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INSIDE

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Reversible Cerebral Vasoconstriction Syndrome (RCVS)

ABSTRACT & COMMENTARY

By John J. Caronna, MD
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Dr. Caronna reports no financial relationship relevant to this field of study.

Synopsis: *RCVS occurs in a variety of clinical settings, and should be considered and investigated in any person with sudden severe headache that is unexplained by other disorders.*

Source: Ducros A, Boukobza M, Porcher R, et al. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain* 2007;130(Pt 12):3091-3101.

DUCROS AND ASSOCIATES HAVE REPORTED THE LARGEST SERIES OF cases of the so-called "reversible cerebral vasoconstriction syndrome" (RCVS). RCVS is characterized by the association of severe or "thunderclap" headaches with or without neurological deficits, and a string of beads appearance of cerebral arteries that resolves spontaneously in 1-3 months. The authors prospectively followed 67 consecutive patients diagnosed at Lariboisiere Hospital in Paris with angiographically confirmed RCVS. There were 43 women and 24 men, with a mean age of 42 years (range, 19-70 years). RCVS was spontaneous in one-third and secondary in two-thirds of patients. More than one-half of the patients (n=37) reported the previous use of vasoactive substances (cocaine, cannabis, nasal decongestants, serotonin reuptake inhibitors, interferon, nicotine patches), which in some cases was combined with binge drinking. Five patients (12%) were just postpartum; only one had received bromocriptine after delivery to inhibit lactation.

Severe headache, by definition, was the presenting symptom in all patients and was the only symptom of RCVS in 51 patients (76%). Sixty-three patients (94%) had multiple thunderclap headaches (mean number, 4.5; range, 2-18) that recurred over a mean period of 7.4 days (range, 1-21). In 16 patients with complications, cortical subarachnoid hemorrhage (SAH) (22%), intracerebral

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hemorrhage (ICH) (6%), seizures (3%), and reversible posterior leukoencephalopathy (RPLS) (9%) were early complications that occurred mainly during the first week. Ischemic events including TIA (16%) and stroke (4%) occurred mainly during the second week.

The authors, therefore, hypothesize that the different time course and evolution of thunderclap headaches, SAH, and strokes indicate that the vasospastic disorder starts in small distal arteries and progresses to involve medium and large arteries.

No relapses were observed during the mean follow-up of 16 months. The authors concluded from their data that RCVS is more frequent than commonly thought and is more often than not secondary to exposure to vasoactive substances.

COMMENTARY

RCVS is a term that encompasses a group of disorders sharing angiographic and clinical features, namely reversible segmental and multifocal vasoconstriction of cerebral arteries, and severe headaches with or without focal neurological deficits. The names for this syndrome, among many others, include: benign cerebral angiopathy or vasculitis,[1] Call-Fleming syndrome,[2] and thunderclap headache with reversible vasospasm.[3] The pathophysiology of RCVS is not understood and the cause probably is multifactorial, given the numerous and heterogeneous precipitating events that may or may not be causally related to the syndrome. *(See Table.)*

In an editorial accompanying this report, van Gijn doubts that RCVS is a nosological entity because of the overlap with other syndromes such as migraine and the multitude of precipitating factors, as well as interobserver variation in what constitutes arterial narrowing on cerebral angiograms.[4] Nevertheless, Ducros and associates have done clinicians a great service by reporting their large series of RCVS patients in useful detail, thereby stimulating further research into this sometimes not-so-benign entity. ■

Table.
Conditions Associated with RCVS

- **I. Postpartum**
  - Postpartum alone and exposure to drugs, eclampsia, pre-eclampsia
- **II. Exposure to drugs**
  - Cannabis, cocaine, ecstasy, amphetamines, LSD
  - Binge alcohol drinking
  - SSRIs
  - Nasal decongestants, phenylpropanolamine, pseudoephedrine, ephedrine
  - Ergot derivatives, including triptans
  - Tacrolimus, cyclophosphamide, erythropoietin, IVIg, RBC transfusion
  - Interferon alpha
  - Nicotine patches
- **III. Catecholamine-secreting tumors**
  - Pheochromocytoma, bronchial carcinoid
- **IV. Miscellaneous**
  - Hypercalcemia, porphyria, head trauma, spinal subdural, post carotid endarterectomy, neurosurgery
- **V. Large artery lesions**
  - Cervical artery dissection, unruptured cerebral berry aneurysm, cerebral artery dysplasia

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1. Snyder BD, McClelland RR. *Arch Neurol* 1978;35:612-614.
2. Call GK, et al. *Stroke* 1988;19:1159-1170.
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Can Patients Accurately Report Seizure Frequency?

ABSTRACT & COMMENTARY

By Cynthia Harden, MD
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Dr. Harden reports no financial relationships relevant to this field of study.

Synopsis: *Patients with epilepsy are unaware of most of their seizures. Video-EEG is the most reliable method to accurately determine seizure frequency.*

Source: Hoppe C, Poepel A, Elger CE, et al. Epilepsy: accuracy of patient seizure counts. *Arch Neurol* 2007;64:1595-1599.

THIS STUDY AIMED TO DETERMINE IF REMINDING ADULT epilepsy inpatients to record seizure occurrence would improve documentation accuracy when compared to actual seizure occurrence on inpatient video-EEG recording. Ninety-one consecutive adult partial epilepsy patients were asked to document the occurrence of seizures during inpatient video-EEG monitoring. This information was then compared for accuracy against the actual recorded seizure occurrence. Out of 582 partial seizures recorded, patients failed to document 55.5% of seizures; daily reminders to record seizures did not improve the documentation rate. Seizures originating in the left hemisphere, either frontal or temporal, complex partial seizures, and seizures during sleep were associated with patients' documentation failure.

Important exclusion criteria were a history of pseudoseizures, prolonged subclinical seizure activity, and generalized epilepsy, for which an aura or immediate seizure warning usually would not occur. Not surprisingly, reminding the patients did not improve seizure documentation as compared to a group of patients randomly assigned not to have daily reminders.

The striking finding of this report is that the detection rate of seizure occurrence by patient report is very low, with patients reporting only about one-half of the seizures recorded on video-EEG. This was not improved by encouraging vigilance for seizure occurrence; therefore, this gap in reporting is likely accounted for by the patients' lack of awareness of the events, not by lack of effort. This assumption is supported by the finding that seizures during sleep were especially poorly remembered by patients, with only 14% reported. Furthermore, complex partial seizures, which often involve mesial temporal structures important for recall, were only reported 27% of the time compared to video-EEG capture. The authors do not speculate as to why left frontal and temporal seizures were less frequently remembered than right sided seizures, but do suggest a role of the left hemisphere in seizure awareness.

COMMMENTARY

This study brings to light what neurologists working in epilepsy have long realized—people with epilepsy simply do not know how many seizures they are having. The seizures reported during office visits are a distillation of the patient's seizure experience and must be considered as a surrogate for the actual number of seizures that have occurred. This is the reality for persons with epilepsy and for epileptologists who have time and again watched video-EEG recordings of seizures for which the monitored patient has no recall.

The frequency of unreported seizures in persons with epilepsy due to lack of awareness of their occurrence illustrates the importance of long-term video EEG monitoring or overnight ambulatory EEG monitoring. These procedures can inform the neurologist about the frequency, severity, and localization of seizures and can extend, validate or refute the report by the patient. Frequent unreported seizures may be associated with several important comorbidities in epilepsy such as injury and sudden unexpected death in epilepsy patients. Video-EEG or ambulatory EEG monitoring should be considered for a broad spectrum of seizure patients to help the neurologist further understand the epilepsy syndrome in that particular patient, such as how many and what type of seizures actually are occurring. This would help to improve care for patients, in terms of guiding medical and surgical treatments for epilepsy.

How Often Are MRI Abnormalities Found in Asymptomatic People?

ABSTRACT & COMMENTARY

By Matthew E. Fink, MD

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

Synopsis: *In an adult population older than age 45, brain MRI reveled that 1.8% had asymptomatic aneurysms, 1.6% had benign tumors, and 7.2% had silent brain infarcts.*

Source: Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. *N Engl J Med* 2007;357:1821-1828.

THE USE OF BRAIN MRI BY GENERAL PHYSICIANS HAS increased dramatically for a variety of non-specific complaints such as headaches, dizziness, and minor head trauma. As a result, neurologists frequently are consulted to explain unexpected abnormalities that are found on brain imaging studies, and these findings often result in considerable anxiety and worry by referring physicians and their patients. Therefore, the study by Vernooij and colleagues from Rotterdam, the Netherlands, provides us with important information regarding the background frequency of brain pathology in an asymptomatic general population.

The subjects included 2000 people (mean age, 63.3

years; range, 45.7-96.7; 52.4% were women) from a population-based Rotterdam study that was designed to look at healthy aging. All scans were obtained with a 1.5-T GE scanner with an eight-channel head coil. The MRI protocol included four axial sequences: 3-D, T_1-weighted sequence; 2-D proton-weighted sequence; 2-D FLAIR sequence; and 3-D T_2-weighted gradient-echo (GRE) sequence. Slice thickness was 1.6 mm for all sequences except the FLAIR, which was 2.5 mm. Magnetic resonance arteriography (MRA) was not performed. Two trained reviewers, a resident in radiology and a resident in neurology, interpreted all scans. The reviewers were unaware of any clinical information about the subjects. Two experienced neuroradiologists reviewed the reported abnormalities, as well as an additional random sample of 230 scans to ensure accuracy and reliability of the interpretations.

Asymptomatic brain infarcts were present in 145 persons (7.2%); 112 were diagnosed as lacunar infarcts and 41 as cortical infarcts. The asymptomatic brain infarcts were found at increasing frequency with increasing age as evidenced by the following: 45 to 59 years (4.0%); 60 to 74 years (6.8%); and 75 to 97 years (18.3%).

The study identified 35 aneurysms (1.8%) and 31 (1.6%) primary benign tumors (18 meningiomas, 4 vestibular schwannomas, 2 lipomas, 1 trigeminal schwannoma, and 6 pituitary adenomas). There was one possible malignant tumor (low-grade glioma). Other findings included 7 cavernous angiomas, 1 metastases, 1 subdural hematoma, 22 arachnoid cysts, 18 Type-I Chiari malformations, 9 major vessel stenoses, 1 dermoid cyst, and 1 fibrous dysplasia. Regarding the brain aneurysms, all except 2 were in the anterior circulation and all except 3 were less than 7 mm in diameter. Four aneurysms were intracavernous. None of the persons with incidental brain findings reported any symptoms, except for 2 with hearing loss (vestibular schwannoma and transvestibular lipoma). The only urgent finding was a large, chronic subdural hematoma in an asymptomatic person who, in retrospect, had a minor head injury 4 weeks before the MRI scan was performed. The only other person who was referred for treatment had a 12 mm middle cerebral artery aneurysm.

COMMENTARY

It has been the common experience of neurologists that incidental findings on MRI that have no relation to a patient's complaints are common, and this study bears that out. The frequency of incidental small aneurysms and benign tumors is consistent with other literature, and does not raise our concern. Only one aneurysm was large enough (12 mm) to warrant referral for possible treatment, and none of the benign tumors required treatment. It is possible that the addition of MRA to these studies may have identified some additional small aneurysms, but they would not have been clinically significant. The asymptomatic subdural hematoma occurred in a setting of minor head trauma, and the brain metastases occurred in a person with known lung cancer.

The authors' report of asymptomatic brain infarcts in 7.2% of persons is a more difficult issue to address. We were not given any information about risk factors for vascular disease in this population, and it would be important to correlate the MRI findings with rates of hypertension, cardiac disease, smoking, etc. However, the authors have not explained why they diagnosed all of these lesions as infarcts. Are all parenchymatous lesions that have the signal characteristics of cerebrospinal fluid (CSF) infarcts? In adults older than age 45, how many of the white matter lesions are non-ischemic demyelinating lesions? The authors have followed an arbitrary rule used by many neuroradiologists that diagnose the cause of "white matter hyperintensities" according to age; if the patient is older than age 50, the lesions are "infarcts." We need more objective imaging criteria for differentiating white matter hyperintensities to better understand cause and effect, and to make accurate diagnoses of our patients. In a middle-aged asymptomatic person, I believe that we still do not know what these white matter lesions represent pathologically. ■

Migraine: More Than Just a Headache

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: *The neuronal activation that triggers migraine headaches produces more than just head and face pain. Symptoms of disordered visual processing, disequilibrium, and delayed gastric emptying occur in migraine patients as either a headache accompaniment or as a separate symptom.*

Sources: Vincent MB, Hadjikhani N. Migraine aura and related phenomena: beyond scotomata and scintillations. *Cephalagia* 2007;27:1368-1377; Vukovíc V, Plavec D, Galinovíc I, et al. Prevalence of vertigo, dizziness, and migrain-

ous vertigo in patients with migraine. *Headache* 2007;47:1427-1435; Aurora S, Kori S, Barrodale P, et al. Gastric stasis occurs in spontaneous, visually induced, and interictal migraine. *Headache* 2007;47:1443-1446.

As questioning of migraine patients reveals, a migraine is much more than just pain. It is a complex constellation of complaints that is often presaged by premonitory symptoms; segueing into an aura; evolving into head, face, and neck pain and its many accompanying symptoms; and finishing with symptoms of fatigue or euphoria. Migraine accompaniments mirror the gamut of neurologic complaints, with some symptoms more easily recognized than others. Migraine patients also are more susceptible to their environments, even in between painful attacks, and often report interictal sensitivity to bright lights, strong scents, and the motion of cars and boats. These three papers reveal myriad of neurological and systemic symptoms that vulnerable migraine patients learn to recognize as part of their disorder.

The most frequent migraine aura is visual, consistent with underlying spreading depression that is initiated in the occipital cortex. While the most common visual auras are bright flashes of light or expanding, zigzagging horseshoes with loss of vision, Vincent and Hadjikhani describe subtler visual symptoms related to colors and complex visual phenomena. More than one-half of their patients with migraine, who responded to an e-mail questionnaire, reported abnormalities discerning faces and colors, language and memory abnormalities, irritability, or sleep disturbances that generally were related to the migraine attack or persisted interictally. While the symptoms were more common in patients with migraine with aura, these symptoms, especially cognitive complaints, also occurred in patients who did not have migraine aura. Visual symptoms included prosopagnosia, dyschromatopsia, and visual agnosia, which were manifested as disturbances of visual naming, stimulus appreciation, or meaning attribution. The authors hypothesize a variable clinical expression threshold that determines how spreading depression, which begins in occipital regions and expands into visual association areas, translates into different visual processing symptoms in migraine patients.

Complaints of dizziness, disequilibrium, and motion intolerance, while noted in the general population, are significantly more common in migraine patients. Episodic vertigo, not associated with headache, frequently occurs in patients who also have migraine headaches. Vukovíc and associates compared the retrospective prevalence of dizziness and vertigo in predominantly female migraine patients (327) and non-headache controls (324). The lifetime prevalence of a sense of vertigo or dizziness was 51.7% in migraine patients, as compared to 31.5% in the controls ($p<0.0001$). Almost one-fourth of migraine patients had migrainous vertigo, which was defined as episodic vestibular symptoms accompanied by migraine head pain or its accompanying symptoms. Dizziness and vertigo as migraine accompanying symptoms were associated with migraine with aura, more than migraine without aura.

Impaired gastric motility during a migraine attack is associated with the migraine's characteristic nausea and vomiting, and gastric stasis leads to decreased absorption of oral acute migraine medications. Aurora and colleagues showed previously that delayed gastric emptying, present during a migraine attack, also occurs between migraine attacks and during induced migraine attacks triggered by an alternating black and white checkerboard pattern. The authors performed gastric emptying studies on three patients during spontaneous migraine, visually induced migraine, and between migraine attacks. Using two different techniques, time to half emptying was delayed during spontaneous migraine, induced migraine, and between migraine, as compared to normative values. However, the results were variable, as one older patient did not show delay during any testing, and a delay in emptying was found during spontaneous migraine in only one patient. Since the patients were tested at a mean interval of almost 7 hours after the onset of a spontaneous migraine, as opposed to almost immediately after an induced migraine, time from onset of migraine symptoms may affect gastric stasis. Other factors such as age and concomitant medication use may factor into the correlation of gastric stasis with migraine.

COMMENTARY

Migraine phenomenology reveals a disorder that expands beyond the pain and its usual accompanying symptoms. Patients with migraine may experience a multitude of symptoms that are both associated with and distinct from the headache. The variety of migraine-associated visual phenomena indicates an involvement of cortical spreading depression beyond its initiation in the occipital cortex, migrating into neighboring areas subserving cognitive interpretation of visual symptoms. The clear association between migraine and vertigo and dizziness is not easily explained, with vascular, cerebellar, and hypotensive mechanisms proposed. Studies of gastric dysfunction during and distinct from migraine headaches provides evidence of autonomic dysfunction in a subset of migraine patients; this correlates with the crucial role of the hypothalamus in triggering primary headaches, including migraine. What is clear is that migraine is much more than a disorder of blood vessel diameter.

Migraine is a neuronal, as distinct from a vascular, disorder that involves many separate but connected areas of the brain. We need to recognize the many different symptoms experienced by migraine patients to help them with a disorder that extends beyond their headache. ■

Low Back Pain: Are We Offering Too Much?

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Medical College, Cornell University

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

Synopsis: *Patients with acute low back pain receiving acetaminophen and standard advice do not benefit from the addition of NSAIDs or spinal manipulative therapy.*

Source: Hancock MJ, Maher CG, et al. Assessment of diclofenac or spinal manipulative therapy, or both, in addition to recommended first-line treatment for acute low back pain: a randomised controlled trial. *Lancet* 2007;370:1638-1643.

ACUTE LOW BACK PAIN IS A COMMON CHIEF COMPLAINT in general practice as well as in neurology. Treatment guidelines for acute low back pain at this time recommend using acetaminophen and advising patients of moderate physical activity and avoidance of bed rest. Many physicians prescribe nonsteroidal anti-inflammatory drugs (NSAIDs) and/or spinal manipulative therapy for acute low back pain. This study was designed to assess whether NSAIDs or spinal manipulative therapy would result in faster recovery when used in addition to acetaminophen and patient teaching.

The trial enrolled 240 patients with moderate, non-radiating, or radiating low back pain of less than six weeks duration presenting to general practitioners in Australia. Of note, patients with two or more radicular findings on examination (including myotomal weakness, dermatomal sensory loss, or reflex loss) were excluded. All patients were given paracetamol 1 gram four times daily and standard advice. Patients were subsequently randomized into four groups: spinal manipulation plus diclofenac, placebo manipulation plus diclofenac, spinal manipulation plus placebo diclofenac, or placebo manipulation plus placebo diclofenac. Placebo spinal manipulation was carried out with detuned pulsed ultrasound. Active spinal manipulation was delivered using joint mobilization and high velocity thrust procedures that could be adjusted at the therapist's judgment depending on the clinical presentation. Primary outcome was the number of days to recovery.

The results of the study demonstrated that neither diclofenac nor spinal manipulation therapy used individually or in combination significantly hastened recovery time. Across all groups, the median time to recovery was approximately 2 weeks. Of the patients, 99% recovered completely by 12 weeks after randomization. Neither diclofenac nor spinal manipulation therapy had a significant effect on any of the secondary outcomes, which included pain, disability, daily functioning, or global perceived effect. No statistically significant differences in adverse reactions were noted in this trial. One patient had a hypersensitivity reaction to diclofenac.

■ COMMENTARY

This study demonstrates a generally well-known fact about acute radiating or nonradiating back pain: it is almost always self-limiting. The study suggests that NSAIDs and spinal manipulation do not really offer any benefit over basic counseling and acetaminophen. General practitioners and other physicians encountering these patients have further evidence that conservative management is indeed appropriate as long as there is no evidence of significant nerve root compression on neurological examination. Patients with acute low back pain should be offered reevaluation at four weeks time if the symptoms are not resolved. In the small group of patients in whom pain persists at four weeks, modalities such as imaging, spinal manipulative therapy, and NSAIDs could be discussed. ■

Brachial Plexopathy: Patterns and Pathogenesis

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, NewYork-Presbyterian Hospital, Cornell Campus

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

Synopsis: *The most common etiology of brachial plexopathy is Parsonage-Turner syndrome.*

Source: Moghekar AR, Karli N, et al. Brachial plexopathies: etiology, frequency, and electrodiagnostic localization. *J Clin Neuromuscl Dis* 2007;9:243-247.

BETWEEN FEBRUARY 1999 AND OCTOBER 2003, 203 patients evaluated at the Electromyography (EMG)

Laboratory of Johns Hopkins Hospital were diagnosed with brachial plexopathy, based on a history of acute or subacute onset of weakness or numbness in one or more regions of the brachial plexus that was confirmed electrodiagnostically. Nerve conduction studies encompassed study of the median and ulnar motor nerves, and the median, ulnar, radial, and medial and lateral antebrachial cutaneous sensory nerves. Needle EMG encompassed examination of all muscles necessary for localization, and electrodiagnostic criteria for plexus localization included a combination of sensory and motor nerve amplitude loss with evidence of denervation in appropriate muscles. Etiology was determined through records obtained from the referring physicians.

Men outnumbered women 125 to 78. Plexopathy was unilateral in 181, without side predominance, and bilateral in 22, of which 19 were idiopathic (Parsonage-Turner syndrome), and 3 were radiation induced. Overall, Parsonage-Turner syndrome was the most common etiology, diagnosed in 81 patients (40%). Birth trauma, usually affecting the upper trunk; or direct trauma, most often involving all 3 trunks, accounted for 22% and 20%, respectively (n=45 and 40). Post-surgical plexopathy due to faulty positioning (n=16, 8%), post-radiation (n=11, 5%), neoplastic (n=7, 3.5%), and cervical rib (n=3, 1.5%) accounted for the remaining cases. Supraclavicular localization involving the trunks (n=189, 93%) was more frequent than infraclavicular involvement affecting the cords and branches (n=14, 7%). Purely upper trunk plexopathy (n=54, 27%) was more prevalent than involvement of all 3 trunks (n=51, 25%) or only the lower trunk (n=23, 11%). Exclusive middle trunk plexopathy was not seen. Nerve conduction studies revealed motor abnormalities more often than sensory, always axonal, and never primarily demyelinating in nature.

Of note, 47% of Parsonage-Turner syndrome patients experienced no pain prior to onset, and 57% had no identifiable antecedent precipitant. Focal involvement of a single trunk or nerve branch (bilateral phrenic nerve [n=4], suprascapular [n=3], long thoracic [n=7], was more likely in Parsonage-Turner syndrome than in other causes of brachial plexopathy. Post-radiation plexopathy most often involved all 3 trunks (8/11); however, post-surgical cases were more diverse in localization, with almost any combination equally likely. Pain was a feature in only 3 of 11 post radiation patients and 1 of 7 neoplastic cases.

COMMENTARY

Depressed sensory nerve action potential (SNAP) amplitude or absent sensory response on nerve conduction studies identifies a lesion as distal to the dorsal root ganglion. When documented in the appropriate clinical setting, such findings confidently localize the lesion to the brachial plexus. In the absence of sensory nerve abnormalities, a radicular localization remains possible. In a retrospective study of 56 brachial plexopathy patients (in the interest of full disclosure, published by this reviewer), the yield of sensory nerve abnormalities was increased (up to 82.5%) when sensory nerves sharing the distribution of motor nerve abnormalities were specifically studied.[1] For example, the lateral cutaneous nerve of the forearm should be included in any study of suspected upper trunk lesions, and the medial cutaneous nerve of the forearm in suspected lower trunk/medial cord plexopathy. Targeting sensory nerves for study in this manner enhances the accuracy of brachial plexopathy diagnosis. ■

Reference

1. Rubin M, Lange DJ. *Eur Neurol* 1992;32:245-247.

Nonmotor Symptoms in PD after Deep Brain Stimulation of the Subthalamic Nucleus

ABSTRACT & COMMENTARY

By Panida Piboolnurak, MD
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Dr. Piboolnurak reports no financial relationship relevant to this field of study.

Synopsis: *It is well accepted that subthalamic nucleus deep brain stimulation is effective in improving motor function in Parkinson's disease. However, the effect of DBS (deep brain stimulation) on non-motor symptoms still needs to be further studied.*

Source: Zibetti M, Torre E, Cinquepalmi A, et al. Motor and nonmotor symptom follow-up in parkinsonian patients after deep brain stimulation of the subthalamic nucleus. *Eur Neurol* 2007;58:218-223.

ALTHOUGH MOTOR SYMPTOMS CONSTITUTE THE CARDINAL features of Parkinson's disease (PD), non-motor symptoms, including neuropsychiatric conditions (depression, anxiety, psychosis, and cognitive impairment), autonomic disorders (orthostatic hypotension, urinary dysfunction, and gastrointestinal disturbance), sleep disorders, and sensory symptoms (pain and dysesthesias) also contribute greatly to disability and quality of life. Many studies have provided compelling evidence of long-term benefit of subthalamic nucleus deep brain stimulation (STN DBS) on motor symptoms. However, the influence of STN DBS on

non-motor symptoms is less well established.

In this study, the authors investigated the impact of STN DBS on motor and non-motor symptoms in 36 PD patients (14 women and 22 men) at 12 and 24 months after DBS surgery. Mean age at surgery was 61.2 ± 6.2 years. Mean disease duration was 16.7 ± 4.4 years. Unified Parkinson's Disease Rating Scale (UPDRS) was used as an assessment tool. Data concerning constipation and urological dysfunction were collected from clinical charts in the form of nominal data (presence or absence). Daily PD medication requirement data were collected in the form of levodopa equivalent dosage.

Comparing between preoperative off-medication and postoperative off-medication/on-stimulation condition, UPDRS III (objective motor scores) improved 52% and 55% at 12 and 24 months after surgery, respectively. Total UPDRS II score (motor and non-motor items of activity of daily living) improved 60% and 59% at 12 and 24 months, respectively. Off-duration was reduced by 92% and 98% at 12 and 24 months. Levodopa equivalent daily dosage was reduced by 60% and 59% at 12 and 24 months, comparing to the preoperative dosage. Postoperative total UPDRS I score and subscores (intellectual impairment, thought disorder, depression, and motivation) were not different compared to preoperative scores. However, when analyzing each patient individually, 3 patients developed moderate memory loss at 24 months, 3 patients developed benign hallucinations, 6 patients developed depression, and 6 patients developed motivation impairment.

Preoperatively, UPDRS II non-motor subscores for salivation, swallowing, and sensory complaints were improved by medications. Postoperatively, these scores also were improved by the combination of medication and stimulation comparable to preoperative medication effect, while PD medication dosage was markedly reduced. In addition, sleep-related problems and constipation improved after surgery. However, falling unrelated to freezing, nausea, symptomatic orthostatic hypotension, and urological dysfunction were unchanged.

The authors concluded that STN DBS improved motor symptoms and some non-motor symptoms such as salivation, swallowing, sensory complaints, sleep problems, and constipation. The improvement in those non-motor symptoms was explained by the improvement in bradykinesia, relatively constant motor control, and dopaminergic medication reduction. The authors also pointed out that this study had some weak points, including a small number of patients, low prevalence of some non-motor symptoms, and limitation of UPDRS in capturing the extent of non-motor features.

COMMENTARY

Although non-motor symptoms of Parkinson's disease are less visible than motor symptoms, they can be very disruptive for the patients and are more difficult to treat. Moreover, PD medications frequently can worsen or induce those symptoms. This study provided the evidence that STN DBS can improve motor symptoms and some of non-motor symptoms, including: saliva drooling, swallowing difficulty, sensory symptoms related to parkinsonism, sleep-related problems, and constipation. However, some non-motor symptoms may not be purely non-motor. For instance, saliva drooling is more likely due to a reduction in saliva swallowing. Difficulty in swallowing can be due to malfunction of voluntary pharyngeal muscles and/or involuntary smooth muscles of pharynx and esophagus. Possible causes of a fall include postural instability, freezing, and orthostatic hypotension. Moreover, sleep disturbances can result from both motor and non-motor symptoms as well as from medication side effect. As the authors pointed out, further study using a more specific assessment tool for non-motor symptoms, with a larger number of patients, will be able to give a better answer whether STN DBS can improve non-motor symptoms. ■

CME Questions

1. **During the second week after the onset of RCVS, all of the following are likely to occur, *except:***
   a. Recurrent thunderclap headache
   b. TIA
   c. Vasospasm involving medium and large cerebral arteries
   d. Cortical subarachnoid hemorrhage or intracerebral hemorrhage
   e. Ischemic stroke

2. **Patients with epilepsy can accurately report how often they are having seizures.**
   a. True
   b. False

3. **Nocturnal epilepsy is rarely reported by patients.**
   a. True
   b. False

4. **Brachial plexopathy:**
   a. is more common in men than women.
   b. is usually bilateral.
   c. is more often right sided than left sided.
   d. is most often due to trauma.
   e. is most often infraclavicular in localization, affecting the cords and branches, rather than supraclavicular, involving the trunks.

Answers: 1. d; 2. b; 3. a; 4. a

In Future Issues: **Vasculitis of the Central and Peripheral Nervous System**

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.

FDA Warnings Dominate Pharmaceutical News

In this issue: *FDA warnings for existing drugs dominate pharmaceutical news this month. The FDA and its advisory committees have issued warnings on erythropoiesis-stimulating agents, oseltamivir (Tamiflu) and zanamivir (Relenza) for the treatment of influenza, rosiglitazone (Avandia) for the treatment of type 2 diabetes, varenicline (Chantix) to help stop smoking, the beta agonist salmeterol (Serevent), and modafinil (Provigil) for use in children. The FDA has also asked for marketing suspension of Bayer's aprotinin (Trasylol). These warnings represent a new push by the FDA to regulate existing drugs for safety after they have been approved for marketing. It also comes at a time when the FDA is cleaning up its advisory committee processes, especially with regard to limiting potential conflict of interest by advisory committee members. A summary of the new committee processes can be found at www.FDA.gov.*

Erythropoiesis-stimulating agents (ESAs) are the subject of new warnings from the FDA. The drugs, Aranesp, Epogen, and Procrit are used to treat anemia associated with cancer chemotherapy and chronic kidney failure. For cancer patients, several studies have shown that the drugs promote tumor growth and decrease survival rates in patients with advanced breast, head neck, lymphoid, and non-small cell lung cancer when given in doses that achieve a hemoglobin level of 12 g/dl or greater—the target in clinical practice. There is currently no evidence to know whether the ESA's promote tumor growth or shorten survival in patients who achieve hemoglobin levels less than 12 g/dl. The warning also specifically states that ESA's should only be used in cancer patients to treat chemotherapy-related anemia, not other causes of anemia associated with cancer and stress, and that the drug should be discontinued once chemotherapy is discontinued. For patients with chronic kidney failure, the new warnings states that ESA's should be used to maintain hemoglobin levels between 10 to 12g/dl. Higher hemoglobin levels increase risk for death and serious cardiovascular events such as stroke, heart attack, or heart failure. Finally, the new labeling emphasizes that there is no data that demonstrates that ESA's improve symptoms associated with anemia such as quality of life, fatigue, or patient well-being for patients with cancer or for patients with HIV undergoing AZT therapy.

An FDA panel is recommending new warnings on the flu drugs oseltamivir (Tamiflu-Roche) and zanamivir (Relenza-Glaxo) regarding abnormal psychiatric behavior associated with the drugs. This issue came up last year with a number of reports from Japan of erratic behavior including jumping from buildings resulting in deaths in patients taking the

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drugs. Many of the cases involved children. Japan has already taken the step of warning prescribers not to use the drugs in those aged 10 to 19. The panel reports 700 cases of psychiatric adverse events associated with both drugs, and 25 potential deaths in patients taking Tamiflu. No fatalities have been reported with Relenza. Both companies insist their drugs are safe and suggest that it is difficult to know if symptoms are caused by influenza or by medications. In the meantime Roche has agreed to stronger warnings for Tamiflu. Both medications reduce the symptoms of influenza and reduce the duration by approximately one-and-a-half days.

The manufacturers of rosiglitazone (Avandia-GlaxoSmithKline) have agreed to add new information to the existing black box warning regarding the potential increased risk of heart attacks associated with drug. The FDA's press release states that "People with type 2 diabetes who have underlying heart disease or who are at high risk of heart attack should talk with their health-care provider about the revised warning as they evaluate treatment options. FDA advises health-care providers to closely monitor patients who take Avandia for cardiovascular risks." Rosiglitazone is approved for treatment of type 2 diabetes as single therapy or in combination therapy with metformin, sulfonylureas or other oral anti-diabetes treatments. GSK has been asked by the FDA to conduct a long-term study to evaluate the potential cardiovascular risks of rosiglitazone.

The FDA has issued an "Early Communication" regarding varenicline (Chantix), Pfizer's prescription medication to help adults stop smoking. Pfizer has received reports describing suicidal ideation and erratic behavior in some patients taking the drug which have been submitted to the FDA. The Agency is soliciting any additional similar cases from Pfizer and will complete analysis when more data is available and then communicate conclusions and recommendations. In the meantime the FDA recommends health-care providers monitor patients taking Chantix for behavior and mood changes.

An expert panel of the FDA is also recommending a new warning for the long acting beta agonist salmeterol (Serevent-GlaxoSmithKline) regarding use in children. Nine new adverse event reports including five deaths in children using the drug had been reported in the last year as well as reports of increased hospitalizations and asthma-related deaths in children. Before a final recommendation is made by the FDA, review of other long-acting beta agonists will also be included, including formoterol (Foradil), Novartis' long-acting beta agonist and GlaxoSmithKline's Advair which is a combination inhaler of salmeterol and fluticasone. There is some evidence that steroid inhalers mitigate the risk of asthma-related deaths in patients taking long-acting beta agonists.

An FDA panel is recommending stronger warnings for use of modafinil (Provigil) in children. The drug is approved to treat certain sleep disorders in adults, and is not approved for use in children, but is occasionally used off label for the treatment of attention deficit hyperactivity disorder. The drug's labeling was recently updated to warn of serious skin reactions and psychological problems such as hallucinations and suicidal ideation.

Bayer Pharmaceuticals is complying with the FDA's request for a marketing suspension of aprotinin (Trasylol). The drug, which is used to control bleeding during heart surgery, is the subject of a large Canadian study, the preliminary results of which have shown an increased risk of death associate with the drug.

FDA Actions

The FDA has approved over-the-counter sales of cetirizine 5 mg plus pseudoephedrine HCL 120 mg (Zyrtec-D) for adults and children aged 12 years and older. The product has been available as a prescription drug since 2001 for the treatment of upper respiratory allergies.

The FDA has approved several new generics for marketing. Oxcarbazepine (Trileptal) will soon be available as a generic in 150, 300, and 600 mg strengths the treatment of partial seizures in adults and children. Hydrocodone/ibuprofen (Vicoprofen) is also approved as a new generic. The drug is approved for short-term treatment of acute pain. Rivastigmine (Exelon) will be available in generic 1.5, 3, 4 .5, and 6 mg strengths for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia assisted with Parkinson's disease. ■