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# Occipital Nerve Stimulation for Medically Refractory Hypnic Headache

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**Objective:** Hypnic headache is a rare, primary headache disorder that exclusively occurs regularly during sleep. We present a case of hypnic headache successfully managed with occipital nerve stimulation.

**Materials and Methods:** A 64-year-old female presented with a four-year history of a right occipital headache that regularly awakened her from sleep. The headache, which was dull and throbbing, would awaken her regularly at 4:00 AM, five hours after bedtime at 11:00 PM. No photophobia, nausea or vomiting, lacrimation, or other autonomic symptoms were present. The headache was refractory to various medical treatments, including indomethacin, flunarizine, propranolol. She underwent a trial of occipital nerve stimulation with a lead electrode using a medial approach.

**Results:** During the ten-day trial stimulation, she reported almost complete relief from hypnic headache. Chronic occipital nerve stimulation replicated the trial results. The attacks of hypnic headache recurred in one year with loss of stimulation-induced paresthesia; a subsequent x-ray showed electrode migration. After revision of the electrode to the original location, the effectiveness of the occipital nerve stimulation against hypnic headache was achieved again, and this effect has been consistent through 36 months of follow-up.

**Conclusion:** Occipital nerve stimulation was effective in a patient with chronic, refractory hypnic headache.

**Keywords:** Hypnic headache, neuromodulation, neurostimulation, occipital nerve stimulation, peripheral nerve stimulation

**Conflict of Interest:** The authors have reported no conflicts of interest.

## INTRODUCTION

Hypnic headache (HH), first described by Raskin in 1988 (1), is a primary dull headache that awakens the patient from sleep. Generally described as a primary headache of the elderly (2), it has also been called clockwise headache or alarm clock headache. The attacks are usually of short duration (30 minutes) and awaken the patient at a constant time each night. According the *International Classification of Headache Disorders*, second edition (3), HH must fulfill the following criteria:

1. A dull headache fulfilling criteria 2–4;
2. Develops only during sleep and awakens the patient; and
3. At least two of the following characteristics:
   (a) Occurs >15 times per month,
   (b) Lasts >15 min after waking,
   (c) First occurs after the age of 50 years,
   (d) No autonomic symptoms and no more than one of nausea, photophobia, or phenophobia, and
   (e) Not attributed to another disorder.

The incidence is very low; <100 cases have been published to date. However, HH is probably more common than previously thought (2). The pathophysiology of HH remains unclear, but due to its circadian nature as well as its reported responsiveness to lithium (1), a disturbance of chronobiologic rhythms is a putative factor. According to polysomnographic studies, it is speculated that HH might be a rapid eye movement (REM) sleep disorder caused by impaired function of parts of the antinociceptive system of the brainstem (4). Randomized double-blind studies do not exist, but according to a detailed review (2), the most efficient treatment is lithium, with a good response in 26 out of 35 cases. Alternatively, partly successful prophylactic strategies include indomethacin, caffeine, flunarizine, and melatonin (2).

Peripheral nerve stimulation (PNS) for primary headaches involves applying electrical impulses to specific terminal branches of afferent nerves supplying the trigeminocervical complex. Occipital nerve stimulation (ONS) is the most studied of the PNS for primary headaches. ONS has been applied for chronic migraine, hemicranias continua, chronic cluster headache (CH), paroxysmal hemicranias, and short-lasting unilateral neuralgiform headaches with conjunctival tearing and injection (SUNCT). According to a review (5), the overall efficacy of ONS in primary headaches is about 59%, and it has been effective in a variety of primary headache conditions. We describe a 64-year-old woman with chronic HH who responded to chronic ONS.

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## CASE DESCRIPTION

A 64-year-old female presented a four-year history of a right occipital headache that regularly awakened her from sleep. The headache would awaken her regularly at 4:00 AM, five hours after bedtime at 11:00 PM. The headache was described as dull, throbbing, of right occipital localization and of moderate severity (4/10 on the numerical rating scale from 0 to 10), making the patient sit on the bed and squeeze her occipital area. It occurred 28–30 days/month and lasted for one hour. No photophobia, phonophobia, or nausea and vomiting were reported. Lacrimation and other autonomic symptoms were absent. The patient did not complain of visual disturbance or other neurological symptoms.

She had tried various kinds of over-the-counter drugs on her own initiative and reported a mild effect of acetylsalicylic acid, which reduced the intensity of pain slightly but did not influence the occurrence of the headache. She has been treated for migraine, and medical treatment including propranolol, lorazepam, diazepam, zolmitripam was ineffective. Indomethacin and fluoxetin were also not effective. Amitriptyline 30 mg before bedtime at 11:00 PM was effective in reducing the intensity (2–3/10) and frequency (15–25 days/month) of HH; however, she could not continue amitriptyline because of excessive somnolence during the daytime. She refused lithium therapy because she feared side effects.

She did not use caffeine or tobacco and had no allergies. Her family history was noncontributory. Laboratory evaluations, including erythrocyte sedimentation rate, complete blood count, and chemistries, were unremarkable. Magnetic resonance imaging of the brain and the cervical spine showed no abnormalities (Fig. 1a). Unfortunately, the patient refused the proposed polysomnography. The trial of oral indomethacin (up to 75 mg tid, for two weeks) and intramuscular injection of indomethacin (100 mg bid, for two days) did not prevent the occurrence of nocturnal headache. Repeated blocks of greater and lesser occipital nerves were effective in reducing severity and duration of HH but could not prevent the occurrence of HH.

After getting informed consent from the patient, we performed a trial of ONS. A percutaneous electrode (Pisces Quad®, Medtronic, Minneapolis, MN, USA) was placed via a Tuohy needle at the level of C-1, where subcutaneous stimulation of a transversely placed electrode should produce an appropriate paresthesia pattern. Temporary stimulation was given to verify proper electrode position and paresthesia pattern. Then, the electrode was anchored to the underlying fascia, and a strain-relief loop was created. The extension wire was tunneled for trial stimulation (contact polarity – ± +, 210 μsec, 100 Hz) (Fig. 1a).

During a seven-day trial, stimulation was given at 11:00 PM before bedtime. The patient fell asleep after having elicited the stimulation-induced paresthesia in her painful area. This nocturnal stimulation was quite effective and almost completely blocked the occurrence of HH; she could sleep well. After confirming the effectiveness of ONS, the pulse generator (Itrel II®, Medtronic) was implanted in the right infraclavicular chest wall through subcutaneous tunneling of extension cable. The stimulator was turned on at 11:00 at night and was turned off in the morning by the patient herself. This nocturnal ONS was quite effective, and the frequency of HH remarkably reduced to 1–3 days/month, and the intensity also declined to 1–2/10. Even if she awoke with a HH attack, with increasing the intensity of stimulation, i.e., more strong paresthesia in the painful area, she could sleep readily again without sitting and squeezing the occipital area for one hour. She could stop all medication, and the effectiveness of ONS was fairly consistent. At one year after ONS, she suddenly could not feel the stimulation-induced paresthesia for one month, and the frequency of HH increased to 12 days/month. She subsequently visited our outpatient clinic again. An x-ray of the cervical spine showed migration of the lead and wound revision including lead relocation was performed (Fig. 1b,c). The analgesic effect against HH was restored again. The effectiveness of chronic ONS against HH in this patient has been fairly consistent through 36 months of follow-up.

## DISCUSSION

HH is a headache disorder, described in 1988 by Raskin (1), characterized by recurrent attacks occurring exclusively during sleep. Other primary headache disorders that may actually awaken people from sleep are migraine, CH, and chronic paroxysmal hemicranias (CPH) (6). The most obvious association between sleep and headache is HH. It is unique in that it only occurs during sleep. CH and CPH are

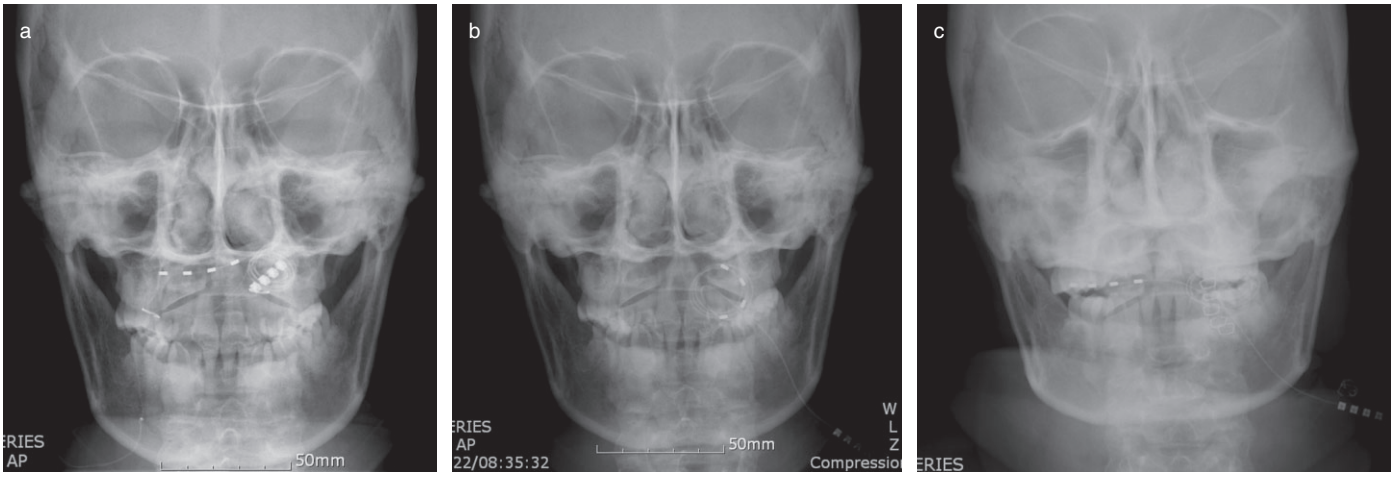


**Figure 1.** Occipital nerve stimulation for hypnic headache. a. The x-ray film showing the location of a percutaneous electrode at C1 level. b. The x-ray film showing migration of the electrode during loss of occipital nerve stimulation against hypnic headache. c. The x-ray film taken following the revision of the electrode and restoration of occipital nerve stimulation effectiveness in the treatment of the patient's hypnic headache.



  

classified as trigeminal autonomic cephalgia and present with characteristic parasympathetic autonomic features (3). HH will not have these autonomic features and typically presents in the fifth to sixth decades of life (4). Migraine headache will tend to have a duration of 4–72 hours, whereas HH tends to resolve within approximately 30 min of awakening (4). Our patient most likely had HH, given the age at onset, frequency, intensity, and type of pain, and the lack of associated autonomic features. Unfortunately, the response to lithium could not be assessed due to the patient's refusal.

The pathophysiology of HH remains unclear. The observation that the onset of HH attacks was associated with REM sleep (7), which has been observed in all but one patient with polysomnography or sleep history suggested that pain-processing structures are activated during REM sleep. In a study of polysomnography in HH (8), no obstructive sleep apnea or other type of nightly deoxygenation was found, and the response to continuous positive airway pressure and oxygen supplementation was inconclusive (9). It was suggested that HH might be a REM sleep disorder due to a disturbance of the sleep-related physiology of brain stem structures, such as the dorsal raphe nucleus, the locus coeruleus, and the periaqueductal gray (PAG) matter (4,7). However, a frequent onset of headache attacks during REM sleep has also been reported for migraine and episodic CH. Thus, the association between REM sleep and HH might be unspecific (2).

HH might be a chronobiological disturbance because most patients experience the headache attack at the same time in the night (alarm-clock headache) (2). The suprachiasmatic nucleus, the most important brain structure for endogenous circadian rhythm, has afferent and efferent connections with the PAG matter, which is one of the most important midbrain structures for antinociception (2). With advanced age, the function of the suprachiasmatic nucleus, which is a part of the hypothalamic–pineal axis, is diminished, and melatonin secretion is impaired (10). Lithium indirectly increases the level of melatonin and is able to affect serotonin metabolism by downregulating serotonin receptors and increasing serotonin release. Thus, serotonin metabolism is affected in HH (10,11).

According to a comprehensive review (2), the most efficient treatment is lithium. Alternatively, partly successful prophylactic strategies included indomethacic, caffeine, flunarizine, and melatonin (2). Recently, case reports of treatment with botulium toxin type A and application of a mandibular advancement appliance for obstructive sleep apnea have been reported to be effective in HH (12,13).

Occipital nerve block (ONB) transiently reduced the severity and duration of HH in our patient, but it could not prevent the occurrence of HH. Although the mechanism of action of ONB is not completely elucidated, antinociceptive effect may be secondary to direct anesthetic effects, mechanical effects of the injection itself, or to blockade of neurogenic inflammation. Like ONS, it may alter nociceptive trafficking into trigeminocervical complex. ONB has been shown to reduce head pain and brush allodynia in maigraineurs (14). It has been hypothesized that ONB reduces trigeminal hyperexcitability by blocking the conduction of noxious stimuli and by blocking the antidromic flow of nociceptive vasoactive neuropeptides such as substance P and calcitonin gene-related peptide (15). Although ONB was effective in our case with HH, analgesic response to ONB has not been shown to be predictive of the therapeutic effect from ONS in patients with medically refractory chronic headaches (16).

The mechanism of the analgesic effect of peripheral neurostimulation likely affects multiple pain processing circuits in the central nervous system, resulting in analgesic effects (17). Direct effects of electrical stimulation on peripheral nerve excitability have been described, including a transient conduction velocity decrease, increase in electrical threshold, and decrease in response probability (18). However, ONS did not significantly modify pain thresholds in CH patients (19). Neuromodulatory effects on the spinal segmental network have been suggested (20,21). Indeed, the somatosensory neurostimulation of afferent Aβ fibers block nociceptive transmission on a segmental level (22). Activation of descending pain inhibitory supraspinal structures, such as PAG, is also involved in mediating the antinociceptive effects of neurostimulation. As γ-amino butyric acid (GABA)ergic neurons in the PAG exert a tonic inhibitory effect on the activity in descending pain inhibitory pathways, including trigeminovascular inputs (23), a decreased GABA level in the PAG following spinal cord stimulation may lead to activation of descending antinociceptive projections with subsequent pain reduction (24).

Nociceptive input from afferents in the trigeminal nerve and cervical afferents (C2-C3) converge on the same nociceptive second-order neurons in the trigeminocervical complex that extends as a functional unit from the level of the trigeminal nucleus caudalis to at least the C2 segment. The resulting loss of spatial specificity helps to explain why ONS may have an antinociceptive effect in the territory of the trigeminal as well as occipital nerves (25). A functional positron emission tomography study of the antinociceptive effect of ONS in patients with chronic migraine showed changes in cerebral blood flow in the dorsal rostral pons, anterior cingulated cortex (ACC), and cuneus in a pain state, sites that are known to be activated during migraine (26,27). In the paresthesia state with ONS, ACC and left pulvinar activation were observed, indicating that ONS can modulate activity in the thalamus. Thus, gate control at the segmental levels, as well as activation of descending pain inhibitory pathways, in addition to, modulation of brain stem structures involved in central nociceptive trafficking via trigeminocervical complex, such as dorsal rostral pons, thalamus, and ACC are thought to be involved in the mechanism of ONS.

ONS is a promising treatment for disabling refractory primary headache syndrome. The technique of ONS for medically intractable headache was introduced by Weiner and Reed in 1999 (28). In the past decades, a number of case reports, case series, and some prospective studies have emerged on the application of ONS in the treatment of primary headache disorders as well as in secondary headache disorders, including posttraumatic headache, and cervicogenic headache, and cranial neuralgias, including occipital neuralgia (19,26,29–35). The procedure can be performed under local or general anaesthesia, with a subcutaneous lead (either a cylindrical or paddle electrode) inserted to cross the greater, lesser, and least occipital nerves via an incision on the midline or a lateral incision close to the mastoid process (36). Alternatively, a miniaturized Bion device can be implanted in the suboccipital region (34). The stimulation parameters, including frequency and pulse width with voltage, are adjusted such that patients experience mild paresthesia in the stimulated area.

Results of ONS in intractable chronic migraine, often in the context of medication overuse, have been encouraging (26,30,31), with 43 of 51 patients (84%) experiencing at least 50% improvement. In recent data from a multicenter, prospective, randomized, single-blind, controlled feasibility study (ONSTIM trial), the responder rate was 39% intractable chronic migraine patients with ONS, compared with 6% in a control stimulation group and a 0% responder rate in the medical management group (37). Trigeminal autonomic cephalalgias, including CH, paroxysmal hemicranias, and SUNCT, can be devastating, medically intractable conditions (25). In the two largest case series for ONS for drug resistant chronic CH, one retrospective (35) and one prospective (19), at least 50% improve-



  

ment was noted in 1/3 to 2/3 of patients, respectively. Hemicrania continua, an indomethacin-responsive primary headache, may experience the most robust response to ONS, as so far 7/9 patients (77%) reported at least 50% improvement after a mean follow-up of little over a year. Some patients with paroxysmal hemicranias, SUNCT, and new daily persistent headache have been implanted, but their data are too preliminary to draw any conclusion (25,38).

Despite the good effect of ONS in this patient, several unresolved issues in ONS for HH and other headache disorders remain. Although refractory HH of occipital localization in our patient responded to ONS, we still do not know whether ONS would be beneficial to HH in which the most prevalent pain location is frontal and temporal. It is still difficult to identify headache disorders with higher likelihoods of responding to ONS and to identify predictors of success with ONS, as response to an ONB certainly is not (16,37,38). No specific electrode has been developed for ONS yet. As seen in our patient, lead migration in a highly mobile region such as the neck is a significant technical issue in ONS. In a series of 15 patients treated with ONS, all patients had lead migration and required revision within three years of follow-up (32). A paddle electrode, rather than a cylindrical electrode, may be associated with less migration (30). Rechargeable and miniaturized technology, such as the Bion device, needs to be further explored (34). Additionally, optimal stimulation parameters need to be determined.

## CONCLUSIONS

HH is a rare, primary headache disorder that exclusively occurs during sleep and for which medical treatment has been reported to be effective. In a patient with chronic, medically-refractory HH, we report long-term effectiveness of ONS.

### Authorship Statements

Drs. Son and Yang recruited the patient and attended the operation. Dr. Hong analyzed the data and reviewed the references. Dr. Lee made a critical review of this article. Drs. Son, Yang, and Hong wrote the manuscript. Dr. Yang procured the institutional review board approval. All authors have approved the submitted version of the manuscript.

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