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INSIDE

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Does a Lower Vitamin D Level Increase the Risk of Relapse in Inflammatory Spinal Cord Disease?

ABSTRACT & COMMENTARY

By Jai S. Perumal, MD

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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 retrospective analysis of 77 patients with monophasic and recurrent inflammatory spinal cord disease, the authors report significantly lower vitamin D levels in patients with recurrent disease.*

Source: Mealy MA, et al. Low serum vitamin D levels and recurrent inflammatory spinal cord disease. *Arch Neurol* 2012;69:352-356.

The role of vitamin D in autoimmune diseases, including multiple sclerosis (MS), is increasingly recognized. There is growing evidence that lower levels are associated with a higher risk of developing MS and a higher risk of relapses in patients with established MS. Potential molecular mechanisms for the role of vitamin D in immune modulation also have been proposed. Although several studies have shown an inverse relationship between the risk of a relapse and vitamin D level in MS, its role in other central nervous system inflammatory diseases has not been reported. The present study explored the potential relationship between serum vitamin D level and the risk of recurrence in inflammatory spinal cord disease.

This retrospective analysis of 77 patients with inflammatory spinal cord disease included 44 patients with monophasic transverse myelitis and 33 patients with recurrent transverse myelitis. The recurrent group comprised 20 patients with neuromyelitis optica spectrum disorders (NMO), including those with concomitant SLE or Sjogrens disease, and 13 NMO IgG negative patients with recurrent transverse myelitis. The main objective of the study was to investigate a potential association between low serum vitamin D levels and recurrent spinal cord disease. For the analysis,

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patients were divided into those with monophasic transverse myelitis and recurrent disease. Along with serum 25-hydroxyvitamin D levels, data on patient characteristics (including age, sex, disability level, and the season when vitamin D levels were checked) were collected. In determining the association between vitamin D level and risk of recurrence, the analysis was adjusted for age, race, and sex, since these variables have been independently associated with vitamin D levels in earlier studies.

There were 44 patients in the monophasic transverse myelitis group and 33 patients in the recurrent group. The two groups were similar in several demographic characteristics. When compared with the patients in the monophasic group, patients in the recurrent group had significantly lower vitamin D levels. The mean (SD) 25-hydroxyvitamin D levels were 33 (11.1) ng/mL in the monophasic group and 18 (11.8) ng/mL in the recurrent group. At the Johns Hopkins Hospital laboratory where the analysis was done, vitamin D deficiency is defined as level < 20 ng/mL. After adjusting for demographic characteristics, patients with recurrent disease had a mean (SD) 25-hydorxy vitamin D level that was 10 (3.1) ng/mL lower than patients with monophasic disease.

■ COMMENTARY

There is growing evidence for an immune modulatory role of vitamin D in autoimmune disorders including multiple sclerosis. Several studies have investigated environmental risk factors for developing MS and reported an increased risk with lower vitamin D levels. Studies also have looked at the association between serum vitamin D levels and risk of a relapse in patients diagnosed with MS and found an inverse relationship. The present study is the first to explore a potential role for vitamin D in inflammatory spinal cord disease. The authors found significantly lower levels of vitamin D in patients with recurrent spinal cord disease compared to patients with monophasic disease. There are several limitations to this study, including the retrospective nature of the analysis and the variable times from disease onset when vitamin D levels were measured. Even though the analysis was adjusted for known variables that could have influenced vitamin D levels, there could have been other factors that influenced the disease course. Despite the limitations, this study does show significantly lower vitamin D levels in patients with recurrent disease compared to those with monophasic disease. This study warrants further prospective long-term studies, which might help establish an inverse causative association between lower vitamin D levels and the risk for a relapse and if intervention with vitamin D supplementation in those with low vitamin D levels decreases the risk of subsequent relapses in MS and patients with inflammatory spinal cord disease. ■

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Clinicopathological Features of Pure Autonomic Neuropathy

ABSTRACT & COMMENTARY

By Joshua Weaver, MD, and Norman Latov, MD, PhD

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Dr. Weaver reports no financial relationships relevant to this field of study. Dr. Latov has served as consultant to Grifols, Novartis, CSL Behring, Pfizer, Octapharma, Sanofi, Baxter Biotherapeutics, Elan Pharmaceuticals, Depomed, and Eisai Inc. He owns stock in Therapath LLC, and is beneficiary of a licensing agreement between Cornell University and Teva Pharmaceuticals for a patent related to the use of MSR1 antibodies in inflammatory diseases.

Synopsis: *The clinicopathological features of nine patients with pure autonomic neuropathy, with or without antiganglionic acetylcholine antibody, were assessed. There was considerable variability in the clinical manifestations, course, unmyelinated nerve fiber loss, and response to therapy.*

Source: Koike H, et al. The spectrum of clinicopathological features in

pure autonomic neuropathy. *J Neurol* 2012 DOI 10.1007/s00415-012-6458-x.

PURE AUTONOMIC NEUROPATHY IS RARE. IT SELECTIVELY AFfects only sympathetic and/or parasympathetic nerves, leaving motor and sensory functions intact. Known causes include diabetes, amyloidosis, Sjogren's syndrome, or cancer. Recent identification of antiganglionic acetylcholine receptor (AChR) antibody suggests an autoimmune etiology in some cases previously categorized as idiopathic.

Patient selection criteria included autonomic dysfunction, normal nerve conduction studies, and evidence for peripheral involvement including antiganglionic AChR antibody, denervation supersensitivity evidenced by pupillary or blood pressure responses, or sural nerve biopsy showing unmyelinated fiber damage. Patients with neurodegenerative or systemic disorders associated with autonomic neuropathy were excluded.

Of nine patients, six were men and three were women, with mean age of onset 50.4 years (± 18.1 SD). Four had antecedent events of fever and/or infection. Four had antiganglionic AChR antibodies. Orthostatic symptoms with syncope were the most common (in eight of the nine patients), followed by gastrointestinal symptoms, abnormal perspiration, urinary symptoms, mydriasis, dry mouth and eyes, and erectile dysfunction. Of those patients with antiganglionic AChR antibodies, autonomic symptoms tended to be more widespread with the notable exception of one patient who only had orthostatic symptoms.

Autonomic testing revealed orthostatic hypotension, reduced baseline plasma norepinephrine concentration, electrocardiographic abnormalities, supersensitive pupillary and blood pressure responses to the administration of catecholamines, decreased lacrimal and salivary secretions, and decreased perspiration in the majority of the patients tested.

Sural nerve biopsies done in six patients showed normal densities of large and small myelinated nerve fibers with no evidence of axonal degeneration, demyelination, or remyelination. Electron microscopic findings revealed decreased unmyelinated fiber densities in three patients, and two showed increased amount of collagen pockets indicative of decreased sympathetic efferents. Those with longer duration showed more unmyelinated fiber loss.

Of four patients who were negative for the antiganglionic AChR antibody, one spontaneously recovered without immunomodulatory treatment, one received intravenous methylprednisolone with complete recovery, and two showed initially spontaneous recovery with later recurrence of symptoms. Three of the patients with antiganglionic AChR antibody received intravenous immunoglobulin; one showed significant improvement; one showed mild improvement; and one did not improve.

■ **COMMENTARY**

This study documents the variable and overlapping clinical manifestations of patients with idiopathic or antiganglionic AChR antibody associated pure autonomic neuropathy. It also adds to the scarce literature on the pathological changes seen in these patients.[1-3]

The study raises a number of questions regarding both the diagnosis and treatment of pure autonomic neuropathy. Given that neurodegenerative central nervous system disease processes, such as multiple system atrophy, can present overlapping symptoms and signs, testing for antiganglionic AChR antibodies or sudomotor denervation could help distinguish between central and peripheral causes of dysautonomia.[4]

Some of the patients who were seronegative for ganglionic AChR antibodies had antecedent infections or an acute monophasic course, suggesting an autoimmune etiology as in an atypical form of Guillain–Barré syndrome. As such, immunomodulatory therapy may prevent irreversible ganglionic or small fiber damage. Further studies will be needed to identify those patients who are likely to respond to therapy. ■

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Inhaled Anesthetics Have Differential Experimental Effect on Memory Mechanisms

ABSTRACT & COMMENTARY

By Halinder S. Mangat, MD

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

Synopsis: *Isoflurane causes mitochondrial disruption and apoptosis in neuronal and hippocampal cells, and*

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*

Potent Antiplatelet Medication Causes Excessive Intracranial Bleeding

Source: Morrow DA, et al. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 2012;366:1404-1413. DOI: 10.1056/NEJMoa1200933.

VORAPAXAR IS A POTENT ANTIPLATELET MEDICATION WITH a novel action that works by inhibiting thrombin activation of platelets through the protease-activated receptor PAR-1. In an international trial of 26,449 patients who had a history of myocardial infarction, ischemic stroke, or peripheral arterial disease, vorapaxar 2.5 mg daily or placebo was randomly administered and patients were followed for a median of 30 months. The primary endpoint was a composite of death from cardiovascular causes, myocardial infarction, or stroke. However, after 2 years of enrollment, the safety monitoring board recommended termination of the study because of an excess of intracranial hemorrhage in the treated group, compared to placebo.

After 3 years of follow-up, the primary endpoint occurred in 1028 patients (9.3%) in the vorapaxar group and in 1176 patients (10.5%) in the placebo group (hazard ratio [HR] = 0.87; 95% confidence interval [CI] 0.80-0.94; $P < 0.001$). Moderate-to-severe bleeding occurred in 4.2% of patients treated with vorapaxar and 2.5% of those who received placebo (HR = 1.66; 95% CI, 1.43-1.94; $P < 0.001$) with an increase in the rate of intracranial hemorrhage in the vorapaxar group (1.0% vs 0.5%; $P < 0.001$). Although vorapaxar reduced the risk of secondary cardiovascular death and ischemic events, there was an increased risk of serious bleeding complications, including intracranial hemorrhage. ■

Bridging Therapy with Thrombolysis Appears to Be Safe and Effective

Source: Mazighi M, et. al. Bridging therapy in acute ischemic stroke. A systematic review and meta-analysis. *Stroke* 2012;43:1302-1308.

THERE ARE NO DEFINITIVE, RANDOMIZED, CONTROLLED clinical trials that have been reported regarding intravenous to intra-arterial bridging therapies with thrombolytics in patients with acute ischemic stroke. The in-

decreases memory consolidation in mice. Such effects are not seen with desflurane. This may impact selection of anesthetic agents for patients with Alzheimer's disease undergoing surgical procedures.

Source: Zhang Y, et al. Anesthetics isoflurane and desflurane differently affect mitochondrial function, learning, and memory. *Ann Neurol* 2012;71:687-698.

THERE ARE A LARGE NUMBER OF PATIENTS WITH ALZHEIMER'S disease (AD) who need and undergo surgery and anesthesia every year. Cognitive dysfunction has been reported postoperatively, placing patients with AD at increased risk. Therefore, these investigators studied cellular mechanisms that may play a role.

The authors studied caspase 3 activation, mitochondrial destabilization via reactive oxygen species (ROS) generation, and decreased levels of ATP. Hippocampal neurons and neuroblastoma cell line B104 were used. Behavioral testing in mice treated with isoflurane or desflurane was done using fear conditioning test.

Results showed isoflurane but not desflurane increased ROS generation, lowered mitochondrial membrane potential, increased caspase 3 activation, and lowered ATP levels. Many of these were mediated via opening of the mitochondrial permeability transition pore (mPTP). These effects were attenuated by cyclosporine A, a potent mPTP blocking agent. Behavioral testing showed decreased fear conditioning by isoflurane, likely from decreased memory consolidation.

The inference from this study is that isoflurane activates pathways that have been shown to be involved in the pathogenesis of AD and mimics failure of memory consolidation. This would make desflurane an anesthetic of better choice over isoflurane in patients with AD. Therefore, it would be important to emphasize the selection of anesthetic agents in patients with AD who undergo surgery.

■ COMMENTARY

Inhaled anesthetics, such as isoflurane and desflurane, affect cognitive function in humans. In a clinical trial involving 45 patients undergoing non-neurological surgery, isoflurane anesthesia was associated with higher impair-

vestigators performed a meta-analysis of 15 studies and used pooled data to determine if this therapy was effective and safe.

The pooled estimate for recanalization was 69.6% (95% CI, 63.9-75.0). Pooled estimates of clinical outcomes were 48.9% for favorable outcome, 17.9% for mortality, and 8.6% for symptomatic intracranial hemorrhage. In a meta-regression analysis, the shorter the mean time to intravenous treatment, the greater the recanalization rate and the lower the mortality. By comparing bridging therapy with published results of intravenous alteplase alone, bridging therapy was associated with a favorable outcome (OR = 2.26) with no difference in mortality or symptomatic intracranial hemorrhage. Time to intravenous treatment remains the most important determinant of outcome. ■

Elderly Women with Atrial Fibrillation Have a Greater Risk of Stroke Than Men

Source: Avgil Tsadok M, et al. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. *JAMA* 2012;307:1952-1958.

The reasons for the higher risk of stroke in women who have atrial fibrillation (AF), compared to men, is unclear, but under-treatment with warfarin has been suggested as a cause. In a population-based cohort study of patients 65 years or older admitted to the hospital with recently diagnosed AF in Quebec, Canada, from 1998-2007, administrative data were used to link hospital discharge diagnoses with warfarin use. The cohort comprised 39,398 men (47.2%) and 44,115 women (52.8%). On admission, women were older and had a higher CHADS score. At 30 days post-discharge from the hospital, 58.2% of men and 60.6% of women had filled a prescription for warfarin. Adherence to warfarin treatment was good in both male and female groups. Crude stroke incidence was 2.02 per 100 person-years in women (95% CI, 1.95-2.10) vs 1.61 per 100 person-years in men (95% CI, 1.54-1.69, $P < 0.001$) and was driven by the population of patients 75 years or older.

In a multivariate Cox regression analysis, women had a higher risk of stroke than men (HR = 1.14, 95% CI = 1.07-1.22, $P < 0.001$) after adjusting for comorbid conditions, individual components of the CHADS score, and warfarin treatment. The risk of stroke was higher in elderly women, compared to men, regardless of warfarin use, but the causes remain undetermined. ■

ment in cognitive tests compared to spinal anesthesia or desflurane.[1] The latter also has a lower incidence of cognitive impairment compared to propofol.[2]

The mechanisms behind such cognitive impairment may be numerous. Isoflurane causes increased generation of Aβ.[3] It has been shown to cause loss of neural stem cells and decreased neurogenesis in young rodents. These effects were not seen in adult rodents, implying an age-dependent mechanism.[4] In the opposite spectrum, it induces NMDA receptor NR2B subunit composition. This is responsible for LTP in hippocampal CA1 neurons and memory formation.[5] In another study, isoflurane induced cognitive impairment in mice with the lowest administered dose, but this did not persist at 56 hours post anesthesia.[6]

This study examines the effects of isoflurane and desflurane on some of the pathways that are involved in pathogenesis of AD. The test of memory used in this experiment is that of associative memory. A more elaborate test of memory would be a Morris water maze or a radial T-maze.

Caspase 3 activation and mitochondrial ATP depletion are important mechanisms. There are other pathological mechanisms that are also affected by isoflurane as above. The overall balance seems to indicate a detrimental effect on cognition. That the pathways of injury seem to be similar to those seen in AD should make the use of isoflurane a matter of caution in patients with AD. ■

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Variable 'Faces' of Facioscapulohumeral Muscular Dystrophy

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: *With the advent of specific genetic tests, atypical forms of facioscapulohumeral muscular dystrophy can be reliably diagnosed.*

Source: Hassan A, et al. Focal and other unusual presentations of facioscapulohumeral muscular dystrophy (FSHD). *Muscle Nerve* 2012; DOI: 10.1002/mus.23358.

EASILY IDENTIFIED IN ITS CLASSIC FORM, FACIOSCAPULOhumeral muscular dystrophy (FSHD) usually begins in the second or third decade with facial weakness impairing eye closure, whistling, or smiling; shoulder girdle weakness with marked biceps and triceps atrophy; and scapular winging with accompanying foot drop in the scapuloperoneal variant. What are the uncommon phenotypes? How might they present?

Retrospective review of the Mayo Clinic electronic database between 1996-2011 disclosed 139 cases of FSHD, all of whom had been seen at least once in the Neuromuscular Clinic, of which seven were atypical, yet genetically confirmed. Encompassing four men and three women, ranging in age of onset from 18-63 years, the presenting symptom comprised monomelic leg or arm weakness, in three and two patients respectively, while two patients presented with axial weakness. One patient reported a post-traumatic onset of trapezius weakness, but a positive family history raised suspicions of a possible alternate diagnosis. Family history of FSHD was documented in only two, but all gave a history of having a "weak family member." Initial examination confirmed weakness in five patients. Concomitant peripheral neuropathy and dyspnea were seen in one patient each, and two patients had S1 radicular pain with gastrocnemius atrophy on presentation. Serum creatine kinase was normal in two, and at most thrice the upper limit of normal, while needle electromyography revealed myopathic changes consisting of low amplitude, short-duration, motor unit potentials with an early recruitment pattern, initially in all but two patients, but developing eventually in all. Atypical presenting features of FSHD should be expanded to include monomelic weakness, axial weakness, and dyspnea.

■ **COMMENTARY**

With the advent of genetic testing for FSHD, the existence of atypical case presentations has been confirmed and includes FSHD with facial sparing, limb-girdle, or distal myopathy forms, or camptocormia (an abnormal posture with marked flexion of the thoracolumbar spine that abates when recumbent). Myoglobinuria is reported, but this patient had both a heterozygous mutation in calpain3 gene (CAPN3) exon 4, as well as an FSHD 4q35 deletion.[1] Epilepsy, speech delay, and mental retardation were seperately seen as the presenting complaints of different individuals in a single family,[2] and bilateral Coats' disease (idiopathic telangiectasia with intraretinal or subretinal exudation in the absence of retinal or vitreal traction) was reported in an aymptomatic 39 year-old woman.[3] Muscle pain, tongue atrophy, hearing loss, and cardiomyopathy are also reported. ■

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Clinical and Radiological Features Associated with Rhombencephalosynapsis

ABSTRACT & COMMENTARY

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

Synopsis: *This study presents a large group of new cases of rhombencephalosynapsis and carefully describes correlations to other associated morphological abnormalities as well as to outcomes.*

Source: Ishak GE, et al. Rhombencephalosynapsis: A hindbrain malformation associated with incomplete separation of midbrain and forebrain, hydrocephalus and a broad spectrum of severity. *Brain* 2012;135:1370-1386.

Rhombencephalosynapsis (RES) is a rare disorder of cerebellar formation, characterized by partial or complete loss of the vermis. As the name implies, in RES the left and right cerebellar hemispheres are fused. This is in contrast to other cerebellar vermian hypoplasia syndromes, such as Joubert syndrome or Dandy-Walker malformation, where the lobes remain separated. The pathogenesis is unknown, with most of the occurrences appearing de novo, but there is also evidence for autosomal recessive inheritance in a few cases.

RES can occur in isolation, but in Gomez-Lopez-Hernandez syndrome (GLH), RES is found together with parietal alopecia, trigeminal anesthesia, and can include dysmorphic facies, short stature, and skull shape abnormalities. Occasionally RES is found together with one or more features also found in VACTERL association (vertebral anomalies, anal defects, cardiovascular anomalies, tracheoesphageal fistula, renal/radial anomalies, and limb defects).

This study by Ishak et al describes 42 new cases of RES. Ten cases were found via review of the Seattle Children's Hospital imaging database of more than 15,000 reports by searching for RES. An additional five cases were found in the database after a re-review of 56 MRIs with aqueductal stenosis. Twenty-seven cases were obtained via referral from outside clinicians. The authors qualitatively evaluated several anatomical characteristics of the MRIs: the infratentorium for cerebellar size, shape, morphology and vermian deficiency pattern; the posterior fossa for size and fourth ventricle shape; the superior cerebellar peduncles for orientation and presence of ectopic tissue; the superior medullary velum for thickness and presence of ectopic tissue; the posterior commissure for thickness; the cerebral aqueduct for patency; the pons for size; the inferior and superior colliculi for fusion or presence of ectopic tissue; the supratentorium for interhemispheric fusion, migrational disorders, presence of the septum pellucidum, corpus callosal integrity, fusion of fornices, integrity of mammillary bodies, pituitary gland, and olfactory bulbs; and presence of ventriculomegaly.

Cases were grouped into four clinical categories 1) a diagnosis of GLH, 2) at least one VACTERL feature but not GLH, 3) RES which occurred together with holoprosencephaly who were not in the first two groups, and 4) RES not otherwise specified. Finally, cases were assessed a clinical outcome rating of mild, moderate, or severe based on an intake form and records review.

Whereas the existing literature typically has described RES as either partial or complete, the authors were able to identify a spectrum in the pattern and severity of cerebellar fusion. In general, mild cases involved only the posterior vermis (in approximately 30%), while the anterior vermis and then the nodulus were also fused or absent in the moderate (20%) and severe cases (20%) respectively, with complete absence of all parts of the vermis (20%) or an atypical pattern (10%) in the remaining cases.

The severity of RES and severity of outcome were correlated. In addition, outcomes were worse in the clinical categories of either RES with holoprosencephaly and RES with VACTERL compared to those in the GLH or RES NOS category. However, the severity of RES did not correlate with clinical category. There were no significant sex-specific differences.

The authors describe several non-vermian abnormalities found in conjunction with RES. The posterior fossa was generally small, and small size correlated with severity of RES. The pons was variably flat, hypoplastic, or had a compressed appearance. In complete RES, the cerebellum tended to be hypoplatstic. In contrast, in more than half the cases of partial RES, the cerebellum extended upward through the supratentorial notch while inferior cerebellar ectopia (i.e., Chiari I malformation) was present in about a third of the cases. This was attributed to a normal cerebellar size in an otherwise small posterior fossa.

Approximately half of the cases had aqueductal stenosis, which was strongly associated with fusion of midbrain structures at the level of the stenosis such as the inferior or superior colliculi. This fusion occurred across the midline, in the craniocaudal direction, or both. Aqueductal stenois was also associated with superior cerebellar peduncles that were too close to the midline. Nineteen of the cases with aqueductal stenosis required shunting due to obstructive hydrocephalus. Ventriculomegaly was not correlated with the severity of RES; however, it was correlated with worse clinical outcome.

The study identified the presence of several forebrain abnormalities. More than half the cases had an absent septum pellucidum and three quarters had a thin, dysplastic, or otherwise abnormal corpus callosum. Many cases had absent mammillary bodies (30%), fused fornices (50%), or absent olfactory bulbs (30%). Although these types of forebrain abnormalities can be secondary to a destructive process resulting from hydrocephalus, the authors attribute the findings to a developmental defect, given that these features were also seen in those without hydrocephalus. In addition, prenatal imaging was available for some cases, which confirmed the abnormality prior to the development of hydrocephalus.

Seven patients had cortical abnormalities: two with bilateral frontal polymicrogyria with heterotopia, two with periventricular heterotopia, and three with holoprosencephaly. Two of the subjects had an unusual form of holoprosencephaly with fusion of occipital lobes, thalami, basal ganglia, and hypothalamus.

■ COMMENTARY

The new cases of RES described in this study provide

significant new information on this rare disorder. Patients with aqueductal stenosis should be carefully evaluated for RES, with particular attention given to the posterior vermis so as not to miss the mild cases. The authors suggest that RES also should be sought in those with cerebellar herniation, a small cerebellum, and an absent septum pellucidum. Although it seems intuitive that those with severe or complete RES, or those with concomitant holoprosencephaly or VACTERL features will have worse outcomes, sampling bias somewhat limits the prognostic data. This is particularly true in mild cases, given we have limited information about the overall prevalence of RES.

Although the etiology is not known, RES clearly is not a disorder limited to the cerebellum, and this careful description of the spectrum of RES will help to identify additional cases. This hopefully will lead to an increased understanding of RES, including the identification and development of appropriate genetic mouse models of abnormal dorsal midline signaling. ■

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:

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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!

CME Questions

1. Vitamin D deficiency is associated with:

a. a higher rate of MS relapses.
b. a higher rate of relapses in myelitis.
c. Both of the above

2. The clinical features of pure autonomic neuropathy include all of the following *except*:

a. orthostatic syncope.
b. constipation.
c. bladder disorders.
d. dry mouth and eyes.
e. numbness and paresthesias.

3. Some inhalation general anesthetic agents may cause prolonged memory impairments.

a. True
b. False

4. Unusual presentations of facioscapulohumeral muscular dystrophy include:

a. monomelic weakness.
b. axial weakness.
c. dyspnea.
d. All of the above
e. None of the above

5. Which of the following structures can be abnormal in cases of rhombencephalosynapsis?

a. Olfactory bulbs
b. Corpus callosum
c. Pons
d. Septum pellucidum
e. All of the above

6. Vorapaxar, a potent antiplatelet medication, is safe and effective for secondary prevention of ischemic cardiovascular events.

a. True
b. False

7. Intravenous-to-arterial thrombolytic bridging therapy is less effective and more dangerous than intravenous therapy alone.

a. True
b. False

8. Women with atrial fibrillation have a higher risk of stroke than men.

a. True
b. False

In Future Issues:

Mechanisms of Apraxia

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.*

Critical Drug Shortages Are on the Rise

In this issue: Drug shortages; metformin and cancer prevention; migraine prevention guidelines; and FDA actions.

What's causing the shortages?

Drug shortages are happening at an unprecedented rate. Just in the last 2 months, we have seen shortages of diazepam, methotrexate, leucovorin, naltrexone, oxymorphone, mitomycin, fentanyl, metoclopramide, pantoprazole, ondansetron, and dexamethasone among others. What is causing the shortages and is there any end in sight? Although it seems like a new problem, we have seen an increasing number of drug shortages going back to 2005. But while there were about 50 drug shortages in the mid 2000s, last year more than 260 drugs were in short supply, including many commonly used and clinically vital drugs. The cause of these shortages is multifactorial. Some sources in the industry blame price controls, especially for generic drugs. Medicare and Medicaid impose strict controls on most generics, squeezing pharmaceutical companies' ability to make a profit. Some companies have simply decided to drop out of the generic market altogether. Others blame fewer manufacturers. The *Wall Street Journal* reports that there were 26 vaccine makers in the United States in 1967, while currently there are only six. But even these issues do not explain the severe shortages we are seeing. Most experts agree the two major issues causing the current shortages are supply chain disruptions, especially disruptions in raw materials, and problems with manufacturing, especially safety issues, which force the FDA to shut down production of a product line or an entire factory. Safety shutdowns are the most common cause of shortages of sterile injectable drugs. But in other cases, companies limit production themselves when they either have an absolute shortage of raw materials or they decide to divert limited supplies of raw materials from less expensive generics to more expensive brand-name drugs. This is a current issue with some of the attention deficit hyperactivity disorder drugs that have been in short supply for several months. Last month, the FDA initiated a series of steps to increase the supply of critically needed cancer drugs, including allowing the importation of drugs in shortage from Europe and elsewhere. The agency is also fast tracking approval of new manufacturers for short-supply drugs like methotrexate. The FDA, as well as the Obama administration, is also requiring companies to give early warning of potential drug shortages. Finally, the Justice Department will aggressively pursue possible incidences of collusion or price gouging among drug distributors who may be taking advantage of shortages. Despite these steps, there will likely be no short-term easing in drug shortages. ■

Does metformin prevent cancer?

Last month, we reported that low-dose aspirin may be protective against some cancers. Now it looks like metformin may have similar properties. A new study from the American Association for Cancer Research suggests that the diabetes drug may improve the prognosis with pancreatic cancer. In a retrospective study, researchers at the University of Texas studied 302 patients with diabetes and

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pancreatic cancer; 117 of these patients were taking metformin. The 2-year survival rate was 30.1% for the metformin group vs 15.4% for the non-metformin group ($P = 0.004$; x^2 test). The pancreatic cancer patients on metformin lived 4 months longer than non-metformin patients (15.2 months vs 11.1 months). The authors suggest that metformin should be evaluated as a supplemental therapy for patients with pancreatic cancer (*Clin Cancer Res* published online March 31, 2012; doi: 10.1158/1078-0432.CCR-11-2994). Data presented at the AACR meeting in Chicago earlier this year suggest that the drug may also be beneficial for men with prostate cancer, although further research is needed. ■

Migraine prevention in adults

The American Academy of Neurology and the American Headache Society have published their new guideline on pharmacologic treatment for episodic migraine prevention in adults. The highest level (Level A) recommendation for prevention was given to antiepileptic drugs, including divalproex sodium, sodium valproate, and topiramate. Other level A drugs included the beta-blockers metoprolol, propranolol, and timolol as well as the triptan frovatriptan, but this last agent is just for short-term use for menstrually associated migraine (MAM) prevention. Level B drugs included the antidepressants amitriptyline and venlafaxine, the beta-blockers atenolol and nadolol, and the triptans naratriptan and zolmitriptan (also only for short-term MAM prevention). Possibly effective medications included lisinopril, candesartan, some beta-blockers, and carbamazepine. There was little or no evidence to support any other drugs including selective serotonin reuptake inhibitors, calcium channel blockers, or acetazolamide. Drugs that should not be offered include lamotrigine and clomipramine. In a separate section on nonsteroidal anti-inflammatory drugs (NSAIDs) and complementary treatments, Petasites hybridus (butterbur) were given recommended status, while NSAIDs were listed as probably effective (*Neurology* published online April 24, 2012; doi: 10.1212/WNL.0b013e3182535d20, and doi: 10.1212/WNL.0b013e3182535d0). ■

Fibrate use in elderly patients

Fibrate use in elderly patients is associated with worsening renal function and increased risk of hospitalization, according to a new study. Researchers reviewed data from a large Canadian database of patients over the age of 65 who were started on a fibrate or ezetimibe (comparator). Many patients in both groups were also on statins. Fibrate users were more likely to be hospitalized for an increase in serum creatinine (odds ratio [OR] 2.4 [95% confidence interval (CI), 1.7 to 3.3]). Fibrate patients were also more likely to consult a nephrologist, but there was no difference in all-cause mortality or need for dialysis. In a subgroup of 1110 patients in which serum creatinines were available at baseline and within 90 days, 9.1% of fibrate users and 0.3% of ezetimibe users had an increase in serum creatinine of 50% or more (OR 29.6 [CI, 8.7 to 100.5]). The risk was higher if patients had chronic kidney disease. The authors conclude that new fibrate use in the elderly is associated with an increase in serum creatinine and a small increase in hospitalization and nephrology consultation (*Ann Intern Med* 2012;156:560-569). ■

FDA actions

The FDA has approved the first PDE5 inhibitor in a decade for the treatment of erectile dysfunction (ED). Avanafil (Stendra) joins sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) as the fourth drug approved for this indication. Avanafil will be marketed as having a shorter onset and a shorter half-life than the other drugs in this class. Men should take avanafil as needed 30 minutes before sexual activity with onset of action as quickly as 15 minutes. The approval was based on three randomized, placebo-controlled clinical trials of 1267 patients with ED in which 57% of men achieved erections sufficient for intercourse, up from a baseline of 15% (compared to 27% with placebo). Like other PDE5 inhibitors, avanafil should not be taken with nitrates. Commonly reported side effects include headache, flushing, nasal congestion, nasopharyngitis, and back pain. Avanafil will be marketed by VIVUS of Mountain View, California, as Stendra.

The FDA is requiring new labeling on finasteride — Merck's testosterone blocker used for the treatment of benign prostatic hypertrophy (5 mg as Proscar) and male pattern baldness (1 mg as Propecia). The new labeling addresses sexual adverse events such as libido disorders, ejaculation disorders, orgasm disorders, and even male infertility and poor semen quality. Some of these issues, such as libido disorders and ejaculation disorders, may continue after stopping the drug, while infertility and poor semen quality improve or normalize after discontinuation. The labeling change is based on event reports filed with the FDA, although a clear causal relationship has not been made. Still, the agency is recommending that a discussion of the risks and benefits of finasteride include the possibility of sexual side effects. ■

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.*

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Statins and Dyslipidemia: Should we be Looking Beyond LDL?

Source: Boekholdt SM, et al. *JAMA* 2012;307:1302-1309.

TREATMENT OF DYSLIPIDEMIA WITH STATINS produces consistent, durable lowering of low-density lipoprotein cholesterol (LDL-C), which is associated with substantial reductions in myocardial infarction and stroke. Other lipoprotein markers — in particular apolipoprotein B (apoB) and non-high-density lipoprotein cholesterol (non-HDL-C) — are also associated with vasculopathy. Indeed, the putative pathogenetic role of apoB has garnered some enthusiasm from lipidologists who encourage more routine measurement and modulation of apoB as a primary goal.

Risk reduction with statins is imperfect. That is, substantial risk for vascular events and death exists even with excellent LDL-C reduction. Might levels of apoB or non-HDL-C in patients already on a statin help us to discern which ones remain at high risk?

Boekholdt et al performed a meta-analyis of statin trials (n = 62,154) that included data on apoB and non-HDL-C, examining the relationship between on-treatment levels of LDL-C, apoB, non-HDL-C, and cardiovascular outcomes. For each increase of one standard deviation in the level of any of these three markers, the risk for a cardiovascular event increased, and to a very similar degree (13%-16% increase per standard deviation). However, when comparing the three markers with one another, non-HDL-C showed a statistically significantly greater association with increased risk than the other two markers. The authors suggest that based on this and other data, stronger consideration should be given to promoting non-HDL-C as an important target for reduction in subjects with dyslipidemia. ■

When Thiazides are Associated with Hyponatremia

Source: Rastogi D, et al. *J Clin Hypertens* 2012;14:158-164.

CONTROL OF HYPERTENSION IS REWARDED with important reductions in myocardial infarction, stroke, and cardiovascular death. Yet, the job of hypertension control is daunting, since on a worldwide basis it is estimated that more than one-fourth of all adults have hypertension! It has been known for more than 5 decades that thiazides can produce electrolyte disarray, including hypokalemia, hyponatremia, and hypomagnesemia, any of which can result in serious adverse effects and/or hospitalization. Rastogi et al performed a retrospective case-control study to elucidate risk factors for hyponatremic hospital admission while on a thiazide diuretic. They compared 1802 cases of hospitalized thiazide-associated hyponatremia with controls (n = 9003).

Risk for hyponatremic hospitalization doubled with each 10-year increase in age. The only other statistically significant associations were coadministration of an ACE inhibitor and concomitant hypokalemia. The coadministration of an ARB had a strong trend toward increased risk, but was marginally non-significant. Patients with comorbid diabetes, dyslipidemia, and gastroesophageal reflux disease were also more likely to be admitted for hyponatremia. Hopefully, recognition of these associations will assist clinicians to prevent hyponatremia, or at least detect its presence earlier. ■

Broadening Perspectives on Maintaining Healthy Erectile Function

Source: Meldrum DR, et al. *Int J Impot Res* 2012;24:61-68.

FOR MORE THAN A DECADE, IT HAS BEEN recognized that nitric oxide (NO) is critical in the attainment and maintenance of an erection. Accordingly, pathology that induces endothelial dysfunction, and hence impaired generation of NO, is consistently associated with erectile dysfunction (ED). Traditional cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, and cigarette smoking are each associated with increased prevalence and incidence of ED. Increases in oxidative stress appear to be a common denominator for many of the paths that lead to endothelial dysfunction.

Additional lifestyle factors that have been associated with endothelial dysfunction include insufficient exercise, obesity, and specific dietary components (e.g., high carbohydrate diet).

Many of the risk factors associated with endothelial dysfunction are modifiable. For instance, obesity is associated with insulin resistance, which lowers vascular NO. Exercise improves NO levels systemically. A high-fat intake may in-

crease oxidative vascular wall stress.

There is some literature support for multifactorial intervention in men with ED to help restore sexual function. Meldrum et al suggest a list of factors that might favorably impact endothelial health (and hence, sexual functionality), including: 1) maintenance of healthy weight; 2) regular aerobic exercise; 3) low-fat, low glycemic-index diet; 4) smoking cessation; 5) alcohol moderation; 6) folate and omega-3 fatty acid supplementation; and 7) ARB rather than ACE treatment of hypertension. ■

Cancer Risks Associated with Diagnostic X-rays

Source: Linet MS, et al. *CA Cancer J Clin* 2012;62:75-100.

Within a few years after the initiation of diagnostic X-rays, toxic effects were noted, including increased risk for skin cancer, leukemia, dermatitis, and cataracts. In this early period, doses of X-ray, especially from fluoroscopy, were high. Protective devices for patients as well as persons occupationally exposed to diagnostic radiation demonstrably reduced such adverse consequences.

The dose of radiation that is required to induce cancer is not clearly known. However, populations who have been exposed to calculable levels of radiation through wartime exposure (i.e., Japanese atomic bomb survivors) and subjects receiving radiation therapy help us to predict a dose-response relationship. It is not yet clear to what extent the high-dose radiation exposure and subsequent development of cancer reflects cumulative lower dose exposures. Nonetheless, because radiation toxicity may be related to total exposure, peak exposure, or both, radiation from commonly used diagnostic procedures has stimulated concern.

For instance, a CT of the abdomen, commonly used investigationally for persons with acute or chronic abdominal pain, incurs the same amount of radiation exposure as 750 chest X-rays. Linet et al quote recent estimates suggesting that the 70 million CT scans performed each year in the United States could lead to 29,000 additional cancers.

The authors recommend a number of steps to reduce unnecessary radiation exposure, including 1) learning about radiation doses associated with various imaging techniques, 2) consideration of imaging without radiation (i.e., ultrasound, MRI), and 3) avoidance of elective X-rays in pregnant women. ■

The REDEEM Trial: Dutasteride for Management of Localized Prostate Cancer

Source: Fleshner NE, et al. *Lancet* 2012; 379:1103-1111.

Prostate cancer (PCA) comprises 25% of all newly diagnosed cancers in men in the United States. PCA chemoprevention trials with 5-alpha-reductase inhibitors have had mixed results. The first major PCA prevention trial with finasteride showed a 25% decrease in total PCA vs placebo, but an increase in more aggressive (high Gleason score) cancers. A similarly designed large prevention trial with dutasteride again found a 25% decrease in total PCA, but there was an increase in more aggressive cancers (albeit not statistically significant in this trial). Based on these mixed results, clinicians have been reluctant to use 5-alpha-reductase inhibition for PCA prevention.

Might 5-alpha-reductase inhibitors prove more useful for treatment of PCA rather than prevention? The REDEEM trial randomized men with localized PCA (n = 300) who had elected active surveillance for their disease to dutasteride 0.5 mg/d or placebo. At 3 years time, the risk of PCA progression was reduced by 38% in men on dutasteride.

Because dutasteride is generally well tolerated, men with non-aggressive Gleason scores (six or less) who might otherwise select active surveillance for localized disease may have reduced risk of disease progression with the addition of dutasteride. ■

Amantadine for Traumatic Brain Injury

Source: Giacino JT, et al. *N Engl J Med* 2012;366:819-826.

In young adults (age 15-30), traumatic brain injury (TBI) is the most common cause of death and disability. As many as one in seven TBI hospital admissions leaves the hospital in a vegetative state. Amantadine (AMT) has achieved some popularity for inclusion in pharmacotherapy regimens for disorders of consciousness, although the mechanism by which AMT effects positive change is uncertain. Certainly it has been shown that AMT blocks N-methyl-D-aspartate, and is an indirect agonist of dopamine, but what these pharmacologic effects do to enhance outcomes is unclear. In any case, initial trials have supported its use, and a major observational trial indicated better outcomes in TBI for persons who had received AMT.

Patients who had sustained TBI (n = 184) and who were either vegetative or minimally conscious for at least 1 month (and no longer than 16 weeks) after injury were randomized to AMT or placebo. AMT was administered initially at 100 mg b.i.d., and titrated to 200 mg b.i.d. if the Disability Rating Scale had not shown improvement. The course of treatment was 4 weeks in duration, and patients were monitored for 2 weeks after continuation of treatment.

AMT treatment was associated with statistically significantly better functional recovery outcomes than placebo. AMT is not a new medication, so its adverse effects profile, characterized by mild, transient adversities, is well known. These data support the inclusion of AMT in the pharmacologic regimen of serious TBI. ■

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