Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches

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Anticonvulsant and antidepressant medications have demonstrated efficacy in migraine treatment. Vagus nerve stimulation (VNS) is an effective treatment for drug-refractory epilepsy and possibly depression and it also has documented analgesic effects. These observations suggested a possible role for VNS in treating severe refractory headaches, and led to a trial of VNS in patients with such headaches. VNS was implanted in four men and two women with disabling chronic cluster and migraine headaches. In one man and one woman with chronic migraines VNS produced dramatic improvement with restoration of ability to work. Two patients with chronic cluster headaches had significant improvement of their headaches. VNS was well tolerated in five patients, while one developed nausea even at the lowest current strength. In conclusion, VNS may be an effective therapy for intractable chronic migraine and cluster headaches and deserves further trials. □*Migraine, cluster headache, vagus nerve stimulation, epilepsy*

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Introduction

Migraine is one of the most common neurological diseases with a prevalence of 12% in the US population (1). Epidemiological data from the USA and other countries indicates that a surprising 4% of the population suffers from daily headaches (2). Many safe and effective therapies are available for the management of an acute migraine attack, but prophylactic pharmacotherapy of frequent, prolonged or refractory migraine headaches is much more limited. A variety of drugs are used for this purpose, but many are marginally effective, while others often cause unacceptable side-effects. Among the drugs that are effective for prophylaxis of migraine attacks are antidepressants and anticonvulsants, such as divalproex sodium, gabapentin and topiramate. The latter are used not only for migraine prophylaxis, but also for mood disorders.

Vagus nerve stimulation (VNS) has proven to be effective for drug-resistant epilepsy and it is undergoing clinical trials for the treatment of refractory depression. The efficacy of VNS in epilepsy and possibly depression strongly suggests a further possible therapeutic effect in refractory migraines. A potential antimigraine effect of VNS is suggested by observations made in epilepsy studies. VNS has been shown to alter cerebral metabolism and blood flow in the limbic system, and to affect neurotransmitter systems involved in migraine. A patient with refractory epilepsy and severe migraine was treated with VNS and, while the seizures persisted, the migraine improved from 3 per month to 3 in 13 months (3). We reported our first patient with chronic migraine who benefited from VNS () and 1 we have since treated another five patients with VNS. In all patients, the left vagus nerve was stimulated. MIDAS is a migraine disability scale, but we also used it in our cluster patients because of

the lack of such a scale for patients with cluster headaches.

Case reports

Migraine

Patient 1

This 45-year-old-male presented to the New York Headache Center in March of 1996 with a history of migraine attacks that started at the age of 13. The frequency of attacks was two a week, and each one was preceded by a visual and sometimes sensory and motor auras. The prodrome consisted of severe depression and slurred speech for 24 h prior to the attack and at times some drooling. The pain was always left-sided and lasted for about 24 h. He had associated photophobia, phonophobia and worsening with light physical activity. Sumatriptan injections had been effective in relieving his head pain and vomiting. He was not overusing analgesics or caffeine. His initial visit was prompted by a change in his headaches. The patient began to have vertical diplopia as part of his aura. Diplopia was present only with both eyes open. On several occasions he had episodes of involuntary twitching of his thumb that lasted several minutes. These were not accompanied by alteration of consciousness. Over the ensuing years frequency and severity of his attacks increased. He developed near-syncopal attacks during his migraines (feeling as if he is about to pass out and having to lie down) and almost every migraine was followed by hemisensory deficit and hemiparesis for 24 h following the attack. This made him experience some degree of impairment almost continuously. The patient was on the verge of leaving his job and applying for disability benefits. His mother had migraine headaches.

Physical examination was normal, except when he was examined after a severe migraine attack when he had a mild hemiparesis and hemi-sensory deficit.

Two MRI scans of the brain one year apart were normal. He had abnormal interictal cerebral perfusion on a SPECT scan with an irregular perfusion pattern including bi-frontal and bi-occipital hypoperfusion. Multiple EEGs, including a 48-h video EEG were normal.

Sumatriptan injections have remained effective for pain and vomiting, but not other symptoms. He failed to exhibit sustained response or did not tolerate prophylactic therapy with propranolol, verapamil, nifedipine, gabapentin, divalproex sodium, tiagabine, amitriptyline, bupropion, paroxetine, riboflavin and short courses of prednisone. Doses of all drugs were escalated to the highest tolerable level. Botulinum toxin injections were given on three occasions with a modest decline in headache frequency. Abortive therapy with nifedipine provided inconsistent relief of his aura symptoms.

Because of continued deterioration with secondary anxiety and depression, a vagus nerve stimulator was implanted in November of 1999. The patient began to improve within 2–3 months following the implantation. The stimulation parameters have been intermittently increased because of some deterioration, including the most recent adjustment in November 2001. The VNS first resulted in a reduction in frequency of migraine attacks, elimination of prodromal depression and shortening of his aura symptoms. After seven months, attacks of diplopia had decreased in duration to a few seconds instead of minutes, and the frequency of migraine attacks went down to two or three a month. A year after implantation he no longer had near-syncopal attacks, slurred speech or diplopia and the frequency of his attacks declined to 2–3 a month. The remaining attacks respond to 20 mg of sumatriptan nasal spray. Increases in the stimulation settings have been prompted by the return of aura with slurred speech, near-syncopal attacks and diplopia. Eighteen months after implantation, VNS remains highly effective in controlling symptoms and allowing the patient to remain very functional and employed.

Patient 2

This 26-year-old woman presented with a complaint of headaches since childhood, but then she developed migraine attacks in 1997. In 1998 they became daily and in the summer of 2000 became very severe. The headaches were bilateral, nonpulsatile, associated with nausea, rarely vomiting, accompanied by neck pain, photophobia, phonophobia and were not made worse by light physical activity. The patient had no aura or any associated neurological symptoms. MRI scan and a lumbar puncture were normal. Treatment was tried using divalproex sodium, topiramate, nortriptyline, metaxalone, opioids, magnesium infusion and botulinum toxin, type A injections with little success. The patient also suffered from interstitial cystitis for which she was taking pentosan, nortriptyline, 75 mg, and intermittently oxycodone. Her family history was positive for headaches. Because of severe disability VNS was implanted in July 2002 with a dramatic improvement in her headaches. Her MIDAS score went from 100 to 13 (on 10/15/02) and she became able to work full time, while before VNS she was completely disabled.

Patient 3

This woman was 37 years old in October of 1996 when first seen for daily episodes of loss of balance with inability to walk, speech impairment, diplopia and bilateral headache. She had had these incapacitating attacks for five years. Extensive testing at several leading institutions failed to determine the aetiology of these attacks and the diagnosis of basilar migraine was made based on IHS criteria. Trials of multiple anticonvulsants, antidepressants, alpha, beta and calcium channel blockers, muscle relaxants, opioids, benzodiazepines, zafirlukast, dopamine agonists, amantadine, acetazolamide and indomethacin failed to significantly relieve her symptoms. She has remained on trazodone, acetazolamide and clonazepam with mild relief. VNS was implanted in November 2001. Despite repeated attempts the patient was unable to tolerate even minimal current due to nausea. She has remained disabled.

Patient 4

This man was first seen in October 1998, when he was aged 41 years and had suffered from chronic migraine for the previous 17 years. The headaches were right-sided, very intense, pulsatile, often associated with nausea, but not photophobia or phonophobia, and were made worse by light physical activity. They were present daily and almost continuously. He also had multiple sclerosis, which was only mildly disabling and had a grand mal seizure in 1993. His headaches were treated with divalproex sodium, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, verapamil, propranolol, methysergide, indomethacin, lithium, amantadine, montelukast, baclofen, naratriptan around the clock, magnesium infusion, fentanyl patch, sustained release morphine, botulinum toxin type A injections, dihydroergotamine, meperidine and sumatriptan injections. Because of lack of relief from all of these therapies VNS was implanted in June 2002. In the first three months his MIDAS improved from 100 to 14, but then worsened to the baseline in the following month. VNS current and other parameters are still being adjusted. He remains on levetiracetam 1500 BID daily and frequent sumatriptan and meperidine injections.

Cluster

Patient 5

This 33-year-old-man developed typical left-sided cluster headaches in 1986. Five years later they became chronic. The headaches were very intense, associated with agitation, ipsilateral lacrimation and nasal congestion. The headache frequency varied from 1 per day to 10 per day and the duration of an untreated attack was up to 90 min. He was first treated at the NYHC in 1997. The following medications were tried at the highest tolerable dose: tiagabine, divalproex sodium, gabapentin, topiramate, levetiracetam, carbamazepine, lithium, verapamil, propranolol, baclofen, melatonin, methysergide, methadone, sustained-release morphine, and the following abortive drugs: dihydroergotamine (IV, SC, NS), sumatriptan (SC, NS, PO), zolmitriptan, rizatriptan, naratriptan, almotriptan, frovatriptan, hydromorphone, meperidine, methadone, hydromorphone and prochlorperazine. He also failed to respond to botulinum toxin type A injections. Excessive use of sumatriptan injections (up to 60 mg in 24 h) led to hospital admission for intravenous histamine desensitization, which provided temporary relief on two occasions. The patient made a suicidal gesture, which led to a further admission. He has remained depressed, to various extent, despite aggressive pharmacotherapy. He also suffered from attention deficit disorder and was treated with stimulants. VNS was implanted in November 2001 and his cluster headaches markedly improved within two months. He has had some neck pain at the site of the vagus nerve stimulator, especially upon increasing the current strength. Depression has remained difficult to manage and brief periods of cluster headaches have returned. However, a year after implantation the patient considers VNS to be highly effective in reducing his attacks. His MIDAS dropped from 265 to 15. The patient remains on Zyprexa, Adderall, lorazepam and continues to try various antidepressants. He also intermittently needs sumatriptan injections or oxycodone.

Patient 6

This 48-year-old man presented in 1995 complaining of headache of 4 years duration. The headaches were right-sided, very intense, pulsatile, not associated with nausea, vomiting, photophobia or phonophobia, but with agitation, nasal congestion and lacrimation. They used to occur 1–5 times per day and last 1 h. Oxygen helped somewhat. He was being treated with divalproex sodium, verapamil, indomethacin, amitriptyline and daily dihydroergotamine injections. His family history was negative for headaches. Physical examination was normal. The patient went through trials of divalproex sodium, gabapentin, lamotrigine, topiramate, tiagabine, propranolol, verapamil, indomethacin, lithium, melatonin, amanta-

dine, montelukast, baclofen, tizanidine, bupropion, nefazodone, lorazepam, NSAIDs, naratriptan around the clock, fentanyl patch, magnesium infusion, botulinum toxin type A injections and courses of intravenous histamine desensitization. Sumatriptan injections have been effective, but on several occasions he took up to 10 injections (60 mg) in 24 h. He was on gabapentin, 2400 mg a day, and fentanyl patch, 50–75 μg for both headaches and severe back spasms of unclear aetiology as well as leg pain. After implantation of VNS in May 2002, his MIDAS score decreased to 8 from a pretreatment scores of up to 210. An attempt to reduce the fentanyl dose caused an increase in headaches with an increase in the need for Imitrex and the dose was increased. The VNS current strength is being increased, with the last adjustment occurring in September 2002. The patient's overall functional level has remained poor, mostly due to fatigue, weakness, back muscle spasms, anxiety and depression.

Discussion

Excellent response in two and good response in another two of our six patients demonstrates the potential utility of VNS in the treatment of refractory migraine and cluster headaches (Table 1). The maximal therapeutic benefit in epilepsy patients occurs in up to a year after implantation, so it is possible that further benefit can be observed in patients 4, 5 and 6. All patients had daily symptoms, which included headaches as well as other neurological and systemic symptoms prior to VNS treatment, while after treatment four patients stopped having these daily. Data on the number of headache-free days, frequency, duration and severity of headaches and analgesic consumption before and after treatment was not collected.

Despite normal EEGs, it is possible that some or all of these patients in fact had been suffering from epilepsy with migraine or cluster headaches as the main clinical manifestation of the disease. However, this is unlikely since over such a long duration of illness one would expect an occasional focal or generalized seizure or other suggestive symptoms to occur, or an abnormal EEG to be recorded, or the patient to respond to an anticonvulsant medication.

Migraine and cluster attacks involve dysfunction of intracranial vasculature, sympathetic nervous and pain modulation systems. Intracranial vasculature is supplied with parasympathetic fibres, which originate in the sphenopalatine and otic ganglia, sympathetic fibres, which originate in the superior cervical ganglion and sensory fibres from the trigeminal ganglion. In addition to these neural influences blood vessel size is controlled by endothelial cells through the release of endothelium-relaxing agents, such as prostacyclin, endothelium-derived hyperpolarizing factor (EDHF) and nitric oxide (NO).

Parasympathetic dysfunction has been reported interictally in migraine patients based on an altered heart rate response to a Valsalva maneuver combined with unaltered cardiovascular tests reflecting sympathetic function (4). More pronounced sympathetic dysfunction is present in patients with cluster headaches. VNS directly affects the parasympathetic nervous system and in turn affects intracranial vasculature. In humans, VNS has been shown to change blood flow in several brain structures, including the thalamus, posterior temporal cortex, putamen, inferior cerebellum (5), and thalamus, postcentral gyrus, hypothalamus, insular cortex, inferior cerebellum, hippocampus, amygdala, posterior cingulate gyrus (6). These effects are complex, and it is difficult to pinpoint what effect VNS might have, but many of these brain structures are involved with migraine. VNS has been shown to suppress experimentally induced pain (7). These vascular and analgesic effects of VNS may be responsible for the observed beneficial effect in four of our patients.

VNS is clearly a treatment of last resort and needs further study. Its use was prompted and is justified

5 **Table 1** Response to VNS in 4 migraine and 2 cluster headache patients

Patients	Age	Sex	Diagnosis	Duration of illness (years)	VNS current (mA)	VNS pulse width (s)	VNS on/off s/min	Response
1	45	M	Chronic migraine	32	1.25	0.250	7/0.2	Excellent
2	26	F	Chronic migraine	5	2.75	0.250	60/0.8	Excellent
3	37	F	Basilar migraine	10				Poor
4	45	M	Chronic migraine	17	1.5	0.250	30/5	Poor
5	33	M	Chronic cluster	15	1.25	0.250	7/02	Good
6	55	M	Chronic cluster	11	1.25	0.250	30/5	Good

by the desperate nature of our patients' illness. These patients are completely disabled, often depressed and at times suicidal and have exhausted other non-invasive treatments.

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