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## INSIDE



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# Peripheral Neuropathy in Small Vessel Systemic Vasculitides

ABSTRACT & COMMENTARY

***By Michael Rubin, MD, FRCP(C)***

*Professor of Clinical Neurology, Weill Cornell Medical College*

*Dr. Rubin is on the speaker's bureau for Athena Diagnostics, and does research for Pfizer and Merck.*

***Synopsis:*** *Axonal neuropathy is common in patients with biopsy-proven small vessel systemic vasculitis (SVSV), and responds to immunosuppressive therapy.*

**Source:** Cattaneo L, Chierici E, Pavone L, et al. Peripheral neuropathy in Wegener's granulomatosis, Churg-Strauss syndrome and microscopic polyangiitis. *J Neurol Neurosurg Psychiatry* 2007;78:1119-1123.

SMALL VESSEL SYSTEMIC VASCULITIS (SVSV), CHARACTERIZED BY serologic positivity of antineutrophil cytoplasmic antibodies (ANCA) and inflammatory involvement of venules, capillaries, and arterioles, includes Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS), and microscopic polyangiitis (MP). Any organ system, including the peripheral nervous system (PNS), may be affected. Among the 64 consecutive patients with SVSVs included in this study, periodic neurologic and electrodiagnostic studies were performed to determine differences of PNS involvement with these conditions. Inclusion into this cohort study was based on a definitive diagnosis of vasculitis and clinical and serologic parameters, using American College of Rheumatology criteria for WG and CSS, and Chapel Hill Consensus Conference criteria for MP. Exclusionary criteria comprised other causes for neuropathy, including diabetes mellitus, alcoholism, paraproteinemia, HIV or Lyme disease, hypothyroidism, vitamin deficiency, heavy metal intoxication, cancer, celiac disease, or family history of neuropathy. Periodic follow-up for up to 88 months (mean 37 months) encompassed a neurological examination, electrodiagnostic studies of 3 motor and 4 sensory nerves with needle electromyographic study of distal leg muscles, functional disability score, and Birmingham Vasculitis Activity Score type 1 (BVAS). Statistical analysis was performed using univariate factorial ANOVA and Bonferroni corrected t tests, with statistical significance placed at 0.05

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In the 64-patient cohort, 26 were diagnosed with WG, 26 with CSS, and 12 with MP. Neuropathy was seen in 27 patients, more frequently in men ($p<0.01$) only in the CSS group; was always axonal; and occurred early, within 2 months of systemic disease onset, in 16. Mononeuropathy or mononeuropathy multiplex was present in 16 patients, 4 presented with cranial neuropathy, and distal symmetric polyneuropathy occurred in 11. WG and MP comprised 6 each, and CSS 15. No correlation was seen between disease subset, form of neuropathy, age of onset, or antineutrophil cytoplasmic antibodies (ANCA) positivity or pattern. WG patients tended to develop neuropathy later in the course of their disease compared to CSS and MP; they also were older than non-neuropathy WG patients at the time of disease onset and diagnosis. Steroids and cyclophosphamide resulted in clinical and electrophysiologic improvement, improved functional disability score, and decreased BVAS. Only 1 WG patient experienced a relapse 4 years later.

## COMMENT

Leukocytoclastic vasculitis, the histopathologic hallmark of SVSV, is characterized by angiocentric segmental inflammation, endothelial cell swelling, postcapillary venular wall fibrinoid necrosis, and a predominantly neutrophilic cellular infiltrate around and within dermal blood vessel walls showing fragmentation of nuclei (karyorrhexis or leukocytoclasia).[1] Most forms of SVSV are idiopathic (45-54%), but bacterial and hepatitis B antigens may be present within small vessel walls, and infections (10-36%), including hepatitis B (5%), influenza vaccination, and medications (10-45%), particularly beta-lactam antibiotics and diuretics but also aspirin, interferons, and sulfonamides, may be causative. Immunoglobulin deposits within the vessel walls are scarce, engendering the designation of these disorders as pauci-immune small-vessel vasculitides. ANCA are closely associated, useful for diagnosis, and at least in some patients, correlate with disease severity and may be helpful in predicting relapse. Proper treatment can induce remission of active disease and prevent irreversible end-organ damage. ■

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# Transient Ischemic Attacks: A Neurologic Emergency?

ABSTRACT & COMMENTARY


***By Dana Leifer, MD***

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*Dr. Leifer reports no financial relationship relevant to this field of study.*



***Synopsis:*** *Two recent studies suggest that rapid TIA evaluation and treatment can reduce stroke risk.*


**Sources:** Lavallée PC, Meseguer E, Abboud H, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. *Lancet Neurology* 2007;6:953-960; Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet* 2007;370:1432-1442.

Recent evidence suggests that there is a significant risk of stroke after transient ischemic attack (TIA) and that TIAs precede as many as a quarter of strokes. The risk of recurrent stroke in the first week after a TIA or minor stroke is as high as 10%. Nevertheless, patients with a TIA often do not receive a rapid, comprehensive evaluation. Two recent studies provide evidence that rapid intervention after TIA actually does reduce the risk of stroke.

In the SOS-TIA trial, Lavallée and colleagues randomized patients between standard medical care and rapid evaluation at a specialized TIA clinic located in Paris, France. This clinic was available 24 hours per day, 7 days

per week. The clinic was advertised in mailings to physicians and emergency departments throughout the Paris metropolitan area. Patients received evaluation within 4 hours of admission, including examination by a vascular neurologist, CT or MRI, carotid duplex ultrasound, transcranial Doppler, and ECG. Echocardiography was performed when cardiac embolism was suspected. Blood tests, including fasting lipid panel and glucose, hemoglobin A1c, C-reactive protein, creatinine, and CBC, were performed. Patients who were not fasting returned at a later time for lipid studies and glucose measurement. Antithrombotic therapy was started in almost all patients, and therapy to lower blood pressure and cholesterol were begun when appropriate. Patients with atrial fibrillation were admitted for anti-coagulation, and patients with high-grade carotid stenoses were admitted for revascularization.

During the three years of the study, 1085 patients were evaluated, with the number increasing from 316 in the first year to 407 in the last year. As expected from prior studies, symptoms were short in duration, with a median length of 10 minutes in the 535 patients with definite clinical TIAs and no brain damage on imaging, and 15 minutes in the 108 patients with definite clinical TIAs and brain tissue damage. The main finding was that the 90-day risk of stroke was only 1.24%; the expected risk based on $ABCD^2$ scoring[1] was 5.96%. When the sample was limited to the 552 patients seen within 24 hours of their TIA, the 90-day stroke risk was 1.63% compared to an expected risk of 6.49%. These results suggest that rapid evaluation of TIA patients is effective in reducing stroke risk, although the lack of a control group is admittedly a shortcoming of the study. The results appear to reflect a variety of interventions. Of those with TIA or minor stroke, 98% were started on antithrombotic therapy. Thirty patients were started on oral anticoagulation for atrial fibrillation. Antihypertensive therapy was started or modified in 28% of the 701 patients with definite TIA or minor stroke, and lipid-lowering therapy was started or modified in 45%. Carotid revascularization was performed in 43 patients, with a median delay of 6 days.

Another recent study by Rothwell and co-workers provides additional evidence for the efficacy of rapid evaluation of TIA patients. In the initial baseline period, TIA patients were referred to a specialized clinic but received scheduled appointments, with a median delay of 3 days from referral. Subsequent tests were generally scheduled within a week of the initial clinic appointment, and treatment recommendations were made to the referring physician but not started by the TIA clinic. In the second phase of the study, referring physicians were instructed to send suspected TIA patients directly to the clinic on a walk-in basis. Antithrombotic treatment was begun in the clinic after brain imaging, which was performed on the day of evaluation in the clinic when appropriate. The main finding was that the 90-day risk of stroke fell from 10.3% in the first phase to 2.1% in the second phase (p=0.0001). The findings appear to reflect several differences in treatment between the two phases. At 30-day follow-up, patients in the second phase were more likely to be receiving statin treatment, to be on antihypertensive therapy, and to be treated with aspirin and clopidogrel in combination. Mean blood pressures were lower at 30 days in phase 2. Similar numbers of patients underwent carotid surgery, but surgery was performed more quickly in phase 2.

In conclusion, these two papers both provide evidence that rapid evaluation and treatment (within 24 hours) of TIA patients are likely to reduce the risk of stroke. The results suggest that additional efforts to educate the general population and health care providers about the importance of dealing with TIAs as an emergency will reduce the incidence of stroke. ■

### Reference


1. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. *Lancet* 2007;369:283-292.


### *Correction*

In the January 2008 (Vol. 26, No. 5) issue of *Neurology Alert,* Dr. Cynthia Harden's disclosure information was incorrectly listed. It should have been: Dr. Harden reports that she has received grant/research support from UCB and Eisai Inc.; is a retained consultant for GlaxoSmithKline; and is on the speaker's bureau for UCB, GlaxoSmithKline, and Pfizer. ■

# Limb Girdle Muscular Dystrophy

ABSTRACT & COMMENTARY


***By Michael Rubin, MD, FRCP(C)***

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*Dr. Rubin is on the speaker's bureau for Athena Diagnostics, and does research for Pfizer and Merck.*



***Synopsis:*** *Proteomic and molecular genetic testing is a critical part of the diagnostic algorithm for limb girdle muscular dystrophy (LGMD).*


**Source:** Norwood F, de Visser M, Eymard B, et al. EFNS guideline on diagnosis and management of limb girdle muscular dystrophies. *Eur J Neurol* 2007;14:1305-1312.

Molecular biology has evoked a peaceful revolution in neurology, particularly in the delineation and classification of the various forms of limb girdle muscular dystrophy (LGMD). It's time for an update. First described by Walton and Nattrass,[1] 21 forms are currently classified based on linkage studies and are divided between those that are autosomal dominant (n = 5), designated LGMD1A-E, or autosomal recessive (n = 14), designated LGMD2A-N. Two of the dominant forms may, in rare instances, be recessive. Such molecular diagnosis has more than only nosological value, as certain forms carry cardiac or respiratory complications that may warrant early intervention. Based on a MEDLINE, Cochrane database, and EMBASE search, among others, the following consensus recommendations for the management of LGMD were devised by the European Federation of Neurological Societies (EFNS).

Although all LGMDs demonstrate pelvic and shoulder girdle involvement, thorough clinical assessment remains the backbone of evaluation and should guide further investigation. Some clinical pearls of note will be listed here. Neonatal hypotonia, commonly seen in congenital muscular dystrophy and myopathy, is seen only in LGMD1B, involving the lamin A/C gene mutation. Neonatal contractures are not seen in LGMD, but may occur later in childhood, along with spinal rigidity, most commonly in LGMD1B and more mildly in LGMD2A (calpain 3 gene mutation). Purely distal muscle involvement may be seen in early LGMD2B (Miyoshi type dysferlin deficiency), LGMD1B, or LGMD1C (caveolin 3 gene mutation). Scapular winging most frequently is seen in LGMD2A and 2C-F (sarcoglycan gene mutations), while hip abductors are relatively preserved in LGMD2A. Muscle hypertrophy may be seen, usually involving the gastrocnemius, but it may involve other muscles as well. This may include the tongue in LGMD1C, LGMD2C-F (where scoliosis is most often seen among the LGMD), and LGMD2I (fukutin-related protein gene mutation, FKRP, one of the most common forms of LGMD). LGMD2I muscle hypertrophy, associated with cardiac and respiratory compromise, may be misdiagnosed as Becker's muscular dystrophy. Geographically, only Brazilians are reported with LGMD2G (telethonin gene mutation) and only Canadians with LGMD2H (TRIM32 gene mutation). Finland had the first LGMD2J (titin gene mutation) cases. Cardiomyopathy or dysrhythmias are common in LGMD1B, LGMD2C-F, and LGMD2I. Respiratory muscle weakness is common in LGMD2C-F and LGMD2I.

Patient workup should include serum creatine kinase (CK) measurement. CK is normal or mildly elevated in LGMD1A and 1B; moderately elevated in LGMD1C, 2A, 2C-F, and 2I; or more than ten-fold elevated in LGMD2B. Electrodiagnostic studies add little but will exclude neuropathy. Muscle imaging does not yet warrant the expense or trouble, but can preempt selecting an end-stage muscle for biopsy. Muscle tissue is best obtained by open biopsy, and standard histological techniques as well as immunohistochemistry and immunoblotting should be performed. DNA analysis remains the gold standard for diagnosis and allows for carrier identification and presymptomatic diagnosis.

Consultation with pulmonologists for LGMD2C-F and 2I, and cardiologists for LGMD1B, 2C-F, and 2I, is critical, as these forms are associated with hypoventilation, respiratory failure, conduction defects, or cardiomyopathy. Physical therapy is probably beneficial but no papers specifically address this issue. Genetic counseling is appropriate. No drug is of profound benefit for LGMD but creatine produced a 3% benefit in 6 patients with sarcoglycanopathy. Co-enzyme Q10 (ubiquinone) has not been studied. Prednisone has been empirically used with some benefit in LGMD2C-F because of its reported benefit in Duchenne dystrophy. More recently, prednisolone (0.35 mg/kg/d) was reportedly beneficial in two LGMD2I patients.[2] Although both developed dilated cardiomyopathy during treatment, this was felt to be a consequence of the disease rather than the treatment.

## COMMENTARY

Any online literature search quickly reveals that the LGMD medical literature is overwhelming, making it barely possible to keep abreast given the sheer number of papers published. Novel mutations are reported weekly, as are variant phenotypes, but most are irrelevant to the average busy practitioner. Yet a recent literature review yielded this clinically relevant question: Should testing for the protein deficiency be performed before or after DNA analysis? The answer is: Before. Nevertheless, it appears that although molecular diagnosis has greater success when a protein alteration already has been detected, efficiency varies between LGMD forms.[3] Doubling of the LGMD2A mutation detection rate was achieved when the calpain 3 protein test was previously performed, whereas sarcoglycanopathy diagnosis was 20-fold greater when molecular testing followed muscle biopsy immuno-fluorescence. Let the clinician beware.

## References


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3. Darin N, Kroksmark AK, Ahlander AC, et al. *Neuromuscul Disord* 2007;17:810-811.

# Post-craniotomy Headaches After Surgery

ABSTRACT & COMMENTARY

***By Dara G. Jamieson, MD***

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*Dr. Jamieson is a consultant for Boehringer Ingelheim and Merck, and is on the speaker's bureau for Boehringer Ingelheim, Merck, Ortho-McNeil, and Pfizer.*

***Synopsis:*** *Acute and chronic head and face pain occur after craniotomies for a variety of intracranial lesions. Persistent postoperative pain is more common in women and is associated with depression and anxiety.*

**Sources:** Rimaaja T, Haanpää M, Blomstedt G, et al. Headaches after acoustic neuroma surgery. *Cephalalgia* 2007;27:1128-1135; Rocha-Filho PA, Gherpelli JL, de Siqueira JT, et al. Post-craniotomy headache: characteristics, behaviour and effect on quality of life in patients operated for treatment of supratentorial intracranial aneurysms. *Cephalalgia* 2007;28:41-48; Rocha-Filho PA, Fujarra FJ, Gherpelli JL, et al. The long-term effect of craniotomy on temporalis muscle function. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;104:e17-e21.

SOME NEUROSURGICAL PATIENTS LEAVE THE HOSPITAL with more than just a scalp scar and the reassurance of having a resected acoustic neuroma or a clipped aneurysm. Post-craniotomy headaches can be frustrating for neurosurgeons and their referral neurologists, but are especially so for patients who thought that brain surgery would end their neurological symptoms. The International Headache Society (IHS) recognizes chronic post-craniotomy headache as a headache, maximal in the surgical area, that develops within 7 days of the craniotomy and persists for at least 3 months. An acute post-craniotomy headache has the same characteristics but lasts for less than 3 months. Both supra- and infratentorial surgeries for multiple types of intracranial lesions can cause craniofacial pain that persists postoperatively. These three papers, two from the University of San Paulo and one from Helsinki University, review the chronic head and face pain syndromes that can result from craniotomy.

Rimaaja and researchers noted that preoperative headaches occur in a variable percentage of patients undergoing acoustic neuroma surgery, but postoperative headaches persist in up to one-third of patients a year after resection. The aim of this study, which reviewed the charts of 241 patients who underwent acoustic neuroma surgery from January 1995 to September 2002 at Helsinki University Hospital, was to assess headaches after the operation. The authors sent out questionnaires to evaluate pre- and postoperative headache characteristics as well as symptoms of depression in 228 living, traceable patients, of whom 84% responded. About one-third of patients had preoperative headaches, but twice that number had postoperative headaches. Of the 122 patients who reported any postoperative headache, 110 noted either only post-craniotomy headaches or distinctly different, new post-craniotomy headaches. Three quarters of the patients with new postoperative headaches had headaches that persisted for at least a year after surgery. Possible predictors of chronic postoperative headache were female gender ($p=0.04$), lack of previous headache ($p=0.005$), and small tumor size ($p<0.0001$). All patients with new postoperative headaches had acoustic neuroma resection with a retrosigmoid approach. Of the new postoperative headache patients, one-third of those with continuing headaches had depression; however, only 9% of the patients without continuing postoperative headaches had depression, as assessed by the Beck Depression Inventory. Physical stress, bending, or coughing typically aggravated the headaches, which may relate to sensitization of dural sensory pathways. The authors suggested simple analgesics for acute pain relief and tricyclic antidepressants or gabapentin for preventative therapy.

Rocha-Filho and coworkers evaluated craniofacial pain after resection of supratentorial cerebral aneurysms. In one paper, they retrospectively evaluated the jaw movements and masticatory muscles of 71 patients at 4-6 months after craniotomy by a pterional approach. About 48% of post-craniotomy patients complained of craniofacial pain with normal jaw movement or activities. More than half of the patients complained of pain in muscle of mastication. Those patients with post-craniotomy headache were more likely to have marked masticatory muscle tenderness than those without headache after surgery.

The same group at the University of San Paulo prospectively followed 79 patients who survived operative treatment of a supratentorial aneurysm between October 2002 and October 2003. The patients, who all had a Glasgow Coma Scale score of 15 prior to surgery, were divided into a group without subarachnoid hemorrhage (SAH), a group with SAH but no pre-operative headache, and a group with SAH and a preoperative headache. They were followed for up to 6 months after surgery, with chronic post-craniotomy headaches defined by IHS criteria as occurring at 3 months. Headaches were observed in more than 90% of patients after surgery, decreasing to 60% at a week postoperatively. An increase in mean headache frequency was observed postoperatively, with a decrease in headache frequency over time in all study groups. Using IHS criteria, the incidence of

acute (< 3 months) post-craniotomy headache was 10.7%, with a 29.3% incidence of chronic (> 3 months) headache. Headaches were both migrainous and non-migrainous in description. While 40% of patients who did not have SAH had chronic post-craniotomy headache, almost all of those patients had a primary headache disorder prior to aneurysm resection. Increasing the time period for the onset of post-craniotomy headache from 7 days to 30 days increased the number of patients defined as suffering from a post-craniotomy headache. There was a significant, positive correlation between anxiety and depression and headache frequency. Pain intensity was higher in women and in patients with more symptoms of anxiety. Post-craniotomy headache had significant negative effects on patients' quality of life.

## COMMENTARY

These two groups published papers that assessed the prevalence and characteristics of post-craniotomy headaches associated with different intracranial lesions. Any evaluation of a post-craniotomy headache must take into account the high prevalence of primary headaches (migraine and tension-type) in the population, as well as the headaches associated with the underlying intracranial lesion that necessitated surgery. However, chronic headaches related to the surgery commonly occur in patients after craniotomy. While a rare immediate postoperative headache may be due to surgical complications, the vast majority of acute and chronic post-craniotomy headaches have no underlying anatomic correlate and may be related to a disturbance of dural nociceptive receptors. Patients should be prepared prior to surgery for the possibility of persistent headaches, and given reassurance that headaches developing after surgery are expected and treatable. Recognition of the common occurrence of these post-craniotomy headaches can forestall unnecessary invasive interventions to diagnose or treat the acute or chronic headache precipitated by neurosurgery.

# Serum Concentrations of Retinol-binding Protein and Retinol in Patients with and without IIH

ABSTRACT & COMMENTARY

***By Erik J. Kobylarz, MD, PhD***

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*Dr. Kobylarz reports no financial relationship relevant to this field of study.*

***Synopsis:*** *Increased levels of retinol in CSF in patients with IIH suggests that vitamin A may be involved in the pathogenesis of IIH.*

**Source:** Warner JE, Larson AJ, Bhosale P, et al. Retinol-binding protein and retinol analysis in cerebrospinal fluid and serum of patients with and without idiopathic intracranial hypertension. *J Neuroophthalmol* 2007;27:258-262.

IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH), OR pseudotumor cerebri, is a neurologic condition with increased intracranial pressure (ICP) in the setting of normal cerebrospinal fluid (CSF) composition. This condition causes headache and papilledema, often resulting in progressive vision loss. In an effort to further understand the potential role of vitamin A-related compounds in the pathogenesis of IIH, Warner and colleagues compared CSF and serum concentrations of retinol and retinol-binding protein (RBP) in patients with and without IIH.

CSF and serum samples were collected from 87 patients, 28 of whom had been diagnosed with IIH. Of the remaining patients, 42 had non-IIH neurologic conditions and 17 had no known neurologic conditions but were undergoing preoperative lumbar punctures for anesthesia. RBP levels were determined using radial immunodiffusion (RID), and retinol levels were measured by means of high-performance liquid chromatography (HPLC).

In this study, higher serum retinol levels and lower CSF RBP levels occurred in the IIH patients, compared with those in controls. In addition, there was a more significant elevation in the CSF retinol/RBP ratios compared with those in serum in patients with IIH.

## COMMENTARY

A number of studies have implicated vitamin A compounds in the pathogenesis of idiopathic intracranial hypertension.[1-4] However, this is the first study comparing serum and CSF concentrations of both retinol and RBP in patients with and without IIH.

In this article, Wagner and coworkers report significantly increased unbound CSF and serum retinol levels, elevated retinol to RBP ratios more significantly in CSF, and significantly decreased CSF RBP levels in patients with IIH. When controlling for increased body mass index (BMI), the IIH patients had significantly increased serum RBP and free retinol, as well as decreased CSF RBP levels and elevated CSF retinol/RBP ratios compared with the controls. These results provide further evidence for the involvement of vitamin A in this disease process.

Additional studies with a larger number of subjects are needed to elucidate the pathophysiology of IIH (i.e.,

the specific role of vitamin A, such as its potential toxicity to arachnoid villi, resulting in decreased CSF reabsorption). These studies should take into account the concurrent effects of BMI, estrogen levels, and age. In addition, due to the multivariate statistical relationships demonstrated by this group, further investigation of the correlations between vitamin A and retinol and RBP levels in CSF and serum is warranted. ■


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3. Tabassi A, Salmasi AH, Jalali M. *Neurology* 2005;64:1893-1896.
4. Warner JE, Bernstein PS, Yemelyanov A, et al. *Ann Neurol* 2002;52:647-650.


# Toward a Functional Anatomy of Tourette Syndrome

ABSTRACT & COMMENTARY


***By Claire Henchcliffe, MD, DPhil***

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*Dr. Henchcliffe reports that she is on the speaker's bureau for the following companies: GlaxoSmithKline, Teva, Boehringer Ingelheim, Schwarz Pharma, and Allergan.*


***Synopsis:*** *Functional MRI (fMRI) measurements in unmedicated children with Tourette syndrome during cognitively difficult tasks suggest increased "direct" pathway activity in the basal ganglia, and possible compensatory mechanisms involving the subthalamic nucleus and prefrontal cortex.*



**Source:** Baym CL, Corbett BA, Wright SB, et al. Neural correlates of tic severity and cognitive control in children with Tourette syndrome. *Brain* 2008;131(Pt 1):165-179.


THIS STUDY ADDRESSES TWO CRITICAL YET POORLY understood issues in Tourette syndrome (TS): the association of cognitive deficits with TS, and the nature of the neuronal networks that are disrupted in this developmental disorder. Eighteen children with TS (mean age 10.42 years, range 7-13 years, 15/18 boys), were recruited through the Tourette Syndrome Association, advertisements, referrals, and UC Davis; and were compared with 19 healthy matched volunteers (mean age 10.33 years, 11/19 boys) recruited via local schools, recreational centers, and fliers. TS diagnosis was based upon DSM-IV criteria. Of the 18 children with TS, 16 had never taken medication for the condition, 1 had taken no medication for 1 month, and 1 had withdrawn medication 40 hours prior. All children with TS scored higher on evaluation of tic severity, executive dysfunction, OCD and ADHD symptomatology, anxiety, and behavioral and social communication. In all subjects, fMRI data were acquired during response to 3 types of tasks representing aspects of cognitive control: 1) task-switching; 2) response selection (ignoring competing information); and 3) rule representation. In TS subjects, tic severity correlated with increased activation of the substantia nigra/ventral tegmental area (SN/VTA), striatum and globus pallidus pars interna (GPi), thalamus, motor cortex, nucleus accumbens, and subthalamic nucleus (STN). Moreover, during task performance, TS subjects displayed higher activation of the left prefrontal cortex compared with control subjects.

## ■ COMMENTARY

TS is a developmental disorder characterized by motor and vocal tics (the latter may be words, phrases, or more complex sentences or simply grunts or throat-clearing). However, individuals with TS typically suffer from an array of "non-motor" symptoms, including ADHD and OCD (in this study using the Conners' and CY-BOCS rating scales, 7/18 TS subjects scored in the clinical range for OCD, 1/18 for ADHD, and 2/18 for OCD/ADHD), and problems with cognitive flexibility and inhibitory control have been particularly evident. The present study builds upon evidence pointing to deficits in TS in processing in the prefrontal cortex and striatum, regions important for cognitive control. Unlike previous studies though, children were unmedicated, arguing against changes simply representing medication effects. fMRI measurements defined several important regions of increased activation correlating with tic severity (i.e., presumed associated with TS and not its comorbid conditions). 1) Increased activation of the SN/VTA (containing abundant dopaminergic neurons) fits with previous data implicating dopamine dysfunction in TS. 2) The authors suggest that heightened activation in the striatum, GPi, thalamus, and motor cortex may be linked, representing activation of the "direct" pathway, important in motor control. 3) The nucleus accumbens demonstrated increased activation in this study, which may be consistent with a role in reinforcing behavior. 4) While activation of the STN might initially seem coun-

terintuitive, the authors hypothesize that the "hyperdirect" pathway from cortex to STN would compensate for "direct" pathway activation. In summary, despite limitations inherent to this type of neuroimaging study, these data represent an important step toward dissecting the complex neural changes occurring in TS. This is critical. Since as novel therapeutic approaches such as deep brain stimulation are now being developed for TS, it is imperative that the neural underpinnings and any cognitive comorbidities are better understood. ■

## CME Questions

5. **Small vessel systemic vasculitides (SVSVs):**
   a. are characterized by serologic positivity of antineutrophil cytoplasmic antibodies (ANCA).
   b. are characterized by inflammatory involvement of venules, capillaries, and arterioles.
   c. include Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis.
   d. demonstrate leukocytoclastic vasculitis as their histopathologic hallmark.
   e. All or none of the above are correct

6. **Rapid evaluation and initiation of treatment of transient ischemic attacks reduces the risk of stroke.**
   a. True
   b. False

7. **Which of the following may result in reduction of the risk of stroke after TIA?**
   a. Rapid initiation of antithrombotic therapy
   b. Rapid initiation of statin therapy
   c. Rapid initiation of antihypertensive therapy
   d. Rapid carotid revascularization
   e. All of the above

8. **Which of the following statements regarding limb girdle muscular dystrophies (LGMDs) is correct?**
   a. All LGMDs demonstrate pelvic and shoulder girdle involvement.
   b. Among LGMDs, neonatal hypotonia is seen only in LGMD1B, involving the lamin A/C mutation.
   c. Neonatal contractures are not seen in LGMDs
   d. Muscle hypertrophy, usually involving the gastrocnemius, also may involve other muscles.
   e. All of the above

9. **Persistent craniofacial pain after craniotomy:**
   a. is uncommon and rarely disabling.
   b. is only seen with posterior fossa lesions.
   c. is only seen in patients with preoperative headaches.
   d. may be correlated with anxiety and depression.
   e. rarely lasts a year after surgery.

10. **Wagner and colleagues found all of the following results in patients with IIH *except*:**
    a. elevated CSF retinol to RBP ratio.
    b. elevated CSF free retinol.
    c. elevated serum free retinol.
    d. decreased serum RBP.
    e. elevated serum retinol to RBP ratio.

11. **fMRI identifies increased activation in *all but which* of the following structures during cognitive control task performance in Tourette syndrome?**
    a. Substantia nigra-ventral tegmental area (SN/VTA)
    b. Subthalamic nucleus (STN)
    c. "Direct" pathway
    d. "Indirect" pathway
    e. Striatum

Answers: 5. e; 6. a; 7. e; 8. e; 9. d; 10. d; 11. d

## CME Objectives

The objectives of *Neurology Alert* are:

- To present the current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;
- To discuss the pathogenesis and treatment of pain;
- To present basic science lessons in brain function;
- To discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs;
- To discuss nonclinical issues of importance to neurologists, such as the right to die and the physician's legal obligation to patients with terminal illness. ■



## In Future Issues:

**Genetic Causes of Epilepsy**

# PHARMACOLOGY WATCH

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


## Another Study Implicates Avandia

***In this issue:*** *Rosiglitazone (Avandia) implicated in yet another study; Prilosec and Nexium not associated with cardiac events; Anastrozole (Arimidex) shown more effective than tamoxifen for treatment of early-stage breast cancer; antibiotics show no effect on sinusitis; FDA actions.*

THE HANDWRITING MAY BE ON THE WALL FOR GlaxoSmithKline's rosiglitazone (Avandia) with yet another study implicating the drug with an increased risk of heart failure, cardiovascular events and mortality when compared to other oral hypoglycemic agents. The study was a nested case-control analysis of a retrospective cohort study using health care databases in Ontario. The patient population was nearly 160,000 older (>65 years of age) type 2 diabetics on at least one oral agent. The primary outcome was emergency visit or hospitalization for congestive heart failure, while secondary outcomes were AMI and all-cause mortality. After a mean follow-up of 3.8 years, monotherapy with rosiglitazone was associated with an increased risk of CHF (RR 1.60; 95% CI 2.10; *P*<.001), AMI (RR 1.40; 95% CI, 1.05-1.86; *P*=.02), and death (RR 1.29; 95% CI, 1.02-1.62; *P*=.03). Thiazolidinediones in general were evaluated in the study, but the adverse effects were limited to rosiglitazone. Adverse effects were found in patients who took the drug as a single agent or in combination with other hypoglycemic drugs (*JAMA*. 2007;298:2634-2643). Meanwhile, two large pharmacy benefit managers, Prime Therapeutics and HealthTrans, have dropped rosiglitzone from their formularies and the Department of Veterans Affairs is severely limiting the drug's use. Sales of the drug dropped 27% in the second quarter of 2007 and 39% in the third quarter.

### *Prilosec and Nexium Cleared*

Omeprazole (Prilosec) and esomeprazole (Nexium) are not associated with increased rates of cardiac events, according to statements on the FDA web site. Concern was raised after AstraZeneca submitted data from two long-term studies in patients with severe gastroesophageal reflux to assess treatment with either drug vs surgery. Evaluation of secondary outcomes raised the question of whether long-term use of these drugs increased risk of cardiovascular events including sudden death. In a statement published on the FDA web site (www.fda.gov) on December 10, the agency states that it has completed a comprehensive scientific review of known safety data for both drugs. Based on review of the two studies presented by AstraZeneca and analysis of 14 comparative studies of omeprazole, no evidence of increased rate of cardiac events was seen. "Therefore, FDA continues to conclude that long-term use of these drugs is not likely to be associated with an increased risk of heart problems. The FDA recommends that health-care providers continue to prescribe, and patient's continue to use, these products as described in the labeling for the two drugs."


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## Anastrozole over Tamoxifen for Breast Cancer

Anastrozole (Arimidex) is more effective than tamoxifen as adjuvant treatment for early-stage breast cancer according to a study published online as an early release in the *Lancet Oncology*. The study looked at 6241 women with locally invasive breast cancer who were randomized to anastrozole or tamoxifen and followed for a median of 100 months. Primary endpoints were disease-free survival, and secondary endpoints were time to recurrence, incidence of new contralateral breast cancer, time to distant recurrence, overall survival, and death after recurrence. Endpoints were evaluated in the total population and in the hormone-receptor-positive subpopulation. The primary endpoint and all secondary endpoints favored anastrozole except for deaths after recurrence and overall survival for which there is no significant difference. Fracture rates were higher in patients receiving anastrozole compared to tamoxifen. There was no difference in cardiovascular morbidity or mortality between the two treatment groups. The authors conclude that the study "establishes long-term efficacy of anastrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with hormone sensitive, early breast cancer, and provide statistically significant evidence of a larger carryover effect after five years of adjuvant treatment with anastrozole." (*Lancet Oncology* early online publication, 50 December 2007).

## Antibiotics and Steroids Not for Sinusitis

Antibiotics and topical nasal steroids are of no benefit for patients with acute maxillary sinusitis according to a new randomized controlled trial of 240 adults. Patients with acute non-recurrent sinusitis were randomized to treatment with antibiotics and nasal steroids, placebo antibiotic and nasal steroid, antibiotic and placebo nasal steroids, or placebo antibiotic and placebo nasal steroid. Amoxicillin 500 mg three times a day for seven days and budesonide spray once daily were the active drug use in the study. The main outcome was proportion of clinically cured at 10 days and the duration of symptoms. Antibiotics made no difference in the proportion of patients with symptoms lasting 10 days or more (29% with antibiotics, 33.6% with no antibiotics). Use of nasal steroid also made no difference for the same measure (31.4% with budesonide, 31.4% with no budesonide). The authors conclude that neither an antibiotic nor topical steroid alone or in combination was effective as the treatment for acute sinusitis in the primary care setting (*JAMA*. 2007;298:2487-2496).

## FDA Actions

An expert advisory panel of the FDA has recommended against approving Merck's petition to take lovastatin (Mevacor) over-the-counter. This was the third request in 7 years for OTC status for the cholesterol-lowering drug. The advisers voted 10-2 against approval citing concerns whether patients were capable of determining if they are appropriate candidates for the medication. The FDA generally follows the advice of its advisory panels.

The FDA has approved yet another beta-blocker for the treatment of hypertension. MylanBertek's nebivolol (Bystolic) is a selective beta-1-adrenoreceptor blocker with vasodilating effects. The drug is the 19th beta-blocker approved in the United States.

Wyeth has received an approvable letter for bazedoxifene, a new selective estrogen receptor modulator (SERM) for the prevention of osteoporosis in postmenopausal women. In issuing the letter, the agency asked for more data on the risk of blood clots and stroke, problems that have plagued the other marketed SERM for this indication (raloxifene-Evista). The agency did not ask for new studies however. Wyeth is also seeking the indication for treatment of osteoporosis in postmenopausal women. When approved, bazedoxifene will be marketed as Viviant.

The FDA has issued a safety warning on fentanyl skin patches after several reports of deaths and life-threatening side effects associated with inappropriate use. The warning stresses that the patches are only for patients who are opioid-tolerant and have poorly controlled pain on other narcotic pain medications. The patches are not for postoperative pain or sudden or occasional pain. Patients who used the patch should be aware of the signs of fentanyl overdose. Patients and physicians should be aware of potential drug interactions and physicians and pharmacists need to instruct patients on appropriate use of the patch. Patients also need to be aware that heat sources such as heating pads, electric blankets, saunas, heated waterbeds, hot baths, sunbathing and even fever may result in sudden increases in blood levels of fentanyl.

The FDA has approved a new volume expander for the treatment of volume loss during surgery. German drugmaker Fresenius Kabi's Voluven utilizes a new synthetic starch that is insoluble in water. In clinical trials the product was found to be as safe and effective as Hespan, a currently approved starch solution volume expander. ■