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The use of positive airway pressure and transauricular vagus nerve stimulation in a paroxysmal hemicranias and assessment of sympathetic skin response

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Abstract

Paroxysmal hemicrania is characterised by severe short-term unilateral headaches that are associated with ipsilateral cranial autonomic symptoms. A rare headache type, paroxysmal hemicrania is included in the trigeminal autonomic cephalgia group of primary headache. The relationship between paroxysmal hemicrania and sleep apnoea has not been previously reported in the literature. Non-invasive vagus nerve stimulation offers an alternative treatment option for patients who cannot tolerate indomethacin or other traditional treatments. We report the case of a female patient with sleep apnoea and paroxysmal hemicrania who could not use indomethacin and other therapies. Her headaches temporarily regressed with positive airway pressure treatments and positively responded to transauricular vagus nerve stimulation. We evaluated the stimulatory effect of this treatment by examining the patient's sympathetic skin responses.

Keywords: Vagus nerve stimulation, trigeminal autonomic cephalgia, headache, sleep apnoea

INTRODUCTİON

Paroxysmal hemicrania (PH) is a type of trigeminal autonomic cephalalgia that responds well to indomethacin treatment and which can recur 5–40 times a day. PH is characterised by ipsilateral cranial autonomic features and 2–30 minutes of severe unilateral throbbing, stinging or boring pain in the ocular, temporal or frontal regions. Acute treatment options include indomethacin, sumatriptan, oxygen, nerve blockage, methylprednisolone, piroxicam, rofecoxib, prednisone, valdecoxib, etoricoxib, naproxen and betamethasone. Long-term treatment options include indomethacin, topiramate, verapamil, carbamazepine, flunarizine, nerve blockage, piroxicam, amitriptyline, gabapentin, valproate, propranolol, phenytoin, acetylsalicylic acid, lithium, ergotamine, dipyrone, acetazolamide, baclofen, methysergide, doxepin, betamethasone and methylprednisolone.[1] However, these treatment options are often associated with side effects. Thirty percent of patients reported dose-limiting side effects with indomethacin; approximately 20% could not continue treatment because they could not tolerate the drug.[2] Non-invasive vagus nerve stimulation (nVNS) offers an alternative treatment option for patients who cannot tolerate standard medical treatments. We report the case of a female patient with PH and intolerant to standard medical treatments. Her sleep apnoea and headaches were temporarily relieved by positive airway pressure (PAP). The subsequent resumption of a less severe head pain was then successfully treated with transauricular vagus nerve stimulation (ta-VNS). We evaluated the stimulatory effect of this treatment by examining the patient's sympathetic skin responses.

CASE REPORT

A 35-year-old female patient was admitted to the neurology outpatient clinic with a severe headache [visual analogue scale (VAS) of 10], accompanied by nasal congestion and ipsilateral lacrimation that was located around the right eye. The symptoms had occurred over the past two and half months. The episodes lasted for 5–20 minutes and recurred up to five times a day, at least five days a week. The patient had a microadenoma in the pituitary gland and had been prescribed cabergoline. The neurological examination, laboratory tests, cranial magnetic resonance imaging (MRI) and magnetic resonance venography were normal. A pituitary MRI revealed a 7 x 5 mm microadenoma in the right posterior of the pituitary gland. Due to the risk of allergic reactions, the patient could not

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use indomethacin, topiramate or gabapentin. A polysomnography test was performed because the headaches frequently occurred during night sleep and were accompanied by morning fatigue, excessive daytime sleepiness and snoring. The polysomnography test was conducted using an Alice 6 polysomnography device (Philips) in the sleep laboratory and scored according to the American Academy of Sleep Medicine (AASM) 2.3 version (2016) rules. The apnoea hypopnea index was 9.1, and a mild obstructive sleep apnoea syndrome was diagnosed. The respiratory events increased when the patient was in a supine position. Surgery for nasal septal deviation was recommended, but the patient declined the operation. After a PAP titration was performed, the apnoea hypopnea index reduced to 0.7. The patient had no headaches after the PAP titration. Automatic continuous positive airway pressure (Auto CPAP) treatment of 5-7 cm H2O was recommended to the patient, who had been having symptoms for eight months. The sleep efficiency was 65.2% in the first polysomnography, and increased to 81.7% in a subsequent PSG performed with PAP. The sleep latency decreased from 22 minutes to 5.5 minutes and total wakefulness period after sleep onset decreased from 148 minutes to 69 minutes. The REM stage percentage decreased from 14.2% to 10.1%, N1 stage percentage decreased from 18.6% to 10.1%, N2 stage percentage increased from 47.2% to 58.1% and N3 stage percentage increased from 20.1% to 21.7.

After the PAP therapy, the patient had no headaches for two and a half months. Then, the patient had headaches that lasted for five minutes, four times a day, being VAS of 6, for 15 days in a month. A pituitary MRI showed a partial enlargement of the adenoma (9 x 6 mm); the patient's prolactin was in the normal range. As the patient could not be given standard medical treatments, a ta-VNS was planned. Twice a day for one month (morning and evening), the stimulus was applied to the right ear. Each application lasted for 30 minutes at 50 μs, 5 Hz frequency and 5 volts. The patient's headaches regressed to a VAS of 5 and lasted for five seconds once a day; there was no need to use nVNS during these headaches. During the follow-up period, a 7-volt stimulus was applied for one and a half months. The patient's headaches regressed to a VAS of 1; they occurred once a day and lasted for 1–2 seconds. During a two-week period when she could not use the stimulator, she had severe pain that lasted four hours one night and short-term pain 1–2 times daily. The patient returned to a stimulus intensity of 5 volts, because 7 volts caused a pain in her ear; she used 5 volts for one month and 6 volts for one month. The patient continues to use 6.5 volts. Her headaches have regressed to a VAS of 1–2, last for 1–2 seconds once a day and occur 2–3 days a week. When the patient's headaches resumed after the PAP therapy, we examined the bilateral sympathetic skin responses of the hand, face and neck with an electromyography (EMG) device (Medelec) before using the stimulator. The amplitudes of the patient's sympathetic skin responses from the left face (asymptomatic) and the neck were lower than the amplitudes of the right (symptomatic). After five months of nVNS, the response amplitude on the right face was lower than the response amplitude on the left face, and the response amplitudes on both sides of the neck were similar (Table 1).

DISCUSSION

PH is characterised by the sudden onset of headaches that are associated with cranial autonomic features, such as ipsilateral conjunctival injections, nasal congestion, rhinorrhoea, ptosis and eyelid oedemas. These cranial autonomic features can occur in the ocular, temporal, maxillary or frontal regions. PH onset most commonly occurs in the second and third decades of life and is a rare syndrome in all ages and both sexes. Typically, 20% of PH cases are episodic, while 80% are chronic paroxysmal hemicranias.

Table 1: Patient's sympathetic skin responses from the face and neck

	Before treatment		After treatment	
	Latancy (s)	Amplitud (mV)	Latancy (ms)	Amplitud (μV)
R face	0.82	**4.1**	830	**723.3**
L face	0.84	**2.2**	850	**1380**
R neck	0.95	**6.1**	810	2775
L neck	0.66	**1**	800	3108.3

R: Right L: Left

Previous reports have indicated that PH may be associated with pituitary tumours; consequently, if the PH presents with atypical features, abnormal examination findings or treatment resistance, a pituitary MRI should be examined.[3] Our patient had a pituitary adenoma that had been followed up for four years, and she had been regularly using cabergoline.

The vagus nerve is a mixed nerve that includes both sensory and motor nerves. The role of the vagus nerve in trigeminal pain has been reported in the literature.[2,4] There are two forms of nVNS, ta-VNS and transcervical (tc-VNS).[5] The ta-VNS form causes a neuromodulatory effect by transcutaneously stimulating the auricular branch of the vagal nerve.[6] nVNS induces antinociception that affects the peripheral and central nociception, the opioid response, inflammation, autonomic activity and pain-related behaviours by modulating the pain-related structures in the brain and spinal cord.[6] The efficacy of nVNS was first investigated for acute migraine treatment, followed by cluster headaches. Nesbitt *et al*. reported the efficacy of nVNS as both an acute and preventive treatment in cluster headache patients.[4,7] In a study, 8 patients with PH who had developed intolerance to indomethacin received nVNS. There was a decrease in the frequency and severity of the patients' pain, with a mean improvement of 64.3–71.8%, and no adverse effects.[2] In another study, stimulation was used for three months to five years on PH and hemicrania continua patients; cutaneous irritation at the stimulation site was reported as a side effect. That study reported that 67% of the patients experienced a reduced frequency and severity of attacks.[8] These studies demonstrate that nVNS can be used as a preventive treatment in PH patients who cannot tolerate indomethacin.[2,8]

Sympathetic skin responses are triggered by pre- and post-ganglionic nonmyelinated C fibres. Altiokka *et al*. evaluated sympathetic skin responses in patients with cluster headaches, comparing the extremity and facial responses during both episodic and remission periods. They found that the latency of the sympathetic skin responses on the symptomatic side of the facial region during an episode was longer than that of the asymptomatic side and the control. A report from a cluster headache clinic suggested that facial sympathetic hypoactivity may be more pronounced and that facial sympathetic skin responses obtained during the autonomic dysfunction evaluation of a cluster headache may be more sensitive than the responses detected in the hand.[9] Sympathetic skin responses are also thought to affect patients with paroxysmal hemicrania headaches. In the present case, sympathetic skin responses were examined in the hand, face and neck before the use of the stimulator, and the response amplitudes in the face and neck on the symptomatic side were higher than those on the asymptomatic side. Higher amplitude responses were obtained from the face and neck on the painful side, indicating that the increased sympathetic activity was related to the pain. The lower amplitude responses on the pain side of the face after treatment were comparable to those of the non-pain side of the face, and the response amplitudes on both sides of the neck were similar. These results indicate that the decreased sympathetic activity was related to the pain relief and demonstrate the modulating effect of nVNS on the pain pathways. Clancy *et al*. found that muscle sympathetic nerve activity decreased during ta-VNS in 48 healthy subjects.[10] It was reported that increased sympathetic activity was associated with pain and that nVNS decreased that pain by increasing parasympathetic activity while decreasing sympathetic activity; consequently, nVNS could alleviate pain by autonomic modulation.[6,11] The results reported in these publications explain the changes in the sympathetic skin responses in our case.

Previous polysomnographic studies have demonstrated that cluster headaches are associated with rapid eye movement (REM) sleep and obstructive sleep apnoea syndrome (OSAS), but many questions remain. In one study, cluster headache episodes were associated with sleep apnoea.[12] OSAS causes recurrent hypoxemia, hypercapnia, excessive negative intrathoracic pressure and increased intracranial pressure, as well as sudden changes in the sympathetic system. These changes may trigger cluster headache attacks.[13] The hypothalamus may affect the OSAS pathophysiology. Specific areas of the hypothalamus, such as the preoptic area, affect sleep. Hypothalamus dysfunction causes a decrease in the activity of the carotid body and may trigger the autonomic system. Activation of the hypothalamus (posterior hypothalamus), the most important structure in maintaining homeostasis, may play a role in cluster headaches. The different parts of the hypothalamus are thought to be related to the pathophysiology of the two disorders.[14,15] Although the relationship between cluster headaches and sleep apnoea has previously been reported, no reports have evaluated the relationship between paroxysmal hemicrania

and sleep apnoea. Since cluster and paroxysmal hemicranias are both included in the trigeminal autonomic cephalgia group of primary headache, PH headaches, such as cluster headaches, may also be related to sleep apnoea.

PH, cluster headache and hypnic headache were previously reported to be associated with the REM sleep phase . It could be explained by suppression of the anti-nociceptive network of the periaductal gray (PAG), locus ceruleus and dorsal raphe nucleus, which are effective in REM sleep formation.[16] The REM phase may the phase of sleep with the lowest pain arousal threshold.[17] In our patient, it was observed that the percentage of REM in PSG made with PAP decreased compared to the first PSG. It raises the question of whether the reduction in our patient' s headache may be related to the decrease in the duration of the REM phase.

Our patient did not have any headaches for two and a half months after the PAP treatment. Once the pain returned, the recurrence frequency, as well as the severity and duration of the attacks, was lower than before the PAP treatment, suggesting that PH headaches may be related to sleep apnoea. This case demonstrates that nVNS may offer an alternative treatment option to control pain in patients who cannot tolerate the traditional medical treatments for PH. Notably, the skin responses in our patient support the theory that the autonomic system is affected in PH patients and that autonomic system modulation may be achieved with nVNS. Larger case series are needed to explore these issues.

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