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INSIDE

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Vascular Endothelial Growth Factor and Neuropathy

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: *VEGF is elevated in the serum and plays a role in the pathogenesis of neuropathies associated with monoclonal gammopathies.*

Source: Briani C, Fabrizi GM, Ruggero S, et al. Vascular endothelial growth factor helps differentiate neuropathies in rare plasma cell dyscrasias. *Muscle Nerve* http://www.ncbi.nlm.nih.gov/pubmed/21082697

CAN MEASUREMENT OF SERUM VASCULAR ENDOTHELIAL GROWTH FACTOR (sVEGF) aid in the diagnosis of neuropathy and predict disease course? sVEGF is increased in POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes), less so in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (in spite of a similar demyelinating pathology), and is not significantly elevated in multiple myeloma or monoclonal gammopathy of undetermined significance (MGUS). sVEGF levels in amyloidosis have not been systematically studied.

To evaluate sVEGF levels in amyloidosis and its response to treatment, 25 patients (18 men and 7 women, mean age 66.8 years) with biopsy-proven amyloidosis were evaluated, including 17 (10 men and 7 women) with primary amyloidosis (AL-A), 7 men with transthyretin amyloidosis (TTR-A), and 1 man with senile systemic (wild-type TTR) amyloidosis. TTR-A was diagnosed by molecular analysis and confirmed with sural nerve biopsy. TTR-positive immuno-histochemistry confirmed the diagnosis of senile (wild-type TTR) amyloidosis, whereas primary AL-A was diagnosed by the presence of monoclonal light chain protein in urine or serum, abnormal serum free light chain ratio, or monoclonal plasma cells in bone marrow with negative immuno-histochemistry for TTR and absence of TTR mutation on DNA analysis. Seven TTR-A patients and 3 AL-A patients had an axonal sensory polyneuropathy, and 6 TTR-A patients had

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autonomic polyneuropathy. sVEGF levels were measured by ELISA (enzyme-linked immunosorbent assay). Statistical analysis included the Mann-Whitney U-test and the Kruskal-Wallis test, with significance set at $P < 0.05$.

sVEGF levels were significantly lower in patients with AL-A (median 420 pg/ml) and TTR-A (median 179 pg/ml) compared to those with POEMS syndrome (median 2580 pg/ml). Multiple myeloma median sVEGF level, 260 pg/ml, was also significantly lower than seen in POEMS syndrome. Presence or absence of neuropathy in AL-A did not affect sVEGF level and it did not vary with disease status or therapeutic response. sVEGF measurement can assist in differentiating POEMS from CIDP, MGUS-neuropathy, and amyloidosis, and should be measured in patients with plasma cell dyscrasias and neuropathy.

■ COMMENTARY

Angiogenesis and lymphangiogenesis, critical processes during embryogenesis, tissue growth, wound healing, and disease pathogenesis, are regulated via activation of three receptor tyrosine kinases, VEGFR-1, 2, and 3, by vascular endothelial growth factors (VEGFs). Vascular permeability and vessel dilatation are regulated by these receptors, and VEGF also has, both in vivo and in vitro, direct trophic effects on neuronal cells. Demyelinating neuropathy in POEMS may result from blood-nerve barrier dysfunction mediated by increased levels of circulating VEGF. Yet the mechanism for POEMS remains a puzzle. It is unclear why lambda light chain predominates in POEMS, as opposed to kappa light chain that predominates in MGUS, though both present similar demyelinating neuropathies. Vascular leakage is suggested by the presence of hepatomegaly and splenomegaly in POEMS, attributed to elevated circulating VEGF levels, but other factors, including interleukin-1β, interleukin-6, and tumor necrosis factor α, are also elevated in POEMS and may play a role in pathogenesis. ■

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The ABCs of Anosognosia for Hemiplegia

ABSTRACT & COMMENTARY

By John Caronna, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Anosognosia is an important, but often neglected, part of the neurological examination in a patient with stroke.*

Source: Vocat R, Staub F, Stroppini T, Vuilleumier, P. Anosognosia for hemiplegia: A clinical-anatomical prospective study. *Brain* 2010;133:3578-3597.

The term anosognosia was introduced by Babinski to describe unawareness of hemiplegia, a phenomenon that he thought was caused by sensory deafferentation.[1] Anosognosia occurs in other conditions such as hemianopia, cortical blindness, hemineglect, prosopagnosia, amnesia, aphasia, and dementia. Unawareness of hemiplegia is the most common form of anosognosia and occurs most frequently after damage to the right parietal lobe.

Vuilleumier has proposed that denial of hemiplegia is the result of a combination of disturbances, including not only sensory deafferentation, neglect, and phantom sensations, but also deficits in putative belief and check systems that prevent verification of experiential evidence of motor deficit.[2]

In the present study, Vuilleumier and associates evaluated the incidence, clinical presentation, time course, and neuroanatomical correlates of anosognosia for hemiplegia. Fifty-eight patients with right hemisphere stroke and significant left hemibody motor deficits, were examined using a comprehensive neuropsychological battery at 3 days, 1 week, and 6 months after stroke onset. Fifty patients (22 women, mean age 65 ± 14 years, all right-handed) were examined in the hyperacute phase (mean 2.7 days, range 1-5); 44 patients were examined in the subacute phase (mean 8.3 days, range 7-12); 19 patients

were examined in the chronic phase (mean 223 days, range 180-273). Only 14 patients participated in all three evaluations.

Anosognosia for hemiplegia was frequent in the hyperacute phase (32%), declined by almost one-half at 1 week (18%), and was present at 6 months in only 5%. The phenomenon correlated with the severity of other deficits: loss of proprioception, spatial neglect, and disorientation. Proprioceptive loss was the most determinant factor in the hyperacute period; visuospatial neglect and disorientation were more determinant in the subacute phase. Patients with both proprioceptive loss and neglect had a higher incidence of anosognosia for hemiplegia than those with no or only one deficit.

Personality and emotional traits did not reveal any association with anosognosia. However, certain behaviors closely related to the definition of anosognosia for hemiplegia (confabulation, passivity, and unconcern) were noted in the hyperacute but not the subacute stage.

The location and extent of brain damage were delineated in each patient, based on either a CT or MRI scan obtained after the first week post-stroke. Damage to the insula (particularly its anterior part) and adjacent subcortical structures was determinant for unawareness of motor deficit in the hyperacute period. Additional lesions in the premotor cortex, cingulate gyrus, parietotemporal junction, hippocampus, and amygdala were associated with persistence of anosognosia for hemiplegia in the subacute stage.

These results suggest that anosognosia for hemiplegia reflects a multicomponent disorder, due to lesions affecting a distributed set of brain regions that can lead to several co-existing deficits in sensation, attention, bodily representation, error monitoring, memory, and others, with different combinations in different patients. The authors, therefore, propose a "two-factor theory"[2] or ABC hypothesis[2] of anosognosia for hemiplegia, according to which impairments in components necessary for "Appreciation" of the deficits (e.g., proprioception and spatial attention) might or might not cause unawareness of hemiplegia depending on the severity of addition dysfunction in "Belief" and "Check" components related to self- and reality-monitoring and verification processes.

■ COMMENTARY

For most of us, the examination of a patient with hemineglect by a senior neurologist is a well-remembered highlight of neurology student clerkship or residency training. If the examiner had a flair for the theatrical like the late Fred Plum, then the patient-physician encounter became the source of endless anecdotes, told and retold by his trainees.

Recently, physicians have recognized that patients with right hemisphere strokes are much less likely to receive rTPA than those with left hemisphere strokes. The reasons are twofold; patients with hemineglect fail to recognize the signs of left hemiparesis resulting in prehospital delay; likewise, physicians may not detect anosognosia because of a lack of standardized scores for neglect.[4] Gurol et al have pointed out that the NIH Stroke Scale is biased toward left, i.e., dominant, hemisphere deficits.[5] Ostrow and Llinas, therefore, have proposed the Eastchester Clapping Sign as a screening test for neglect in the acute stroke setting.[6]

Vocat et al have provided an exhaustive review of the phenomenon of anosognosia for hemiplegia and a prospective assessment of a large group of stroke patients with the disorder. The ABC combinatorial rule is clinically useful and explains the present of anosognosia for hemiplegia in some patients, despite a minor loss of proprioception and an absence of hemineglect. In such cases, the primary deficit is in "Belief" or "Check" components. The authors have provided clinicians with useful insights about the multifactorial determinants and temporal evolution of anosognosia for hemiplegia following stroke. ■

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Sleep Disorders and Restless Legs Syndrome in Friedreich's Ataxia

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, DPhil

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

Synopsis: *Restless Legs Syndrome (RLS) was present in 50% of patients with Friedreich's ataxia (FA),*

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*

Risk of Stroke and Cardiovascular Death from Non-Steroidal Anti-Inflammatory Medications (NSAIDs)

Source: Trelle S, Reichenbach S, Wandel S, et. al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: Network meta-analysis. *BMJ* 2011;342:c7086. doi:10.1136/bmj.c7086

The authors reviewed all large-scale, randomized controlled clinical trials comparing any NSAIDs or placebo, and performed a meta-analysis looking at the rates of myocardial infarction, stroke, death from cardiovascular cause, and death from any cause. They reviewed 31 trials in 116,429 patients with more than 115,000 patient years of follow-up. Patients were allocated to naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib, lumiracoxib, or placebo.

Compared with placebo, rofecoxib was associated with the highest risk of myocardial infarction (rate ratio [RR] = 2.12, 95% confidence interval [CI] 1.26 – 3.56). Ibuprofen was associated with the highest risk of stroke (RR = 3.36, CI 1.00 – 11.6), followed by diclofenac. Naproxen was associated with the lowest risk of stroke (RR = 1.76, CI 0.91 – 3.33) and its use was not associated with an increased risk of cardiovascular death. It appears that the entire class of NSAIDs is associated with an increased risk of cardiovascular events, and alternatives should be considered in the management of pain. ■

Cervical Artery Abnormalities are Common in Children with Stroke

Source: Ganesan V, Cox TC, Gunny R. Abnormalities of cervical arteries in children with arterial ischemic stroke. *Neurology* 2011;76:166-171.

Ischemic stroke is rare in children, and etiologies have been varied. The authors reviewed all cases admitted to their hospital in London from 2002-2009, and performed time-of-flight MR imaging of the cervical and intracranial arteries, in addition to MR imaging of the brain, with special attention to infarct presence and location, nature of the arterial disease, risk factors, antecedent trauma, and the presence of cervical arterial disease.

Sixty children (31 boys, median age 5 years 3 months) were included. Fifty children had anterior circulation infarcts only, and nine had posterior circulation infarcts. Cervical arterial abnormalities were found in 15/60 (25%) and intracranial abnormalities were identified in 26. Cervical arterial disease was characterized as definite arterial dissection in 2 cases, probable dissection in 7, nonspecific occlusive arteriopathy in 5, and migrated cardiac occlusive device in 1. In a logistic regression analysis, the presence of posterior circulation infarct predicted the presence of a cervical arterial abnormality (P = 0.04). A history of antecedent trauma was not predictive. The cervical vessels should be imaged in all children with acute ischemic stroke. ■

Continued on page 45

a disorder of intramitochondrial iron accumulation. This study suggests that RLS treatment will potentially help the sleep disorder in appropriately screened FA patients.

Source: Frauscher B, Hering S, Hogl B, et al. Restless legs syndrome in Friedreich ataxia: A polysomnographic study. ePub Dec 13 2010. *Mov Disord* DOI: 10.1002/mds.22769

Friedreich ataxia affects 1/50,000 individuals and is the most common inherited ataxia. In addition to ataxia, it may result in cardiomyopathy, diabetes, and skeletal abnormalities, but this is the first study to systematically assess sleep disturbance as a non-motor feature of FA. Consecutive patients at Innsbruck Medical University with genetically proven FA underwent evaluation for RLS by a board-certified neurologist, assessment of severity by International RLS Study Group Rating Scale (IRLS), and associated periodic limb movements of sleep (PLMS) and of wakefulness (PLMW) were evaluated by 8-hour polysomnographic studies over two consecutive nights. Of 16 patients (mean age 35.4 ± 11.1 years, FA disease duration 16.5 ± 7.0 years), 8 met standard criteria for a diagnosis of RLS. Mean RLS duration was 8.4 ± 9.1 years, and in 7/8 RLS followed FA diagnosis. None were taking medication for RLS; 3 took antidepressant medications without temporal association with RLS onset, but other prescribed and over-the-counter medications were not reported. Polysomnographic studies recorded a PLMS index of > 15/hour in 7/16 subjects, and PLMW index of > 15/hour in all subjects. Only PLMW index associated with diagnosis of FA with RLS. FA with RLS was associated with lower serum ferritin (male: 124.8 ± 28.3 mg/L

Do Patients with Isolated Vertigo Have a Higher Risk for Stroke?

Source: Lee, CC, Su YC, Ho HC, et.al. Risk of stroke in patients hospitalized for isolated vertigo. A four-year follow-up study. *Stroke* 2011;42:48-52.

In a study from Taiwan, all patients hospitalized with a principal diagnosis of vertigo (n = 3,021) were compared to an age- and sex-matched control group of patients hospitalized for appendectomy, and the two cohorts were followed for 4 years to ascertain cardiovascular risk factors and subsequent stroke.

During the 4-year follow-up period, 185 (6.1%) patients from the study group were admitted with stroke, and 58(1.9%) from the control group had a stroke. The vertigo group had statistically-significant higher rates of hypertension, diabetes, coronary disease, and hyperlipidemia, and the risk of stroke was determined by the presence of these risk factors, plus age > 55 years and male sex. The patients were divided into three groups, based on risk factors, and the 4-year cumulative risks for stroke were 1.9 (no risk factors), 7.7 (1-2 risk factors) and 14 (3 or more risk factors). Vertigo may be a clinical symptom of vertebrobasilar disease and cardiovascular risk factors should be identified and treated, to prevent future stroke. Isolated vertigo, without these risk factors, is rarely associated with any type of stroke. ■

Stroke-Type May Determine Outcome After Treatment with Thrombolysis

Source: Mustanoja S, Meretoja A, Putaala J, et.al. Outcome by stroke etiology in patients receiving thrombolytic treatment. Descriptive subtype analysis. *Stroke* 2011;42:102-106.

In a population-based study from Helsinki, Finland, investigators looked at outcomes after intravenous thrombolysis from a single hospital from 1995–2008, and analyzed outcomes based on stroke-type, using a multivariate logistic regression. Good outcome was defined as modified Rankin Scale less than or equal to 2. Stroke classification was based on the TOAST trial.

Of 957 ischemic stroke patients treated with intravenous thrombolysis, 41% (389) had cardioembolism, 23% (217) had large-artery atherosclerosis, and 11% (101) had small-vessel disease (SVD). A good outcome was more common with SVD than with any other subtype. Patients with SVD were more often male, had a lower baseline NIH Stroke Scale score, lower mortality, and had no episodes of intracranial hemorrhage. Common vascular risk factors—hypertension, diabetes, hypercholesterolemia, and transient ischemic attacks—were equally distributed across all stroke subtypes. After adjustment for baseline NIHSS, glucose level, and hyperdense artery sign, patients with SVD still had better outcomes. ■

vs. 193.7 ± 98.2 mg/L; female: 27.8 ± 15.8 mg/L vs. 72.0 mg/L, $P = 0.043$). In addition to RLS, 1/16 had witnessed apneas, 2/16 had sleepwalking and reported confusional arousals, and REM sleep without atonia was recorded in polysomnographic studies in 2/16 (considered by the authors due to trazodone and fluoxetine intake).

■ COMMENTARY

This is the first study to systematically investigate sleep disorders in FA using polysomnography. Although the number of subjects is low, the high prevalence of RLS in these 16 subjects, and the presence of other disorders (sleep apnea, rapid eye movement sleep without atonia) strongly suggests that this bears further study, both to better understand the disorders (FA and RLS) themselves and to directly impact patient care. FA displays autosomal recessive inheritance and is caused by GAA-trinucleotide repeat expansions in the frataxin gene. The corresponding protein, present in mitochondria, is critical to iron homeostasis. In FA, frataxin expression is reduced and iron accumulates in the nervous system, heart, and other tissues: indeed, attempts to translate this into novel therapies (including idebenone, and desferiprone) are ongoing. Iron dysregulation also occurs in RLS, with low ferritin levels in many. It is therefore tempting to postulate that aberrant iron homeostasis/metabolism is the underlying link between FA and RLS. The relationship, though, is obviously complex and by no means suggests extrapolating iron supplementation treatment sometimes given in RLS to FA with RLS. The anatomical underpinnings of RLS in FA may also be complex. The authors strongly suggest spinal cord pathology as the primary link between FA and RLS. Again, this is far from clear, as pathology in FA is widespread, involving the spinal cord, but also the cerebellum, brainstem, and cerebral hemispheres. It is therefore intriguing that Synofzik and colleagues,[1] in addition to diagnosing RLS in 32% subjects with FA, reported sonographic hypoechogenicity likely reflecting decreased iron content present in the substantia nigra, that was significantly associated with RLS, as well as FA severity. Given the multi-system nature of FA, possible links to other sleep disorders need to be seriously

considered—the authors suggest that REM sleep without atonia was medication-related in their subjects, but this will need further characterization. Finally, this study is important in that, together with Synofzik and colleagues,[1] it supports close questioning of patients' sleep habits in FA, with sleep studies where appropriate, and with a view to alleviating a subset of symptoms in this challenging disorder. ■

Reference

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Gait Ataxia in Essential Tremor Modulated by Thalamic Deep Brain Stimulation

ABSTRACT & COMMENTARY

By Jordan Dubow, MD, and Claire Henchcliffe, MD, DPhil

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Dr. Dubow reports no financial relationships relevant to this field of study, Dr. Henchcliffe reports she is on the speaker's bureau and advisory board for Allergan and Teva; speaker's bureau for Boehringer-Ingelheim, GlaxoSmith-Kline, and Novartis; advisory board for Merz, and is a consultant for Gerson Lehman Group and Guidepoint Global.

Synopsis: *Thalamic deep brain stimulation improves ataxia in subjects with essential tremor at therapeutic stimulation parameters, and worsens ataxia at supra-therapeutic parameters.*

Source: Fasano A, Herzog J, Raethjen, J et al. Gait ataxia in essential tremor is differentially modulated by thalamic stimulation. *Brain* 2010;133:3635-3648.

ESSENTIAL TREMOR (ET) IS THE MOST COMMON FORM OF pathological tremor. However, older patients with ET and those with more than five years of disease duration have abnormalities of gait as well as limb ataxia. Tremor refractory to medication typically responds exquisitely to deep brain stimulation (DBS) of the thalamic ventral intermediate nucleus (VIM), but DBS effects on ataxia remain to be characterized.

In the present study, 11 patients with ET (age 69.8 ± 3.9 years, disease duration 24.4 ± 11.2 years) were evaluated 24.7 ± 20.3 months after bilateral thalamic DBS and compared to 10 age- and gender-matched healthy controls. Tremor was assessed with a modified version of the Fahn-Tolosa-Marin Tremor Rating Scale (TRS). Ataxia was rated using the International Cooperative Ataxia Rating Scale (ICARS), a 100-point scale that quantifies ataxia in four categories of movement, with higher scores indicating worsened ataxia. Normal gait speed and tandem gait speed were measured, and gait analysis was also performed on a motor-driven treadmill, recorded with an infrared movement analysis system. To quantify ataxia of gait, an ataxia ratio was computed, and coefficients of variation of gait cycle time and swing phase duration were calculated. Assessments were performed in ET subjects during three stimulation conditions: "stimulation ON," "stimulation OFF," and supra-therapeutic stimulation.

Thalamic DBS resulted in a 66% reduction of the TRS score under "stimulation ON" compared to the "stimulation OFF" conditions. Supra-therapeutic stimulation also reduced tremor severity, but worsened spiral drawing due to stimulation-induced ataxia. The ICARS score was significantly higher in the "stimulation OFF" compared to the "stimulation ON" state, and "stimulation ON" also significantly reduced the number of missteps compared to "stimulation OFF" and supra-therapeutic stimulation. Velocity of tandem gait was significantly faster in the "stimulation ON" compared to the supra-therapeutic stimulation, and velocity of routine walking was significantly faster in the "stimulation ON" compared to "stimulation OFF" and supra-therapeutic stimulation.

On treadmill gait analysis, the foot trajectories of patients with essential tremor were highly variable (ataxic) during "stimulation OFF." During "stimulation ON," foot trajectories improved and were indistinguishable from controls in some patients. During "stimulation ON," the ataxia ratio and the coefficient of variation during swing phase were significantly lower than during "stimulation OFF" and supra-therapeutic stimulation. The ataxia ratio and the coefficient of variation of swing phase were significantly higher during "stimulation OFF" and supra-therapeutic stimulation compared to "stimulation ON."

■ COMMENTARY

This study confirms that essential tremor, now felt to be a neurodegenerative condition, is not a monosymptomatic disorder—advanced patients may develop a cerebellar disorder with both midline and hemispheric cerebellar signs compared to healthy controls. The fact that thalamic stimulation improved cerebellar symptoms at therapeutic parameters, and worsened ataxia at supra-therapeutic stimulation parameters, offers insight into both clinical treatment of ataxia and to the anatomical localization of ataxia in ET. Critically, this study raises the question of whether DBS of the VIM nucleus of the thalamus may be beneficial for patients with other causes of ataxia, such

as multiple system atrophy or the spinocerebellar ataxias. One strength of the study lies in its careful, precise, and objective motor evaluations, but none of the study subjects had ataxia that interfered with their walking or day-to-day function, and improvements were seen only on scales and not with functional assessment. Therefore, we do not know if thalamic DBS would indeed provide meaningful impact in patients with much more severe ataxia. Further study is certainly warranted, and this is underlined by Earhart and colleagues.[1] who reported that DBS effects upon gait and balance are highly variable in individuals with ET. Finally, another observation of this study was that patients with essential tremor had slower gaits in routine walking compared to controls. Some individuals with ET progress to Parkinson's disease, and it would be fascinating to determine whether motor measures used in this study could be early predictors of later ET subtypes. ■

Reference

1. Earhart GM, Clark BR, Tabbal SD, Perlmutter JS. Gait and balance in essential tremor: Variable effects of bilateral thalamic stimulation. *Mov Disord* 2009;24:386-391.

A Hereditary, Childhood Form of Parkinsonism

ABSTRACT AND COMMENTARY

By Sabiha Merchant, MD, and Steven Weinstein, MD

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Neither Dr. Merchant and Dr. Weinstein report any financial relationships relevant to this field of study.

Synopsis: *Dopamine transporter deficiency (DAT) is a rare inherited disorder that causes a Parkinsonian syndrome in infants and young children.*

Source: Kurian MA, Li Y, Zhen J, et al. Clinical and molecular characterisation of hereditary dopamine transporter deficiency syndrome: An observational cohort and experimental study. *Lancet Neurol* 2011;10:54-62.

PARKINSONIAN DISORDERS TYPICALLY PRESENT IN ADULTS but rare forms exist in early infancy. A multitude of etiologies exist and this paper describes a cohort of children with a deficiency of the dopamine transporter (DAT) due to mutations of SLC6A3. The identification of the molecular basis of this disorder has the potential to lead to specific therapeutic strategies and perhaps allelic variations to provide insight into adult onset disorders.

An international multicenter study was performed to characterize the clinical and molecular characteristics in 11 children with hereditary dopamine transporter deficiency syndrome (DAT). Patients were identified from seven pediatric neurology centers, movement disorder and neurotransmitter specialists, laboratories performing CSF neurotransmitter analysis, and a review of published cases in PubMed.

Patients presented between 0.5 and 7 months of age with Parkinsonism, hyperkinesia, or a combination. Video movies of the children created by the parents and the clinics were reviewed independently by three neurologists. The history was reviewed to identify any risk for intrauterine and perinatal injury (cerebral palsy), and, although the results were not provided, an evaluation was performed to exclude a metabolic basis for the neurological findings—assessment for a mitochondrial disorder, MRI search for iron accumulation, and measurement of CSF neurotransmitters to exclude a biosynthesis defect. An elevated ratio of homovanillic acid to 5-hydroxyindoleactic was suggestive of DAT and prompted further genetic evaluation for SLC6A3 mutations.

The clinical phenotype was an early infancy presentation with irritability, feeding difficulty, and movement disorders. All children had generalized dystonia within one year of clinical presentation. As the disease progressed, axial hypotonia and pyramidal tract features became more obvious. By age 3 years, all had pyramidal tract findings and severe gross motor delay. Basal ganglia, as visualized on MRI, had no gross structural defects or signal abnormalities. GI motor deficits, sleeping difficulties, pneumonias, and orthopedic complications developed. Features of DAT were almost indistinguishable from patients who had defects of dopamine biosynthesis, but may be suggested by the high incidence of dystonic crises in DAT. Cognitive impairment was mild and speech delays were thought to be due primarily to the motor difficulties. Death occurred in 4 of 5 children who survived to age 9 due to respiratory complications and cardiac failure.

Evaluation of CSF neurotransmitters was the most sensitive indicator of the disorder that prompted genetic analysis. An elevated homovanillic acid to 5-hydroxyindoleactic ratio distinguished DAT from synthesis defects in which both levels were low. Mutations in the autosomal recessive gene SLC6A3 were found in each case leading to defective trafficking of dopamine reuptake into the presynaptic neuron resulting in cerebral dopamine deficiency. It is postulated that dopamine accumulates extraneuronally, resulting in dopamine degradation. Serotonin

biosynthetic pathways were unaffected.

Therapeutic interventions that had little of no efficacy, including muscle relaxants, dopamine agonists, anticholinergics, antiglutaminergics, GABA agents, and deep brain stimulation in one child. Partial response to carbidopa was seen in two patients with residual DAT activity.

■ COMMENTARY

The paper emphasizes that many of childhood movement disorders require an extensive evaluation both to identify systemic metabolic disorders and disorders of dopamine synthesis, transport, and metabolism. Correct identification may allow for more accurate prediction of the time course of a progressive disorder. The authors did not discuss whether acquired enzymatic deficits may develop in adults in response to environmental factors. We do not know what effect the aging process has on this enzyme system. ■

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

- Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

- After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

CME Questions

40. Serum vascular endothelial growth factor (sVEGF) is highest in which of the following disorders?

a. Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS)
b. Chronic inflammatory demyelinating polyradiculoneuropathy
c. Multiple myeloma
d. Monoclonal gammopathy of undetermined significance

41. Anosognosia for hemiplegia occurs in most patients with right-hemisphere stroke.

a. True
b. False

42. Sleep-associated movement disorders are common in patients with Friedreich's Ataxia.

a. True
b. False

43. Which statement is not true about essential tremor?

a. Essential tremor is the most common form of tremor.
b. After many years, patients with ET may develop gait ataxia.
c. Essential tremor does not become worse over time.
d. DBS targeted at the thalamus is effective treatment for ET.
e. Thalamic DBS improves the ataxia that accompanies ET.

44. Children with DAT are expected to live a normal lifespan.

a. True
b. False

45. Naproxyn, compared to other NSAIDs, has the lowest reported association with cardiovascular events, including stroke.

a. True
b. False

46. Compared to adults, children with ischemic stroke have a high prevalence of cervical arterial abnormalities.

a. True
b. False

47. Isolated vertigo is a benign condition that does not require vascular evaluation.

a. True
b. False

48. Stroke due to cardioembolism has the best outcome after intravenous thrombolysis.

a. True
b. False

Answers: 40. a, 41. b, 42. a, 43. c, 44. b, 45. a, 46. a, 47. b, 48. b.

In Future Issues:

More on Headache Management

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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Immunochemical FOBT and low-dose aspirin

Source: Brenner H, et al. Low-dose aspirin use and performance of immunochemical fecal occult blood tests. *JAMA* 2010;304:2513-2520.

IMMUNOCHEMICAL FECAL OCCULT BLOOD testing (i-FOBT) is becoming increasingly popular as a screening tool for colorectal cancer (CRC). At the same time, the number of persons taking long-term low-dose aspirin (ASA) for CV disease risk reduction is also increasing. Concern has been expressed that the predictable increase in GI bleeding associated with ASA would decrease the specificity of i-FOBT by increasing false positives. At the same time, it has been suggested that consequences of i-FOBT to detect upper GI bleeding may have been overestimated, since the globin chains detected by i-FOBT typically are degraded progressively during passage through the GI tract, and are hence less available for i-FOBT identification than bleeding more distal in the GI tract. Finally, utilization of ASA might also increase the risk of bleeding of CRC, thus enhancing likelihood of detection.

To assess the relationship between ASA, i-FOBT, and results of CRC screening, Brenner et al reported on almost 2000 adults who underwent CRC screening, 12% of whom were regular ASA users.

Sensitivity (the number of positive tests in persons confirmed to have advanced GI neoplasms) of i-FOBT was greater in ASA users than non-users. i-FOBT specificity (the number of negative tests in persons without advanced GI neoplasms) was minimally reduced.

Chronic low-dose ASA does not appear to compromise the ability of i-FOBT to detect advanced GI neoplasia, with a modest decrease in specificity. ■

Aerobic vs resistance exercise for type 2 diabetes

Source: Church T, et al. Effects of aerobic and resistance training on hemoglobin A1c in patients with type 2 diabetes. *JAMA* 2010;304:2253-2262.

MOST PERSONS WITH TYPE 2 DIABETES (DM2) are overweight or obese. Exercise is routinely advised for DM2, although whether a particular method of exercise has an advantage for optimization of glycemic control is not well defined.

Church et al compared the effects of aerobic exercise (AER), resistance training (RES), or the combination (AER + RES) vs placebo in previously sedentary mid-life DM2 adults (mean age = 56 years). Participants engaged in the prescribed activities for 9 months. The primary outcome was change in A1c from baseline.

At the conclusion of the trial, only the AER + RES provided statistically significant reduction in A1c compared to placebo; AER alone or RES alone did not.

It would be unfortunate if clinicians were to interpret this trial as indicating a lack of value of either AER or RES alone. All exercise groups had favorable changes in anthropomorphic metrics, and exercise has been shown to be associated with a favorable impact upon cardiovascular risk in large population studies, an effect that may be independent of glycemic effects. ■

Atrial fibrillation risk: Choose your parents wisely

Source: Lubitz SA, et al. Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. *JAMA* 2010;304:2263-2269.

A FAMILIAL COMPONENT CONTRIBUTES to atrial fibrillation (a-FIB) risk, such that independent of other risk factors (e.g., hypertension), having a first-degree relative with a-FIB increases risk.

Using data from participants (n = 11,971) in the Framingham Heart Study, Lubitz et al examined the relationship between having a first-degree relative (sibling or parent) with a-FIB and subsequent development of a-FIB during an 8-year window of observation.

Subjects with a positive family history had an increased risk of a-FIB compared to those without a family history (5.8% vs 3.1% over 8 years). Risk increased further with the number of family members affected by a-FIB. The younger the age of a-FIB onset in a family member, the greater the increase in a-FIB risk.

Overall, having a positive family history for a-FIB increased risk of new-onset a-FIB by 40%. Of all risk factors for a-FIB, hypertension is responsible for the largest population-attributable risk; whether treatment of hypertension in persons with demonstrated increased

risk for a-FIB because of family history might provide reduction in a-FIB risk remains to be determined. ■

The effects of obesity upon activity of short-acting insulin analogs

Source: Gagnon-Auger M, et al. Dose-dependent delay of the hypoglycemic effect of short-acting insulin analogs in obese subjects with type 2 diabetes: A pharmacokinetic and pharmacodynamic study. *Diabetes Care* 2010;33:2502-2507.

The most recent ADA/EASD algorithm for management of type 2 diabetes (DM2) indicates basal insulin as an appropriate next step if glycemic goals are not attained with metformin and lifestyle interventions. After fasting glucose levels are controlled on basal insulin regimens, it is common to use prandial bolus insulin (especially short-acting insulin analogs) if A1c goals have not been reached. The activity profile of short-acting insulin analogs has been established by trials in either lean healthy subjects or type 1 diabetics; neither population may be pharmacokinetically or pharmacodynamically concordant with DM2, and most are overweight or obese. To examine these issues, obese DM2 subjects (n = 7) received lispro insulin and were monitored for time to peak insulin concentration, maximal attained insulin concentration, and efficacy for reducing glucose.

Absorption of low-dose lispro (10 units) was similar in DM2 and controls, but its hypoglycemic effect was less in obese persons. At higher doses (30 units and 50 units), however, both absorption and efficacy were diminished in obese DM2 subjects. The authors challenge the current perceptions of the utility of short-acting insulin analogs in DM2, reminding us that the purpose of prandial insulin is to provide rapid rise and rapid glucose-lowering effects, both of which appear to be diminished in obese individuals. In any case, these data confirm that clinicians might anticipate proportionately less "bang-for-the-buck" as they up-titrate short-acting insulin analog doses in obese DM2. ■

Capitalizing on the second-meal effect in type 2 diabetes

Source: Chen JM, et al. Utilizing the second-meal effect in type 2 diabetes: Practical use of a soya-yogurt snack. *Diabetes Care* 2010;33:2552-2554.

It is probably not widely known that Mom was right — at least as it pertains to diabetes — that you should NOT skip breakfast. Why? Because of the "second-meal effect," a little-recognized physiologic response that can have a potentially favorable effect on glucose.

The way the "second-meal effect" works is like this: When breakfast is eaten, the degree of hyperglycemia seen after lunch is less than if the same amount of calories are given without having eaten breakfast. It has been suggested that the improved glucose level is related to a reduction in preprandial free fatty acids, which allows for greater storage of muscle glycogen during a second meal (and hence a greater disappearance of glucose from the plasma). This phenomenon occurs in both diabetic and non-diabetic individuals. Based upon this observation, Chen at al hypothesized that perhaps providing a pre-breakfast snack would reduce post-breakfast hyperglycemia.

Diabetic subjects (n = 10) were administered a snack of soya beans and yogurt 2 hours before breakfast. For scheduling convenience, the snack was administered at 8 am, and breakfast at 10 am.

Plasma glucose 2 hours after breakfast was significantly lower in the group who received the snack. Since postprandial glucose levels have been associated with adverse cardiovascular outcomes in diabetics, it might be both desirable and possible to manipulate post-meal hyperglycemia without using medications. ■

Seeking the best diet for weight-loss maintenance

Source: Larsen TM, et al. Diets with high or low protein content and glycemic index for weight loss maintenance. *N Engl J Med* 2010;363:2102-2013.

Identifying the "best" diet to achieve and maintain weight loss in overweight persons has been an elusive task. Even if a person is successful at reducing weight using a highly calorie-restricted diet over the short term, the choice of a preferred maintenance diet over the long term is ill-defined.

Larsen et al enrolled overweight adults who had successfully lost at least 8% of their initial body weight, and randomized them into diets based upon protein content and glycemic index. Five subgroups were thus defined based upon high or low protein (PRO) and glycemic index (GIN): high GIN + high PRO, high GIN + low PRO, low GIN + high PRO, low GIN + low PRO, and control). All subjects followed their respective diets for 26 weeks.

Both high PRO and low GIN were independently associated with lesser weight regain. Overall, adherence to diet and maintenance of weight loss was best with the high PRO + low GIN diet. It is possible that even greater benefit could have been achieved in relation to protein, because the actual separation of protein content between high PRO and low PRO of 5.4% was substantially less than the intended 12%. ■

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Statin Use in Patients with Abnormal Liver Function

In this issue: Statins and liver function; dosing timing for thyroxine; rivaroxaban for VTE, DVT, and stroke; echinacea and the common cold; and FDA actions.

Statins and liver function

Most physicians are hesitant to use statins in patients with abnormal liver function tests (ALT or AST less than three times the upper limit of normal). A new study suggests that not only are statins safe and effective, they may improve liver abnormalities in patients with fatty liver. In a study recently published in the *Lancet*, 437 patients enrolled in the Greek Atorvastatin and Coronary Heart Disease Evaluation study population were noted to have moderately abnormal liver tests at baseline, which were possibly associated with non-alcoholic fatty liver disease. Of that group, 227 were treated with a statin (atorvastatin) and 210 were not. Patients treated with a statin had substantial improvement in liver tests ($P < 0.0001$), whereas the group not treated with a statin had further increases in liver enzyme concentrations. Cardiovascular events occurred in 10% of atorvastatin-treated patients vs 30% of the non-statin group (60% relative risk reduction; $P > 0.0001$). This was a greater improvement in benefit than seen in patients with normal liver function tests. Fewer than 1% of the participants who received a statin had to discontinue statin treatment because of transaminase concentrations more than three times the upper limit of normal. The authors concluded that "statin treatment is safe and can improve liver tests and reduce cardiovascular morbidity in patients with mild to moderately abnormal liver tests that are potentially attributable to nonalcoholic fatty liver disease" (*Lancet* 2010;376:1916-1922). ■

Dosing timing for thyroxine

When is the best time to take thyroxine? Patients are generally told to take it on an empty stomach in the morning and wait at least 30 minutes before eating. A new study suggests that taking thyroxine at bedtime might be a better option. Over 6 months, 105 patients were randomized to take 1 capsule in the morning and 1 capsule at bedtime (one containing levothyroxine and the other a placebo), with a switch after 3 months. Taking levothyroxine at bedtime lowered thyrotropin levels and increased free thyroxine and total triiodothyronine levels (the primary outcome). Treatment did not change secondary outcomes including quality of life. The authors concluded that taking levothyroxine at bedtime is a good alternative to morning intake (*Arch Intern Med* 2010;170:1996-2003). This would likely benefit patients who find it difficult to wait 30 minutes to eat after taking their thyroxine each morning. ■

Rivaroxaban: an oral, factor Xa inhibitor

Rivaroxaban is an oral, direct factor Xa inhibitor that is approved in several countries for the prevention of venous thromboembolism (VTE) after orthopedic surgery. It is currently being evaluated by the FDA for this indication. Based on the findings of the EINSTEIN study, it appears the drug is also effective for the treatment of acute deep vein thrombosis (DVT). EINSTEIN consists of three randomized trials of rivaroxaban, one for the treatment of acute DVT, one for treatment of acute pulmo-

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nary embolism, and one for continued, long-term treatment in patients who have received treatment for acute DVT or pulmonary emboli. The results of the first and third wings of the study were recently reported in the *New England Journal of Medicine*.

In the DVT treatment arm, 3449 patients with acute DVT were randomized to rivaroxaban (50 mg twice daily for 3 weeks, followed by 20 mg once daily) or subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months. In the continued treatment wing of the study, patients were randomized in a double-blind fashion to rivaroxaban 20 mg once daily or placebo for additional 6 or 12 months after completion of 6-12 months of treatment for VTE. The primary outcome for both studies was recurrent DVT. For the treatment of acute DVT, rivaroxaban was non-inferior to enoxaparin-vitamin K antagonist (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.44-1.04; $P < 0.001$). In the continued treatment study, rivaroxaban had superior efficacy compared to placebo (8 events [1.3%] vs 42 events [7.1%] with placebo; HR 0.18; 95% CI, 0.09-0.39; $P < 0.001$). There were four patients in the rivaroxaban group with non-fatal major bleeding vs none in the placebo group. The EINSTEIN authors concluded that "Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation" (*N Engl J Med* 2010;363:2499-2510).

Rivaroxaban is also being evaluated for the prevention of stroke in patients with nonvalvular atrial fibrillation based on the ROCKET AF study, which was presented at the American Heart Association meetings in November 2010. If approved, it will join the recently approved direct thrombin inhibitor dabigatran (Pradaxa®) for this indication. Both drugs have the advantage over warfarin of not requiring ongoing lab monitoring. ■

Echinacea and the common cold

The National Center for Complementary and Alternative Medicine (NCCAM), a division of NIH, has been in existence for nearly 20 years, much of the time under the intense scrutiny of the mainstream medical community. Despite NCCAM's attempts to verify the effectiveness of alternative healing practices, most if not all rigorously studied modalities have been shown to be ineffective. The benefit of another alternative staple, echinacea, is questioned with the publication of a NCCAM-sponsored study testing the benefit of the herbal remedy for treating the common cold. More than 700 patients in Wisconsin with new-onset common cold were assigned to one of four groups: no pills, placebo pills (blinded), echinacea pills (blinded), or echinacea pills (unblinded). The primary outcome was severity of the cold by self reporting with secondary outcomes of interleukin-8 levels and neutrophil counts from nasal washes. The comparison of the two blinded groups showed a trend toward benefit for the echinacea group (an average decrease in duration of cold of 7-10 hours out of 1 week; $P = 0.089$), but no difference in mean illness duration. There were no differences in the secondary outcomes. The authors concluded that the differences in illness duration and severity were not statistically significant with echinacea compared to placebo (*Ann Intern Med* 2010;153:769-777). ■

FDA Actions

The FDA is removing the breast cancer indication for bevacizumab (Avastin-Genentech). The somewhat unusual move was made after an FDA advisory panel suggested last summer that the drug did not provide a survival benefit for patients with breast cancer and at the same time caused serious side effects. The drug is still approved for treating cancer of the brain, colon, kidney, and lung.

The **FDA advisory panel is recommending approval for the first new diet pill in a decade. Orexigen Therapeutics' Contrave® is a combination of the antidepressant bupropion and the opioid antagonist naltrexone.** The drug was recommended for approval by a vote of 13-7, with some committee members voicing concern about potential side effects of the drug and recommending close post-marketing follow-up and studies to assess the risk of major cardiac events. The recommendation to approve the drug was based on studies that show an average weight loss 4.2% greater than placebo.

The **FDA has approved denosumab for the prevention of skeletal related events (fracture and bone pain) in patients with bone metastases from solid tumors.** The drug, which is given as a once monthly injection, was approved after a 6-month priority review. Denosumab is a monoclonal antibody to RANKL, a protein essential for the formation, function, and survival of osteoclasts. Denosumab in a lower-dose formulation was recently approved for the treatment of osteoporosis under the trade name Prolia™. Amgen Inc. will market the drug for this new indication under the trade name Xgeva™. It is expected to compete strongly with Novartis Pharmaceutical's zoledronic acid (Zometa®), which is approved for the same indication. ■