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INSIDE

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What are the Causes of Late-Life Cognitive Decline?

ABSTRACT & COMMENTARY

By Richard S. Isaacson, MD

Associate Professor of Neurology (Education), Weill Cornell Medical College

Dr. Isaacson reports that he is a scientific advisor/consultant for Novartis and Accera.

Synopsis: *Contrary to popular belief, a longitudinal study has found that much of late-life cognitive decline was* not *secondary to the three most common neurodegenerative disease pathologies.*

Source: Boyle PA, et al. Much of late life cognitive decline is not due to common neurodegenerative pathologies. *Ann Neurol* 2013; online at wileyonlinelibrary.com. DOI: 10.1002/ana.23964.

With the first wave of the baby boomer generation nearing their 70s, and considering that age is the number one risk factor for cognitive decline, determining the causal relationships behind progression of dementia is essential. Managing pre-symptomatic cognitive decline from a standpoint of both risk reduction and prevention of dementia is crucial, and targeted therapies may be defined by the most common disease pathologies.

The three most common causes of dementia in older age include dementia due to Alzheimer's disease (AD), vascular dementia (VD), and Lewy body dementia (LBD). These three diseases also account for the majority of cases of mild cognitive impairment (MCI). AD is the most common neurodegenerative dementia and affects millions of individuals, with many millions more affected as caregivers and family. Because the pathology of AD precedes symptom onset sometimes by decades, there is significant interest in developing preventive intervention strategies that target earlier stages of disease. Although vascular risk factor modification may be associated with reduced rates of VD, disease modification in LBD is less clear. The pathologic indices of AD, VD, and LBD accumulate in the brains of older persons with and without dementia, but the extent to which they account for late-life cognitive decline remains unknown. Ear-

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lier identification of at-risk individuals could lead to faster diagnoses, better stratification of patients, and ultimately to more effective preventive treatments.

In the current study, the authors tested the hypothesis that these pathologic indices account for the majority of late-life cognitive decline. Using participants from two large and highly regarded longitudinal clinical-pathologic studies, with > 95% follow-up participation rates for survivors and autopsy rates > 80% (the Rush Memory and Aging Project; Religious Orders Study), postmortem neuropathologic examinations provided quantitative measures of three measures of AD (global AD pathology, tangles, and amyloid), two measures of VD (macroscopic infarcts and microinfarcts), and one measure of neocortical Lewy body pathology, in 856 participants. Detailed annual cognitive function data were available for up to 18 years, and included a mean of 7.5 annual evaluations (including 17 cognitive tests), with participants in both studies undergoing uniform, structured, annual clinical evaluations (including detailed annual cognitive testing and neurologic examinations). The authors also used random coefficient models to examine the linear relation of pathologic indices with global cognitive decline. Since cognitive decline may accelerate in the few years prior to death, analysis was further conducted via random change point models to first determine when the rate of cognitive decline increased prior to death (indicating the onset of terminal decline) and characterize rates of cognitive decline before and after its onset. They then examined the relation of the pathologic indices with the onset of terminal decline and rates of change before and after its onset.

Results showed that while the pathologic indices of the three most common causes of dementia are important determinants of cognitive decline in their older aged cohort, contrary to the hypothesis, they only explained a total of 41% of the variation in cognitive decline (even when multiple pathologic indices of AD, VD, and LBD were examined simultaneously). The authors concluded that the majority of the variation in cognitive decline remained unexplained. This suggests that a large proportion of late-life cognitive decline is driven by factors *other* than the pathologic indices of AD, VD, and LBD, which are the primary focus of scientific efforts to prevent cognitive impairment and dementia. Further, in random change point models, the common pathologic indices accounted for less than one-third of the variation in the onset of terminal decline, and rates of preterminal and terminal decline.

■ COMMENTARY

New research focused on the neurobiological basis of pathologically unexplained cognitive decline is imperative. Strategies are urgently needed to effectively combat the ever-growing public health crisis posed by cognitive decline in older age. This study had several limitations (e.g., measures of disease processes, especially particularly cerbrovascular disease, were incomplete; additional pathologic indices were not quanified) and several additional factors that also likely contributed to the high rate of unexplained causes (e.g., indices may lack specificity, measures of cerebrovascular disease were incomplete, inability to examine the contribution of small vessel disease, not accounting for hippocampal sclerosis or other recently described pathologies). However, even considering these limitations, investigation of an alternative explanation is warranted. Along these lines, one recent study published in *Science Translational Medicine* discovered that deficiency of the histone-binding protein RbAp48 was related to age-related memory loss (ARML), with its expression deteriorating with age.[1] ARML, an area of active research, may be one of the more common syndromes apart from AD, VD, and LBD associated with cognitive decline. ARML is just one example of a condition with unclear neuropathologic indices, and implications for diagnosis, treatment, and prevention of cognitive decline. ■

Reference

1. Pavlopoulos E, et al. Molecular mechanism for age-related memory loss: The histone-binding protein RbAp48. *Sci Transl Med* 2013;5:200ra115.

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Hypertension in the Elderly May Be Associated with Progressive Brain Atrophy

ABSTRACT & COMMENTARY

By Michael T. Lin, MD

Assistant Professor of Neurology and Neurosciences, Weill Cornell Medical College

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

Synopsis: *Mid-life hypertension may be a risk factor for late-life brain atrophy and may exacerbate neurodegeneration. However, lowering blood pressure too aggressively in those with advanced atherosclerotic vascular disease may also result in late-life brain atrophy.*

Source: Jochemsen HM, et al. Blood pressure and progression of brain atrophy: The SMART-MR study. *JAMA Neurol* 2013;70:1046-1053.

HYPERTENSION IS WELL ESTABLISHED AS A RISK FACTOR FOR vascular brain lesions. There is also emerging evidence that abnormal blood pressure may be a risk factor for neurodegeneration. Several cross-sectional studies have shown that high blood pressure in midlife is associated with more brain atrophy later in life, whereas in late life, low blood pressure is associated with more brain atrophy. However, there is little prospective evidence relating blood pressure and brain atrophy.

The SMART-MR (Secondary Manifestations of ARTerial disease-Magnetic Resonance) study in the Netherlands is a prospective, cohort study on MRI brain changes in patients with arterial disease — coronary artery disease, cerebrovascular disease, peripheral artery disease, or abdominal aortic aneurysm. Of 1309 patients enrolled from 2001-2005, 663 had MRIs at baseline and during follow-up from 2006-2009. Average follow-up time was 3.9 years, average age was 57, and 81% were men. The ventricular fraction was used as a measure of subcortical brain atrophy, and the ventricular fraction increased with time in all blood pressure groups.

The key findings were 1) that in those with low diastolic blood pressure (DBP) at baseline, the increase in ventricular fraction was greater than in those with high DBP at baseline (this finding was driven primarily by patients with coronary artery disease); and 2) in those with normal or high DBP at baseline, the increase in ventricular fraction was less if DBP decreased over time than if it increased. Findings were adjusted for demographic factors, other vascular risk factors, alcohol consumption, baseline brain volume, and baseline burden of strokes and white matter lesions.

Of note, previous studies found that low blood pressure was associated with increased brain atrophy in late life, whereas this study observed low DBP to be associated with increased brain atrophy in mid-life in patients with arterial disease. The authors hypothesized that patients with arterial disease have early vascular aging with increased arterial stiffness, impaired endothelial function, and impaired cerebral autoregulation, making them more vulnerable to low blood pressure. Because this association of low blood pressure and increased brain atrophy occurred primarily in patients with coronary artery disease, baseline low DBP might represent poor cardiac output and insufficient brain perfusion. On the other hand, in those with higher DBP at baseline, the association of decline in blood pressure over time with less brain atrophy suggests that treating abnormally high blood pressure will be beneficial.

■ COMMENTARY

Strengths of this study include its prospective design and large numbers of patients. The poor follow-up rate is a weakness, and it is not clear whether these findings will generalize to patients without arterial disease. Nonetheless, many patients do have arterial disease, and this study further emphasizes the emerging understanding of how vascular risk factors are related to neurodegeneration as well as stroke. Practically, the study suggests that blood pressure should be treated in patients with hypertension, but should not be lowered further in patients who already have normal or low blood pressure, particularly in the setting of an acute intercurrent illness. ■

Relevance of Aquaporin 4 Antibodies in Longitudinally Extensive Transverse Myelitis

ABSTRACT & COMMENTARY

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Perumal is a consultant for Biogen Idec and Genzyme, and is on the speakers bureau for Teva and Biogen Idec.

Synopsis: *Based on a review of data from 76 adult patients with longitudinally extensive transverse myelitis, the authors highlight the importance of considering a differential diagnosis in those patients with longitudi-*

Stroke Alert: A Review of Current Clinical Stroke Literature

By Matthew E. Fink, MD, *Professor and Chairman, Department of Neurology, Weill Cornell Medical College, and Neurologist-in-Chief, New York Presbyterian Hospital*

Prehospital Triage to Primary Stroke Centers Improves Treatment

Source: Prabhakaran S, et al. Prehospital triage to primary stroke centers and rate of stroke thrombolysis. *JAMA Neurol* 2013;70:1126-1132. doi:10.1001/jamaneurol.2013.293.

The city of Chicago, IL, has 2.85 million residents who are ethnically diverse, and a single 911 emergency care provider system, the fire department, that takes all suspected stroke victims to the local hospitals. In 2009, the state of Illinois legislated that all suspected stroke patients be triaged to a designated primary stroke center certified by the Joint Commission, and the authors of this paper evaluated the impact of this policy in a multicenter cohort study that began in September 1, 2010 to August 31, 2011. Data were collected using the American Heart Association Get-With-The-Guidelines database and the main outcome measured was the fraction of patients with ischemic strokes who received intravenous tPA.

There were 1075 stroke and TIA patients admitted in the pretriage 6-month period, and 1172 patients in the post-triage period. Demographic characteristics (age, sex, risk factors) were similar for the two groups (mean age = 65 years; 53% female). Compared with the pretriage period, EMS services increased from 30.2% to 38.1%, and prenotification increased from 65.5% to 76.5%, after implementation of the new policy. Rates of intravenous tPA use were 3.8% before triage and 10.1% after triage ($P < 0.001$), and onset-to-treatment times decreased from 171.7 minutes to 145.7 minutes ($P < 0.03$). Symptomatic intracranial hemorrhage and in-hospital mortality were not significantly different between the two periods. Implementation of a triage policy for stroke patients, directing them to a specialized stroke center, was independently associated with increased tPA use for patients with ischemic stroke. ■

More Good News About the Mediterranean Diet!

Source: Psaltopoulou T, et al. Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. *Ann Neurol* 2013; online DOI: 10.1002/ana.23944.

In a comprehensive meta-analysis, the authors reviewed all published studies that looked at the association of adherence to the Mediterranean diet and the risk of stroke, depression, cognitive impairment, and Parkinson's disease. Studies were included if they provided a relative risk estimate for the use of the Mediterranean diet and the above outcomes, and further analysis was performed to assess the effects of high and moderate adherence. Twenty-two eligible studies were included (11 covered stroke, 9 depression, 8 cognitive

nally extensive transverse myelitis who are aquaporin 4 negative, yet who meet the diagnostic criteria for neuromyelitis optica.

Source: Kitley et al. Longitudinally extensive transverse myelitis with and without aquaporin 4 antibodies. *JAMA Neurol* Online doi:10.1001/jamaneurol.2013.3890.

Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system with selective involvement of the optic nerves and spinal cord. Classic NMO, or Devic's disease, is characterized by concurrent episodes of optic neuritis (ON) and transverse myelitis (TM). The current criteria for a diagnosis of NMO requires the presence of ON and TM and two out of the three supportive criteria: 1) MRI evidence of a contiguous spinal cord lesion extending three or more vertebral segments, 2) initial brain MRI not diagnostic for multiple sclerosis (MS), and 3) NMO IgG seropositivity. The identification of aquaporin 4 antibody (NMO IgG ab) led to an expansion of the disease phenotype, and, currently, patients with isolated ON or TM and who are NMO-antibody positive are classified as having an NMO-spectrum disorder.

In the present study, Kitley et al report their findings from analysis of data of 76 patients with longitudinally extensive transverse myelitis (LETM) in the context of the presence or absence of aquaporin 4 antibody. They report the similarities and differences between the two groups. They also describe the differential diagnosis of aquaporin 4 negative LETM patients who meet the criteria for a diagnosis of NMO as described above.

Seventy-six adult patients with LETM were selected from a database of patients at an outpatient neuroinflammatory specialty center and from inpatient records. Longitudinally extensive spinal cord lesions were those extending three vertebral segments or more. All of these patients had been tested for aquaporin 4 antibody at least

impairment, and 1 Parkinson's disease). High adherence to the Mediterranean diet was associated with reduced risk for stroke (relative risk [RR], 0.71; 95% confidence interval [CI], 0.43-0.83), depression (RR, 0.68; 95% CI, 0.54-0.86), and cognitive impairment (RR, 0.60; 95% CI, 0.43-0.84). Moderate adherence was also associated with reduced risk for depression and cognitive impairment; the effects on stroke were marginal. Regression analysis indicated that the effects on stroke of the Mediterranean diet were more robust among men compared to women. The effects of the diet on depression seemed independent of age. Data were inadequate to make any statements regarding the effects of the Mediterranean diet on Parkinson's disease. On balance, the diet had many favorable effects on the major diseases of the aging brain. ■

Combined Intravenous Therapy with tPA and Eptifibatide is Reported as Safe

Source: Pancioloi AM, et al. for the CLEAR-ER investigators. Combined Approach to Lysis Utilizing Eptifibitide and Recombinant Tissue Plasminogen Aactivator in Acute Ischemic Stroke – Enhanced Regimen Stroke Trial. *Stroke* 2013;44:2381-2387.

At the present time, there is no other treatment for acute ischemic stroke that has been proven safe and effective, other than intravenous tPA. Yet this therapy has many shortcomings, and intra-arterial therapy is still being developed and not yet proven to be more effective than intravenous tPA. In addition, activation of the endovascular team, in the best of hands, still takes hours, and it is likely that these delays are unavoidable. So the search continues for more effective intravenous therapy that can be administered quickly in the emergency department. The combination of intravenous tPA with a GPIb/IIIa inhibitor has been an attractive combination and was tested successfully in the CLEAR-ER trial, reported this month in *Stroke*. The investigators used a dose of IVtPA of 0.6 mg/kg followed by IV eptifibitide (bolus 135 mcg/kg and a 2-hour infusion at 0.75 mcg/kg per minute) compared to standard dose IVtPA (0.9 mg/kg). The randomization was 5:1, with the majority given combined therapy. Of 126 total subjects, 101 received combined therapy and 25 received standard dose IVtPA. Two patients (2%) in the combination group and three (12%) in the standard group had symptomatic intracranial hemorrhage. At 90 days, 49.5% of the combination group had a modified Rankin score of ≤ 1 or return to baseline, compared to 36% in the standard group (NS).

The study was powered and designed to determine safety, and the investigators proved their primary hypothesis that combination therapy is safe. It still remains to be determined if this combination therapy with be more effective than IVtPA alone, and this will require a phase 2-3 trial with 1:1 randomization. ■

twice. Forty-four out of 76 patients (58%) tested positive and 32/76 (42%) tested negative. When demographic data were analyzed, the aquaporin 4 positive group was older at disease onset (45.30 years vs 37.74 years), had a higher proportion of women (86% vs 44%), and had a greater frequency of patients with coexisting other autoimmune diseases (27% vs 3%) when compared to the aquaporin negative group. The severity of the initial presentation and recovery from the episode were similar between the two groups. On analysis of the MRI images, there was no difference in the mean length of the lesion between the two groups, but the conus was involved significantly more in the aquaporin negative group. On follow up, aquaporin positive patients were more likely to have a subsequent episode of central nervous system inflammation when compared to aquaporin negative patients (74% vs 31%, $P = 0.001$).

Among the 32 LETM patients who were aquaporin negative, alternate causes were explored. Six patients tested positive for MOG-Ab, and one each had the following diagnoses — CNS vasculitis; leptomeningeal syndrome associated with connective tissue disease; infections including tuberculosis, mycoplasma, Epstein-Barr virus, west Nile virus; paraneoplastic syndrome due to mesothelioma; and spinal cord infarction. Five patients had acute disseminated encephalomyelitis (ADEM), and three patients went on to have typical MS. In the remaining 10 aquaporin negative patients, despite extensive workup, no specific cause was found. Five of these patients had a history of at least one episode of optic neuritis, met the diagnostic criteria for classic NMO, and were considered seronegative NMO, and five patients were classified as idiopathic transverse myelitis.

The authors further performed an analysis of those LETM patients who met the diagnostic criteria for NMO. Thirty-five of 76 (46%) met the criteria for NMO. Out of

these 35 patients, 20 were aquaporin positive and 15 were negative. The authors point out that among the aquaporin negative patients who met the NMO diagnostic criteria, four patients were MOG-ab positive, three patients had ADEM, and three patients had MS.

■ **COMMENTARY**

The discovery of the highly specific serum aquaporin 4 antibody has expanded our knowledge of the immunopathogenesis of this group of disorders and has led to the identification of the NMO-spectrum of disorders. One of the important findings is that the aquaporin positive group was at a higher risk for subsequent relapses, which has implications for treatment. In determining prognosis in a patient with LETM, the presence of aquaporin 4 antibody predicts a higher risk of recurrence compared to a patient who does not have the antibody and, therefore, initiation of immunosuppressive treatment may be warranted at the time of the initial event in these patients.

The authors report that patients who fit the description of classic NMO, or Devic's disease, with the simultaneous occurrence of bilateral ON and TM, were likely to be aquaporin 4 negative. These patients tended to have a monophasic disease course. Enrolling these patients in clinical trials aimed at gauging the benefit of disease-modifying treatments in NMO-spectrum disorders could lead to inaccurate results.

Finally, the authors demonstrate that a significant proportion of aquaporin 4 negative LETM patients who met the criteria for classic NMO had an alternate diagnosis. This emphasizes the importance of excluding other etiologies before a diagnosis NMO is confirmed. ■

Dietary Association with Phenoconversion in Huntington's Disease Carriers

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

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

Synopsis: *Dairy intake, but not adherence to Mediterranean diet, was associated with increased risk of phenoconversion from mutation carrier to manifesting status in individuals with Huntington's disease.*

Source: Marder K, et al. Relationship of Mediterranean diet and caloric intake to phenoconversion in Huntington disease. *JAMA Neurol* 2013; online doi:10.1001/jamaneurol.2013.3487.

This study aimed to identify dietary risk factors in developing symptoms of Huntington's disease (HD) in individuals carrying the mutation for this disorder. The Prospective Huntington At Risk Observational Study (PHAROS) enrolled approximately 1000 individuals over almost 5 years. Participants were deemed at 50:50 risk of developing HD based on their family history, but 93% of those enrolled had non-specific or no motor abnormalities. The present study describes a subset of 211 individuals in this cohort who were known to have a significant expansion of CAG repeats in the huntingtin gene. Of these 211 individuals, 31 reached the point of at least 99% confidence in clinically definite HD using the Unified Huntington Disease Rating Scale (UHDRS), which was defined as phenoconversion for this study. Mean time to phenoconvert was 2.5 ± 1.7 years. Those who did not phenoconvert were followed for 4.3 ± 1.7 years, that is until the end of the study or until lost to follow up. All data were reported according to degree of adherence to the Mediterranean diet, in which fruits, fish, cereals, legumes, and vegetables are considered beneficial, and meat and dairy are considered detrimental. Mean age ranged from 42.8-44.1 years, with no significant difference between groups. Age and CAG repeat length were both significantly associated with increased risk of phenoconversion during the time period studied. Although Mediterranean diet adherence did not associate in a statistically significant manner with altered risk of phenoconversion, when broken into subcomponents, high dairy intake was significantly associated with a hazard ratio of 2.36 (1.00-5.57, $P = 0.05$) for phenoconversion.

■ **COMMENTARY**

HD is caused by a CAG repeat expansion, encoding glutamine, in the huntingtin gene. The expansion mutation is highly penetrant, is inherited in an autosomal dominant fashion, and thus allows identification of a high-risk cohort for developing HD that is ideal for studying factors that may associate with phenoconversion. In this regard, the PHAROS study and similar studies enrolling at-risk individuals for neurodegenerative diseases are invaluable. It is disappointing that the Mediterranean diet was not found to be associated with decreased risk of phenoconversion from HD carrier to manifesting status. A potential problem is that diet was self-reported and not validated, and the questionnaire was administered more than 30 months after study start up. The authors state that there was just 50-85% power to detect hazard ratios of 2.0 to 3.0, meaning that some signals may have been lost. The same type of dietary analysis has previously demonstrated a positive

association of the Mediterranean diet with decreased risk of Alzheimer's disease, mild cognitive impairment, Parkinson's disease, and cerebrovascular disease. However, after adjustment for age, caloric intake, and CAG repeat expansion, there was approximately a 2-fold greater risk of phenoconversion associated with higher dairy intake. A similar finding has been reported for risk of Parkinson's disease. The authors highlight the association of higher urate levels with lower dairy intake: Of note, higher urate levels have been associated with slower progression of HD over a 2.5 year period in one study and also with decreased risk and slower progression of Parkinson's disease (at least in men). Whether this is indeed a valid explanation or whether dairy intake is a surrogate marker for intake of another harmful substance (pesticides, hormones, or other chemicals used in the U.S. agricultural industry) remains to be seen. Nonetheless, this study supports an idea that is gaining traction — that genetic factors in neurodegeneration may be modulated by diet and/or lifestyle. This potentially presents ideal opportunities for developing preventive strategies. ■

Guillain-Barré in Children

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: *Guillain-Barré syndrome in children presents in a very similar way as in adults, and is treated with either intravenous immunoglobulin or plama exchange, even though there are no large randomized treatment trials of children.*

Source: Devos D, et al. Guillain-Barré syndrome during childhood: Particular clinical and electrophysiological features. *Muscle Nerve* 2013:48;247-251.

With an incidence of up to 2.4 cases per 100,000 in the general population, and up to 1.34 cases per 100,000 in children under 15 years of age, Guillain-Barré syndrome (GBS) is the most common cause of acute flaccid paralysis in previously healthy infants and children. Males are affected more often than females in all age groups, with approximately two-thirds of patients giving a history of antecedent respiratory or gastrointestinal tract infection, most frequently, campylobacter. Does childhood GBS present any specific characteristics that may be identified?

Medical records, including clinical, laboratory, and electrophysiological data, of all 19 children diagnosed with GBS between January 2000 and June 2011, at Nantes University Hospital, Nantes Cedex, France, were reviewed. All subjects fulfilled GBS diagnostic criteria. Electrodiagnostic studies were performed using standard techniques and, for children ≥ 3 years of age, compared to healthy adult values. For those < 3 years of age, normal nerve conduction velocities and motor amplitudes were set at 80%, and distal latencies at 120%, of adult values, to allow for the incomplete myelination of nerves in this age group. Based on electrodiagnostic findings, patients were grouped into either acute inflammatory demyelinating polyradiculoneuropathy (AIDP) or acute motor axonal neuropathy (AMAN). None presented with Miller-Fisher syndrome or acute motor and sensory axonal neuropathy (AMSAN).

Among the 19 children (13 boys and 6 girls), 12 were < 5 years of age, the youngest presenting at 18 months of age. Five children were between 5-10 years of age, and two were older, the oldest presenting at 13 years of age. Most (80%) developed GBS in the winter (n = 7) or spring (n = 8), with 68% (n = 13) reporting an antecedent infection within the prior 4 weeks, respiratory in 8, and gastrointestinal in 2. None reported receiving a vaccination in the prior 4 weeks, and all but one presented as AIDP, while one presented as AMAN. Limb weakness was reported in all patients, and 74% complained of limb pain. Walking ability was lost in 10, and another eight had ataxia. Facial weakness was present in only a single child, three had some cranial nerve involvement, and eight were found to have autonomic abnormalities, with persistent hypertension in five and urinary dysfunction in three. Areflexia or hyporeflexia was found in all. Cerebrospinal fluid cytoalbuminogenic dissociation was found in 17, and MRI scans of brain and spinal cord were normal in the four children so studied. Nerve conduction studies were never normal, even when performed within 3-6 days (n = 9), with decreased motor amplitudes, and prolonged distal and F wave latencies being the most frequent early abnormalities. Leg pain and gait abnormalities in children suggest GBS and electrodiagnostic studies are essential to confirm the diagnosis. Prognosis is generally excellent.

■ COMMENTARY

There are no large clinical therapeutic trials for childhood GBS, and current recommendations, including plasmapheresis or intravenous immune globulin, are based on studies with adults. As in adults, and even prior to initiating specific therapy, a decision must be made regarding admission to an intensive care unit and when to consider mechanical ventilation. Patients require close monitoring of motor strength, blood pressure, heart rate, and sphincteric and respiratory function, and any patient admitted with GBS should be evaluated frequently. Children with

reduced vital capacity (< 20 ml/kg), bulbar palsy, or rapidly progressive weakness should be admitted to a pediatric intensive care unit. ■

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

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- 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.

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CME Questions

1. Late-life cognitive decline may be caused by:
a. Alzheimer's disease.
b. vascular dementia.
c. Lewy body disease.
d. All of the above

2. Hypertension affects the brain in all of the following *except*:
a. risk factor for ischemic stroke.
b. risk factor for hemorrhagic stroke.
c. may induce an acute encephalopathy.
d. improves cerebral perfusion.

3. Diagnostic criteria for NMO-spectrum disorder include all of the following *except*:
a. the presence of optic neuritis.
b. the presence of transverse myelitis.
c. myelitis extending over at least three spinal cord segments.
d. All of the above

4. Which of the following correctly describes the risk of phenoconversion from carrier to manifesting disease phenotype in Huntington's disease genetic mutation carriers?
a. Phenoconversion risk is higher in individuals with lower CAG repeat number.
b. Younger age is associated with increased risk of phenoconversion.
c. Adherence to a Mediterranean diet with high levels of legumes, fruit, and vegetables significantly increases time to phenoconversion.
d. Higher diary intake is associated with increased risk of phenoconversion.

5. Children with Guillain-Barré syndrome:
a. present with leg pain and gait abnormalities.
b. usually have abnormal nerve conduction studies even early in the course of disease.
c. will usually show cerebrospinal fluid cytoalbuminogenic dissociation.
d. may be treated with intravenous immunoglobulin.
e. All of the above

6. Triage of stroke patients to a specialized stroke center does *not* improve outcomes.
a. True
b. False

7. High adherence to the Mediterranean diet results in a decreased risk of stroke and cognitive impairment.
a. True
b. False

8. Combined therapy with IVtPA and a GPIb/IIIa inhibitor for the treatment of acute ischemic stroke has been proven effective.
a. True
b. False

In Future Issues:

New Information Regarding Autism

Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

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.*

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Our Newest Pharmacologic Class for Treatment of Diabetes: SGLT2 Inhibitors

Source: Polidori D, et al. *Diabetes Care* 2013;36:2154-2161.

The role of the kidney in glucose regulation has been underappreciated. Although perhaps counterintuitive, after persistent exposure to elevated glucose levels in the glomerular filtrate presented to the proximal renal tubule, the kidney adapts by reabsorbing *increased* amounts of glucose, thereby *increasing* blood sugar. The sodium glucose cotransporter (SGLT2) receptor is the primary pathway for renal tubular glucose reabsorption; blockade of this receptor results in enhanced urinary glucose excretion. Currently, the only FDA-approved agent for blockade of the SGLT2 receptor is canaglifozin.

In addition to potent SGLT2 receptor blockade, it has been suspected that canaglifozin might affect intestinal absorption of glucose by its modest inhibition of intestinal SGLT1. Polidori et al tested the impact of canagliflozin SGLT1 inhibition by examining the rate of gastrointestinal glucose absorption in healthy volunteers following a 600-kcal mixed-meal tolerance test.

Canagliflozin produced a very modest reduction in glucose absorption over a 6-hour interval (about 6%). The effects were accentuated in the early postprandial intervals, indicating a slowed absorption of glucose that was not attributable to delayed gastric emptying. Blunting of early postprandial glucose absorption should have a favorable effect on postprandial glucose excursions in diabetics.

Although enhanced urinary glucose excretion is the primary mechanism of plasma glucose lowering by SGLT2 inhibitors, modest gastrointestinal SGLT1 inhibition also appears to impact postprandial glucose excursion. ■

Bariatric Surgery vs Intensive Medical Therapy for Diabetes

Source: Kashyap SR, et al. *Diabetes Care* 2013;36:2175-2182.

The benefits of bariatric surgery (BAS) are increasingly recognized for obese patients with type 2 diabetes mellitus (T2DM). Indeed, the mechanisms by which diversionary surgery (e.g., gastric bypass) produces such prompt and dramatic remission in diabetic patients are still being elucidated. Long-term observational data on BAS for persons with severe obesity (body mass index [BMI] > 40) confirm durable weight reduction, improved control of diabetes, and even suggest reduced mortality.

Few trials have directly compared the efficacy of BAS with intensive medical treatment (IMT). Kashyap et al randomized T2DM subjects (n = 60) with moderate obesity (mean BMI = 36) to one of two BAS interventions (gastric sleeve or gastric bypass) or IMT in the Surgical Therapy And Medications Potentially Eradicate Diabetes (STAMPEDE) trial. Currently reported data include outcomes at 24 months.

In essentially every category assessed, BAS patients had superior outcomes to IMT. No BAS-related deaths occurred. At 2 years, degree of A1c control, LDL, HDL, total cholesterol, triglycerides, and CRP were all more improved in the BAS patients than in the IMT patients.

When comparing outcomes in the two BAS groups, even though weight loss was similar between gastric sleeve and bypass surgery, the latter achieved greater improvements in truncal fat reduction, leptin, insulin sensitivity, beta cell function, and incretin responses. BAS is more effective for multiple metabolic markers than IMT over the long term in T2DM patients. ■

Psoriasis and Risk for New Onset Diabetes

Source: Khalid U, et al. *Diabetes Care* 2013;36:2402-2407.

Inflammatory disorders like rheumatoid arthritis (RA) and psoriasis (PSOR) have recently been confirmed to be risk factors for adverse cardiovascular (CV) events, although the precise pathways through which such risk occurs remain controversial. Some have even gone so far as to say that RA should be considered an independent CV risk factor of equal potency to the already registered risk factors like hypertension, history of premature cardiovascular death, etc. Since PSOR and RA share common inflammatory pathways, it's perhaps not surprising that both are associated with CV adversity.

To date, the relationship between PSOR and diabetes mellitus (DM) has been controversial. Since DM is a major contributor to CV events, if PSOR and

DM are related, that would account for some of the increased CV risk.

Khalid et al report on an analysis of the PSOR-DM relationship discerned through a 12-year follow-up of Danish persons ≥ 10 years (n = 4,614,807). They studied the incidence of new-onset DM in PSOR subjects vs controls. A graded linear association between PSOR and new onset DM was found. Compared to the reference population, the incidence of DM in persons with mild PSOR was almost doubled, and in severe PSOR, nearly tripled. ■

Osteoporosis: Are Two Drugs Better Than One?

Source: Tsai JN, et al. *Lancet* 2013;382: 50-56.

Most women today who are receiving pharmacotherapy for treatment of osteoporosis receive oral bisphosphonates (e.g., alendronate, risedronate). Other effective treatments, like teriparatide (TERI) and denosumab (DENO) are usually reserved for more severe cases, in some part because they require parenteral administration.

Even though osteoporosis treatments have shown risk reduction for fracture and improved bone mineral density (BMD), restoration of full bone integrity remains a challenge. As one of the few anabolic tools (as opposed to anticatabolic tools like bisphosphonates), some investigators have tried to augment the favorable activity of TERI by combination with bisphosphonates, but the results have been disappointing. Whether the addition of DENO to TERI might be beneficial was the subject of investigation by Tsai et al. Postmenopausal women with osteoporosis (n = 100) were randomized to DENO, TERI, or both for 6 months. The primary outcome of the study was improvement in BMD.

Combination TERI+DENO appeared to be synergistic, with improvements in BMD greater than either agent alone and arithmetically greater than the anticipated benefit of combined monotherapies. For example, BMD increases at the hip were 4.2% for TERI+DENO, 0.8% for TERI, and 2.1% for DENO. These data support the consideration of TERI+DENO in highest-risk patients, those unable to take other treatments, or patients who fail to respond to other regimens. ■

Long-Term Impact of Weight Management on Blood Pressure

Source: Tyson CC, et al. *J Clin Hypertens* 2013;15:458-464.

The weight loss maintenance (WLM) trial randomized adults (n = 741) with hypertension (HTN) and/or dyslipidemia — but without evidence of cardiovascular disease — to one of several weight loss management programs. Although the initial outcome reports from WLM addressed the relative efficacies of different weight loss strategies over time, this report stratified study participants into those who lost, maintained, or gained weight over the 5-year study period. Tyson et al compared blood pressure effects between the three categories of weight impact, irrespective of which particular method of weight loss had been applied.

At study end, the weight-stable group had gained 0.6 kg, as compared with a 9.1 kg increase in the weight-gain group, and a 7.1 kg decrease in the weight-loss group. The weight-stable and the weight-gain groups were noted to have similar increases in systolic blood pressure (SBP) over 5 years (SBP increase mean 4.2 mmHg), whereas the weight-loss group SBP was not statistically significantly changed.

In contrast to some other trials that report a "legacy effect" (prolonged beneficial impact of early intervention, even after the intervention has ceased), initial weight loss in WLM was not associated with favorable SBP effects if weight was regained. On the other hand, sustained modest weight reduction (< 10% of baseline BMI) had a sustained effect to maintain SBP. Although simply maintaining weight over the long term might appear to be a laudable goal, it is apparently insufficient to favorably affect SBP. ■

The WEAVE Study: Does Special Training in Domestic Violence Improve Outcomes?

Source: Hegarty K, et al. *Lancet* 2013; 382:249-258.

Intimate partner violence (IPV) is a public health problem that knows no boundaries of age, country of residence or origin, economic status, or education. Primary care clinicians, particularly family physicians, are often the first point of clinical contact for victims of IPV, but may lack confidence in their ability to identify and/or address IPV. Hegarty et al report on a trial from Australia in which women who screened positive for concerns about fear of their partner (n = 272) received care from family physicians who were randomized to receive special training in IPV or no intervention. The intervention group physicians participated in the Healthy Relationships Training program, which is intended to provide the ability to respond effectively to women who have experienced IPV and give brief counseling. The primary outcomes of the trial were changes in quality of life (as per the WHO QOL-BREF), safety planning and behavior, and mental health (as per the SF-12) at 1 year.

At 1 year, there was no difference in the primary endpoint between the intervention group and controls. A favorable impact on depression (a secondary endpoint) was seen. However, since the primary endpoint was not achieved, the potential for benefits on depression must remain considered as hypothesis generating. ■

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PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

More Side Effects of Fluoroquinolones Coming to Light

In this issue: New side effects of fluoroquinolones; probiotics and antibiotic-related diarrhea; prostate cancer risk and 5-ARIs; and FDA actions.

New study finds dysglycemia risk

Fluoroquinolones, such as levofloxacin, ciprofloxacin, and moxifloxacin, are useful broad-spectrum antibiotics, but they have been associated with tendinopathy, including tendon rupture and QT interval prolongation. Now, two new potential side effects are coming to light. In a new study from Taiwan, more than 78,000 diabetic patients who received fluoroquinolones were monitored for dysglycemia, including hyperglycemia and hypoglycemia. The study looked at users of levofloxacin, ciprofloxacin and moxifloxacin, cephalosporins, and macrolides. The absolute risk of hyperglycemia was 6.9 per 1000 for moxifloxacin and 1.6 for macrolides. The risk for hypoglycemia was 10.0 for moxifloxacin and 3.7 for macrolides. The adjusted odds ratios for hyperglycemia compared to macrolides were: moxifloxacin 2.48 (95% confidence interval [CI], 1.50-4.12), levofloxacin 1.75 (95% CI, 1.12-2.73), and ciprofloxacin 1.87 (95% CI, 1.20-2.93). For hypoglycemia, the adjusted odds ratios were moxifloxacin 2.13 (95% CI, 1.44-3.14), levofloxacin 1.79 (95% CI, 1.33-2.42), and ciprofloxacin 1.46 (95% CI, 1.07-2.00). The risk of hypoglycemia associated with moxifloxacin was even higher if patients were taking insulin. The authors suggest that fluoroquinolones, especially moxifloxacin, are associated with severe dysglycemia in diabetic patients and that clinicians should "prescribe quinolones cautiously" in diabetic patients (*Clin Infect Dis* published online August 14, 2013. DOI: 10.1093cid/cit439). In related news, the FDA is requiring labeling changes for fluoroquinolones regarding the risk of neuropathy. The FDA Drug Safety Communication states that "serious nerve damage potentially caused by fluoroquinolones may occur soon after these drugs are taken and may be permanent." The warning is for both oral and parenteral forms of the drugs, but not topicals. The FDA recommends that if a patient develops symptoms of peripheral neuropathy associated with a fluoroquinolone, the drug should be stopped immediately and the patient should be switched to a non-fluoroquinolone antibiotic. Further information can be found at the FDA's website at www.fda.gov/Safety/MedWatch. ■

Probiotics and antibiotic-related diarrhea

Probiotics may not prevent antibiotic-associated diarrhea (AAD), including *Clostridium difficile* infections. That was the finding of a randomized, double-blind, placebo-controlled trial in nearly 3000 inpatients aged ≥ 65 years who were exposed to one or more oral or parenteral antibiotics. Patients were randomized to a multistrain preparation of lactobacilli and bifidobacteria or placebo for 21 days. The rate of AAD was 10.8% in the probiotic group and 10.4% in the placebo group ($P = 0.71$). *C. difficile* was uncommon and occurred in 0.8% of the probiotic group and 1.2% of the placebo group ($P = 0.35$). The authors state that "we identified no evidence that a multistrain

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preparation of lactobacilli and bifidobacteria was effective in the prevention of AAD or CDD." (*Lancet* published online August 8, 2013. doi: 10.1016/S0140-6736(13)61218-0). An accompanying editorial wonders if this study can tip the balance of probiotic evidence, as it was a rigorously performed study vs previous small studies showing a positive effect. But, the current study used only two types of non-pathogenic bacteria (doi: 10.1016/S0140-6736(13)61571-8). Still, the cost effectiveness of routine probiotic use must be questioned based on this study. ■

Prostate cancer risk and 5-ARIs

The debate regarding 5-alpha reductase inhibitors (finasteride [Proscar] and dutasteride [Avodart]) and the risk of prostate cancer continues. Despite good evidence that the drugs reduce the overall risk of prostate cancer, there is also evidence that the drugs may increase the risk of high-grade prostate cancers (Gleason score 7-10). This was a finding of the Prostate Cancer Prevention Trial (PCPT) that was published in 2003. That finding was recently questioned in a study published in the *British Medical Journal* that found no risk of higher-grade prostate cancers (*BMJ* 2013;346:f3406, reported in the August *Pharmacology Watch*). Now, 10 years after the PCPT was originally published as an 8-year study, the 18-year follow-up has been published in the *New England Journal of Medicine*. Of the nearly 19,000 men who underwent randomization in the PCPT, prostate cancer was diagnosed in 10.5% of the finasteride group and 14.9% of the placebo group, a 30% reduction in the rate of prostate cancer (relative risk 0.70; 95% CI, 0.65-0.76; $P < 0.001$). But all of the reduction was in lower-grade prostate cancers. There was a slightly higher rate of high-grade cancer in the finasteride group (3.5% vs 3.0%, $P = 0.05$), but there was no difference in overall mortality. There was also no increase in mortality in men diagnosed with high-grade prostate cancer. The authors conclude that finasteride reduced the risk of prostate cancer by about one-third, and although high-grade cancer was more common in the finasteride group, there was no difference in overall mortality or survival after the diagnosis of prostate cancer (*N Engl J Med* 2013;369:603-610). Dutasteride was also studied in the REDUCE trial and similarly found lower rates of low-grade prostate cancers but increased rates of higher-grade cancers (*N Engl J Med* 2010;362:1192-1202). Some have argued that the higher rate of high-grade cancers is due to higher surveillance and "detection bias," but regardless of the cause, it is reassuring to know that there is no higher risk of mortality, at least in the PCPT. The FDA changed the labeling to both finasteride and dutasteride in 2011 regarding the increased risk of high-grade prostate cancers. ■

FDA actions

The FDA has issued a Drug Safety Communication regarding a case of progressive multifocal leukoencephalopathy (PML) in a patient who was taking fingolimod (Gilenya) for the treatment of multiple sclerosis. This is the first reported case of PML associated with fingolimod in patients who had not previously taken natalizumab (Tysabri). The patient, who lives in Europe, had been on the drug for about 8 months and had previously taken interferon beta-1a, azathioprine, and steroids. Novartis, the manufacturer of fingolimod, indicated it is possible that the patient had PML prior to starting the drug. PML is a rare neurologic disease caused by latent infection with the JC virus. It has been associated with immunosuppressive drugs, including natalizumab.

The FDA has approved a new topical agent to treat facial redness in adults with rosacea. Brimonidine, an alpha-2 agonist, is currently used as an ophthalmic preparation for treating glaucoma. The drug constricts dilated facial blood vessels for up to 12 hours. It is approved in a 0.33% topical gel that is applied once daily. Patients with depression, coronary artery disease, Raynaud's, or other conditions that may be exacerbated by an alpha agonist should use the drug with caution. Brimonidine gel is marketed by Galderma as Mirvaso.

The FDA has approved dolutegravir, a new once-daily HIV integrase inhibitor. It is the third integrase inhibitor on the market after raltegravir and elvitegravir. The drug is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infections in adults and children ≥ 12 years of age weighing at least 40 kg. It may be used in treatment-naïve patients or treatment-experienced patients, including those who have previously taken an integrase inhibitor. Approval was based on four trials in more than 2500 patients that showed efficacy in combination with other antiretrovirals. A fifth trial showed efficacy in HIV-infected children as young as 12 who had not taken an integrase inhibitor. Dolutegravir is marketed by ViiV Healthcare as Tivicay. ■