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INSIDE

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Spontaneous Intracranial Hypotension May Be More Than Just a Postural 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: *Although spontaneous intracranial hypotension (SIH) generally causes a benign, self-limited, postural headache, subdural hematomas may occur in SIH with serious sequelae.*

Source: Lai TH, et al. Subdural haematoma in patients with spontaneous intracranial hypotension. *Cephalalgia.* 2007:27:133-138.

SPONTANEOUS INTRACRANIAL HYPOTENSION (SIH) CAUSES THE new onset of a daily persistent headache with the distinctive feature of prominent increase of pain while upright and marked improvement in pain while recumbent. This striking exacerbation of pain with sitting or standing is distinct from the worsening of headache pain with head movement that migraine patients describe as a peripheral sensitization phenomenon. Despite its name, SIH may not always be truly spontaneous as minor trauma, especially in susceptible individuals, can cause the development of cerebrospinal fluid leakage with decreased intracranial pressure. The headache is due to the downward movement of the brain in the erect position with traction on pain-sensitive structures, including cerebral veins and sinuses. An MRI of the brain with contrast may be normal, but it can show meningeal enhancement, low-hanging cerebellar tonsils, or decreased ventricular and cisternal size. Rarely, subdural fluid collections, hematomas and hygromas, are seen. MRI of the spine, myelography, and cisternography, as well as low opening pressure on lumbar puncture, may also be used to diagnose SIH and identify the location of the dural tear. The treatment of SIH is generally conservative management (hydration, caffeine, pain medication, time) or epidural blood patching. Although patients are often quite disabled over the short-term by the severe postural head pain, the long-term prognosis is generally favorable with resolution of the headache in days to weeks.

The radiological features and time-course of SIH is not well documented in this relatively rare cause of headache. Lai et al reviewed

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records of a tertiary medical center in Taiwan and found 40 patients (18 women, 22 men, age ranging from 24-78 years) with SIH. They all had at least one MRI study, with 8 patients having a subdural hematoma (SDH) and 9 patients having nonhemorrhagic subdural fluid collections. Of the 8 patients with SDHs, 6 patients had bilateral SDHs and the other 2 had unilateral SDH with contralateral nonhemorrhagic subdural fluid collections. Two patients who had nonhemorrhagic subdural fluid collections converted the collections to hematomas on repeat MRIs. The presence of a subdural fluid collection did not correlate with age or headache intensity. However, having a SDH was more likely to be associated with neurological deficits and headache recurrence during the disease course. A patient with SDH was more likely to be a man. Although SIH is generally considered to be a benign condition, it can result in change in level of consciousness and focal neurological symptoms, especially when associated with a SDH. One patient had bilateral hand numbness that resolved after the SDH was evacuated. Another patient with a SDH became unconscious with transtentorial herniation, requiring blood patch, hematoma evacuation, and suboccipital decompression. Only 2 of the 8 SDH patients required surgical intervention and the 3 patients with midline shift > 5 mm had total recovery without surgery. Overall there was good symptomatic recovery at 3 months in all 3 groups: no SDH or nonhemorrhagic subdural collection. Mild headaches persisted in one patient without a subdural fluid collection, but the patient with transtentorial herniation was severely disabled. The presence of a SDH increased the chance of neurological deficits and recurrence of severe headaches.

COMMENTARY

This paper highlights a rare but dramatic cause of new onset headache, which may also be associated with a subdural fluid collection. Etiologies of the SDH in SIH include traction on bridging veins, development of new dural vessels in delayed SDH, or evolution of nonhemorrhagic to hemorrhagic subdural collections. The pathogenesis of the SDH may be variable, especially since a diagnostic lumbar puncture could cause a delayed SDH. The authors of this relatively large series of patients conclude that while most patients with SIH have a benign headache, patients with both SIH and SDH are not without risk. Headaches caused by SIH are probably under recognized and SDH may not be found in patients with SIH who do not undergo multiple imaging studies over time. If a patient with a headache characteristic of SIH does not improve consistently over days to weeks, or if the patient has a worsening of the headache, especially if accompanied by focal neurological symptoms or signs, then the patient may have an associated SDH. ■

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Which is Better, the Older or the Newer Antiepileptic Drugs?

ABSTRACT & COMMENTARY

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

Synopsis: *These 2 clinical trials comparing Standard and New Antiepileptic Drugs (SANAD) showed that for partial epilepsy, lamotrigine was clinically better than carbamazepine, and that for generalized and unclassifiable epilepsy, valproate was better tolerated than topiramate and more efficacious than lamotrigine. Due to the potential adverse effects of valproate during pregnancy, the authors were cautious about the interpretation of their results regarding valproate.*

Sources: Marson AG, et al; and the SANAD Study Group. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet.* 2007;369:1000-1015.
Marson AG, et al; and the SANAD Study Group. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet*. 2007 ;369:1016-1026.

THESE 2 LARGE CLINICAL TRIALS CARRIED OUT IN the United Kingdom aim to answer an important

question for physicians treating epilepsy, that is, which is better, the older or the newer antiepileptic drugs (AEDs)? For that purpose, in these studies, the "standard" AED deemed to be appropriate therapy for partial epilepsy treatment was carbamazepine, and for generalized and presumably generalized epilepsy (unclassifiable), it was valproate. The investigators evaluated these standard treatments alongside several newer AEDS, including gabapentin, lamotrigine, oxcarbazepine, and topiramate for partial epilepsy, and lamotrigine and topiramate for generalized and unclassifiable epilepsy.

Patients at least 4 years of age and older were included, and had either newly diagnosed epilepsy, failure on AED monotherapy but not with one of the study AEDs, or were previously in remission but relapsed after withdrawal of AED treatment. The choice of AED was centrally randomized but was not blinded for either the physician or the patient. The AED starting dose, titration and dose adjustment after recurring seizures was performed by the treating physician in an open, unblinded manner. The aim of AED treatment was to control seizures using the lowest monotherapy dose.

The primary outcomes were 1) time to treatment failure, an outcome which included stopping the randomized AED due to inadequate seizure control, side effects, or the addition of another AED, which ever came first, and 2) the time from randomization to a one-year period of seizure remission. Secondary outcomes included quality of life and cost-effectiveness of the AED.

For the partial epilepsy portion of SANAD (arm A), 1721 patients were randomized, with the smallest treatment arm being oxcarbazepine since this arm was added later to the ongoing study. For time-to-treatment failure, lamotrigine was significantly better than carbamazepine, gabapentin and topiramate, and was slightly but not significantly better than oxcarbazepine. Lamotrigine provided better seizure control than gabapentin, and had fewer adverse effects than carbamazepine, topiramate or oxcarbazepine. Time to 12-month remission, however, was significantly better for carbamazepine over gabapentin, and carbamazepine had a non-significant advantage for this outcome over lamotrigine, topiramate and oxcarbazepine. Rash was more common with carbamazepine and oxcarbazepine than with lamotrigine. No differences between AEDs were found on the quality-of-life scale; patients with continued seizures had worse quality of life, including mood subscales. Lamotrigine was associated with a trend for reduced risk of depression compared to other AEDs. The lowest-cost-per-quality-adjusted-life year (QALY) was for lamotrigine and carbamazepine.

For the generalized and unclassifiable epilepsy portion of SANAD (arm B), 716 patients were randomized. For time-to-treatment failure, valproate was significantly better than topiramate, mostly accounted for by adverse effects from topiramate. For time to 12- month remission, valproate was significantly better than lamotrigine only. For the subset of patients with clear evidence of idiopathic primary generalized epilepsy, valproate was significantly better than lamotrigine and topiramate for time-to-treatment failure, but was only better than lamotrigine regarding time to 12-month remission. The authors interpret these results as indicating that valproate was better tolerated than topiramate and more efficacious than lamotrigine.

COMMENTARY

The impact of these large and ambitious studies is undeniable, and for those of us working intimately with epilepsy patients every day, there is a sense of validation in these results; they do reflect what is seen in clinical epilepsy practice. Without declaring AED "winners" or "losers" in these reports, since the response of patients must be considered on an individual basis, results emerge that lamotrigine is a well-tolerated and often effective AED for partial epilepsy, and valproate, despite its adverse metabolic and teratogenic potential, is a very effective AED for generalized epilepsy. Furthermore, this study confirms that persons with epilepsy who have continued seizures have a poor quality of life compared to those whose seizures are controlled.

Regarding the advantages of the "standard" vs the "newer" AEDs, one newer AED, lamotrigine, appears somewhat advantageous over carbamazepine, but there was, overall, little difference in treatment arms in the partial epilepsy study, with the exception that efficacy outcomes were most withering with gabapentin. As a "standard" AED in generalized epilepsy, valproate holds its own against the 2 newer AEDs. This finding, when extrapolated to clinical practice, goes a long way toward explaining why valproate, with its myriad of adverse effects, largely due to enzyme-related metabolic alterations, and its teratogenic risk, remains a widely prescribed AED even in the pediatric and adolescent populations where generalized epilepsy commonly occurs.

Drawbacks of these studies are obvious; they are unblinded and dosing and titration was not controlled. This can lead to bias in both directions: too cautious a titration can be associated with lack of efficacy and too high a starting dose or rapid titration can lead to adverse effects. Each AED has its own profile of risk regarding dose, titration, efficacy and adverse effects; some are more prone to one risk than another. Notably, the doses achieved in this study for lamotrigine were relatively low with a mean dose of 249 mg per day for long-term stable partial epilepsy patients and 203 mg per day for long-term

stable generalized epilepsy patients. Doses reported for other AEDs seem very reasonable, with relatively small standard deviations, suggesting that dose and dose ranges in these studies are similar to standard practice in the United States. Also, it now seems like the lack of such information with levetiracetam is a gaping hole in our assessment of "standard" vs "newer" AEDs due to levetiracetam's wide use and broad-spectrum of indications.

The "real world" methodology of this study, where each physician starts and titrates the AED with a large degree of independence within the clinical trial, is in some way reassuring and suggests that these results can be readily extrapolated to clinical practice. Keeping in mind the lack of strict control on dosing in these studies, the results are a stronger endorsement of valproate as an effective and well-tolerated drug for generalized epilepsy than they are discouraging for carbamazepine or the other newer AEDs evaluated as effective treatments for partial epilepsy. Therefore the "standard" AEDs do not fail when compared to "newer" AEDs; however, lamotrigine has advantages for partial epilepsy. The use of valproate in women of child-bearing potential remains a difficult situation. The SANAD results support the effectiveness of valproate for generalized epilepsy, but the teratogenic and neurocognitive risk to the offspring with in utero valproate exposure are also becoming clear. The best choice of AED for women with generalized epilepsy remains a severe clinical challenge, not yet fully informed by known rates of teratogenic risk of valproate alternatives. ■

Intravenous Immunoglobulin (IVIG) for Myasthenia Gravis and Miller Fisher Syndrome

ABSTRACT & COMMENTARY

By Michael Rubin, MD

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

Synopsis: *IVIG is safe and effective for worsening MG, but has no effect on the natural course of Miller Fisher syndrome*

Sources: Zinman L, et al. IV immunoglobulin in patients with myasthenia gravis. A randomized clinical trial. *Neurology*. 2007;68;837-841.
Mori M, et al. Intravenous immunoglobulin therapy for Miller Fisher syndrome. *Neurology*. 2007;68:1144-1146.

Despite reports touting the apparent benefits of intravenous immunoglobulin (IVIG) in myasthenia gravis (MG), level 1 evidence has been lacking until now. Between March 2004 and May 2005, the University Health Network Neuromuscular Clinic of the University of Toronto, Ontario, enrolled 51 MG patients with progressive weakness, 18 years of age or over, into a randomized, placebo-controlled, double-blind study, comparing IVIG to placebo (IV dextrose 5% in water, D5W). MG diagnosis was based on clinical evaluation, positive findings on single-fiber electromyography (SFEMG), previous response to treatment, and positive acetylcholine receptor antibodies and muscle-specific tyrosine kinase antibodies. Progressing weakness was defined as increasing ptosis, diplopia, dysarthria, chewing or swallowing difficulties, or limb weakness important enough to warrant change in medication. Exclusionary criteria included weakness due to intercurrent infection or medication, respiratory failure requiring intensive care admission, dysphagia with aspiration risk, recent (2 week) change in steroid dosage, renal, hepatic, or cardiac disease, hypercoagulable or hyperviscosity states, pregnancy, and lactation. Patients received either 2 G/kg of IVIG or D5W over 2 days, were premedicated in all instances with acetaminophen and diphenhydramine, and were evaluated by clinical examination at baseline, day 14, and day 28 by the same blinded examiner. Clinical assessments included the Quantitative Myasthenia Gravis (QMG) Score for Disease Severity and the Post-Intervention Status classification, with all anti-cholinesterase medication held for 12 hours prior to evaluation. Change in QMG Score for Disease Severity from baseline to day 14 was the primary outcome measure whereas changes from day one to 28, and from day 14 to 28 served as secondary outcome measures, as did day 14 and 28 Post-Intervention Status, and changes in SFEMG and repetitive nerve stimulation studies from baseline to day 14. Student t test, x2 or Fisher exact test, and analysis of covariance (ANCOVA) were used for statistical analysis.

IVIG provided a small but significant improvement of QMG Score, compared to placebo, at day 14, which persisted, though it failed to reach significance, at day 28. All the benefit was accrued by those with more severe disease, whose QMG score was > 10.5 at baseline. No IVIG patient worsened, compared to 4% on placebo, while 23% vs 42% experienced no change, respectively. Post-Intervention Status was also significantly improved by IVIG compared to placebo, 23% vs 8%, again appreciated only in the more severe cases, with none vs 6% worsening, respectively. No serious adverse events were experienced in either group, with headache, easily treated with over-the-counter medication, being the most common side effect.

COMMENTARY

In contrast to its proven efficacy in myasthenia gravis and Guillain-Barré syndrome, intravenous immunoglobulin (IVIG) appears to be less useful for Miller Fisher syndrome (MFS). Among 92 MFS patients seen between 1979-2005 at the Chiba University Hospital and its affiliates in Japan, and treated with IVIG (n = 28), plasmapheresis (n = 23) or supportive care alone (n = 41), Mori et al reported no significant difference between the treatment groups. Only 4 (4%) remained symptomatic one year after disease onset: one each from the IVIG and control groups, and 2 from the plasmapheresis group. They all had persistent diplopia, and one patient also experienced persistent ophthalmoplegia. MFS is a terrifying but relatively benign condition and does not appear to benefit from IVIG. Almost all patients recover with or without treatment.

Antibodies and Limbic Encephalitis

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

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

Synopsis: *In addition to previously identified antibodies that cause limbic encephalitis, novel antibodies directed against cell membrane antigens may cause many of the "antibody-negative" cases, and these cases seem to respond favorably to immunosuppressive treatment.*

Sources: Bataller L, et al. Autoimmune limbic encephalitis in 39 patients: Immunophenotypes and outcomes. *J Neurol Neurosurg Psychiatry.* 2007;78:381-385.

Bien CG. Limbic encephalitis: extension of the diagnostic armamentarium. *J Neurol Neurosurg Psychiatry.* 2007;78:332-333.

Samarasekera SR, et al. Course and outcome of acute limbic encephalitis with negative voltage-gated potassium channel antibodies. *J Neurol Neurosurg Psychiatry.* 2007;78:391-394.

Limbic encephalitis is an immune-mediated disorder with an acute or subacute presentation of seizures, short-term memory loss and psychiatric symptoms. The neurological symptoms can be explained by specific damage to the medial temporal lobes and hippocampi. Limbic encephalitis has traditionally been considered one of the major paraneoplastic syndromes. However, case reports and case series in the literature over the past 10-15 years have described a group of patients with a clinical presentation of limbic encephalitis without an occult malignancy or detectable antibodies, and others with antibodies not considered to be of paraneoplastic origin—voltage-gated potassium channel antibodies (VGKC). More recently, a novel set of limbic encephalitis-related antibodies targeting novel cell membrane antigens (nCMAg) have been described.

The paper by Bataller and colleagues is a prospective clinical case study of the immunophenotypes and outcomes of 39 patients with limbic encephalitis identified over a 4-year period. Nineteen of these patients demonstrated the presence of previously characterized antibodies, including anti-Hu, anti Ma2 and anti-VGKC. Seventeen patients demonstrated novel antibodies that were detected only with immunohistochemical methods, all demonstrating intense labeling of nCMAg. These antibodies strongly labeled rat hippocampal cell membranes in live culture. Only 3 patients had no detectable auto-antibodies. In all, 82% of patients demonstrated CNS directed antibodies.

There were some differences among the immunophenotypes in the 39 patients reported. The patients with nCMAg antibodies were less likely to demonstrate the typical MRI changes characteristic of limbic encephalitis. Additionally and interestingly, 76% of patients with nCMAg antibodies had teratomas or thymic tumors. The majority of these teratomas were ovarian. Clinically, patients with nCMAg antibodies had a high frequency of hyperkinetic movements (41%), and depressed level of consciousness with hypoventilation (59%). Of the 39 patients, treatment response and follow-up was available for 35. Treatment of the patients included therapy for the underlying tumor, if one was present, and immunosuppression with corticosteroids and other agents. At median follow-up of 19 months, a significant association with response to treatment was noted in those patients with antibodies to VGKC and nCMAg, compared to those with the more traditional paraneoplastic antibodies, Hu and Ma2.

The paper by Samarasekera and colleagues summarizes the cases of 4 patients with limbic encephalitis, who did not demonstrate the presence of paraneoplastic antibodies or anti-VGKC antibodies. These patients did not demonstrate the presence of an underlying malignancy with a median of 18-months of follow-up. These 4 patients all demonstrated an infective prodrome followed by an acute presentation of limbic encephalitis, all demonstrating the typical MRI changes. CSF analysis in these 4 patients demonstrated minimal or no pleocytosis (range 0-5 WBC), normal to mildly elevated protein and negative oligoclonal banding. All 4 patients demonstrated variable recovery, all with persisting residual cognitive deficits and epilepsy. Of note, these patients were not screened for nCMAg antibodies.

COMMENTARY

These studies shed new light on the diagnostic

approach to limbic encephalitis. It is likely that many previously "antibody negative limbic encephalitis" cases are not antibody negative at all, but instead represented cases caused by antibodies directed against neuronal cell membrane antigens. Testing for the novel antibodies directed against nCMAg is not commercially available. However, given the large number of patients with limbic encephalitis who might have these antibodies, and the fact that these patients tend to improve with treatment, the ability to test for these antibodies would represent a significant benefit to patients.

In light of these findings, what should be the neurologist's approach to a patient who presents with limbic encephalitis? The patient should undergo testing for the commercially available antibodies known to be associated with this condition from the serum and the CSF. An age appropriate malignancy screen should be initiated. If an underlying tumor is found, initial treatment should be directed against the tumor. In all cases, whether or not a tumor or antibodies are detected, a trial of immunotherapy, with corticosteroids, IVIG or plasma exchange, should be considered and initiated. In addition, serum should be stored for future assay of novel antibodies. ■

REM Sleep Behavior Disorder and "Paradoxical Kinesis" in Patients with Parkinson Disease

ABSTRACT & COMMENTARY

By Charles P. Pollak, MD

Professor, Clinical Neurology, Weill College of Medicine

Dr. Pollak is a stockholder for Merck, and is on the speaker's bureau for Merck.

Synopsis: *Many patients with Parkinson disease have normalization of movement during REM sleep, similar to the beneficial effects of levodopa while they are awake.*

Source: De Cock VC, et al. Restoration of normal motor control in Parkinson's disease during REM sleep. *Brain.* 2007;130: 450-456.

A PECULIAR FEATURE OF PARKINSON DISEASE (PD) that is familiar to most neurologists is the ability for patients to briefly regain the capacity for rapid movement under urgent conditions, such as a dangerous fire from which it is necessary to escape. First described in 1921, the mechanism of this "paradoxical kinesis" remains unknown. It has now been discovered that the capacity for normal movement may also be regained in PD during REM sleep in those PD patients who develop REM sleep behavior disorder (RBD). Normally, the capacity for movement is lost during REM sleep owing to inhibition of motor systems at the brainstem level. In RBD, this inhibition is lost, enabling movements to arise that correspond to the events of REM dreams (dream enactment). In this investigation, these movements were compared to the waking movements of PD patients and were found to be greatly improved,

Of 100 non-demented PD patients that were interviewed, 59 were found to have RBD. Their bed partners were asked to evaluate the quality of movements, voice and facial expression and compare them to the "ON" levodopa state. Fifty-three of the 59 had bed partners who were able to evaluate them, and all reported improvement of at least one component of motor control during RBD. Video monitoring during polysomnography confirmed that movements in REM sleep (talking, laughing, yelling, reaching, gesturing, punching, kicking) were "surprisingly fast, ample, coordinated and symmetrical," though also "jerky, violent and often repetitive". Dreams during RBD often involved fighting or running/fleeing and commonly resulted in injuries to self or co-sleepers. Interestingly, all patients had asymmetrical PD when awake and used the disabled arm, hand and leg more during RBD.

COMMENTARY

This is an imaginative, wonderfully interesting investigation that makes its point convincingly. RBD is a valuable "experiment of nature," but it is well to remember that it was first created in cats by Sastre and Jouvet by means of brainstem lesions. The cats then appeared to "act out their dreams" whenever they entered REM sleep. This remained a laboratory curiosity until an apparent clinical counterpart was described in 1986 by Schenck and others. PD is one of several disorders that may be associated with RBD. In the present study, RBD was present by history in 60% of the PD patients. In 22%, it had developed before the onset of PD, by a few months to as long as 4 years. The normalized movements of paradoxical kinesis and those associated with RBD seem to differ, because the latter were also observed by the authors when PD patients were acting out dreams with little or no emotional content. RBD dreams are nevertheless usually intensely emotional. The authors speculate that RBD movements have cortical origin and follow the pyramidal tract, bypassing the parkinsonian extra-pyramidal system. ■

Is the Tingling on My Scalp Helping My Headaches? Occipital Nerve Stimulation for Cluster Headaches

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD
Associate Professor of Clinical Neurology, Weill Medical College

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

Synopsis: *Occipital nerve stimulation appears to decrease the cluster pain and attack frequency in most, but not all, patients with chronic drug-resistant cluster headaches.*

Source: Burns B, et al. Treatment of medically intractable cluster headache by occipital nerve stimulation: long-term follow-up of 8 patients. *Lancet*. 2007;369:1099-1106.
Magis D, et al. Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective study. *Lancet Neurology*. 2007;6:314-321.

Patients who suffer from cluster headaches report that the pain is so brutal that they are willing to consider any therapy that promises even slight relief from the agony of unilateral periorbital knife-like pain. Options for successful treatment of cluster headaches are limited. Preventative medication to decrease the frequency and severity of the pain is often only minimally effective. The medications used to treat the acute pain may be used excessively or may not be appropriate for cluster patients with vascular risk factors. Surgical procedures that target the trigeminal nerve or cranial parasympathetic outflow tracts have been attempted with variable results and with risk of significant complications. Deep brain stimulation of the hypothalamus, an area of activation in cluster headaches, has been shown to be effective but the potential surgical complications make this treatment inappropriate for all but the most intractable of patients. While some cluster headaches remit for months to years, the patient with chronic cluster headaches, without intervening headache-free periods, is particularly disabled by the unremitting excruciating pain. The patient with chronic cluster headaches may either have had episodic cluster periods with time periods of relief or may have always had unrelenting headaches. The patient with chronic cluster headaches is often amenable to any treatment that offers promise of partial pain relief.

These 2 papers, one from Belgium (Magis et al) and one from the United Kingdom (Burns et al) examined the benefit of occipital nerve stimulation in patients with chronic medication-unresponsive cluster headache. Suboccipital injection of steroids or local anesthetics has been of occasional benefit in cluster patients but the effect is transient and repeated injections often loose efficacy. Occipital nerve stimulation has been used in intractable migraine patients and its efficacy in these 2 groups of drug-resistant cluster headache patients was evaluated, even though its mechanism of action is not clear. Peripheral neurostimulation has been beneficial in patients with pain disorders such as neuropathic pain, with possible extrapolation to patients with primary headache disorder. Multiple pain pathways, including cervical, somatic trigeminal, and dural trigeminal vascular afferents, which converge on second-order neurons in the brain stem and on third-order cortical neurons, may be impacted by stimulation of the occipital nerve. The perceived clinical benefit of occipital nerve injection and the appreciation of any relief of pain in patients with cluster headaches served as the impetus for the evaluation of occipital nerve stimulation.

The patient population of the 2 papers was very similar, with 8 patients (one woman and 7 men) of average age in the mid-forties, in each study. All patients had suffered from cluster headaches for years (minimum 7 years) to decades with headache that persisted despite aggressive medical therapy. The stimulation technique differed, as the British patients had bilateral occipital nerve stimulators inserted, whereas the Belgian patients had the stimulator surgically implanted only on the side of the headache. The stimulation parameters were adjusted to obtain paresthesias in the innervation territory of the greater occipital nerve.

The assessment of response differed between the 2 papers but was subjective in both. The patients monitored by Magis et al used headache diaries before and after treatment to assess clinical response. Burns et al used a less quantitative assessment in which the patients were asked to give an overall impression of their response and their use of triptan medications before and after the treatment. They were also asked if they would recommend the treatment to a fellow cluster sufferer. No blinding of treatment was possible since paresthesias indicated that stimulation was occurring. However, frequent technical problems with battery life and electrode migration lead to interruption of the stimulation with increase in cluster-attack frequency and severity. The stimulation was also intermittently discontinued in order to monitor response. These interruptions were not blinded as the patients knew when the stimulation was no longer operating because the paresthesias disappeared.

The outcomes reported by both sets of investigators were encouraging. Both studies found that most patients had decreased cluster attack pain and frequency that per-

sisted over months. Magis et al reported that 2 patients were pain free after follow-up of 16 and 22 months. Three patients had 90% reduction in attack frequency and 2 patients had improvement of around 40%. Length of follow-up was variable but was greater than 3 months for all the patients. One patient who had no benefit at 4 months with intolerable paresthesias discontinued treatment. Seven out of 8 patients were able to decrease medication use. These patients all had unilateral stimulation on the side of the headaches.

Burns et al followed their 8 patients for a range of 6-27 months of bilateral stimulation. Two patients had marked improvement and would recommend treatment. Three patients had only moderate improvement but would still recommend treatment. One patient had only mild improvement and would not recommend treatment. The benefit accrued over weeks but appeared relatively durable.

Both groups of patients had frequent technical malfunctions requiring surgical replacement of batteries and electrodes. However, unlike other surgical treatments, specifically deep brain stimulation of the hypothalamus, there were no serious complications of treatment. Patients were selected based on the refractoriness of the headaches, and the pre-implantation response to occipital nerve block did not seem to predict the outcome of successful occipital nerve stimulation.

COMMENTARY

Patients with drug-resistant chronic cluster headaches have an existence dominated by unpredictable, unrelenting pain, and are desperate for any treatment that offers a modicum of relief. The patients in these studies were taking large quantities of medications with minimal benefit and were willing to undergo multiple surgical procedures to obtain benefit. The results are encouraging, even if the pathophysiological mechanism to explain it is elusive. The technique appears to be safe with only frustrating technical glitches. The lack of blinding was, probably, only of minimal consequence given the refractoriness of the pain. The similar result with either unilateral or bilateral stimulation is curious and needs further study. The results with unilateral stimulation are encouraging enough to indicate that the treatment should be unilateral, at least initially, in the appropriate patient with unilateral symptoms. These 2 papers give hope to a group of patients who are despondent and frustrated. For the appropriate patient who understands the uncertainty of the individual response, occipital nerve stimulation can offer hope of an existence with decreased pain.

CME Questions

20. Subdural hematomas associated with spontaneous intracranial hypotension:
A) Are always associated with a favorable outcome.
B) Are frequently bilateral.
C) Cause the postural head pain in patients with spontaneous intracranial hypotension.
D) Are not associated with postural headache recurrence.
E) Are seen more often in women.

21. Choose the correct statement.
A) IVIG significantly alters the course of Miller Fisher syndrome
B) IVIG is of no significant benefit in myasthenia
C) IVIG has been shown, in placebo controlled, double blind trials, to be of significant benefit in the treatment of mild and moderate myasthenia
D) IVIG has been shown, in placebo controlled, double blind fashion, to be of significant benefit in the treatment of severe myasthenia
E) None of the above are correct

22. Antibodies against which of the following structures have recently been described in patients with limbic encephalitis?
A) Dorsal root ganglion sensory neurons
B) Hippocampal nuclear antigens
C) Mitochondrial membranes
D) Neuronal cell membrane antigens
E) Ribosomal RNA

23. Normalization of movement in Parkinson's disease may be observed during sleep in which of the following disorders?
A) Restless Legs Syndrome
B) REM sleep behavior disorder
C) Levodopa ON condition
D) Levodopa-induced dyskinesia

24. Occipital nerve stimulation for intractable cluster headache patients:
A) Carries an unacceptable surgical risk.
B) Decreases medication use but does not decrease attack frequency and severity.
C) Decreases medication use and decreases attack frequency and severity.
D) Only works with bilateral stimulation.
E) Should only be given to those patients who have responded to occipital nerve block.

Answers: 20.(b) 21.(d) 22.(d) 23.(b) 24. (c)

In Future Issues:

Which is better for the diagnosis of acute stroke - CT or MRI?

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.

Long-Awaited Torcetrapib Will Not Be Released, Too Risky

Torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, has been in development by Pfizer for nearly 15 years. The drug has been shown to elevate HDL levels while reducing LDL levels, prompting hopes that torcetrapib would be the first in a new class of important cholesterol medications. In December, Pfizer abruptly pulled the plug on further development of torcetrapib when the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events trial showed an increase in death from all causes associated with the drug, including an increased rate of cardiovascular events and hypertension. A new study points out a possible mechanism for the lack of cardiovascular benefit. In the international study, 1,188 patients with cardiovascular disease underwent intravascular ultrasonography. They then received atorvastatin and were randomized to receive 60 mg of torcetrapib daily or placebo along with atorvastatin for 24 months. Atorva/torcetrapib resulted in a 61% relative increase in HDL and a 20% further reduction in LDL, resulting in an average HDL higher than LDL. But the drug combination was also associated with an increase in systolic hypertension of 4.6mm Hg, and more importantly an increase in atheroma volume of 0.12%, compared to an increase of 0.19% in the atorvastatin alone group (P = 0.72). The authors conclude that treatment with the CETP torcetrapib was associated with improved lipid endpoints, but was also associated with an increase in blood pressure and no significant decline in coronary atherosclerosis (*N Engl J Med.* 2007;356:1304-1316.). In an accompanying editorial, Dr Alan Tall holds out hope that other CETP inhibitors may not show the same adverse effects but suggests that further development of this class of drugs needs to proceed with caution (*N Engl J Med*. 2007;356:1364-1366). ■

IBS-Drug Treatment Pulled, CV Side Effects

Tegaserod (Zelnorm), Novartis Pharmaceutical's drug for irritable bowel syndrome has been removed from the market by the FDA based on recent findings of increased risk of serious cardiovascular events associated with use of the drug. Tegaserod was approved in 2002 for women with irritable bowel syndrome whose primary symptom was constipation. It was given the additional indication in August 2004 for chronic constipation in men and women under the age of 65. Withdrawal was based on analysis of 29 studies involving more than 18,000 patients that showed a small, but statistically significant increase in the risk of cardiovascular side effects (0.1% serious adverse effects with tegaserod vs 0.01% with placebo). The FDA may allow continued use of the drug in a limited number patients for whom no other treatment options are available and the benefits of tegaserod outweigh the chance of serious side effects. The FDA may consider limited reintroduction of the drug at a later date if the population patients can be identified in whom the benefit of the drug outweighs the risk. ■

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Drug Combo Better for Migraine Treatment

Naprosyn plus sumatriptan is better than either drug alone for the treatment of acute migraine according to a new report. In 2 studies, nearly 3,000 patients with a history of migraine were randomized to sumatriptan 85 mg plus naproxen sodium 500 mg, both drugs alone, or placebo to be used after the onset of a migraine with moderate to severe pain. The primary outcome was headache relief at 2 hours, absence of photophobia, absence of phonophobia, absence of nausea, and sustained pain-free response. Sumatriptan plus naproxen was superior to placebo in all measures and was superior to either drug alone in sustained pain-free response. The incidence of adverse effects was the same for the combination as for the individual medications. The authors conclude that sumatriptan 85 mg plus naproxen 500 mg as a single pill for acute treatment of migraine is more effective than either drug as monotherapy (*JAMA*.2007; 297:1443-1454.). Pozen Pharmaceuticals/ GlaxoSmithKline is developing the combination pill, which is expected to be approved later this year under the trade name Trexima. ■

Pergolide Off the Market, Heart Disease Risk

Pergolide (Permax) is being withdrawn from the market after reports of serious valvular heart disease associated with the drug. Pergolide is a dopamine agonist used for the treatment of Parkinson's disease, hyperprolactinemia and pituitary tumor (?). The action was prompted by 2 reports in the January 4, 2007, *New England Journal of Medicine* that showed increased rates of valvular dysfunction in Parkinson's patients who were taking the drug. These findings coupled with the availability of other dopamine agonists prompted the FDA's action. Valeant Pharmaceuticals is removing Permax brand pergolide as are all generic manufacturers. ■

Hormone Treatment, Does Timing Matter?

Further analysis of the Women's Health Initiative suggests that the timing of the initiation of hormone therapy may have an effect on the risk of cardiovascular disease. The analysis looked at postmenopausal women who had undergone a hysterectomy and were randomized to conjugated estrogen or placebo and women who had not had a hysterectomy who were randomized to conjugated estrogen plus medroxyprogesterone or placebo. The main outcomes were coronary heart disease (CHD) and stroke. Women who initiated hormone therapy within 10 years of menopause had a lower incidence of CHD (HR 0.76 [95% CI, 0.50-1.16]), which equates to 6 fewer events per 10,000 person-years. For women who initiated therapy 10-19 years after menopause the hazard ratio was 1.10 (95% CI, 0.84-1.45), and for women who initiated therapy 20 years after menopause the hazard ration was 1.28 (95% CI, 1.03-1.58) or 12 excess events per 10,000 person years. CHD risk increased when patients were stratified by age as well. Hormone therapy increased the risk of stroke with no significant difference based on time since menopause or age. There was a non-significant trend for improved overall mortality in younger women. The authors conclude that women who initiated hormone therapy closer to menopause had a reduced risk of CHD, with an increase risk among women more distant from menopause although the trends did not meet their criteria for statistical significance (*JAMA*. 2007:297;1465-1477.). ■

FDA Actions

The FDA has approved Cangene's immune globulin to prevent reinfection with the hepatitis B virus in certain liver transplant patients. The product was previously approved for preventing hepatitis B infection after exposure in 2006. It is marketed as HepaGam B.

The FDA has banned rectal suppositories that contain trimethobenzamide due to lack of efficacy in preventing nausea and vomiting. The popular suppositories have been marketed under various trade names including Tigan, Tebamide, T-Gen and others. The drug will still be available as oral and injectable preparations. The evaluation which eventually led to the withdrawal is part of the FDA's ongoing Drug Efficacy Study Implementation (DESI) which evaluates older drugs previously approved based on safety data to make sure that they are also effective.

The FDA has approved Merck's combination diabetes drug Janumet, which combines sitagliptin with metformin. Sitagliptin, which is a dipeptidyl peptidase-4 inhibitor, has been marketed by Merck since last October under the trade name "Januvia." The combination is approved for the treatment of patients with type 2 diabetes; it should be dosed twice daily with meals with gradual dose escalation. ■