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INSIDE

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Sodium Channel Mutations in Idiopathic Small Fiber Neuropathy

ABSTRACT & COMMENTARY

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

Dr. Weaver is a Clinical Neurophysiology Fellow, and Dr. Latov is Professor of Neurology and Neuroscience, and Director of the Peripheral Neuropathy Clinical and Research Center, Weill Cornell Medical College

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, 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: *Gain-of-function mutations in a voltage-gated sodium channel, $Na_v1.7$ that renders dorsal root ganglion neurons hyperexcitable, are present in approximately one quarter of patients with idiopathic small fiber neuropathy. Such mutations might be responsible for the degeneration of small nerve fibers and associated symptoms.*

Source: Faber CG, et al. Gain of function $Na_v1.7$ mutations in idiopathic small fiber neuropathy. *Ann Neurol* 2012;71:26-39.

SMALL FIBER NEUROPATHY (SFN) IS A RELATIVELY COMMON DISORDER THAT AFfects small somatic and/or autonomic nerves. Known causes include diabetes, vitamin B12 deficiency, and Sjogren's syndrome among others, although the condition is idiopathic in most cases.

$Na_v1.7$ is a voltage-gated sodium channel expressed in the ganglia and axons of small-diameter peripheral nerves. Gain-of-function mutations in the SCN9A gene encoding $Na_v1.7$ have been associated with Paroxysmal Extreme Pain Disorder (PEPD)[1] or Inherited Erythromelalgia (IEM),[2] while loss of function mutations of $Na_v1.7$ are associated with insensitivity to pain.[3]

Patients with idiopathic SFN were recruited from the Masstricht University Medical Center in the Netherlands. Eligibility criteria included normal nerve conduction studies and reduced intraepidermal nerve fiber density on skin biopsy. Patients with an associated systemic disorder were excluded.

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Complementary DNA from exons in the SCN9A gene coding for $Na_v1.7$ from each subject was amplified, sequenced, and compared to controls to identify sequence variations. Functional analysis of the $Na_v1.7$ mutation was done via voltage clamp (to assess channel function) and current clamp (to assess dorsal root ganglion neuron firing properties). Of 28 patients tested, eight (28.6%) were found to have mutations in the SCN9A gene. All were heterozygous for the mutation, and all mutations were missense. All eight patients reported skin hyperesthesia and burning feet, and seven patients reported autonomic dysfunction with dry eyes, dry mouth, orthostatic dizziness, and palpitations.

Seven unique mutations were identified (two unrelated patients shared the same mutation); all were gain of function mutations rendering dorsal root ganglion hyperexcitable.

■ COMMENTARY

This is the first study to show that missense mutations in the voltage-gated sodium channel $Na_v1.7$ (distinct from those found previously associated with IEM and PEPD) are present in a large proportion of patients with idiopathic SFN.

The study paves the way for a better understanding of the etiology of SFN, and may lead to better treatment options for patients suffering with pain. As these investigations proceed, additional pain syndromes are being identified and linked to $Na_v1.7$ mutations,[4,5] and at least one study has shown phenotypic variability for a given mutation within the same family.[6] Treatment options recently have focused on medications that affect sodium channel functioning, such as mexiletine (a lidocaine derivative),[7] and new sodium channel blockers are being developed that may more effectively treat these pain syndromes.[8]

Limitations of Faber et al's study include possible selection bias and the lack of diversity among the cohort (all Dutch Caucasians from the same academic center) making it harder to relate to the general population. Larger studies with more diverse patient populations need to be done to confirm and expand these findings. Studies evaluating $Na_v1.7$ mutations in the general population (including asymptomatic patients and those that meet less strict criteria of small fiber neuropathy) will be needed to assess the prevalence and degree of penetrance of $Na_v1.7$ mutations. Future drug trials assessing the efficacy of sodium channel blockers in treating patients with $Na_v1.7$ mutations and SFN will be of particular interest. ■

References

1. Fertleman CR, et al. SCN9A mutations in paroxysmal extreme pain disorder: Allelic variants underlie distinct channel defects and phenotypes. *Neuron* 2006;52:767-774.
2. Yang Y, et al. Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. *J Med Genet* 2004;41:171-174.
3. Goldberg Y, et al. Loss-of-function mutations in the Nav1.7 gene underlie congenital indifference to pain in multiple human populations. *Clin Genet* 2007;71:311-319.
4. Dabby R, et al. Chronic non-paroxysmal neuropathic pain — Novel phenotype of mutation in the sodium channel SCN9A gene. *J Neurol Sci* 2011;301:90-92.
5. Hoeijmakers JG, et al. Small nerve fibres, small hands and small feet: A new syndrome of pain, dysautonomia and acromesomelia in a kindred with a novel Nav1.7 mutation. *Brain* 2012 Jan 26 [Epub ahead of print].
6. Estacion M, et al. Intra- and interfamily phenotypic diversity in pain syndromes associated with a gain-of-function variant of Nav1.7. *Mol Pain* 2011;7:92.
7. Choi JS, et al. Mexiletine-responsive erythromelalgia due to a new Nav1.7 mutation showing use-dependent current fall-off. *Exp Neurol* 2009;216:383-389.
8. Goldberg YP, et al. Treatment of Nav1.7-mediated pain in inherited erythromelalgia using a novel sodium channel blocker. *Pain* 2012;153:80-85.

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Sensory Neuronopathy in Patients with Recessive Polymerase γ Mutations

ABSTRACT & COMMENTARY

By Russell L. Chin, MD

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

Synopsis: *Detailed neuropathological investigation of patients with sensory neuronopathy and polymerase γ mutations revealed evidence of posterior column atrophy in spinal cord sections and marked neuronal cell loss with severe mitochondrial biochemical abnormalities (involving respiratory chain complexes I and IV) in the dorsal root ganglia.*

Source: Lax NZ, et al. Sensory neuronopathy in patients harbouring recessive polymerase γ mutations. *Brain* 2012;135:62-71.

IN THIS STUDY, 12 PATIENTS WITH AUTOSOMAL RECESSIVE POLYmerase γ (POLG) mutations were studied. Eleven of the patients underwent clinical and neurophysiological assessment. Two patients expired and had extensive neuropathological studies of the spinal cord (both patients) and dorsal root ganglia (one patient). Age of disease onset was typically in the second or third decade with a few reporting onset in their early 40s. Five had documented peripheral neuronopathy at presentation with sensory ataxia. Three had features of pure sensory neuropathy (SN) with two also showing evidence of motor involvement. Clinically progressive external opthalmoplegia and ptosis were a common finding in all patients.

Electrodiagnostic studies revealed sensory or mixed sensorimotor findings. Macro-EMG in two patients showed increased fiber density and median macro motor unit potential amplitude, consistent with motor neuronopathy. Four patients also showed evidence of proximal myopathy.

Muscle biopsies, obtained in 11 patients, revealed secondary mitochondrial DNA changes with evidence of mitochondrial DNA deletions in association with focal cytochrome c oxidase (COX) deficiency. Analysis of the spinal cord revealed severe myelin loss in the posterior columns (particularly in the fasciculus gracilis), diminished complex I activity in the posterior horn neurons, and a reduction in the posterior horn interneuron population.

Dorsal root ganglion (DRG) cell density was reduced significantly and the neurons also were smaller when compared with controls. Immunohistochemistry demonstrated reduced expression of protein subunits comprising complexes I and IV of the respiratory chain. Mitchondrial DNA copy number analysis showed DRG neurons with dramatically reduced MT-ND4 and MT-ND1 copy numbers, suggesting a decrease in the number of wild-type mitochondrial and also absolute mitochondrial DNA copy number.

The investigators conclude that neuronal dysfunction and death in the dorsal root ganglia results in loss of their central axonal branches and ascending fibers in the posterior fasciculus and posterior horn neurons in the spinal cord. In this study, SN was not the sole clinical feature, and the age of onset and additional features (chronic progressive external opthalmoplegia, ptosis, dysarthria and epilepsy) were clues to a mitochondrial process.

■ COMMENTARY

The mitochondrial genome is maintained and replicated by the POLG protein. The catalytic domain of this protein is encoded by the POLG gene located on chromosome 15q25. Numerous mutations have been mapped to this gene and are associated with a broad spectrum of neurodegenerative diseases (http://tools.niehs.nih.gov/polg), including Alpers-Huttenlocher syndrome in infancy, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, and mitochondrial recessive ataxic syndrome. SN has been reported as part of the SANDO clinical triad (sensory ataxia associated with dysarthria and opthalmoparesis) and also as a presenting feature of the mitochondrial disease.[1]

SN (or ganglionopathy) refers to primary disease of sensory cell bodies in the dorsal root ganglia.[2] These are some of the longest nerves in the body (> 2 m in tall individuals) with the nerve extending from periphery to the cell bodies (near the intervertebral foramen), entering the spinal cord (specifically the fasciculus gracilis) via the posterior roots, and ascending to its first synapse at the cranio-cervical junction.

Well-recognized causes of SN include paraneoplastic disease (e.g., anti-Hu antibodies associated small cell bronchogenic carcinoma), antimitotic treatments (e.g., cisplatin, carboplatin, oxaliplatin), HIV infection, Sjögren syndrome, vitamin B6 toxicity, anti-disialosyl antibodies (e.g., GD1b antibodies), and celiac disease. A significant percentage of SN cases remain idiopathic. A non-length dependent distribution of sensory loss (with upper limb, trunk, or facial involvement) and almost pure and severe electrophysiologic sensory involvement are characteristic of SN. Patients may have diffuse sensory loss with resulting ataxia and pseudoatheoid movements. Tendon reflexes are reduced or absent.[3]

The molecular mechanisms behind SN are poorly understood and pathologic data are limited given the absence of simple, non-traumatic methods of studying the DRG. Primary degeneration of sensory nerves has been demonstrated pathologically in paraneoplastic and HIV-related SN. In Sjögren's syndrome, mononuclear inflammatory cell infiltrates around individual sensory ganglion cells undergoing degeneration have been noted. GD1b antibodies are reported to bind to the surface of sensory ganglion neurons and paranodal myelin in the ventral and dorsal roots.[4]

The DRG findings in this study provide welcome and intriguing information that could advance our understanding of the mechanisms of SN associated with other (more

Stroke Alert: A Review of Current Clinical Stroke Literature

By Matthew E. Fink, *MD, Interim Chair and Neurologist-in-Chief, Director, Division of Stroke & Critical Care Neurology, Weill Cornell Medical College and New York Presbyterian Hospital*

The DRAGON Score: A Measure to Simplify the Prediction of Outcome After IV Thrombolysis

Source: Strbian D, et al. Predicting outcome of IV thrombolysis-treated ischemic stroke patients. The DRAGON score. *Neurology* 2012;78:427-432.

OF ALL ISCHEMIC STROKE PATIENTS TREATED WITH IV ALteplase (tPA), only about half will achieve recanalization and have a good outcome (mRS 0 to 2). In addition, risk factors for intracerebral hemorrhage and other poor outcomes have been identified and will influence outcomes. The current investigators used known risk factors and applied them to a cohort of 1319 ischemic stroke patients admitted to the Helsinki University Central Hospital, and performed a regression analysis to determine which risk factors had the greatest predictive value. Patients with basilar artery occlusion were excluded. They then developed a score that could be easily based on identifiable risk factors.

The DRAGON score (0–10 points) consists of (hyper)**D**ense cerebral artery sign/early infarct signs on admission CT scan (both = 2, either = 1, none = 0), pre-stroke modified **R**ankin Scale (mRS) score > 1 (yes = 1), **A**ge (> 80 years = 2, 65-79 years = 1, < 65 years = 0), **G**lucose level at baseline (> 8 mmol/L [> 144 mg/dL] = 1), **O**nset-to-treatment time (> 90 minutes = 1), and baseline **N**ational Institutes of Health Stroke Scale score (> 15 = 3, 10-15 = 2, 5-9 = 1, 0-4 = 0).

Proportions of patients with good outcome (mRS score 0–2) were 96%, 88%, 74%, and 0% for 0-1, 2, 3, and 8-10 points, respectively. Use of this score may aid the decision-making process regarding use of IV tPA or more aggressive intra-arterial therapies. ■

The SEDAN Score: A Measure to Simplify the Prediction of Intracerebral Hemorrhage After IV Thrombolysis

Source: Strbian D, et al. Symptomatic intracranial hemorrhage after stroke thrombolysis: The SEDAN Score. *Ann Neurol* 2012: Accepted on-line DOI: 10.1002/ana.23546.

THE SAME LEAD AUTHOR, AS ABOVE, DEVELOPED A SIMILAR scale to help predict the risk of brain hemorrhage after administration of IV tPA. The risk factors were identified in three Swedish cohorts of ischemic stroke patients and regression analysis performed.

The SEDAN score (0 to 6 points) comprises baseline blood **S**ugar (glucose) [8.1-12.0 mmol/L (145-216 mg/dL)=1; >12.0 mmol/L (> 216 mg/dL) = 2], **E**arly infarct signs (yes = 1) and (hyper)**D**ense cerebral artery sign (yes = 1) on admission CT scan, **A**ge (> 75 = 1), and **N**IH Stroke Scale on admission (> 9 = 1). Absolute risk for symptomatic intracranial hemorrhage in the derivation cohort was: 1.4%, 2.9%, 8.5%, 12.2%, 21.7%, and 33.3% for 0, 1, 2, 3, 4, and 5 score points, respectively.

The use of the DRAGON and SEDAN scores may aid the frontline clinician in making rapid decisions regarding thrombolytic therapies in patients with acute ischemic stroke. ■

common) conditions, for which treatment options are currently limited. ■

References

1. Fadic R, et al. Sensory ataxic neuropathy as the presenting feature of a novel mitochondrial disease. *Neurology* 1997;49:239-245.
2. Camdessanché JP, et al. The pattern and diagnostic criteria of sensory neuronopathy: A case-control study. *Brain* 2009;132:1723-1733.
3. Kuntzer T, et al. Clinical features and pathophysiological basis of sensory neuronopathies (ganglionopathies). *Muscle Nerve* 2004;30:255-268.
4. Griffin JW, et al. Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjögren's syndrome. *Ann Neurol* 1990;27:304-315.

Electromyography in Anticoagulated Patients

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: *Needle EMG is safe in patients who are taking therapeutic doses of antiplatelet or anticoagulant medications.*

Source: Boon AJ, et al. Hematoma risk after needle electromyography. *Muscle Nerve* 2012;45:9-12.

Patients on antiplatelet agents or anticoagulants often require needle electromyography (EMG), and the risk of hematoma formation and uncontrolled bleeding is often raised. Many EMG laboratories avoid studying such patients.[1] No evidence-based guidelines exist, although it is generally recommended that EMG not be performed if the platelet count is lower than 50,000/mm^3, the internationalized normalized ratio (INR) is greater than 3, or the partial thromboplastin time (PTT) is greater than twice the control value.[2] What are the evidence-based facts? Is there an increased risk of hematoma formation? Should deep muscles be avoided?

In this Mayo Clinic-based, prospective, case-controlled study, 205 patients referred for EMG were divided into three groups, those on (1) warfarin, (2) clopidogrel or aspirin or both, and (3) neither of the above (who served as controls). In each group, at least 100 muscles, arbitrarily defined as "muscles-of-interest," were studied, including the cervical, thoracic, or lumbosacral paraspinal muscles, flexor pollicis longus, flexor digitorum longus, tibialis posterior, and iliopsoas. Following needle EMG, ultrasound of the muscles-of-interest was performed to determine the presence or absence of hematoma formation. Potential blood-thinning agents, EMG needle size, electromyographer experience level, and time-lapse from EMG to ultrasound also were documented. Statistical analysis was performed using the chi-square test, with $P < 0.05$ considered significant.

No hematomas were detected among 70 control patients, in whom 100 muscles-of-interest were studied. Among 78 aspirin/clopidogrel patients and 58 warfarin patients, in whom 116 and 107 muscles-of-interest, respectively, were studied, only one hematoma each was seen on ultrasound, in the tibialis posterior and flexor pollicis longus, respectively. In both cases, the hematomas were asymptomatic. In both instances, a 50-mm (26-gauge) needle had been used, in the former by the EMG fellow, in the latter by the attending electromyographer. Telephone follow-up 24 hours later confirmed that the patients remained asymptomatic, with no evidence of bruising or swelling at the site. No significant difference in bleeding rate was found between the three groups ($P = 0.43$), with only two hematomas found within 323 muscles studied, or 0.62% among the entire study population. Among the warfarin and aspirin/clopidogrel groups, bleeding risk was 0.93% and 0.85%, respectively. Though caution always must be exercised, needle EMG, even of deep muscles, appears safe to perform among patients taking therapeutic doses of antiplatelet agents or anticoagulants. Should the INR be > 3.0, discretion remains the better part of valor.

■ **COMMENTARY**

As an interesting and relevant finding, the authors note that ultrasound of the flexor digitorum longus and tibialis posterior muscles, the only ones to develop hematoma formation, incidentally revealed the presence of multiple veins within and surrounding the muscle. Since it is impossible to determine the presence and location of veins in advance of a routine EMG study, their penetration with the EMG needle may predispose these particular muscles to bleeding. It behooves electromyographers to be aware of this anatomy, and a lighter touch might be warranted when studying these muscles, particularly in anticoagulated patients. ■

References

1. Gruis KL, et al. Survey of electrodiagnostic laboratories regarding hemorrhagic complications from needle electromyography. *Muscle Nerve* 2006;34:356-358.
2. Bolton CF, et al. Minimum standards for electromyography in Cananda: A statement of the Canadian Society of Clinical Neurophysiologists. *Can J Neurol Sci* 2000;27:288-291.

The Specificity of Anti-aquaporin-4 Antibodies for Neuromyelitis Optica Is Further Validated

ABSTRACT & COMMENTARY

By Susan Gauthier, DO, MS

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Gauthier reports she receives research support from EMD Serono, Biogen-Idec, and Novartis Pharmaceuticals, and is on the speakers bureau for Biogen-Idec and Teva Neurosciences.

Synopsis: *This study validated that anti-aquaporin-4 antibodies are highly specific (99.8%) for Devic's disease and related disorders when tested in a large series of miscellaneous autoimmune and non-autoimmune systemic diseases.*

Source: Dellavance A, et al. Anti-aquaporin-4 antibodies in the context of assorted immune-mediated diseases. *Eur J Neurol* 2012;19:248-252.

The identification of anti-aquaporin-4 antibodies (NMO-IgG) has dramatically changed our approach to neuromyelitis optica (NMO) or Devic's disease, but the specificity of NMO-IgG for Devic's disease has been primarily derived from studies involving central nervous system (CNS) demyelinating diseases and healthy

controls. The aim of this study by Dellavance et al was to determine if NMO-IgG could be detected in non-neurologic immune-mediated systemic diseases. The rationale for this study is based upon two important observations: 1) various neurological syndromes, including CNS demyelination, can occur in systemic autoimmune diseases, such as systemic lupus erythematosus (SLE) and Sjögren's disease (SS), and 2) other auto-antibodies (ANA, anti-SS-A/Ro, and anti-SS-B/La) can be present in patients with Devic's disease suggesting the presence of systemic autoimmunity.

In this study, sera from 673 patients with various clinical conditions were randomly selected from three different sources (a department of Neurology, a department of Rheumatology, and a large clinical laboratory) and were divided into five groups. The specimens from neurological diseases included Group I with 47 Devic's patients and Group II which consisted of patients with multiple sclerosis (MS, 13 pts), longitudinally extensive transverse myelitis (LETM, 17 pts), isolated recurrent optic neuritis (5 pts), and spinal cord inflammatory/vascular diseases (6 pts). The rheumatologic specimens were identified as Group III (220 pts) and included sera from patients with the following diseases: SLE, SS, rheumatoid arthritis, systemic sclerosis, primary biliary cirrhosis, and myasthenia gravis. Group IV (35 pts) included patients with either hepatitis C or other acute viral diseases. Lastly, Group V consisted of 300 specimens from miscellaneous diseases, which were randomly obtained from a clinical laboratory. NMO-IgG was detected in the following: 40/47 Devic's (85.1% sensitivity), 1/13 MS (7.7%), 10/17 (58.8%) LETM, and 3/5 (60%) of patients with isolated recurrent optic neuritis. NMO-IgG was not found in any of the other patient groups. The overall specificity of NMO-IgG for Devic's and related disorders (LETM and isolated recurrent optic neuritis) was calculated to be 99.8%. Neurological manifestations were present in 5/85 SLE and 5/15 SS patients.

■ COMMENTARY

This study further validates anti-aquaporin-4 antibody as a specific marker for NMO or Devic's disease. The strength of this study lies in the large number of samples for which NMO-IgG was tested, but a flaw is the lack of clinical information in nearly half of the samples. Unfortunately, there were very few patients with neurological manifestations of a systemic autoimmune disease and having a larger cohort of these patients would have strengthened the findings. The specificity of NMO-IgG for Devic's disease (and related disorders) reported in this paper is in line with the known specificity from the original studies. NMO-IgG's target antigen is the aquaporin-4 water channel, in which titers have been found to correlate with NMO disease severity and treatment response; this suggests a direct relationship of the antibody to the pathogenesis of the disease.[1] Through the development of this antibody, Devic's is no longer considered a clinical variant of MS but a distinct disease. Importantly, with the advent of this antibody, the spectrum of Devic's can be identified and treatment algorithms can be modified to target B-cell/antibody reduction as opposed to T-cell based therapies that are utilized to treat MS. ■

Reference

1. Takahashi T, et al. Anti-aquaporin-4 antibody is involved in the pathogenesis of NMO: A study on antibody titre. *Brain* 2007;130(Pt 5);1235-1243.

Cognitive, Motor, and Brain Volume Deficits in Children with Growth Hormone Deficiency

ABSTRACT & COMMENTARY

By Sotirios Keros, MD, PhD

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

Synopsis: *Children with isolated growth hormone deficiency have lower IQ, worse motor skills, and several brain regions with smaller volumes than carefully selected controls.*

Source: Webb EA, et al. Effect of growth hormone deficiency on brain structure, motor function, and cognition. *Brain* 2012;135(Pt 1): 216-227.

GROWTH HORMONE (GH) AND INSULIN-LIKE GROWTH FACtor-1 (IGF-1) receptors are located throughout the brain, and are particularly expressed in regions related to learning and memory, such as the hippocampus. GH deficiency leads to smaller brain volumes in animals and contributes to decreased neuronal and glial proliferation. There are a variety of existing studies in both animals and humans that suggest GH deficiency and low IGF-1 levels are correlated with decreased cognitive ability. In addition, exogenous growth factor has been noted to improve IQ in small-for-gestational-age children. The human cognitive data, however, are somewhat contradictory and are limited due to heterogeneous patient groups with multiple etiologies of GH deficiency, non-standard definitions, and wide ranges of the ages of included subjects. Few human studies have examined the role of GH deficiency on brain structure or on motor function.

In the present study, the authors prospectively recruited children aged 5-11 with isolated growth hormone deficiency (IGHD) (n = 15), but with otherwise normal endocrine function. To control for any confounding effects of short stature, children with idiopathic short stature (n = 14) were used as controls. IGHD was defined as a level below 6.7 mcg/L on tests of GH release in children with a height and growth velocity less than two standard deviations below the mean. Idiopathic short stature was defined as a height less than 2 standard deviations below the mean but with normal height velocity and a GH level of greater than 10 mcg/L with stimulation testing and normal brain MRIs and IGF-2 concentrations. In addition to GH levels, IGF-1 and its primary binding protein, insulin-like growth factor binding protein 3 (IGFBP-3), were measured. All patients had extensive cognitive testing, including Full-Scale IQ (Wechsler Intelligence Scales for Children 4th ed. or a subset of the Weschsler Preschool and Primary Scale of Intelligence 3rd ed.). Memory, as well as attention and executive function, were assessed using the NEPSY-II battery and Cambridge neuropsychological test automated battery (CANTAB). Parental checklists were used to assess behavioral differences, and motor skills were assessed using the Movement Assessment Battery for Children Test. 1.5 tesla brain MRIs were obtained to assess for the volume of total brain, basal ganglia, thalamus, hippocampus, and corpus callosum using Freesurfer software analysis. Diffusion tensor fractional anisotropy and mean diffusivity maps were extracted and calculated from the MRI data as markers of white matter tract integrity.

Webb et al discovered several statistically significant differences in the IGHD group compared to controls. Blood levels of IGF-1 and IGFBP-3 were lower in the IGHD group. Full-Scale IQ was lower in IGHD children (92.8 vs 102.6; $P = 0.01$). Lower scores in Verbal Comprehension Index and Processing Speed Index also were noted. Total motor scores were lower in IGHD, specifically in the subcategories of manual dexterity and balance. Total brain volume was similar in both groups, but the volumes of the splenium of corpus callosum, right palladum, right hippocampus, and left thalamus were lower in the IGHD children. Fractional anisotropy of the corpus callosum, as well as the bilateral corticospinal tracts, were lower in the IGHD group, while left corticospinal tract diffusivity was higher. There were no statistically significant differences in behavioral scales or in attention and memory tasks.

Looking only within the IGHD group, the authors found that several findings were significantly correlated when using appropriate statistical analyses. IQ and verbal performance were positively correlated with IGFBP-3 levels. IGF-1 levels also were correlated with verbal scores, but not with IQ. The volume of the splenium of the corpus callosum correlated with verbal scores was well as IGF-1 levels, while white matter integrity of the entire corpus callosum was correlated with IQ. Bilateral thalami and left pallidum volumes were correlated with IGFBP-3. Left and right corticospinal tract fractional anisotropy was correlated with an aiming and catching assessment, while the right corticospinal tract was also correlated with balance. Total movement scores were correlated with the volume of the splenium, left and right pallidum, and left thalamus.

■ COMMENTARY

Although this study has a relatively small sample size, it is well-controlled with tightly defined inclusion criteria and controls. The authors find a clinically relevant reduction of 10 IQ points in children with IGHD. IQ and other cognitive measures were also related to decreased IGF-1 or IGFBP-3 levels as well as the volume of several brain regions. It is a novel finding that children with IGHD have decreased motor function, and that this decreased motor function is correlated to differences in the brain volume of deeper brain structures as well as white matter differences in the corticospinal tract. Children with GH deficiency commonly have other endocrinological abnormalities, which complicates the interpretation of some previous studies.

The GF/IGF-1 axis is involved in several intracellular signaling pathways, primarily stimulating cell growth and preventing apoptosis. IGH and IGF-1 receptors are expressed in the embryonic rodent brain, and IGF-1 pathways regulate prenatal and postnatal differentiation of inhibitory interneurons, which are critical for normal development. This study reinforces that GH treatment should not

necessarily be reserved for short stature, but it remains to be seen whether early treatment with GH in deficient children can prevent cognitive and motor deficits. ■

CME Objectives

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

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

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
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4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
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CME Questions

1. Which of the following statements about small fiber neuropathies (SFN) is *not* true?

a. SFN may be caused by diabetes.
b. The most common symptom of SFN is pain.
c. Nerve conduction studies are abnormal in SFN.
d. SFN is diagnosed by skin biopsy.
e. SFN may affect autonomic function.

2. Sensory neuronopathy is associated with which of the following conditions?

a. Polymerase γ mutations
b. Sjogren's syndrome
c. HIV infection
d. Paraneoplastic anti-Hu disease
e. All of the above

3. The risk of bleeding into muscles after needle electromyography is significantly increased in patients taking therapeutic doses of:

a. aspirin.
b. clopidogrel.
c. warfarin.
d. All of the above
e. None of the above

4. Anti-aquaporin-4 antibody can be found in which of the following clinical conditions?

a. Systemic lupus erythematosus
b. Sjögren's disease
c. Myasthenia gravis
d. Longitudinally extensive transverse myelitis
e. Rheumatoid arthritis

5. Isolated growth hormone deficiency in children is associated with decreased total brain volumes.

a. True
b. False

6. Which of the following risk factors increase the likelihood of poor outcomes in patients with ischemic stroke?

a. Early infarct signs on CT scan
b. Age > 80 years
c. NIS Stroke Scale > 15
d. Elevated blood glucose
e. All of the above

In Future Issues: **Headaches and Migraine**

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.*

Dutasteride and Low-Risk Prostate Cancer

In this issue: New treatment for prostate cancer; avastin and breast cancer; new CMS disclosure rule; and FDA actions.

Adjunct to active surveillance?

Low-risk prostate cancers are nonpalpable, low-grade tumors associated with prostate-specific antigen (PSA) levels less than 10 ng/mL. For these patients, active surveillance is an option, allowing a period of observation to help decide who should be treated or not treated. Generally, this involves repeated biopsy sampling with the option to treat more aggressively if higher grade tumors are found. Active surveillance is more frequently utilized in Europe and Canada than in the United States, where more aggressive treatment is the norm. A new study from the U.S. and Canada investigates the safety and efficacy of the 5α-reductase inhibitor dutasteride on prostate cancer progression in men with low-risk disease. A total of 302 men ages 48-82 with low-volume Gleason score 5-6 prostate cancer were randomized to dutasteride 0.5 mg per day or placebo. Patients were followed for 3 years with prostate biopsies done at 18 months and 3 years with the primary endpoint being time to prostate cancer progression. After 3 years, 38% of men in the dutasteride group and 48% of men in the control group had prostate cancer progression (hazard ratio 0.62; 95% confidence interval [CI], 0.43-0.9; $P = 0.009$). Dutasteride was not associated with an increase in adverse events. There were no prostate cancer-related deaths and no incidence of metastatic disease in either group. The authors conclude that "dutasteride could provide a beneficial adjunct to active surveillance for men with low-risk prostate cancer" (*Lancet* published online January 23, 2012). An accompanying editorial points out the appeal of a safe oral drug that can prevent prostate cancer progression, but the author cannot recommend the drug based on this study due to several limitations — short duration, no evidence of mortality difference, and, most importantly, the risk that 5α-reductase inhibitors may decrease the volume of low-grade, but not high-grade, cancers. (*Lancet* published online January 23, 2012). This study comes at a time when physicians are actively debating the pros and cons of screening for prostate cancer. The recently published PLCO trial showed that PSA screening does not lower the risk for death from prostate cancer while there is evidence of harm (*J Natl Cancer Inst* 2012;104:125-132). Some would argue that rather than treating low-grade prostate cancers, it may be better not to diagnose it at all. This issue is sure to be a topic of discussion at the FDA if GlaxoSmithKline requests approval for dutasteride (Avodart) for the management of low-risk prostate cancer. ■

More to the avastin/breast cancer story?

In November 2011, the FDA revoked the approval of Genentech's bevacizumab (Avastin) for the treatment of breast cancer. The somewhat controversial decision was based on lack of evidence of improved survival with the drug, even though several studies have shown improvement in progression-free survival. This has sparked a debate regarding surrogate clinical endpoints, such

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as progression-free survival or pathological complete response, which is the endpoint used in two new studies recently published in the *New England Journal of Medicine*. The first study from Germany randomly assigned 1948 women with medium-sized tumors to receive neoadjuvant epirubicin and cyclophosphamide, followed by doxetaxel with or without bevacizumab, in patients with HER2-negative breast cancers. Rates of pathological complete response were 14.9% without bevacizumab and 18.4% with the drug (odds ratio 1.29; 95% CI, 1.02 to 1.65; $P = 0.04$). Patients with hormone receptor-negative ("triple negative") tumors did better while patients with hormone receptor-positive tumors saw no improvement (*N Engl J Med* 2012;366:299-309). The other study, supported by the National Cancer Institute, looked at about 1200 patients with operable HER2-negative breast cancer. Patients were given neoadjuvant therapy with docetaxel plus capecitabine or paclitaxel plus gemcitabine followed by doxorubicin-cyclophosphamide. They were further randomized to receive bevacizumab for the first six cycles. Adding capecitabine or gemcitabine to docetaxel had no effect and increased toxicity; however, adding bevacizumab increased the rate of pathological complete reponse (28.2% without bevacizumab vs the 34.5% with bevacizumab, $P = 0.02$). Bevacizumab increased the rates of hypertension, left ventricular systolic dysfunction, hand-foot syndrome, and mucositis. The authors conclude that bevacizumab significantly increased the rate of pathological complete response (*N Engl J Med* 2012;366:310-320). An accompanying editorial points out that the ongoing controversy regarding bevacizumab for the treatment of breast cancer revolves around the issue of using surrogate endpoints in clinical trials as well as broader economic issues in the treatment of cancer. Although the study showed improvement in the surrogate endpoint of pathological complete response (defined as absence of residual tumor in the breast and nodes in the European study and a less stringent criteria of absence of residual tumor in the breast only in the American study), neither study was powered to show differences in survival — the criteria the FDA used to withdraw the approval for bevacizumab (*N Engl J Med* 2012;366:374-375). It is unlikely that either of these studies will influence the FDA to change its decision until more definitive survival data are available. ■

Disclosure rule open for comments

The Centers for Medicare and Medicaid Services is requesting comments on a proposed rule that would require drug and device companies to report all financial relationships with physicians. The new rule is part of the Affordable Care Act. It would require disclosure of payments for food, entertainment, gifts, consulting fees, honoraria, research funding for grants, education or conference funding, royalties or licenses, and insurable contributions. Physicians would also need to disclose stock ownership in pharmaceutical and device companies, with all this information provided on a public website. Failure to disclose this information would mean substantial fines for physicians. Comments will be accepted until mid-February with the final rule expected later in 2012. ■

FDA actions

Responding to concerns about increasing antibiotic resistance, the FDA has issued an order that prohibits the use of cephalosporins in cattle, swine, chickens, and turkeys effective April 15, 2012. This rule is intended to limit the indiscriminate use of cephalosporins and preserve the effectiveness of the drugs in humans.

The FDA has approved a once-weekly, extended-release formulation of exenatide for treatment of type 2 diabetes. The drug is a glucagon-like peptide-1 receptor agonist and is indicated as an adjunct to diet and exercise for improved glycemic control. It is the first once-weekly diabetes drug to be approved. The approval was based on the DURATION-5 trial, which compared once-weekly exenatide with twice-daily exenatide injection. Exenatide extended-release is approved with a Risk Evaluation and Medication Strategy (REMS) because of concerns regarding acute pancreatitis and the potential risk for medullary thyroid cancer, as well as concerns about QT prolongation and cardiovascular risk. Exenatide extended-release will be marketed by Amylin Pharmaceuticals and Alkermes plc as Bydureon.

The FDA has approved vismodegib to treat adult patients with advanced basal cell carcinoma who are not candidates for surgery or radiation, and for patients with metastatic disease. The drug was approved under the agency's priority review program and is the first approved drug for metastatic basal cell carcinoma. The once-a-day oral pill inhibits the Hedgehog pathway, a molecular pathway found in basal cell carcinomas but few other normal tissues. The approval was based on a single, multicenter trial of 96 patients in which 30% of patients with metastatic disease experienced a partial response and 43% patients with locally advanced disease experienced a complete or partial response. Vismodegib is marketed by Genentech as Erivedge. ■

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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Long-Term Effects of Bariatric Surgery: Improved CV Outcomes

Source: Sjostrom L, et al. *JAMA* 2012; 307:56-65.

INCREASES IN BODY MASS INDEX (BMI) above normal are linearly associated with cardiovascular (CV) morbidity and mortality. The increased incidence of hypertension and diabetes in overweight and obese individuals explains some of this association. Since the weight reduction subsequent to bariatric surgery (BARS) is usually accompanied by improvements in blood pressure and metabolic profile, one would hope that this would translate into a reduction of CV events.

The Swedish Obese Subjects study provides data from this prospective controlled study of BARS (n = 2010) vs "usual care" (n = 2037) for adult obese subjects. The minimum BMI for inclusion was 34 kg/m^2 in men and 38 kg/m^2 in women. Subjects were followed for a median of 14.7 years.

The BARS subjects enjoyed a 53% relative-risk reduction in CV deaths (28/2100 vs 49/2037) and a 33% risk reduction in overall fatal and nonfatal CV events (199/2100 vs 234/2037) over the almost 15 years of follow-up.

Although the degree of excess BMI did not correlate with outcomes — i.e., persons who had higher baseline BMI did not enjoy a greater (or lesser) risk reduction than comparators — there was a correlation with insulin resistance. As manifest by baseline plasma insulin concentration, subjects with the highest degree of insulin resistance had the greatest degree of CV risk reduction. This long-term follow-up of a large surgical population is encouraging that BARS reduces CV risk. Demonstration of risk reduction requires both a large population and enduring follow-up, since most of the participants were much younger than are typically enrolled in CV risk reduction trials. ■

Long-Term Survival in SHEP Trial Participants

Source: Kostis JB, et al. *JAMA* 2011;306: 2588-2593.

THE SYSTOLIC HYPERTENSION IN THE ELderly (SHEP) trial was a prospective, randomized, controlled trial of diuretic (chlorthalidone) vs placebo in 4736 subjects with isolated systolic hypertension over the age of 60. At the conclusion of the trial (4.5 years mean follow-up), chlorthalidone resulted in a statistically significant reduction in cardiovascular (CV) *events*, but only a favorable trend (NOT statistically significant) in CV *mortality*. Because of the favorable initial results, at the conclusion of the trial all SHEP participants were advised to use active treatment.

Kostis et al report on 22 years of follow-up of SHEP trial participants. According to their analysis, there was a beneficial difference noted between persons originally assigned to diuretic vs placebo: a statistically significant 11% reduction in CV death, although total mortality was not significantly different between the two groups. Benefits seen years after a clinical trial intervention has ceased are commonly termed "legacy effects," and suggest that a sustained period of blood pressure control with chlorthalidone may extend CV risk reduction over a much longer interval. Because all trial participants were encouraged to receive active treatment post-trial, the favorable between-group differences seen would likely be an underestimate of true attainable benefits. ■

Exercise and Weight Loss in Persons with Pre-existing Coronary Heart Disease

Source: Ades PA, et al. *Chest* 2011;140: 1420-1427.

THERE IS STILL SOME DEBATE ABOUT THE relationship between being overweight and cardiovascular (CV) health, since among overweight individuals there is great diversity in levels of CV fitness as well as CV risk factors (e.g., hypertension, diabetes, dyslipidemia). Much of the insight we have today about the benefit of cardiac rehabilitation programs was gleaned from trial data in the 1970s and 1980s, at which time many fewer study subjects were obese or morbidly obese. Hence, determining the impact of exercise and weight loss in persons more representative of current coronary heart disease (CHD) demographics is pertinent.

Obese adults (mean baseline BMI = 32.3 kg/m^2) with established CHD (n = 38) participated in a regimen of weight loss combined with one of two different intensity exercise programs (walking 45-60 minutes vs 25-40 minutes per session) for 4 months.

Endothelial function, as assessed by flow-mediated dilation, was improved in both groups, but improved more in the group with greater intensity of exercise. The authors also comment that the amount of endothelial functional improvement seen with weight loss was similar in magnitude to that attained with statin treatment. Degree of endothelial functional improvement correlated with amount of weight lost, suggesting a dose-response effect. In an era when more than 80% of persons entering cardiac rehabilitation programs are overweight or obese, it is encouraging that participation in rehabilitation programs that result in weight loss and sustained physical activity improve endothelial function. ■

Predicting Adverse Outcomes in Asthmatics: The Severity of Asthma Score

Source: Eisner MD, et al. *Chest* 2012; 141:58-65.

In the United States, approximately 5,000 persons die each year from asthma. Several metrics for predicting outcomes in asthmatics are available including the asthma control test, work productivity and impairment index-asthma, FEV_1, and severity of asthma score (SOA). The SOA score is a validated questionnaire that incorporates asthma symptom frequency, medication use history, and hospitalizations for asthma among its 13 items. The Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma study is an observational study of omalizumab or placebo in asthmatics with demonstrated inhalant allergen sensitivity. In the placebo arm (n = 2878), the SOA score was compared with the other metrics mentioned above for its ability to predict five asthma-related outcomes: exacerbations, hospitalizations, unscheduled office visits, emergency room visits, and need for systemic steroid treatment.

Of all the metrics chosen, SOA had the best predictive capacity, and was singular in that it had significant positive-predictive value for all five of the adverse asthma-related outcomes, whereas other tools were positively predictive in only a portion of the five outcomes. One of the attractive aspects of the SOA is that no special tools, lab tests, or measurements of pulmonary function are required to score it. ■

Subclinical Atrial Fibrillation

Source: Healey JS, et al. *N Engl J Med* 2012;366:120-129.

I have been a student of atrial fibrillation (AF) for some time, but had never come upon the term "subclinical" AF until this *New England Journal of Medicine* publication. The authors point out that although AF is often brought to our attention by awareness of an arrhythmia, it is often asymptomatic — what they call subclinical. Indeed, it is not uncommon to see patients presenting with ischemic stroke, heart failure, or syncope, only to discover that asymptomatic AF is the underlying etiology.

Healey et al report on a population of hypertensive seniors in whom either a pacemaker or defibrillator had been implanted but who had no prior history of AF (n = 2580). The implanted devices were programmed to report any episode of heart rate 190 beats per minute (bpm) or greater. Subclinical atrial tachyarrhythmia — defined as an asymptomatic occurrence of atrial rate > 190 bpm for more than 6 minutes — was detected in 35% of study subjects over 2.5 years of observation; asymptomatic episodes far outnumbered symptomatic tachyarrhythmia. The risk for ischemic stroke in persons experiencing any atrial tachyarrhythmia was increased by 2.5 fold.

These data may help to explain some of the ischemic stroke cases that have no immediately visible antecedent. On the other hand, the complex terminology that separates AF into persistent, paroxysmal, subclinical, permanent, etc, may not be helpful; the phrase "once a fibber, always a fibber" simplifies the fact that (except for transient AF associated with perioperative stress), any episode of AF, regardless of duration or extinguishability, elevates thrombotic risk. ■

Real-life Use of Sunscreen in Ski Areas

Source: Buller DB, et al. *J Am Acad Dermatol* 2012;66:63-70.

Current recommendations for sunscreen include three fundamental steps: 1) application up to 30 minutes before exposure, 2) use of a sun protection factor (SPF) of at least 15 (higher if ultraviolet [UV] radiation is high), and 3) reapplication every 2-3 hours. Skiing is associated with high UV exposure because of the combination of altitude and snow reflection.

Buller et al interviewed adult skiers in the western United States and Canada (n = 4837). Subjects were interviewed face-to-face while riding on chairlifts and gondolas (I don't ever remember getting offered one of those tough, technical scientific jobs!).

Almost 50% of subjects reported using sunscreen with SPF 15 or higher, and most applied it 30 minutes before sun exposure. Reapplication was only performed by 20%. Only 4% of respondents fulfilled all three components of appropriate sunscreen use. Overall, men were substantially less compliant than women.

Messages about the importance of skin protection appear to be reaching the public, including young athletic adults. Further education about the need for reapplication, coupled with insights about circumstances of increased exposure risk (like skiing), might improve compliance in the future. ■

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