Current Understanding and Treatment of Headache Disorders

Five New Things

BY MICHAEL J. MARMURA, MD
STEPHEN D. SILBERSTEIN, MD

As general practitioners become increasingly adept at prescribing triptans and preventive treatment, neurologists are more likely to see patients who are refractory to standard therapies. The most pressing concern for physicians and patients is excluding secondary headache. Reversible cerebral vasoconstriction syndrome is increasingly recognized as an underdiagnosed cause of headache, and may present as a sudden-onset thunderclap headache. The past few years have brought exciting new advances in the understanding of migraine pathophysiology including new genes for migraine and discovery of a new pathway for light sensitivity. After almost 20 years since the introduction of triptans, calcitonin

gene-related peptide antagonists now appear to be effective as acute migraine treatment for patients with poor response or contraindications to triptans. Finally, onabotulinumtoxin A has become only the 6th medication approved by the US Food and Drug Administration for migraine prevention and the first approved for chronic migraine. This article aims to highlight these exciting new topics in the treatment and understanding of headache disorders, which will help neurologists better treat and explain the disorders to their patients.

REVERSIBLE CEREBRAL VASOCONSTRICTION SYNDROME IS NOT RARE

Thunderclap headache is a neurologic emergency originally defined as a severe, sudden-onset headache; ruptured intracranial aneurysm had to be suspected and ruled out.¹ In addition to subarachnoid hemorrhage, many other disorders, such as spontaneous CSF leak, cerebral venous thrombosis, pituitary apoplexy, sphenoid sinusitis, carotid or vertebral dissection, stroke, hypertensive emergency, third ventricle colloid cyst, and even an unruptured aneurysm, can present with thunderclap headache.² Many patients with thunderclap headache have segmental cerebral vasoconstriction likely related to a disturbance in the con-

From the Jefferson Headache Center, Thomas Jefferson University, Philadelphia, PA.

Address correspondence and reprint requests to Dr. Michael J. Marmura, Jefferson Headache Center, 8130 Gibbon Building, 111 South 11th St., Philadelphia, PA 19107; michael.marmura@jefferson.edu

Author disclosures are provided at the end of the article.

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"The past few years have brought exciting new advances in the understanding of migraine pathophysiology"

trol of vascular tone.³ Originally called Call-Fleming syndrome, it is now known as reversible cerebral vasoconstriction syndrome (RCVS).⁴ In almost all cases, cerebral vasoconstriction resolves within a few weeks. Angiography (conventional, MRI, or CT angiography) is crucial to make the diagnosis.⁵ Transcranial Doppler has been used to monitor cerebral vasoconstriction. Case reports suggest that calcium channel blockers such as nimodipine may help relieve symptoms and prevent stroke.⁶

RCVS may be one of the most common causes of thunderclap headache. Ducros et al⁷ reviewed 67 consecutive patients with angiographically confirmed RCVS. Most (42 of 67) were women, with a mean age of 42 years. Most presented with thunderclap headache: 63 subjects had multiple headache episodes of extreme severity peaking in less than 10 seconds. Transient neurologic deficits occurred in 11 subjects. Visual symptoms were most common, followed by unilateral sensory symptoms or aphasia; 2 patients had seizures. Five patients were diagnosed with stroke: 1 ischemic, 3 hemorrhagic, and 1 with both types. RCVS was due to another disorder in 63% of subjects. Precipitating factors included delivery or early postpartum and the use of vasoactive substances (cannabis, selective serotonin reuptake inhibitors, nasal decongestants, cocaine, or alcohol after binge drinking). Severe headaches resolved in 3–6 weeks, but 24 subjects reported milder persistent headache and 7 developed depression. Based on their data, Ducros et al. concluded that RCVS is greatly underdiagnosed.

Thunderclap headache often occurs without a proven secondary cause. Primary thunderclap headache is recognized by the current International Classification of Headache Disorders⁴ as a sudden-onset headache lasting from 1 hour to 10 days. Chen et al⁸ suggested that primary thunderclap headache is in the same spectrum as RCVS and that nimodipine is also an effective treatment.

ONABOTULINUMTOXIN A IS EFFECTIVE IN THE PREVENTIVE TREATMENT OF CHRONIC MIGRAINE Chronic migraine (CM) is a highly disabling form of chronic daily headache and the most common disorder seen in tertiary headache centers.⁹ Patients with CM have headache at least 15 days per month and have symptoms that meet criteria for migraine on at least 8 of those days.⁴ Many patients with CM overuse acute medication to treat pain and preventive treatment is essential. Most preventive medications

for migraine, such as β -adrenergic blockers, antidepressants, and anticonvulsants, have not been rigorously studied for the treatment of CM. Based on recent clinical trials, onabotulinumtoxin A (BoNTA) is now the first medication with US Food and Drug Administration approval for CM prophylaxis.

The basic pharmacologic actions of BoNTA are fairly well-understood, but the exact mechanism of action in pain relief is unclear. BoNTA binds to nerve terminals, is endocytosed, and cleaves SNAP-25 protein, inhibiting the vesicular release of acetylcholine from nerve terminals, and blocking neuromuscular transmission. Similar phenomena occur in parasympathetic and sensory neurons.¹⁰ Starting a few days after IM injection, BoNTA produces partial chemical denervation of the muscle, resulting in a localized reduction in muscle activity for months. Due to the fact that pain relief in cervical dystonia trials often occurred before any decrease in muscle tension, it has been suggested that BoNTA may have other distinct properties that lead to pain relief. BoNTA administration appears to inhibit the release of glutamate and the neuropeptides, substance P and CGRP, from nociceptive neurons.¹¹ By blocking peripheral sensitization of nociceptive fibers, it may also inhibit central sensitization and allodynia.¹²

Some early studies suggested that BoNTA demonstrated effectiveness for the prevention of chronic daily headache, which includes CM,¹³ but in other studies did not demonstrate a significant reduction in headache-free days compared to placebo.¹⁴ A large, placebo-controlled study for the treatment of episodic migraine failed to show superiority over placebo,¹⁵ due to a greater than expected placebo response. The most common adverse events in headache trials have been cosmetic (ptosis, facial asymmetry) and temporary worsening of headache after injection.¹⁶

Two recent, large, phase 3 multicenter studies, the PREEMPT 1 and 2 trials, evaluated the safety and efficacy of BoNTA for the treatment of adults with CM. These 2 studies enrolled 1,384 subjects with CM in trials consisting of a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week open-label phase. All subjects received at least a minimum dose of 155 units of BoNTA administered at 31 injection sites across 7 head and neck muscles using a fixed-site, fixed-dose injection paradigm with 155 units and up to 40 additional units using a modified follow-the-pain approach.^{17,18} All patients received injections in frontalis, corrugator, procerus, occipitalis, temporalis, and trapezius muscles. In PREEMPT 1, there was no significant difference in the number of headache episodes compared to baseline in the BoNTA and placebo groups, but in PREEMPT 2 BoNTA significantly reduced the frequency of headache days com-

pared to placebo. Based on the pooled analyses, subjects receiving BoNTA in the double-blind phase had statistically significant improvement from baseline after injection compared with placebo treatment in headache episodes and multiple secondary clinical domains, including mean frequency of headache days and headache episodes. BoNTA-treated subjects also had fewer migraine episodes, fewer moderate or severe headache days, and less disability and triptan use than the placebo group.

A BETTER UNDERSTANDING OF PHOTOPHOBIA IN MIGRAINE Migraineurs typically develop worsening pain and migraine symptoms when exposed to light, a phenomenon known as photophobia. Photophobia is also common in ocular disorders, such as iritis¹⁹ and uveitis, and intracranial disorders, such as meningitis. In the classic visual pathway, light activates rods and cones in the retina, which activate retinal ganglion cells that project via the optic nerve, to the lateral geniculate nucleus, superior colliculus, and then the visual cortex. This pathway includes image-forming and non-image-forming data. A new pathway (non-image-forming information) allows maintenance of normal circadian rhythms via the suprachiasmatic nucleus and is regulated by intrinsically photosensitive retinal ganglion cells (ipRGCs). These ipRGCs are independent of the rods and cones and contain melanopsin, a photopigment.²⁰

Nosedá et al.²¹ studied blind individuals who had migraine and correlated these findings with rat models involving tracing of ipRGC projections to areas in perception of pain from the dura. Of the blind patients with migraine, 6 had no light perception due to severe optic nerve damage or bilateral enucleation. These subjects experienced abnormal sleep patterns and poor pupillary light responses. Their migraines did not worsen with light exposure. In contrast, 14 blind subjects who were able to detect light despite minimal perception of images had normal sleep patterns and a normal pupillary light reflex. Despite widespread rod and cone degeneration, these patients had worsening migraine symptoms with light exposure during migraine attacks, suggesting that ipRGCs, and not rods and cones, are important in photophobia.

These retinal projections of non-image-forming brain areas project to the contralateral dorsocaudal

region of the posterior thalamus, as demonstrated by anterograde tracing in the rat.²² ipRGC input to this area modulates dura-sensitive pain neurons, which also project to this region. Thalamic neurons, dually sensitive to dural pain and light input, project widely to multiple cortical regions, including the primary somatosensory cortex, the primary and secondary motor cortices, the parietal association cortex, and the primary and secondary visual cortices.²¹ These cortical projections may help explain other common migraine symptoms, in addition to photophobia, such as motor weakness or incoordination, visual disturbances, and poor concentration.

CALCITONIN GENE-RELATED PEPTIDE ANTAGONISTS EFFECTIVELY TREAT MIGRAINE ATTACKS Stimulation of trigeminal sensory neurons results in the release of neuropeptides (including substance P and calcitonin gene-related peptide [CGRP]), producing blood vessel dilation and mast cell, endothelial, and platelet activation (neurogenic inflammation), which leads to migraine.²³ CGRP is elevated in external jugular venous blood during acute migraine pain,²⁴ and triptans reduce elevated CGRP levels.²⁵ In animal models, mice sensitized to CGRP demonstrate more light-averse behavior when exposed to exogenous CGRP. The administration of olcegepant, a CGRP receptor antagonist, prevented photophobia in these mice.²⁶

Although triptans are currently the gold standard for acute migraine treatment, some patients do not respond or respond inconsistently to them. Triptans may be less effective for attacks with established central sensitization, clinically manifested as allodynia,²⁷ although this has not always been the case in clinical trials.²⁸ Triptans are contraindicated in patients with coronary artery disease, cerebrovascular disease, or significant risk factors due to potential vasoconstrictive effects. Chest tightness and pain after triptan use is a common adverse event and may lead to unnecessary concern or diagnostic testing.²⁹ Frequent triptan use (10 days a month or more) can lead to worsening of headache (medication overuse headache), requiring medication withdrawal.³⁰

CGRP antagonism does not cause vasoconstriction, making it safe for patients with migraine who cannot use triptans. Ho et al.³¹ studied the CGRP antagonist Telcagepant 150 mg and 300 mg and compared it to zolmitriptan 5 mg and placebo in a randomized, parallel-treatment, placebo-controlled, double-blind trial. Telcagepant 300 mg was statistically more effective for complete pain relief after 2 hours and pain relief compared with placebo. It was also more effective in reducing photophobia, phonophobia, and nausea. The efficacy of Telcagepant was similar to that of zolmitriptan but with fewer adverse

Headache: Five New Things

- Reversible cerebral vasoconstriction syndrome is not rare.
- Onabotulinumtoxin A is effective in preventing chronic migraine.
- New pathway for light sensitivity is discovered.
- Calcitonin gene-related peptide antagonists effectively treat migraine attacks.
- New genes causing migraine have been identified.

events. Adverse events seen in the trial included fatigue, dizziness, and abdominal pain. All were similar to placebo. Connor et al.³² confirmed these findings and found that the 150 mg dose was effective. Three patients who used Telcagepant in a previous study developed asymptomatic, transient elevations in liver enzymes. Further studies to determine the safety of frequent Telcagepant use are underway.

The development of CGRP antagonists is hopeful for patients who either do not respond to triptans or cannot take or tolerate them. Further studies are needed to determine the role of CGRP antagonists in migraine and the optimal way to use them.

GENETIC ADVANCES IN MIGRAINE Although clinicians have long recognized the genetic basis of migraine, only a few specific migraine genes have been discovered. Most genetic advances have involved familial hemiplegic migraine (FHM). Mutations involving the *CACNA1A* gene, a P/Q type voltage-gated calcium channel located on chromosome 19, are responsible for about half of FHM cases. In addition to hemiplegic aura, these patients with FHM may have cerebellar ataxia or severe attacks with minor head trauma.³³ Two other FHM genes have been discovered: the *ATP1A2* gene, which produces a loss of function of the alpha-2 N^+/K^+ ATPase pump,³⁴ and *SCN1A*, a neuronal voltage-gated sodium channel gene.³⁵ Mutations in any of these 3 genes involved in ion transport can increase glutamate concentrations and excitatory neurotransmission, resulting in a lower threshold for cortical spreading depression and migraine.

Migraine with aura is a common, debilitating, recurrent headache disorder associated with transient and reversible focal neurologic symptoms. Researchers recently identified a locus for migraine with visual aura in a study of 36 families with visual aura, most commonly scintillating scotoma.³⁶ The implicated gene, found using linkage analysis at chromosome 9q21-q22, overlaps a recently discovered gene for occipitotemporal lobe epilepsy. Like migraine, genetic forms of epilepsy may be related to neuronal excitability and abnormalities in ion channels. The *SCH3* gene in this region is known to be involved in the adaptive response of neurons to environmental stress.³⁷

A role has been suggested for the 2-pore domain (K2P) potassium channel, TWIK-related spinal cord potassium channel (TRESK, encoded by *KCNK18*), in pain pathways and general anesthesia.³⁸ Lafreniere et al.³⁸ examined whether TRESK is involved in migraine by screening the *KCNK18* gene in subjects diagnosed with migraine. They found a frameshift mutation, F139WFSx24, which segregates perfectly with typical migraine with aura in a large pedigree. They identified

prominent TRESK expression in migraine-salient areas, such as the trigeminal ganglion and sensory ganglia. Functional characterization of this mutation demonstrates that it causes a complete loss of TRESK function and that the mutant subunit suppressed wild-type channel function through a dominant-negative effect, thus explaining the dominant penetrance of this allele. These results therefore support a role for TRESK in the pathogenesis of typical migraine with aura and further support the role of this channel as a potential therapeutic target.³⁷

The genetics of more common forms of migraine are less clear. A large, case-control, genome-wide association study including 2,731 migraine patients recently linked the minor allele of rs1835740 on chromosome 8q22.1 to migraine with and without aura.³⁹ This marker is located near 2 genes that could be involved in migraine, metadherin (MTDH) and plasma glutamate carboxypeptidase (PGCP). MTDH regulates the gene that encodes a major glutamate transporter in the brain⁴⁰ and PGCP is involved in glutamate metabolism. In this study, the linkage was strongest for individuals with aura. This study suggests that alterations in glutamate release, transport, and clearance may be a common link in many migraine sufferers.

DISCLOSURE

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