5.

Although the absolute risks for stroke and myocardial infarction in healthy young women who take oral contraceptives is very low, compared to non-users there is an increased risk based on the relative dosage of estradiol, and the particular progestin used in combination does not seem to have a significant effect. This study did not address the possible role of cigarette smoking, obesity, or hypertension as confounding variables. ■

Which factors predict a positive response to intravenous immunoglobulin (IVIG) or plasma exchange (PLEX) in a patient with myasthenia gravis (MG)? To address this question, data were collected from two trials comparing IVIG or PLEX to placebo, that included patients 18 years or older, with a quantitative MG score of 10.5 or greater, whose weakness worsened and thus required alteration of treatment, as determined by a neuromuscular expert. MG diagnosis was based on clinical evaluation and positive findings on repetitive nerve stimulation studies and single fiber electromyography. Negative antibody studies did not preclude the diagnosis. Exclusionary criteria encompassed worsening of symptoms due to infection or medication (e.g., aminoglycosides), hepatic, renal, or cardiac disease, hypercoagulability, hyperviscosity, pregnancy, breastfeeding, or history of anaphylaxis. Patients received either IVIG 1 g/kg/day for 2 consecutive days, or five plasma exchange procedures, performed every other day, with weekend breaks allowed. Change in quantitative MG score from baseline to 2 weeks following full therapy was the primary endpoint measure, and secondary outcome measures included quantitative MG score at 3 and 4 weeks, improvement in repetitive nerve stimulation decremental response and single fiber electromyography jitter, and change in acetylcholine receptor (AchR) antibody titers at days 28 and 60. Statistical analysis included analysis of variance (ANOVA), multivariate ANOVA for repeated measures, and analysis of covariance (ANCOVA). Chi square testing was performed and $P < 0.05$ was considered statistically significant.

Among 63 MG patients treated with IVIG and 42 treated with PLEX, mean age was 57 years, disease duration was approximately 5 years, and gender was equally divided among men and women. Both groups included those with or without AchR and muscle-specific kinase (MuSK) antibodies, prior thymoma or thymectomy, as well as patients currently treated with prednisone, azathioprine, or mycophenolate mofetil. Compared to non-responders, patients who responded to IVIG or PLEX were more likely to be seropositive for AchR, but not MuSK, antibodies, tended to have higher baseline quantitative MG score, and greater jitter on single fiber electromyography, but not more significant decrement of repetitive nerve stimulation studies. Ultimately, using multivariate regression, only baseline quantitative MG score proved to be a significant predictor of response to IVIG or PLEX in MG.

■ **COMMENTARY**

For MG patients refractory to IVIG or PLEX, rituximab (RTX), a chimeric monoclonal antibody against surface B cell protein CD20, appears to be an effective alternative.[1] Among 13 refractory MG patients treated over 2 years in a retrospective, observational, multicenter study in France, 7 were able to discontinue prednisone treatment within a year following RTX induction, accomplished either by administering 375 mg/m^2 weekly for 4 consecutive weeks, followed by 375 mg/m^2 every 3 months, or by administering two 1 g infusions, 2 weeks apart, followed by 1 g infusions, as needed, if symptoms warranted. Refractory patients had all previously undergone thymectomy, had received at least 6 months of prednisone and one other immunosuppressive agent, comprising azathioprine, mycophenolate mofetil, cyclosporine, or cyclophosphamide, and either IVIG or PLEX. RTX was well tolerated with no side effects being reported, except for one case of spondylodiskitis, occurring a year following the last RTX infusion. RTX appears to be a good alternative for refractory MG. It is safe, well tolerated, and demonstrated to be efficacious in a non-randomized case series. ■

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An Advance in the Search for Parkinson's Disease Biomarkers

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

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Dr. Henchcliffe reports she is on the speakers bureau and advisory board for Allergan and Teva; speakers bureau for Boehringer-Ingelheim, GlaxoSmithKline, and Novartis; advisory board for Merz; and is a consultant for Gerson Lehman Group and Guidepoint Global.

Synopsis: *Changes in CSF metabolites reflect dopamine and norepinephrine deficiency in Parkinson's disease, and may be sensitive in early identification.*

Source: Goldstein DS, et al. Cerebrospinal fluid biomarkers of central catecholamine deficiency in Parkinson's disease and other synucleinopathies. *Brain* 2012;135:1900-1913.

PARKINSON'S DISEASE (PD), AND THE LESS COMMON DISORders Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF), are related by pathology involving the protein α-synuclein, and all involve central catecholamine deficiency with well-established decreases in dopamine and norepinephrine. In this study, cerebrospinal fluid (CSF) levels of dopamine and its metabolite, dihydroxyphenylacetic acid (DOPAC), and norepinephrine and its metabolite, dihydroxyphenylglycol (DHPG), were quantitated in individuals with PD (n = 34), MSA (n = 54), PAF (n = 20), and control subjects (n = 38). Ages in the PD, MSA, and PAF groups were similar (63 ± 2, 60 ± 1, and 61 ± 3 years, respectively). Controls comprised three groups: volunteers from the NIH Clinical Center (50 ± 2 years), individuals judged not to have chronic autonomic failure or central neurodegeneration (53 ± 3 years), and volunteers at the University of Washington (≥ 70 years). More men than women were recruited in the patient groups, but gender ratio was not stated for the control group. DOPAC levels were significantly lower in CSF from those with PD, MSA, and PAF (0.86 ± 0.09, 1.00 ± 0.09, and 1.32 ± 0.12 nM, respectively) compared with controls (2.15 ± 0.18 nM), as were DHPG levels (PD: 8.82 ± 0.44 nM; MSA: 7.75 ± 0.42 nM; PAF 5.82 ± 0.65 nM; control 11.0 ± 0.62 nM). Moreover, DOPAC levels could distinguish cases of parkinsonism from controls with 100% sensitivity and 89% specificity. Although DOPAC levels could not distinguish PD from MSA, PD differed from PAF in measures of lower CSF DOPAC and higher CSF DHPG.

■ **COMMENTARY**

Diagnosis of PD and related disorders remains clinical, and although ^{123}I-ioflupane SPECT (DaTscan®) scans were recently approved as adjunctive testing for parkinsonism, there remains a critical need for biomarker development to aid diagnosis, tracking progression, and evaluating treatment response. Measuring CSF catecholamines and their metabolites, although indirect, is attractive based on a strong scientific rationale, but previous studies have failed to yield definitive answers. Now, the authors present compelling data that measures of DOPAC and DHPG, major metabolites of dopamine and norepinephrine, are decreased in CSF of PD, MSA, and PAF, and hold promise as potential future tests and measures of neurodegeneration. The strength of this study is in sophisticated technology using liquid chromatography with electrochemical detection, and although not widely available, the authors state there is an effort to make this resource available for clinicians and researchers. Potential confounders include medications taken by the subjects, which were very different between groups, and it is also difficult to tell from data presented how well the control group was matched for age and gender. Furthermore, patients referred to the NIH, as in this study, may not represent the "typical" cohort we

see in clinical practice. Indeed, one had a rare α-synuclein gene triplication leading to PD, seven of 34 PD subjects initially had been diagnosed with MSA or PAF due to prominent dysautonomia, and almost a quarter of PD subjects were taking midodrine and fludrocortisone (presumably for blood pressure support). The study highlights how important developing standardized biosample collections has become, both in discovery and validation phases of test development, and efforts such as the international Parkinson's Progression Markers Initiative (NCT01140123) have now evolved to fill this need. It is critically important that we see these measures validated in an independent cohort, as these results hold as potential biomarkers of pathway-specific neurodegenerative processes. ■

Outcome of Shunting for Idiopathic 'Normal Pressure Hydrocephalus'

ABSTRACT & COMMENTARY

By John J. Caronna, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Normal pressure hydrocephalus remains a clinical diagnosis and standardized clinical assessments predict a positive response to shunting in most patients.*

Sources: Klinge P, et al. One-year outcome in the European multicentre study on iNPH. *Acta Neurol Scand* 2012; DOI:10.1111/j.1600-0404.2012.01676X. Hellstrom P, et al. A new scale for assessment of severity and outcome in iNPH. *Acta Neurol Scand* 2012; DOI:10.1111/j.1600-0404.2012.01677X.

The authors assessed the 1-year outcome after shunt surgery in patients with idiopathic normal pressure hydrocephalus (iNPH), that is, NPH of unknown cause. Patients (n = 142) were prospectively included in the European Multicenter Study of iNPH that evaluated the predictive value of the CSF tap test (TT) and resistance to CSF outflow studies (to be reported in a separate article). The present study reports outcome in patients in whom the diagnosis of iNPH was based solely on the clinical and radiological findings without regard to the results of CSF TT and CSF outflow studies.

Based on clinical and radiologic criteria, patients were classified as "typical" ($iNPH_t$) in 61% or "questionable" ($iNPH_Q$) in 39%. A diagnosis of $iNPH_t$ by clinical criteria required a gait disturbance affecting tandem walking, turning, stride length, and base. Patients diagnosed as $iNPH_Q$ had less typical gait disturbances. Patients with $iNPH_t$ had mild-to-moderate cognitive impairment (MMSE Score ≥ 21); those with more severe cognitive deficits were classified as $iNPH_Q$. The presence of incontinence was not used for classification.

The MRI criteria for $iNPH_t$ and $iNPH_Q$ were an Evans index > 0.30 and evidence of communicating hydrocephalus. Patients with $iNPH_Q$ also had moderate cortical atrophy and moderate-to-severe leukoaraiosis.

At 12 months after shunt surgery, outcome was assessed in 115 patients by the modified Rankin Scale (mRS) and the iNPH grading scale of four domains: gait, neuropsychology, balance, and continence. Sixty-nine percent of patients had improved according to the mRS by one step or more, and 84% according to the iNPH scale. The improvement by domains was gait 77%, neuropsychology 63%, balance 56%, and incontinence 66%. There were no differences in comorbidities or signs and symptoms between responders and non-responders to surgery. Classification of iNPH as "typical" or "questionable" did not affect level of improvement.

Twenty-eight percent of patients experienced complications of surgery that were either conservatively (13%) or surgically (15%) treated. Only one patient had a hematoma that required evacuation. These results strongly support shunt surgery for patients with clinical and MRI features suggestive of iNPH.

■ COMMENTARY

This study provides evidence that long-term improvement can be sustained in patients after shunt surgery. In the past, it was common for patients who initially did well after shunting to deteriorate over months as the mechanical characteristics of their CSF dynamics changed over time. The present durability of good results is probably, in part, the result of the use of programmable ventriculoperitoneal shunts. In the present series, shunt adjustments were made 76 times in 36 patients (31%).

The remarkable improvement rate in this series was substantially higher than the 50% reported in a review of studies not using any supplementary tests for the selection of patients for surgery.[1] One reason for the high rate of successful shunting may be the early and accurate recognition of the typical clinical and radiological phenotype of iNPH in these patients. Another reason is probably the use of a new, more sensitive iNPH scale to measure outcome. Motor improvement in 69% of patients also was measured by the modified Rankin Scale (MRS).

NPH remains fundamentally a clinical diagnosis. Nevertheless, clinical features alone cannot distinguish between responders and non-responders to shunt surgery.

The evaluation of patients with a suspected diagnosis of NPH has been more hindered than helped by attempts to develop confirmatory tests and procedures to predict the response to shunt surgery. At present, most clinical tests such as CSF drainage have a high positive-predictive value but a poor negative-predictive value. More than half of suspected NPH patients with a negative CSF TT can be expected to respond to shunt surgery.

The decision to refer a patient for shunt surgery remains based on a detailed history and neurological examination, together with an MRI of the brain and a lumbar puncture for CSF examination and pressure measurement. Therefore, we await, with interest, the final results of the European iNPH study that combines clinical and radiologic evaluations with CSF TT and CSF outflow resistance studies and correlates them with outcome after shunt surgery. ■

CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

Reference

1. Marmarou A, et al. Guidelines for management of idiopathic normal pressure hydrocephalus: Progress to date. *Acta Neurochir Suppl* 2005;95:237-240.

CME Questions

1. Primary progressive apraxia of speech is usually associated with Alzheimer's disease.
a. True
b. False

2. Chronic tinnitus appears to respond to which therapy?
a. Cognitive-behavioral therapy
b. Transcranial magnetic stimulation
c. Transcranial direct electrical stimulation
d. Electrical vagus nerve stimulation
e. All of the above

3. Which of the following factors best predicts a positive response to intravenous immunoglobulin or plasma exchange in a patient with myasthenia gravis?
a. Baseline quantitative myasthenia gravis score
b. Severity of decrement on repetitive nerve stimulation at baseline
c. Severity of single fiber electromyography jitter at baseline
d. Acetylcholine receptor antibody titers at baseline
e. Muscle-specific kinase antibody titers at baseline

4. Abnormal CSF findings in Parkinson's disease, multiple system atrophy, and pure autonomic failure include which of the following, when compared with controls?
a. Increased total protein
b. Decreased dopamine and increased norepinephrine
c. Decreased metabolites of dopamine and norepinephrine
d. There are no known abnormalities

5. Which of the following statements is *not* true? Patients classified as $iNPH_Q$ often had:
a. a gait disorder atypical for normal pressure hydrocephalus.
b. moderate cerebral cortical atrophy.
c. leukoaraiosis.
d. an Evans index < 0.30.
e. MMSE Scores < 21.

6. Cardiovascular risk factors, as documented with the $ABCD^2$ score, predict ischemic stroke as a cause for isolated dizziness.
a. True
b. False

7. Warfarin has been shown to be better than aspirin in preventing ischemic stroke in patients with heart failure.
a. True
b. False

8. The use of estradiol-containing oral contraceptives increases the risk of stroke and myocardial infarction.
a. True
b. False

In Future Issues:

Update on Muscle Diseases

Dear *Neurology Alert* Subscriber:

This issue of your newsletter marks the start of a new continuing medical education (CME) semester and provides us with an opportunity to tell you about some **new procedures for earning CME and quicker delivery of your credit letter.**

Neurology Alert, sponsored by AHC Media, provides you with evidence-based information and best practices that help you make informed decisions concerning treatment options and physician office practices. Our intent is the same as yours — the best possible patient care.

The objectives of *Neurology Alert* are:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

The American Medical Association, which oversees the Physician's Recognition Award and credit system and allows AHC Media to award *AMA PRA Category 1 Credit™*, has changed its requirements for awarding *AMA PRA Category 1 Credit™*. Enduring materials, like this newsletter, are now required to include an assessment of the learner's performance; the activity provider can award credit only if a minimum performance level is met.

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1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. *First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.*
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This activity is valid 36 months from the date of publication. The target audience for this activity is neurologists.

If you have any questions about the process, please call us at (800) 688-2421, or outside the U.S. at (404) 262-5476. You can also fax us at (800) 284-3291, or outside the U.S. at (404) 262-5560. You can also email us at: customerservice@ahcmedia.com. On behalf of AHC Media, we thank you for your trust and look forward to a continuing education
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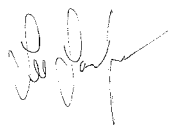

Lee Landenberger
Continuing Education Director
AHC Media

PHARMACOLOGY WATCH

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

Does Azithromycin Cause Cardiovascular Death?

In this issue: Azithromycin and cardiac risk; warfarin and heart failure; aspirin and VTE; effectiveness of long-acting contraceptives; and FDA actions.

New study finds increased risk

Is azithromycin proarrhythmic? Macrolide antibiotics are associated with an increased risk of sudden cardiac death, but azithromycin (Zithromax), the popular "Z pack" macrolide, has been considered safe. That may change based on the results of a new study from Vanderbilt. Researchers reviewed the records of patients in the Tennessee Medicaid cohort to detect an increased risk of death related to short-term cardiac effects of azithromycin and several control antibiotics. Patients with serious noncardiovascular illness and hospitalized patients were excluded. Over the study period, there were almost 350,000 patients who took azithromycin, 1.35 million patients who took amoxicillin, 265,000 patients who took ciprofloxacin, nearly 200,000 patients who took levofloxacin, and nearly 1.4 million control patients. Five days of therapy with azithromycin compared to no antibiotics significantly increased the risk of cardiovascular death (hazard ratio [HR] 2.88, confidence interval [CI], 1.79 to 4.63; $P < 0.001$) and death from any cause (HR 1.85; 95% CI, 1.25 to 2.75; $P = 0.002$). Use of amoxicillin was not associated with increased risk of death. Relative to amoxicillin patients, patients taking azithromycin were at 2.5 times higher risk of cardiovascular death and 2 times higher risk of death from any cause, although the absolute risk was low with an estimated 47 additional cardiovascular deaths per million courses. Patients at risk for cardiovascular disease were at higher risk, with an estimated 245 additional cardiovascular deaths per 1 million courses. Cardiovascular death risk was higher with azithromycin compared to ciprofloxacin, but the death rate from levofloxacin was roughly the same. The authors conclude that 5 days of azithromycin was associated with a small but absolute increased risk of cardiovascular death, which was most pronounced in patients with a high baseline risk for cardiovascular disease (*N Engl J Med* 2012;366:1881-1890). Soon after this study was published, the FDA issued a statement urging patients to continue taking azithromycin unless instructed otherwise by their health care professional. The FDA will review the results of the study and will communicate any new information on azithromycin, including the potential risk of QT interval prolongation, to health care professionals and the public. Health care professionals are urged to report any adverse effects related to the use of azithromycin to the FDA's MedWatch Safety program. ■

Warfarin doesn't prevent death

Warfarin is no more effective than aspirin in preventing mortality in patients with heart failure who are not in atrial fibrillation (AF), according to a new study. More than 2300 patients with a left ventricular ejection fraction less than 35% (average 25%) and a mean age of 61 years were randomized to warfarin with a target INR of 2.0-3.5 or

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

aspirin 325 mg per day. The primary outcome was ischemic stroke, intracerebral hemorrhage, or death from any cause. Patients were followed for up to 6 years with a mean follow-up of 3.5 years. There was no difference in the primary outcome (7.47 events per 100 patient years for warfarin, 7.93 for aspirin; HR with warfarin 0.93, CI, 0.79 to 1.10, $P = 0.40$). Warfarin was associated with a significant reduction in the rate of ischemic stroke but was associated with a higher rate of hemorrhage. The authors conclude that among patients with heart failure who are in sinus rhythm, there was no difference in outcome between warfarin and aspirin, but note that since warfarin was associated with a lower risk of ischemic stroke, the choice between the two drugs should be individualized (*N Engl J Med* 2012;366:1859-1869). An accompanying editorial asks, "Could there be some patients with heart failure who would benefit from warfarin?" Those with AF, a history of cardioembolic stroke, history of left ventricular thrombus, and perhaps those with atherothrombotic coronary artery disease may benefit, but in general, warfarin cannot be recommended for patients with heart failure who are not in AF (*N Engl J Med* 2012;366:1936-1938). ■

Aspirin and venous thromboembolism

Aspirin may be protective in patients who have had an unprovoked venous thromboembolism (VTE) to prevent recurrence after they finish oral anticoagulant therapy. In a double-blind study, patients with first-ever unprovoked VTE who had completed 6-18 months of oral anticoagulant treatment were randomly assigned to aspirin 100 mg daily or placebo for 2 years. The primary endpoint was recurrent VTE with major bleeding being the primary safety outcome. Recurrent VTE occurred in 6.6% of patients on aspirin and 11.2% of patients on placebo (HR 0.58; 95% CI, 0.36 to 0.93). One patient in each group had a major bleeding episode. The authors conclude that aspirin reduces the risk of recurrence in patients with unprovoked VTE after they have finished anticoagulant therapy, with no apparent increase in risk of major bleeding (*N Engl J Med* 2012;366:1959-1967). This study is important because about 20% of patients with unprovoked VTE have a recurrence within 2 years. It also shows that taking low-dose aspirin safely reduces that risk by nearly half. An accompanying editorial points out that a similar but larger study is currently ongoing in Australia and New Zealand with results due later this year (*N Engl J Med* 2012;366:2028-2030). ■

Long-acting contraceptives are better

Long-acting contraceptives, such as IUDs and implants, are up to 20 times more effective than oral contraceptives and other short-acting contraceptive methods, according to a new study. In a large, prospective cohort study, women participants were provided with the reversible contraception of their choice at no cost for 3 years. The endpoint was failure of long-acting reversible contraception (IUDs and implants) compared with commonly prescribed contraceptive methods, including oral contraceptive pills, transdermal patches, contraceptive vaginal rings, and depot medroxyprogesterone acetate injection (DMPA). In the nearly 7500 women participants, there were 334 unintended pregnancies. The failure rate among participants who used pills, patch, or ring was 4.55 per 100 participants years as compared with 0.27 among participants using long-acting reversible contraception (HR after adjustment for age, educational level, and history with respect to unintended pregnancy 21.8; 95% CI, 13.7 to 34.9). The rate for DMPA was also low at 0.22. Younger women (< 21 years) who used a short-acting contraceptive had a pregnancy rate almost twice as high as older participants. The pregnancy rate among women who used DMPA, an IUD, or implant were similarly low regardless of age. The authors conclude that the effectiveness of long-acting reversible contraception is superior to that of contraceptive pills, patch, or ring and is not altered in adolescents or young woman (*N Engl J Med* 2012;366:1998-2007). This study not only points out the reliability of long-acting contraceptives, but also the surprisingly high failure rate of short-acting contaceptives, especially in young women. ■

FDA actions

In the biggest generic launch since last year's atorvastatin (Lipitor), the FDA has approved generic clopidogrel (Plavix). The popular antiplatelet drug, with sales of more than $9 billion last year, will be available from seven generic manufacturers in the 75 mg strength and four manufacturers in the 300 mg strengths. The immediate "multisource" status of the generic approval should result in dramatic cost reductions for patients, from an average of $200 per month to about $40 per month. The drug is approved for treatment of acute coronary syndrome and prevention of thrombotic events in patients who have had a recent myocardial infarction, recent stroke, or peripheral artery disease. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 17, NUMBER 7 PAGES 13-14 JULY 2012

Lose-Dose Abdominal CT for Appendicitis

Source: Kim K, et al. *N Engl J Med* 2012; 366:1596-1605.

RADIATION EXPOSURE FROM CT IS QUITE substantial. A "typical" abdominal CT (AB-CT) examination exposes a patient to X-radiation equivalent to more than 500 chest X-rays. The dose-response relationship between diagnostic/therapeutic radiation and untoward consequences is uncertain; nonetheless, the magnitude of radiation from imaging — combined with the ever-increasing frequency with which high-dose diagnostic imaging is used — prompts concern. Perspicacity for wise use of radiation is imperative, especially in younger persons, in whom the lag time for adverse impact of radiation is most pertinent and in whom the likelihood of additional radiation exposure is increased.

When appendicitis is suspected, AB-CT has become the diagnostic imaging of choice. Standard-dose AB-CT exposes the patient to approximately 500 mGy/cm of radiation. Low-dose AB-CT exposes the patient to approximately 100 mGy/cm, but it is not widely used because of uncertainty about its accuracy (compared to standard AB-CT).

Kim et al randomized young adult patients with suspected appendicitis (n = 891) to low-dose or standard-dose AB-CT. The primary outcome of the study was the number of appendectomies performed that did *not* demonstrate appendicitis.

The negative appendectomy rate did not differ significantly between the two groups (3.2% vs 3.5%). Statistical criteria were satisfied that low-dose AB-CT is noninferior to standard dose AB-CT. Clinicians may wish to ascertain the radiation dose used in AB-CT for appendicitis at their institutions. ■

Degludec, a New Ultra-long-acting Basal Insulin for Diabetes

Source: Garber AJ, et al. *Lancet* 2012; 379:1498-1507.

THE ADVENT OF BASAL INSULINS THAT DO not have a prominent peak plasma level — so-called "flat" pharmacodynamic activity — was a welcome addition to diabetes management, since their predecessor, NPH, was often limited by problematic hypoglycemia. Utilization of glargine and detemir insulins, the two basal insulin analogs most recently available in the United States, has mushroomed in response to their superior tolerability compared to NPH insulin: a reduction of about 20% in hypoglycemic episodes and less weight gain. Degludec has recently been submitted to the FDA for approval. It is considered an ultra-long-acting basal insulin.

Garber et al performed a controlled trial in type 2 diabetic patients (n = 972) to compare degludec with glargine as part of a basal-bolus regimen. The primary endpoint of the trial was achieved A1c, but rates of hypoglycemia were also compared.

Both insulins achieved similar A1c improvement, and the overall rate of hypoglycemia was low in both groups. However, the degludec patients experienced almost 20% fewer hypoglycemic episodes (defined as glucose < 56 mg/dL) than the glargine group.

Degludec insulin, if FDA approved, may provide a superior hypoglycemia risk profile than insulin glargine while achieving a similar level of A1c reduction. ■

Prevention Benefits of Aspirin: Cancer, Vascular, or Both?

Source: Rothwell PM, et al. *Lancet* 2012; 379:1602-1612.

AMERICAN CLINICIANS HAVE TYPICALLY thought of aspirin as a preventive (primary and secondary prevention) for cardiovascular (CV) events. Recently, the role of aspirin for primary prevention of CV events has been embattled because although clinical trial data indicate reduction in CV events, total mortality has not been convincingly favorably impacted.

Aspirin appears to have at least two favorable effects upon cancer. It appears to decrease the incidence of colon cancer, and — as a consequence of what otherwise might appear to be an adverse effect — enhances detection rates of existing colon cancer by increasing their proclivity to bleed.

Rothwell et al performed an analysis of trial data from 51 randomized, controlled aspirin prevention trials. Among almost 70,000 participants, risk of cancer death was reduced by approximately 15%, and incidence of cancer was reduced by about one-fourth. Although there is a reduction in vascular events with the use of aspirin, bleeding events induced by aspirin tend to balance this out in the earliest years of aspirin use.

Since cancer is well-entrenched as the No. 2 cause of death in America (and is inching into the No. 1 slot), when we think of the preventive benefits of aspirin, it is time to reframe our thinking into appreciation of the combined benefits of cancer mortality reduction in addition to CV event reduction. ■

UTI in Long-Term Care Facilities Among Older Adults

Source: Genao L, Buhr GT. *Ann Long-Term Care: Clin Care Aging* 2012;20:33-38.

UNLESS A DRAMATIC DEMOGRAPHIC SHIFT occurs, approximately one in four of us will reside in a long-term care facility (LTCF) during our lifetime. Among LTCF residents, 30-50% of antibiotic utilization is for urinary tract infections (UTIs), resulting in substantial expense, adverse drug reactions, and ever-growing populations of resistant bacteria.

The first guidelines for managing UTI in LTCF were issued in 1991. The McGeer criteria included fever, chills, dysuria, frequency, urgency, flank pain, suprapubic pain, change in urine character, worsening of mental or functional status, and new or increased incontinence. Unfortunately, these criteria (and their subsequent modification, known as the Loeb guidelines) had a sensitivity of only 30%, a positive-predictive value of 57%, and negative-predictive value of 61%. Further modifications of the Loeb guidelines have evolved into an algorithm with major and minor symptoms that have been shown to reduce false-positive diagnoses by 30% and antibiotic use by 20%.

Genao and Buhr do not support treatment of asymptomatic bacteriuria in the LTCF setting for older adults. They remind us of the merit of urine dipstick testing because of its strong negative-predictive value: A dipstick urine test negative for leukocyte esterase and nitrate has an essentially 100% negative-predictive value for the presence of UTI. Although not yet in widespread use, other biomarkers of bacterial infection are gaining support. For instance, serum procalcitonin has been studied as a marker of bacterial infection (including UTI) in young adults, and might perform equally well in older adults. ■

Beyond Glucocentricity: Nonglycemic Effects of Incretin-Based Therapy

Source: Brown NJ. *J Am Soc Hypertens* 2012;6:163-168.

ALTHOUGH GLUCOSE CONTROL IN DIABETES has been consistently demonstrated to improve microvascular outcomes, no randomized clinical trial has shown favorable effects on macrovascular disease (stroke, MI, overall mortality). Whether the failure to achieve macrovascular risk reduction is secondary to adverse effects like weight gain, hypoglycemia, catecholamine activation, or other factors remains to be determined. In the mean time, clinicians would like to use agents that have favorable effects on glucose/A1c, but — at worst — neutral effects on cardiovascular risk factors.

The incretin class of agents is currently comprised of GLP-1 agonists (e.g., exenatide, liraglutide) and DPP4 inhibitors (e.g., sitagliptin, linagliptin, saxagliptin). Although both subgroups blunt glucagon and induce glucose-dependent insulin secretion, only the GLP-1 agonists have sufficient potency to also increase satiety and slow gastric emptying. Incretins are generally weight neutral (DPP4) or associated with weight loss (GLP-1). Accordingly, favorable lipid or blood pressure effects might be associated with incretins compared to other treatments that increase weight. The DPP4 enzyme has also been shown to be responsible for breakdown of some vasoactive peptides; hence, changes in blood pressure could be a direct effect of DPP4 inhibition. Because GLP-1 enhances endothelial function, any medication that augments GLP-1 would be anticipated to at least potentially favorably effect vascular function. We look forward to incretin clinical trials that will define the cardiovascular outcomes associated with this class of therapy. ■

Home BP Monitoring May Assist BP Goal Attainment in the Elderly

Source: Cushman WC, et al. *J Am Soc Hypertens* 2012;6:210-218.

ALTHOUGH CLINIC BLOOD PRESSURE (CBP) has been the primary standard by which the majority of major clinical hypertension (HTN) trials have been measured, home BP (hBP) and ambulatory blood pressure monitoring (ABPM) correlate more closely with outcomes and target organ damage. With the advent of reliable, inexpensive, validated devices for home oscillometric BP measurement, national and international agencies now recommend routine inclusion of home BP monitoring for patients with HTN.

Cushman et al report on a trial in elderly hypertensives (men and women > age 70) which compared hBP monitoring with cBP monitoring (n = 128) over 16 weeks. They determined that hBP measurements were consistent with cBP.

Adherence to HTN medications is suboptimal. Utilization of hBP monitoring enables early detection of hypotension, facilitates dose titration (up or down), and may uncover otherwise unidentified insufficient durability of pharmacotherapy (i.e., nighttime measurements showing a waning of antihypertensive effect). As has been demonstrated in other populations, elderly patients can effectively and reproducibly use hBP, which may enhance long-term adherence. ■

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