Case Report

Chronic Bilateral Sphenopalatine Ganglion Stimulation for Intractable Bilateral Chronic Cluster Headache: A Case Report

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A cluster headache (CH) is an excruciating pain centered on the periorbital region and is accompanied by autonomic symptoms. Despite the best currently available medical therapy, many patients still suffer from these headaches. Some patients also experience CH with side shift of attacks, which makes treatment more difficult.

In light of the pathophysiological mechanism of CH, the sphenopalatine ganglion (SPG) is a promising therapeutic target for its management. SPG ablation and non-ablation techniques have been the preferred treatment for CH in recent decades. However, few articles have reported the effectiveness of acute SPG stimulation for CH, and no studies have demonstrated the safety and efficacy of bilateral continuous SPG stimulation for CH.

In this article, we report on a 59-year-old chronic cluster headache (CCH) patient who had side shifts of attacks and was treated with bilateral continuous SPG stimulation. The patient suffered from CCH for 9 years, and the intensity of pain and the frequency of attacks had gradually increased over time. At the time of admission, he experienced daily attacks. Medical therapy and SPG blocks were offered, but he only achieved transient pain relief.

After a careful preoperative examination and discussion with the patient, we provided bilateral SPG stimulation. The electrode was implanted under C-arm fluoroscopic guidance. After continuous stimulation, the patient experienced significant reductions in headache severity. The frequency of attacks was reduced from daily to less than once per week. He also discontinued all of the related drugs that he was taking.

This is the first report of bilateral continuous SPG stimulation for CCH. This report indicates that continuous SPG stimulation is a feasible therapeutic option for CCH. However, large-scale and long-term studies are required to elucidate the efficacy of SPG stimulation.

Key words: Cluster headache, sphenopalatine ganglion, SPG, neuromodulation, side shift, stimulation

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Cluster headache (CH) is one of the most painful primary headache disorders and is characterized by attacks of severe unilateral periorbital pain associated with autonomic signs. These attacks typically last 15 to 180 minutes and occur once every other day up to 8 times per day. Approximately 10% of patients with CH suffer from chronic cluster headache (CCH), in which attacks occur for more than one year without remission or with remissions lasting less than one month (1). Approximately 14% of CH patients also experience headache with side shifts (2), which makes CH management substantially more difficult.

There are few therapeutic options for the treatment of CH. Intranasal injection of triptans and oxy-

gen inhalation are used for the acute treatment of CH, and steroids, verapamil, lithium carbonate, and valproate are used as preventive medications. However, there are significant side effects for these medications, and approximately 10% – 20% of CH patients are refractory to medical treatment (3). Various surgical interventions have been used to manage drug-refractory CH including sphenopalatine ganglion (SPG) blocks, occipital nerve blocks (4), SPG radiofrequency ablation (5), deep brain stimulation (DBS) (6), occipital nerve stimulation (ONS) (7), SPG stimulation (8,9), non-invasive vagus nerve stimulation (10), and spinal cord stimulation (SCS) (11).

SPG has emerged as a promising therapeutic target in light of the pathophysiological mechanism of CH. Although the block or ablation of SPG is effective in treating CH, some side effects are irreversible, and the benefits are transient. Recent research has demonstrated that SPG electrical stimulation was an effective and safe therapy for headache (8,9,12). However, most studies on CH focus on unilateral acute stimulation following attacks. Here, we report a CCH patient with a side shift of attacks who was treated with continuous bilateral SPG stimulation.

Case Report

A 59-year-old man had experienced CCH for 9 years. The patient was healthy and had no past medical history with the exception of an appendectomy. The neurological examination and cerebral magnetic resonance imaging (MRI) were normal. At the age of 36, he experienced an intermittent headache centered on the periorbital region with side shifts and equally timed attacks on both sides. At each attack, he suffered from unilateral pain without any autonomic signs. The patient did not experience headache occurring on both sides simultaneously during the attacks. The frequency of his headache was once every 2 months. He described the intensity of the headache as tolerable, and the pain was relieved after taking nonsteroidal anti-inflammatory drugs (NSAIDs) at that time. Nine years prior to admission, the headaches became intolerable, and their frequency gradually increased to one to 4 attacks per week. The headache episodes lasted for approximately one to 3 hours and were accompanied by autonomic signs, such as conjunctival injection, lacrimation, rhinorrhea and, notably, vomiting. A diagnosis of CCH was made. During each attack, the patient experienced unilateral headache accompanied by ipsilateral autonomic signs. The side of the headache shifted between attacks, and the patient suffered from an equal number of attacks on both sides. The headaches could be triggered by drinking. Oral sumatriptan could usually relieve his symptoms within 20 – 30 minutes. However, the patient occasionally needed to receive intravenous painkillers to terminate the pain. He had also taken verapamil and valproate for headache prevention, but this approach failed to reduce his symptoms. Despite the above treatment, the frequency and intensity of his attacks worsened. Over the last year, he experienced excruciating headaches with 3 to 5 attacks every day and had an extremely low quality of life. Six months ago, he received a bilateral SPG block that was effective in controlling his symptoms. However, the headache recurred one month later. He was again admitted to our hospital for pain management. We offered several treatments, such as another SPG block, SPG radiofrequency ablation, SPG stimulation, ONS, and DBS. The patient refused an SPG block and SPG radiofrequency for transient effects. He was afraid of intracranial hemorrhage caused by DBS and lead migration in ONS and refused these 2 options. Given that his headaches could be relieved by an SPG block, the patient and his family eventually asked for SPG stimulation.

After written informed consent was obtained, the electrodes were accurately implanted into the pterygopalatine fossa (PPF) bilaterally under C-arm fluoroscopic guidance. The procedure was performed under local anesthesia, and the implantation technique was performed through a standard infrazygomatic approach, as described in the literature (5,8), and was guided via C-arm fluoroscopy. As in previous reports, the patient was maintained in the supine position. Prior to electrode implantation, anteroposterior and lateral side x-ray photographs of the head were obtained to determine the location of the PPF. The first electrode was implanted in the right PPF. After local skin and a subcutaneous injection of 1% lidocaine on the right face, a 14-gauge needle was inserted at an entry point in the coronoid notch just below the inferior edge of the zygomatic arch. The needle was inserted anteriorly along the pterygoid plate and stopped at the beginning of the PPF. Then, the needle stylet was removed, and a 4-contact electrode (Model 3487A, Medtronic, Minneapolis, MN, USA) was implanted with its tip located in the PPF. The needle was removed, and the electrode was connected with an external test stimulator (Model 37022, Medtronic, Minneapolis, MN, USA). The location of the electrode was confirmed with C-arm fluoroscopy and sensory stimulation (2.0 V, 50Hz, 300 μs). The elic-

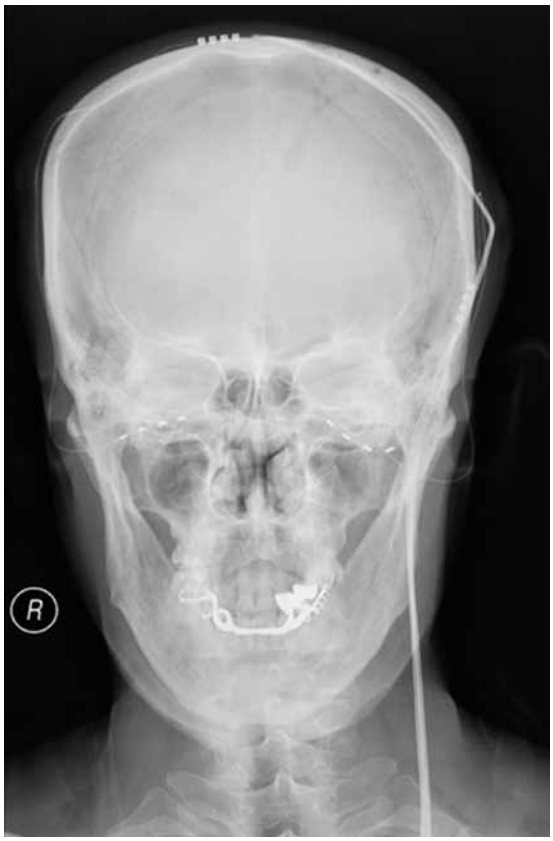

Fig. 1. *Position of the electrode in the postoperative anterior posterior x-ray view.*

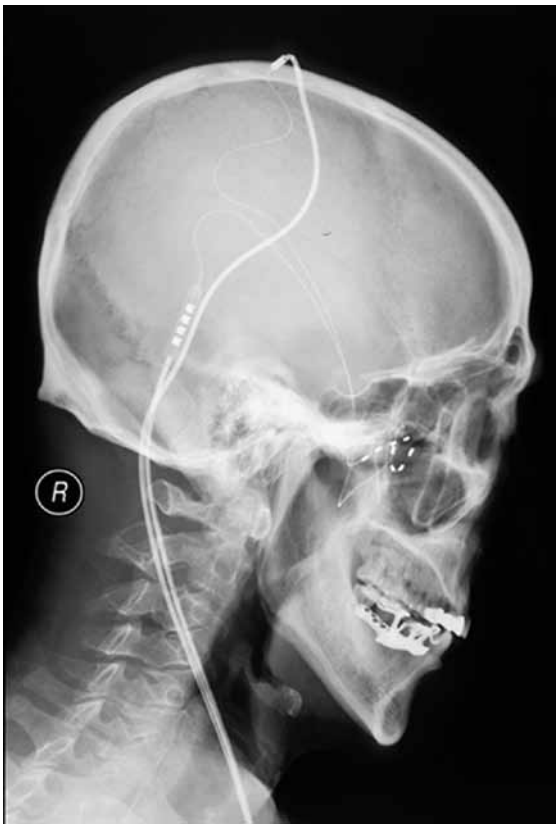

Fig. 2. *Position of the electrode in the postoperative lateral x-ray view.*

ited paresthesia was located at the root of the nose and the deep region behind the nose. Then, local anesthesia and an incision were performed on the right temporal-parietal region. The puncture tunnel was locally anesthetized. The electrode was anchored to subcutaneous tissues with sutures and punctured to the incision subcutaneously. Then, the electrode was connected with a percutaneous lead extension, and the incision was sutured. The left electrode implantation was conducted using the same method as the right electrode and was extended to the left temporal-parietal region with the percutaneous lead extension. Postoperative x-rays were performed to confirm the positioning of the electrode (Figs. 1, 2).

The day after surgery, the test began, and acute stimulation was given when the attacks occurred. The following stimulation parameters were chosen: right 0-, 1+, 50 Hz, 130 μs, 1.0 V; left 8-, 9+, 50 Hz, 130 μs, 1.2 V. After the first 2 days, the patient's symptoms disappeared after 10 minutes to 20 minutes of stimulation. However, on the third day, the patient's headache and autonomic signs could not be relieved following an hour of stimulation, and the pain intensity was the same as that prior to surgery. We adjusted the parameters and eventually chose a frequency of 130 Hz. After stimulation for 15 minutes, the headache dramatically improved. Over another 3 days of testing with 130 Hz, he experienced 13 attacks and achieved pain relief in 7. The remaining attacks were remitted to varying degrees. The patient complained of the remaining headache and the pain of every attack prior to the stimulation in action. In light of his frequent daily attacks, we attempted to give him continuous stimulation similar to ONS. With continuous stimulation on, he did not feel any discomfort. After another 3 days of testing, he only experienced 3 attacks, and the intensity was tolerable. Finally, he reported a significant improvement in symptoms and was satisfied with the thera-

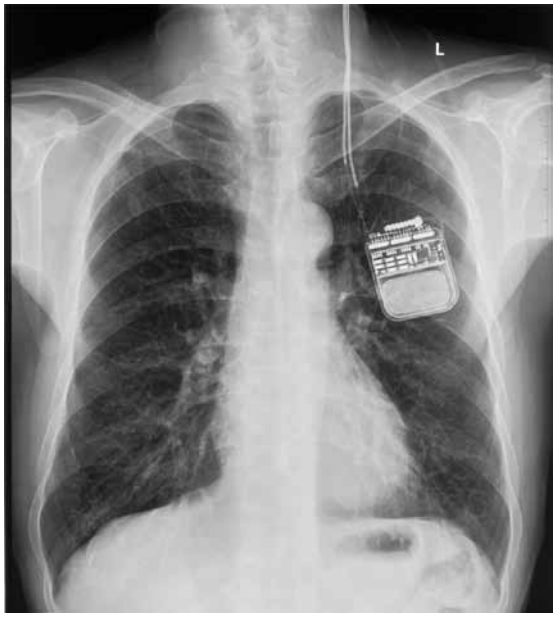

Fig. 3. *The location of the internal pulse generator.*

peutic effects. Then, an internal pulse generator (IPG) (Model 37702, Medtronic, Minneapolis, MN, USA) was implanted under general anesthesia. After sterilization preparation and draping, the bilateral incision on the temporal-parietal region was opened, and the percutaneous lead extension was unloaded. Then, the subcutaneous lead extensions were connected with the leads. The right subcutaneous lead extension was tunneled to the left temporal-parietal incision. The lead extensions of both sides were then punctured subcutaneously to the pocket located in the left infraclavicular region and connected with the IPG (Fig. 3).

The patient was discharged 4 days after stimulator implantation. The stimulation was set to the following final parameters: right 0-, 1+, 130 Hz, 120 μs, 0.7 V; left 8-, 9+, 130 Hz, 120 μs, 0.8 V. The stimulation was non-perceived. In the 4 months of follow-up, his headache frequency was reduced to less than once per week. In addition, the intensity of pain was tolerable and was not accompanied by any autonomic symptoms. The visual analog scale (VAS) intensity of pain prior to surgery was 8 and is one at present. He also discontinued all of the relevant drugs that he had had been taking prior to stimulator implantation. The patient did not experience any serious adverse effects with the exception of a mild numbness in a distinct distribution of the right maxillary nerve. He said that his sensory disturbance gradually disappeared.

Discussion

This is the first report to describe bilateral and continuous SPG stimulation in a patient with CH. Under stimulation, the patient received significant pain relief without any need of pharmacological management and without serious adverse events.

For this patient, many drugs had been tried, but none of them were effective in controlling his headaches. Increasing age has been reported to be a negative predictor of triptan response (13). Therefore, the failure of this patient's drug treatment may have been associated with aging, which results in altered pharmacokinetics. On the other hand, the transportation and permeation of medicine are also affected by the blood-brain barrier (BBB), which can result in low drug concentrations in the brain. For example, verapamil is a substrate of the efflux transporter P-glycoprotein that mediates the clearance of verapamil from the brain (14). The presence of a side shift of attacks may indicate the specificity of the pathophysiological mechanism that results in drug resistance. Moreover, a chronic period with a long duration may also play a role in drug resistance. Further studies are required to elucidate the therapeutic and resistance mechanisms of drugs in the treatment of CH.

The exact pathophysiological mechanisms of CH remain incompletely understood. However, the activation of parasympathetic outflow from the superior salivary nucleus via the facial nerve (predominantly through SPG) constitutes one pathophysiological mechanism of CH (15,16). Additionally, SPG is the largest extracranial parasympathetic ganglion and the primary source of parasympathetic innervation to the face and cranial cavity. These anatomical and physiological features of SPG and the close relationship between CH and autonomic symptoms make it an appropriate target for CH treatment. The effectiveness of various ablative and non-ablative approaches to SPG have been reported; however, most of these procedures have achieved only temporary relief (4) or were associated with irreversible adverse effects (5). Currently, there is growing interest in neuromodulation as a treatment for refractory CH. SPG stimulation for CH has been reported in several studies, and the inhibition of abnormal electrical activity from the SPG and the network-modulating effects of SPG stimulation may explain the benefits of this

approach. In one study on the efficacy of short-term SPG stimulation with a removable electrode for CCH, 61% of attacks were aborted completely, and the associated autonomic features of CH were also resolved along with the pain (8). A multicenter, randomized, sham-controlled trial reported the efficacy and safety of acute SPG stimulation with a novel miniaturized neurostimulator (9). In the randomized experimental period, when the patients were treated with full stimulation, pain relief was achieved in 67.1% of attacks compared with 7.4% for the sham-treated and 7.3% for the subperception-treated attacks. Furthermore, 68% of the patients experienced significant pain remission, and 10 patients had a more than a 50% reduction in attack frequency. However, these studies of SPG stimulation for CH all focused on acute electrical stimulation. In our patient, we also chose acute stimulation at the beginning. More than 50% of the patient's attacks achieved pain relief, and the others were remitted to different degrees. However, the patient complained of residual pain. We then attempted to provide continuous chronic electrical stimulation. To our surprise, the patient achieved significant pain relief and a reduction in attack frequency without any severe side effects. In light of the dramatic frequency reduction, SPG stimulation may have prophylactic properties.

The accurate placement of the electrode in the PPF plays an important role in SPG stimulation effectiveness (8). In previous research, the electrodes were implanted with the assistance of fluoroscopy (8,12). However, the PPF is a narrow and deep space between the posterior wall of the maxillary sinus and the medial plate of the pterygoid process. Fluoroscopy is typically performed to locate the PPF using anatomic landmarks such as the middle turbinate and pterygopalatine fissure; as a result, deviation is unavoidable. Another means to verify the location of the PPF is through stimulation-induced paresthesia. Typically, paresthesias of SPG stimulation have been located at the root of the nose and nasopharyngeal region (8), which could further confirm the position of the electrode. If paresthesia is located in the upper teeth, gums, and hard palate, this means that the maxillary nerve or greater and lesser palatine nerves are being stimulated (5). Under these circumstances, the location of the electrode is not acceptable and the electrode should be redirected. Thus, appropriate lead location can be achieved with the assistance of fluoroscopy and stimulation-elicited paresthesia.

CH attacks always occur unilaterally and affect the same side of the head. However, approximately 14% of CH patients suffer from headaches that shift sides (2). Side shifts also have been reported in patients after unilateral ONS and hypothalamic stimulation. Bilateral CCH also appears to predict a poor response to hypothalamic stimulation (6). In one study, after unilateral ONS, 5 out of 14 side-locked patients experienced side shifting with contralateral attacks that occurred infrequently, either isolated or in short bouts (17). In addition, a severe bilateral CCH patient underwent left hypothalamic stimulation but still had pain on the right side; bilateral electrode implantation was finally required to control the headache (18). Our patient also experienced side shifts without a predominating side; we eventually chose bilateral SPG stimulation. A study on cranial autonomic function revealed that the cranial parasympathetic tone was bilaterally reduced in the remission phase of CH (19). This result implies that central factors play a role in the pathophysiological mechanism of CH. For this reason, unilateral stimulation may not eliminate pain in some patients. Consequently, the occurrence of side shifts should be seriously considered when proposing surgical treatment in CH patients. Bilateral electrical stimulation should be recommended to inhibit attacks in these patients.

Regarding the stimulation parameters, there is no consensus for SPG stimulation. Previous data have focused on acute stimulation. Ansarinia et al (8) reported that the most effective frequency was approximately 50 Hz. However, the mean stimulation frequency was 120.4 ± 15.5 Hz in another study (9). In our patient, the frequency was converted from 50 Hz to 130 Hz for pain management. High-frequency stimulation may achieve a substantially greater effect, and low-frequency stimulation (5 Hz) was shown to induce CH-like attacks that could be terminated by high-frequency stimulation (80 – 120 Hz) (20). Furthermore, low-frequency stimulation of SPG (approximately 10 Hz) was shown to induce the opening of the BBB, cerebral vasodilatation, and plasma protein extravasation (21). Thus, low-frequency stimulation may lead to the activation of parasympathetic efferents that could result in headache attacks. The headaches recurred in our patient on the third day of test stimulation at a frequency of 50 Hz. We believe that the pain relief experienced during the first 2 days may have been a result of the lesion effect of the electrode which frequently occurs after deep brain electrode implantation (22). Stimulation at a frequency of 60 Hz has been reported to also activate the parasympathetic system and increase cerebral blood flow (23). When the frequency was changed to 130 Hz, the

patient experienced significant pain relief. This high-frequency stimulation is thought to act by causing depletion of parasympathetic neurotransmitters (9). SPG stimulation may work predominantly through inhibition of the parasympathetic system in the treatment of CH. Nevertheless, the SPG contains parasympathetic, sympathetic, and sensory components, and the specific effects of high-frequency stimulation on parasympathetic components require further research. However, high-frequency stimulation can also induce delayed attacks. Thus, future studies are needed to elucidate the frequency effect mechanism of SPG stimulation.

Conclusion

We assert that continuous SPG stimulation is promising and feasible for the treatment of CCH. An optimal lead location in the PPF is required for SPG stimulation efficacy. In the future, elucidating the pathophysiological mechanism of CCH and SPG stimulation may support the utility of SPG stimulation, although large-scale multi-center randomized controlled studies are also required to confirm the efficacy of SPG stimulation for CH.

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Kai Zhang and Fang Luo contributed equally to this work

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