Curr Pain Headache Rep (2013) 17:362
DOI 10.1007/s11916-013-0362-7

MIGRAINE (R COWAN, SECTION EDITOR)

Why Does Vomiting Stop a Migraine Attack?

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Published online: 4 August 2013

Abstract Migraine is commonly associated with nausea and vomiting, though, interestingly, vomiting has also been reported by some patients to be therapeutic, and may actually stop a migraine attack. In this review, we will first discuss the epidemiology of nausea and vomiting in migraine. Further, we will briefly review the connections between the enteric nervous system, the autonomic nervous system, and the central nervous system as they pertain to understanding the question of "Why does vomiting stop a migraine attack?"

Keywords Enteric nervous system · Migraine · Nausea · Pain · Vomiting · Vagal nerve stimulation · VNS

Introduction

Migraine is a common neurovascular disorder with associated GI and autonomic symptoms that is frequently treated by neurologists in the clinical setting. Nausea, vomiting, photophobia, and phonophobia are strongly associated with migraine attacks, and are an integral part of the diagnostic criteria for migraine according to International Headache Classification 2 and 3-beta [1]. An interesting phenomenon that has been observed by some migraineurs is the pain-relieving property of vomiting during their migraine attacks. Dozens of public patient forums discuss individuals' experiences on the improvement or cessation of their migraine attacks after vomiting. Some patients have been reported to induce vomiting during a migraine attack with the goal of improving their head pain [2, 3].

Vomiting as a pain-relieving maneuver has been explored throughout history. Over 2,000 years ago, Hippocrates believed that migraine resulted from vapors rising from the stomach to the head [4], and observed that "… vomiting, when it became possible, was able to divert the pain and render it more moderate" [5]. To date, however, there have not been any specific studies or reviews on the pain-relieving effect of vomiting. Further, vomiting is not a universal pain-relieving maneuver for migraineurs, as many migraineurs suffer from headache not relieved by repeated vomiting; additionally, many patients prefer to avoid vomiting. Headache experts appear to agree that the gut–brain interaction is bidirectional and complex, and certainly extends beyond simply the maintenance of daily digestion. More and more experts are embracing the concept that the gut and the brain are closely connected through direct and indirect wiring, and that this interaction may play an important role in certain central nervous system (CNS) pathologies, such as migraine. However, there is still only broad speculation on the various pathophysiologic mechanisms that may contribute to the pain-relieving effect of vomiting.

In this review, we first discuss the epidemiology of nausea and vomiting in migraine. Further, we briefly review the connections between the enteric nervous system (ENS), the autonomic nervous system (ANS), and the CNS in migraineurs. And finally, we attempt to construct theories to answer the question "Why does vomiting stop a migraine attack?".

Epidemiology of Nausea and Vomiting in Migraineurs

One of the first epidemiologic studies linking nausea and vomiting to migraine was in 1960 when Selby and Lance [6] described accompanying symptoms in migraineurs; 87 % of patients reported nausea, while 56 % patients reported vomiting during migraine attacks. Multiple subsequent epidemiologic studies and clinical trials have echoed this result, demonstrating that both nausea and vomiting are reported in at least half of all migraine sufferers [7, 8]. In addition, the

This article is part of the Topical Collection on *Migraine*

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2009 American Migraine Prevalence and Prevention survey by Lipton et al. [9•] suggested that nausea could be taken as a marker for a more severe subset of migraine, and that nausea was associated with more migraine-related disability. However, this study did not evaluate the incidence or prevalence of vomiting in migraineurs.

Two studies were able to specifically identify vomiting as a pain-relieving behavior in migraineurs. In a 2001 study, Martins and Parriera [2] interviewed 100 headache patients with either migraine (n=72) or tension-type headache (n=28), and questioned them concerning their use of non-pharmacological maneuvers to relieve their head pain. The only behavior that was exclusively found in migraineurs (none in the tension-type headache group) was vomiting. Fifty-eight out of 72 migraineurs answered "yes" to vomiting as a behavior to relieve pain, of which 43 experienced spontaneous vomiting and 15 patients induced vomiting. The efficacy of vomiting in stopping their head pain was reported to be 62.1 % (36 of 58 patients, spontaneous or provoked, compared with a reported efficacy of 90 % for taking medication)[2]. A study by Bag and Karabulut [3] reported similar results. Of 130 patients, vomiting was, again, the only pain-relieving maneuver that was reported specifically in migraineurs. Twenty-one out of the 75 migraineurs answered "yes" to vomiting as a behavior to relieve pain, out of which 15 had spontaneous vomiting and six patients used induced vomiting [3].

These studies suggest some specificity in the pain-relieving effect of vomiting in migraineurs compared with patients with tension-type headaches. However, neither study clearly distinguished if the vomiting behavior was performed only by migraine patients who had nausea versus those who did not. They also did not distinguish the efficacy between induced versus spontaneous vomiting on relieving patients' head pain. The degree and duration of their improvement of head pain were vague – it was not clear if the pain improved only temporarily or if the entire migraine attack abated after vomiting. (In the Martins and Parreira [2] study, efficacy was rated as positive—that specific maneuver always or often reduced pain or negative-rarely or never-reduced pain.) Further, the studies did not address the differences in the epidemiology of vomiting in migraineurs with aura versus those without aura.

Finally, Gupta and Bhatia's study [10] compared the pain-relieving effect of vomiting in migraine patients with cranial autonomic symptoms (CAS) versus those without. This study consisted of 78 consecutive patients with migraine, of which 73.1 % had CAS. Vomiting was found to have some pain-relieving effect in both patients with and without CAS (4.8 % vs 5.3 %, $P=1.0$)[10].

In the pediatric population, vomiting was found to be more frequent in younger children suffering from headache [11]. However, no systematic studies have been done to describe the efficacy of vomiting on migraine termination in children.

Brief Overview of the Connections Between the ENS, the ANS, and the CNS

Gastrointestinal function is controlled by ENS, which is heavily influenced by the ANS and receives input from the CNS. The ENS also provides feedback information to the CNS.

The ENS is composed of thousands of small ganglia within the walls of the gastrointestinal tract, the mucosal epithelium, and the arterioles. These cells are developed from neural crest precursors that migrate along the vagus, which then separate and differentiate in the gut [12]. The neurons of the ENS are exposed to a complex internal environment in the gut and allow communication with the CNS [13]. Like neurons in the CNS, enteric neurons are embedded within a matrix of astrocytes [14] and secrete numerous neurotransmitters, such as acetylcholine, dopamine, serotonin, PACAP, and calcitonin gene-related peptide (CGRP) [15]. The transmission of information from the gut to the CNS relies on multiple information carriers, including the vagal and spinal afferent neurons, immune mediators, gut hormones, and gut microbiota-derived signaling. Output from the CNS to the gut primarily utilizes autonomic neurons and neuroendocrine factors [16].

The Anatomy and Physiology of Vomiting

Vomiting, or emesis, involves the contraction of the gut and the thoracoabdominal wall musculature, and produces oral expulsion of gastric content. Retching, in comparison, involves the same sequence of muscular events without expulsion of actual vomitus. The term nausea refers to a subjective feeling of the need to vomit [17].

Evolutionarily, vomiting likely represents a defensive mechanism against the accidental ingestion of toxic materials. However, the neurophysiology of vomiting, as well as nausea and retching, is extremely complex. Most believe that nausea may represent a low intensity activation of pathways that cause vomiting, though certain CNS stimuli can evoke vomiting with little prior nausea [18, 19]. Functional magnetic resonance studies have shown that nausea provoked by visual stimuli is associated with activation of a matrix of brain structures including the amygdala, putamen, and dorsal pons/locus coeruleus, while increasing nausea can subsequently involve the insular, anterior cingulate, orbitofrontal, somatosensory, and prefrontal cortices [20•].

Brain structures subserving emesis lie in the dorsal vagal complex (DVC) of the medulla oblongata comprised of the nucleus tractus solitarius, dorsal motor nucleus of the vagus, and area postrema. Information from the gastrointestinal tract is transmitted by vagal afferents to the nucleus tractus solitarius [21]. When the DVC is activated, the efferent pathways travel within vagal and sympathetic nerves to the

gastrointestinal tract and within spinal nerves to the diaphragm and abdominal muscles [22, 23]. At the onset of vomiting, intrinsic contractions occur in both the duodenum and the stomach, the lower esophageal sphincter relaxes, and vomitus moves from the stomach into the esophagus. Next, the respiratory and abdominal muscles contract to expel the vomitus into the mouth [24].

There are stereotypic physiological changes that accompany nausea and vomiting. Nausea is often associated with cutaneous vasoconstriction and sweating. The act of vomiting parallels the Valsalva maneuver and produces a transiently elevated heart rate followed by decreased heart rate, and additionally causes continued peripheral vasoconstriction [19].

Studies have shown that lesions in certain anatomic areas described in the above emesis reflex can be essential for nausea and/or vomiting. For example, Cisplatin-induced vomiting can be eliminated by ablation of the area postrema in cats [25]. Further, electrical stimulation of the vagal afferent fibers in humans can induce nausea [26]; however, nausea can persist in humans even after sub-diaphragmatic vagotomy [27], and vomiting can occur in the absence of structures rostral to the medulla [28].

Why Does Vomiting Stop a Migraine Attack?

The termination of migraine has received less attention than studies focusing on the initiation and sustenance of migraine pain. A recent review suggests that the termination of a migraine attack may be an active process itself, rather than the result of the passive loss of a trigger [29]. In a recent opinion paper, Shapiro [30] proposes that if the mechanisms for active termination of a migraine exist, "they may lie within neural networks that also subserve the initiation of sleep and/or emesis, as these physiologic changes have been found to terminate migraines". We posed questions relating to the topic "Why does vomiting stop a migraine attack?" to experts in the field. Based on the replies from the experts and current known literature on this topic, we constructed the following hypotheses.

Hypothesis 1: Vomiting as an Adaptive Reaction to Limit Sensory Input During Attacks

Migraine attacks have been reportedly triggered by excessive sensory input (light, sound, lack of sleep, etc.), and migraineurs are known to actively avoid such triggers [31–33]. Gastroparesis has been found in migraineurs during attacks, as well as interictally [34, 35, 36•] and may represent yet another adaptive process to limit gastric input and motion, and subsequently limit sensory input. Dr David Kudrow, while disagreeing with the premise that vomiting has an effect on ameliorating migraine, proposes that migraine may be a cyclic event in which a physiologic avoidance and repulsion of all forms of sensory stimuli takes place. This may apply to the repulsion of any form of movement, including peristaltic movement, and vomiting may merely be an accompanying symptom that occasionally coincides with the termination of headache.

One of the first studies that suggested the presence of gastroparesis in migraineurs during attacks was done by Volans in 1974 [37]. This study found that about 45 % of patients showed impairment in the rate of absorption of aspirin during attacks compared with the absorption rates in the same patients interictally. By utilizing gastric scintigraphy, more recent studies by Aurora et al. [35, 36•] showed not only ictal gastroparesis in migraineurs, but additionally showed slowed gastric emptying interictally in migraineurs compared to control subjects [34]. Nausea, vomiting, and postprandial pain are all prominent symptoms associated with gastroparesis [38], which, perhaps, all lead to a common goal of ridding the body of any food stimuli. Thus, headache in migraineurs may terminate when the sensory stimuli has been successfully eliminated through the act of vomiting.

Hypothesis 2: Nausea and Vomiting May Represent Migraine Symptoms Arising From, and in Turn Modulating, the Activity of the ENS

Another view is that certain events in the ENS might provoke migraine attacks under some circumstances, or that such events may constitute the primary substrates for putative migraine syndromes such as infantile colic, abdominal migraine, or cyclic vomiting. It is thus conceivable that the migraine symptoms of nausea and vomiting may be considered phenomena emerging from a complex interaction of the CNS, ANS, and ENS, where vomiting may be a terminal event of these interactions. This viewpoint was proposed in an early form by Samuel-Auguste Tissot in the eighteenth century [39]. Eadie summarized Tissot's thesis [40]:

> Tissot's view was that in most instances of migraine a primary initial disturbance of the stomach was induced by emotion, diet or other locally acting factors. This stomach disturbance then exerted an effect elsewhere in the body by virtue of 'sympathy' or 'consensus' and brought about irritation of local scalp nerves, mainly the supraorbital nerve and other trigeminal branches. This nerve irritation was responsible for unilateral, mainly frontal, head pain. The neural irritation then extended to other parts of the nervous system, and in particular to the nerve supply of the stomach which was activated to bring about vomiting. The resultant emptying of the stomach's contents led to recovery of

the stomach's function. This corrected the cause of the migraine and so ended the attack. Hence migraine was to be regarded as a 'sympathetic' illness.

The simple dogmatic view that events arising in the alimentary tract are the universal initiators of migraine attacks is unsupported. That is, non-enteric stimuli (e.g. light, odorants, weather changes, etc.) can trigger migraine attacks. However, it is possible that some "functional bowel disorders", such as idiopathic gastroparesis, may actually represent acephalgic "enteric migraine". For example, in one specialty center survey, 59 % of patients with severe symptoms of idiopathic gastroparesis had a co-diagnosis of migraine [41].

Nausea is often a symptom of the premonitory phase of migraine, where it is associated with activation of the DVC, among other brain regions [42]. Such migraine-specific DVC activation might reflect activity arising in the ENS [21], and then reflexively influencing it [43], particularly as the DVC does not appear to be activated following nausea induced by some non-enteric (e.g. visual) stimuli [20•]. Furthermore, enteric astrocytes can propagate intercellular calcium waves [44] comparable to the signaling events observed between brain astrocytes, which are associated with reduced thresholds for cortical spreading depression (CSD) and migraine [45]. It is attractive to speculate that the ENS can also support CSD waves, like some other neural tissues (e.g. retina), and that CSD might thereby contribute to the development of some enteric hypomotility disorders. However, no enteric CSD events have been reported to date.

Hypothesis 3: Stimulation of Vagal Afferents During Vomiting Modulates Head Pain

Migraine symptoms involve the connection between the trigeminal nucleus caudalis and the nucleus tractus solitarius, which receives input from the vagus nerve [21, 46]. Vomiting, much as a Valsalva maneuver, triggers a vagal (parasympathetic) response, which is responsible for the decreased heart rate and peripheral vasoconstriction after the act of emesis. Dr Emeran Mayer suggests that the vomiting-induced vagal nerve stimulation (VNS) may be responsible for the modulation of migraine pain. Vagal nerve activation, according to Dr Mayer, can provide considerable general pain and stress relief.

Holtmann et al. [46] showed that patients who have undergone vagotomy had lower thresholds for pain perception compared to healthy human volunteers, suggesting a pain modulatory role for the vagus nerve. VNS has subsequently been suggested to contribute to the modulation of visceral pain [48, 49] and migraine headache [50–53]. When intractable epilepsy patients receiving VNS were studied retrospectively, those with co-existing migraine reported reduction in frequency and intensity of their headaches [50, 51]. Small prospective case series consisting of non-epileptic patients who underwent VNS implantation specifically for primary headache also showed promising results [52, 53]. Transcutaneous VNS is currently being studied as a treatment for migraine by ElectroCore using the GammaCore stimulator [54].

The activation of vagal afferents, whether by chemical, electrical or physiological means, can actually result in either facilitation or inhibition of nociception [55]. This distinction is likely owing to the stimulation of different types of vagal fibers. The vagus nerve contains three types of fibers (A–C). C-fibers are small, unmyelinated fibers that can be stimulated at a threshold above 2.0 mA. The A-fibers are the large, myelinated fibers, which are recruited at the lowest thresholds of 0.02–0.2 mA [49]. Stimulation of the large A-fibers has been linked to modulation of pain, while the stimulation of small C-fibers has been associated with VNS side effects, such as bradycardia and bronchoconstriction [49].

Vagal stimulation from vomiting is likely very nonspecific, and both large and small fibers of the vagus nerve may be involved. Current available studies on this topic are few. Certainly, more studies are needed to evaluate the efficacy of VNS on migraine pain modulation.

Hypothesis 4: The Neuropeptide Link to Vomiting and Migraine Headache

Enteric neurons secrete numerous neurotransmitters, including acetylcholine, dopamine, serotonin, PACAP, and CGRP. CGRP, specifically, has been implicated in migraine pathophysiology. CGRP receptor antagonists have been tested for their efficacy in acute migraine treatment, and studies are ongoing for the efficacy and safety of antibodies to both free CGRP and the receptor [56–59]. However, no published data have examined the effect of vomiting on the above-mentioned neuropeptides.

Vasopressin (VP) is the only peptide that has been linked with emesis and possibly migraine pain modulation. Emesis has an antidiuretic action and leads to increased arginine–VP (AVP) release [60]. Nausea itself, even without vomiting, is accompanied by intense and rapid AVP release [61]. The specificity of nausea-mediated AVP release is suggested by the absence of significant increases in plasma AVP in rats (which lack an emetic reflex) when they were given relatively large doses of apomorphine [61].

Some migraine precipitants (emotional stress, ethanol, etc.) decrease VP secretion or bioavailability, while some migraine-relieving factors (tricyclic antidepressants, sleep, etc.) have been associated with elevated AVP [62–64]. Gupta [61, 63] has proposed that VP may be implemented in migraine modulation, and its elevation in nausea and/or vomiting

may be viewed as part of the adaptive system that can delay or abort migraine attacks.

However, there is also evidence that refutes the importance of VP in migraine. For example, hypoglycemia, a possible migraine trigger, is a potent stimulus for VP secretion [63]. Chlorpromazine, which is effective in acute migraine treatment, also diminishes VP release from the pituitary and may produce diuresis in humans [65].

Hypothesis 5: Vomiting, by Causing Peripheral Vasoconstriction, May Decrease Blood Flow Through Pain-Sensitized Vessels

Both nausea and vomiting can cause cutaneous vasoconstriction. The act of vomiting and retching can evoke the same physiologic changes as those seen in the Valsalva maneuver. The tightening of abdominal and thoracic musculature initially impedes venous return, causing increased pulse rate and peripheral vasoconstriction in an attempt to increase cardiac output. As the pressure releases at the end of emesis, the pulmonary vessels and the aorta re-expand, and venous blood can again return to the larger venous structures. However, peripheral vascular resistance continues to be elevated even at the end of the Valsalva maneuver [66].

Nociceptive input from peripheral perivascular sensory nerve terminals in the meninges have been strongly implicated to participate in the generation of migraine headache [67]. Migraine pain may be stimulated with arterial dilation by stretching of the arterial wall. This was supported by the observation that the superficial temporal artery (STA) is dilated in migraine attacks [68], and there can be asymmetry of the STAs during a unilateral migraine attack [69]. In addition, epoprostenol has been shown to induce migraine-like attacks in migraineurs and is associated with dilation of both STA and middle cerebral artery (MCA) [70]. Further, studies have suggested the possibility of interrupting migraine pain with compression of the main scalp arteries, hypothesizing that decreased blood flow through the pain-sensitized vessels can perhaps induce a temporary conduction block of periarterial nociceptive fibers [71–74, 75•, 76]. In theory, the effect of meningeal vessel constriction associated with the act of vomiting may modulate the pain sensation by exerting brief episodes of perivascular nociceptive blocks.

However, there have also been numerous studies and increasing evidence against the concept of vasodilatory activation of migraine pain. Kruuse et al. [76] showed a lack of correlation between vasodilatation and the headache with Sildenafil. Amin et al. evaluated magnetic resonance angiograms during spontaneous migraine attacks and did not find vasodilation [77]. Others have looked at the lack of headache with significant vasodilatation when given VIP [78, 79]. Nonetheless, the actions of some anti-migraine agents (e.g. sumatriptan) may include constriction of cerebral vessels [80, 81].

As the debate for the existence of vasodilatory peripheral headache generator becomes better defined, the peripheral vasoconstrictive properties related to vomiting can be further evaluated [82]. It remains to be determined whether emesis-related vascular changes can cause the termination of migraine. If so, one may presume that retching may be just as effective as vomiting in reducing head pain. However, no such epidemiologic studies currently exist to support or refute this idea.

Therapeutic Options

Antiemetic Treatment

If vomiting improves migraine attacks by its fundamental function of limiting sensory input, i.e. limiting food stimuli, medications to quiet abnormal myoelectric activity of the stomach may be helpful in reducing headache impact in migraineurs.

A large portion of migraine medication is in the antiemetic category. There has been a multitude of data demonstrating the efficacy of antiemetics for the treatment of both pain and nausea in migraine headache [83–86]. Ellis et al. [83] demonstrated that migraine patients receiving metoclopramide had better relief of pain than patients receiving only ibuprofen. Metoclopramide, a prokinetic medication often given to patients with gastroparesis to promote gastric emptying, may improve migraine pain in a similar fashion as vomiting.

Interestingly, ondansetron, a selective 5-HT_3 receptor antagonist, which also can provide symptomatic relief to migraineurs, improves nausea without any prokinetic effects. As vagal afferents utilize serotonin receptors, ondansetron may, at least partially, exert its antiemetic effect by inhibiting the afferent vagal pathway that leads to vomiting. As this beneficial effect of ondansetron completely skips the physiologic changes related to vomiting, it would be interesting to compare the efficacy of vomiting versus the use of ondansetron (to prevent vomiting) for the abortion of migraine pain.

Overall, most experts we surveyed support the use of antiemetics with every migraine patient, including those without the symptom of nausea. One of the authors, AR, only uses antiemetics when acute care medications do not effectively relieve nausea and vomiting, or when patients have persistent nausea and/or vomiting.

VNS

Non-invasive, transdermal vagal nerve stimulators have demonstrated some early success in open treatment trials of migraine patients, and large, blinded studies are underway [47]. As many other modalities such as diaphragmatic

breathing also stimulate vagal input, alternative conservative vagal stimulatory maneuvers should also be tried for migraine relief. Currently, no systematic studies exist in the evaluation of vagal stimulatory maneuvers for acute migraine treatment.

Other Treatment Options

Gastric electrostimulation with high-frequency short pulses is a relatively new therapeutic option offered to patients with refractory gastroparesis. It has been shown to improve nausea and vomiting associated with gastroparesis in open-label trials, but not in controlled trials to date [87, 88]. However, its implantation involves an invasive procedure, which may limit its study and use in migraine patients.

Future Directions

Vomiting consists of the complex integration of gastrointestinal, peripheral, and central stimulation, and subsequent activation. If any of these physiologic and chemical changes contribute to the modulation or termination of pain in migraine headache, it would be worthwhile to further investigate the associated therapeutic options. Vagal stimulation, for example, has already been explored for the treatment of migraine.

Epidemiologic studies are needed to further define this interesting phenomenon and shed light on its potential pathophysiology. Patient selection for comparative studies will be key, as vomiting clearly does not improve head pain in all migraineurs. Subsequently, comparative studies can be done to evaluate the above-mentioned aspects of vomiting and their pain-relieving effects. One interesting aspect would be to compare the efficacy of vomiting versus the use of ondansetron (to prevent vomiting) for the termination of migraine pain or even the entire attack. Another question may be the evaluation of pain-aborting effects of vagal stimulatory maneuvers, such as retching, straining, or deep diaphragmatic breathing in migraineurs. Also, what about the relationship of the pain aborting effects of transcutaneous VNS and its effect on nausea and vomiting? It would also be worthwhile evaluating if there is a pain threshold linked to vomiting and if vomiting helps migraine at any stage of the pain intensity scale. Dr David Kudrow suggested a timing study to evaluate the severity of headache at time of first vomiting to time of migraine resolution. Functional magnetic resonance image have been suggested by Dr Leone Massimo to evaluate the functional status of the brain in migraineurs pre- and post-emesis.

Some research limitations exist for this area of study. Many laboratory animals (i.e. rats) do not have an emetic reflex. Additionally, scoring pain and degree of nausea can be difficult, even for a patient with currently existing symptoms.

Conclusion

Migraine is one of the most common neurologic conditions. In addition to medication, many individuals with migraine headaches use non-pharmacological measures to relieve their head pain. Vomiting is a frequent co-existing symptom to migraine head pain, yet it has also been reported by some patients to abort or improve their migraine attacks. Vomiting may exert its pain-relieving effects by fulfilling its fundamental purpose of eliminating sensory input. Or, perhaps, vomiting is merely the terminal event of specific migraine attacks of an enteric onset. Further, vomiting may exert multiple autonomic, chemical, and vascular effects to diminish migraine pain. More epidemiologic studies are needed to better define the patient population amendable to the therapeutic effect of vomiting during a migraine attack.

Acknowledgments We would like to thank the following for their insightful comments and contributions to our survey questions: Dr Allan Purdy (Dalhousie University, Nova Scotia); Dr.David Kudrow (California Medical Clinic for Headache); Dr Emeran Mayer (UCLA); Dr Massimo Leone (Istituto Nazionale Neurologico C. Besta, Milano, Italy); Dr Peter Goadsby (UCSF); and Dr K Ravishankar (Jaslok Hospital and Research Centre and Lilavati Hospital and Research Centre, Mumbai, India).

Compliance with Ethics Guidelines

Conflict of Interest Nu Cindy Chai reported no potential conflicts of interest relevant to this article.

Dr Robert E. Shapiro reported no potential conflicts of interest relevant to this article.

Dr Alan M. Rapoport reported no potential conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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