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Hypothalamic stimulation for trigeminal neuralgia in multiple sclerosis patients: efficacy on the paroxysmal ophthalmic pain

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Abstract

Trigeminal neuralgia is a disorder characterized by paroxysmal pain arising in one or more trigeminal branches; it is commonly reported in multiple sclerosis. In multiple sclerosis patients the ophthalmic branch may be frequently involved and the risks carried by neurosurgical ablative procedures are higher including major adverse effects such as corneal reflex impairment and keratitis. The objective of this works is to assess the role of posterior hypothalamus neuromodulation in the treatment of trigeminal neuralgia in multiple sclerosis patients. Five multiple sclerosis patients suffering from refractory recurrent trigeminal neuralgia involving all three trigeminal branches underwent deep brain stimulation of the posterior hypothalamus. The rationale of this intervention emerges from our earlier success in treating pain patients suffering from trigeminal autonomic cephalalgias. After follow-up periods that ranged from 1 to 4 years after treatment, the paroxysmal pain arising from the first trigeminal branch was controlled, whereas the recurrence of pain in the second and third trigeminal branches necessitated repeated thermorhizotomies to control in pain in two patients after 2 years of follow-up. In conclusion, deep brain stimulation may be considered as an adjunctive procedure for treating refractory paroxysmal pain within the first trigeminal division so as to avoid the complication of corneal reflex impairment that is known to follow ablative procedures.

Keywords

deep brain stimulation, multiple sclerosis, pain, posterior hypothalamus, trigeminal neuralgia

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Introduction

The myriad of complex symptoms and signs of multiple sclerosis (MS) are known to involve numerous neurological pathways with wide variation in temporal and severity patterns. From 20% to 80% of people suffering from MS are known to experience pain, with neuropathic pain (central limb neuropathic pain and trigeminal neuralgia (TN)) being commonly associated with the disease.[1–5] TN is a disorder that is characterized by brief electric shock-like pains that are abrupt in both onset and termination and are limited to the distribution of one or more divisions of the trigeminal nerve.

TN usually commences in the second or third divisions, affecting the cheek or chin, and involves the first division in less than 5% of MS patients. Although this variety of pain is usually evoked by trivial stimuli such as washing, shaving, smoking, talking and/or brushing the teeth (trigger factors), it is also known to occur spontaneously. Small areas in the nasolabial fold and/or the chin seem to be particularly susceptible to the precipitation of pain and are thus thought of as 'trigger areas'. This particular variety of pain is also known to go into remission for variable periods of time.[6]

TN is known to affect 2–5% of MS patients and this usually begins many years after the disease onset and noticeably later than the occurrence of

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non-trigeminal pain.[5,7,8] Although the clinical characteristics of TN-MS are indistinguishable from the idiopathic form (with an absence of sensory loss and the presence of trigger points), the onset of TN-MS does tend to occur at a younger age[9] and the involvement of the first branch is more common. MRI investigations have shown a variety of different kinds of lesions: vascular compression by an artery in the root entry zone,[10] demyelinating lesions affecting pontine trigeminal pathways,[11] and an enlargement of the trigeminal nerve at the root entry zone.[12,13] Furthermore, TN-MS does not seem to be related to activity of the disease revealed by MRI.[12]

It is known that treating MS patients with antiepileptic medications may cause an elevated incidence of adverse effects, even at low dosages, mimicking clinical worsening suggestive of MS relapse.[14–16]

Several neurosurgical techniques were aimed at controlling TN in MS patients, including radiofrequency (RF) lesions,[17] stereotactic radiosurgery,[18] and microvascular decompression (MVD).[19] With that said, however, and in spite of surgical interventions, most of the patients continue to report recurrent pain and demonstrate a need for further neurosurgical interventions. In other words, at present there seems to be no surgical treatment that should be considered as 'definitive' in the control of TN-MS pain. Ablative neurosurgical procedures carry the risk of causing nerve damage and a resulting hypoesthesia/hyperesthesia with the possibility of secondary deafferentation and corneal reflex impairment, corneal anesthesia, neurotrophic keratitis, transitory masticatory weakness and hearing loss.[20] MVD results in MS patients are known to be poor with a late recurrence of paroxysmal pain being highly probable.[19] Deep brain stimulation (DBS) has been effective in reducing pain symptoms in trigeminal autonomic cephalalgias (TACs)[21] although there is no data regarding the efficacy of DBS in TN-MS patients that are suffering from paroxysmal facial pain.[22] Nevertheless chronic stimulation of the thalamus has been the preferred option in the treatment of essential TN and other trigeminal neuropathic pain.[23–25]

Franzini et al.[21] have implanted DBS leads in the posterior nucleus of the hypothalamus (pHyp) to control pain in TACs, a group of primary headaches characterized by disabling, short-lasting pain attacks associated with autonomic phenomena mainly affecting the eye and nose.[6] In subjects suffering from TACs, such as chronic cluster headache (CCH) and SUNCT (Short-lasting Unilateral Neuralgiform Headache attacks with Conjunctival injection and Tearing), pHyp has been targeted particularly when there is radiological evidence suggestive of pHyp metabolic activation and volumetric changes[26,27] and pain on the ipsilateral side. The mid- and long-term clinical outcomes have been encouraging following this treatment with 60% of the treated patients reporting long lasting benefits.[28–31] Similar results have been reported by other authors.[32–34]

Since TN involves the first trigeminal division and since TACs share the same painful territories (i.e. orbital region, forehead and eye), this evidence, the reversibility of the procedure, and the availability of image-guided surgery tools[35] have led us to consider DBS as an appropriate treatment in selected MS patients that have been affected by refractory TN involving the first division of the fifth cranial nerve. This decision has been further supported because of the known risks associated with ablative procedures.

Patients and methods

Five TN-MS patients were implanted with pHyp DBS leads after giving written and signed informed consent prior to surgery. The characteristics of these patients are summarized in Table 1. The five patients consisted of three males and two females with a mean age of 56 years (range 49–65), a mean disease duration of 23 years (range 13–34), and a mean TN duration of 12 years (range 4–21). The Expanded Disability Status Scale (EDSS) scores were as follows: P.G., A.O. and V.M. had 8, while F.D. and P.G. had 7.5 (Table 1). Two patients (P.G. and V.M.) were suffering from referred pain in all three trigeminal divisions, while the pain of the remaining three patients was derived from the first and second divisions. Two patients (P.G. and A.O.) had pain in the right side while the pain of the other three patients was restricted to the left side.

Preoperative MRI scans showed multiple demyelinating lesions involving the hemispheric white matter, the internal capsule, the ponto-mesencephalic region, and trigeminal pathways. Specifically the axial fluid attenuated inversion recovery (FLAIR) images showed a linear hyperintensity at the pontine trigeminal root entry zone. All five patients were unresponsive or refractory to either optimal or maximal pharmacological therapy (carbamazepine 1200 mg × die, phenytoin 400 mg × die, gabapentin 1600 mg × die, lamotrigine 100 mg × die). Prior to DBS implantation, all patients had undergone a variety of neurosurgical procedures. 'P.G.' had three percutaneous balloon compressions and one MVD; 'A.O.' had one percutaneous balloon compression and three termorizothomies; 'F.D.' had three percutaneous balloon compressions and two MVDs; 'B.G.' had four percutaneous balloon compressions; and 'V.M.' had two percutaneous balloon compressions and one termorizothomy. All of these surgical procedures either failed or resulted in only limited pain-free periods (Table 2). Table 2 summarizes the mean duration of pain relief that was achieved by these pre-DBS surgical interventions.

Table 1. Patients' clinical data

Patient	Sex	DBS age (years)	MS type	MS duration (years)	Pre-operative EDSS	TN duration (years)	TN age of onset (years)	Painful Trigeminal branches	Side
P.G.	F	56	SP	32	8	21	35	I-II-III	Right
A.O.	M	65	PP	13	8	13	52	I-II	Right
F.D.	M	55	PP	14	7.5	9	46	I-II	Left
B.G.	M	56	SP	34	7.5	14	42	I-II	Left
V.M.*	F	49	SP	24	8	4	45	I-II-III	Left
Mean (range)		56 (49-65)		23 (13-34)		12 (4-21)	44 (35-52)		

DBS, deep brain stimulation; MS, multiple sclerosis; EDSS: Expanded Disability Status Scale; TN, trigeminal neuralgia; PP: primary progressive; SP: secondary progressive.
*Died of causes unrelated to TN or its treatment

Table 2. Clinical outcomes to neurostimulation

Patient	Number of neurosurgical procedures before the DBS	Mean intervals between pre-DBS surgical procedures (months)	Pre-DBS Barrow scale	Onset of pain relief (days)	Post-DBS Barrow scale	Time pain recurrent (months)	Trigeminal branch involved	Surgery free interval post-DBS (months)	Follow up (months)
P.G.	4	11	V	3	IIIa	12	II-III	20	48
A.O.*	4	3	V	1	IIIa	28	II	48	48
F.D.	5	6	V	1	IIIa	14	II	14	46
B.G.	4	13	V	1	I	12	II	24	51
V.M.**	3	2	V	10	IIIa	11	II-III	11	11
Mean (range)		6 (2-13)		3 (1-10)		15 (11-28)		23 (11-48)	41 (11-51)

*Did not require further surgeries following deep brain stimulation (DBS).
**Died of causes unrelated to trigeminal neuralgia or its treatment

Following DBS implantation, patients were evaluated on a daily basis for the first 2 weeks (assessing neurological evolution and pain severity according to the Barrow Neurological Institute (BNI) scale (see below)) and then followed every 3 months by a phone interview. Clinical follow-ups were made on the basis of the BNI pain intensity scoring criteria (I: no pain; II: occasional pain, not requiring medication; IIIa: no pain but continued medication; IIIb: some pain, controlled with medication; IV: some pain, not controlled with medication; V: severe pain/no pain relief).[36,37] Preoperatively all patients graded their pain as severe and not controlled with medication (BNI scale grade V). Indeed 'efficacy' of the procedure and the recurrence of pain was defined on the basis of at least two points reduction in the BNI scale (from grade V to III).

Surgical procedures

Stereotactic implants (Leksell G stereotactic frame; Elekta, Stockholm, Sweden) were placed under local anesthesia. When necessary, sedation was induced with propofol (0.5–1 mg/kg). Antibiotic treatment was administered to all patients during the perioperative period. Preoperative MRI (brain axial volumetric fast spin echo inversion recovery) was used to obtain high-definition anatomic images, which allowed precise determination of the anterior commissure-posterior commissure line. MRI scans were fused with 2-mm-thick computed tomographic slices obtained under stereotactic conditions, by using an automated technique based on a mutual-information algorithm (Frame-link 4.0, StealthStation; Medtronic Sofamor Danek, Inc., Memphis, TN). The workstation also provided stereotactic coordinates for the target, 3 mm behind the midcommissural point, 5 mm below the midcommissural point, and 2 mm lateral to the midline. A rigid cannula was inserted through a precoronal paramedian burr hole and positioned up to 10 mm from the targeted pHyp. This cannula was used as a guide for placement of the definitive electrode (DBS-3389; Medtronic). Macrostimulation (1–7 V, 60 ms, 180 Hz)

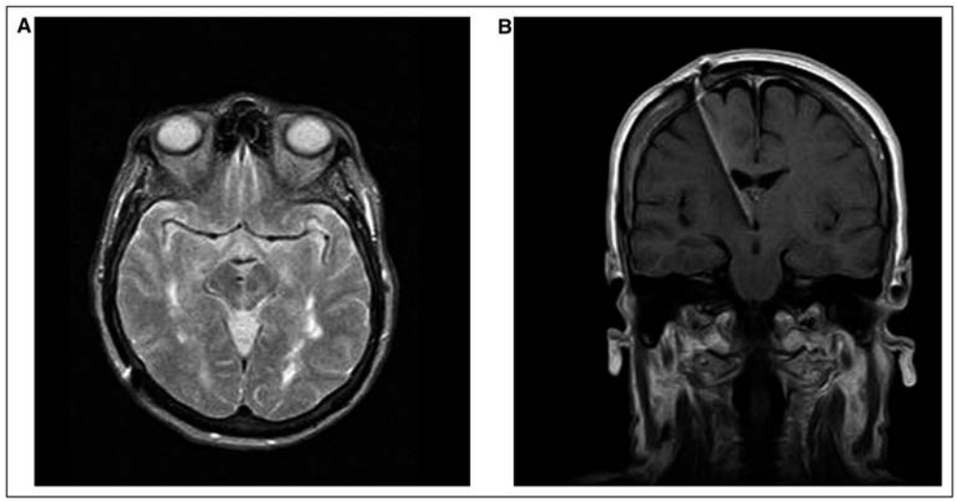

Figure 1. Postoperative MRI scans of a trigeminal neuralgia–multiple sclerosis (TN-MS) patient. (A) MRI T2-weighted axial image shows the deep brain stimulation (DBS) lead in the posterior hypothalamus (pHyp) of a TN-MS patient. Note the presence of signal abnormalities in the supratentorial periventricular white matter. (B) MRI T1-weighted coronal scan showing the lead.

was used to evaluate potential side effects. If no side effects were observed using the standard stimulation parameters (1–2 V, 60 ms, 180 Hz) the guiding cannula was then removed and the electrode was then secured to the cranium with microplates. The extension was then connected to the electrode, tunneled, and brought out percutaneously, for subsequent trial stimulations. On the day after surgery an additional MRI study was performed to confirm the electrode position.

Results

All five patients tolerated the surgery well with no signs of any side effects. Figure 1 shows the results of a post-operative MRI in which the correct placement of the DBS leads within the pHyp of one patient was revealed.

As described in Table 2, we observed the onset of beneficial effects in three out of five patients (A.O., F.D., B.G.) within the first 24 hours after the stimulation was begun. All patients described a reduction of paroxysmal pain attacks within the first trigeminal branch after neurostimulation. P.G. experienced the maximal beneficial effects after 1 month of stimulation (BNI scale grade I), while the four other patients were found to have 'improved' and to have achieved pain 'control' (BNI scale grade IIIa) when DBS was combined with analgesic medication. None of the patients reported any signs of dysesthesia in the territories that are known to be innervated by the three trigeminal branches.

Maximal pain relief was observed in pain that was referred to the ophthalmic branch. None of the patients felt any paroxysmal pain in the first trigeminal branch when the stimulator was turned on. Only one patient (F.D.) experienced a short recurrence of pain in the treated ophthalmic branch after 23 months post-implant. However, when the stimulating parameters were adjusted to slightly higher amplitudes this patient reported an immediate relief of pain. The same patient did experience pain in the ophthalmic branch after the internal pulse generator (IPG) was temporary turned off, but when stimulation was resumed the pain remitted. In another patient (A.O.), when a radiological examination made it necessary to adjust the stimulating parameters he reported pain in the first trigeminal branch which then abated after re-programming the stimulator to the initial parameters. Beneficial effects on pain in the second or/and third branch were limited to a duration that ranged from 11 and 28 months (mean 15 months; Table 2).

Following the DBS implant three patients (P.G., B.G. and F.D.) complained of recurrent pain (BNI scale grade V) and underwent selective RF thermorizothomies to achieve pain relief in either the second or third branch (not in the first). This occurred at varying intervals of time (mean 23 months; range 11–48 months), which are summarized in Table 2. It should be noted that this time interval is longer than the interval that was observed after the neurosurgical procedures that were performed prior to the neurostimulation (mean 6 months; range 2–13 months; Figure 2).

Two patients (A.O. and V.M.) felt that the pain was controlled in all of the affected trigeminal branches with the DBS combined with analgesics (BNI scale grade IIIa), and it should be noted that no further surgical procedures were needed. As of this writing, four patients are still under continued follow-up care

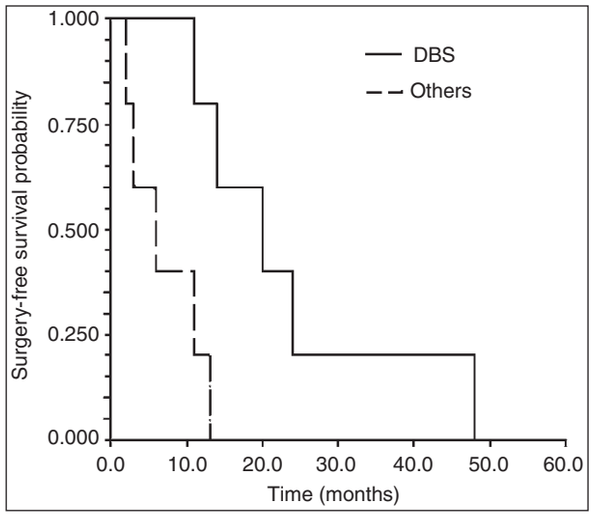

Figure 2. Surgery-free survival curves for the deep brain stimulation (DBS) and other neurosurgical treatments.

(P.G. 48 months; A.O. 48 months; F.D. 46 months; B.D. 51 months;) while one patient (V.M.) died of causes (pneumonia '*ab ingestis*') unrelated to trigeminal neuralgia or our treatment (follow-up 11 months; Table 2).

Discussion

This study describes, for the first time, the successful application of hypothalamic DBS in the treatment of TN in MS patients. Five patients with TN-MS had pain in several trigeminal territories preoperatively. After pHyp DBS implant they were all free of pain 1–10 days after surgery but four out of five continued to require medication in the long term. They had a recurrence of pain in V2, and/or V3, from 11 to 28 months postoperatively but all had sustained pain relief in V1.

The data point towards an efficacy of this procedure in control of paroxysmal pain when it is found to exist in the ophthalmic branch. All five patients reported immediate pain relief, a protracted period of long-term pain control, and a reduced need for analgesic medication without any signs of side effects. In addition all of them reported a subjective improvement in their quality of life. Moreover, when compared with other neurosurgical procedures, DBS achieves longer 'surgery-free intervals'.

Numerous surgical procedures have been used to achieve the control of pain, including MVD, thermal rhizotomy, RF lesions, and gamma-knife radiosurgery. However, all of these surgical procedures report only 'limited' pain-free intervals, in addition to the requirement of further neurosurgical interventions. We believe that any indication of these surgical approaches to the treatment of MS-TN should be based upon an analysis of the risk–benefit profile. There is clear evidence that MS-TN requires significantly more treatments compared with all other non-MS-TN patients[38] and there is also evidence of demyelination in both intra- and extra-mid brain portions of the trigeminal nerve that justifies the chronic and refractory pain.[5]

Broggi et al.[39] have described that only 7 out of 15 MS-TN patients achieved an excellent result following MVD. A similar 'poor' level of efficacy has been also reported by other authors.[40–42] Beneficial effects were reported in 59% of the treated MS patients after percutaneous glycerol rhizotomy.[43] Kanpolat et al.[44] report 'satisfactory' results and 'good' long-term pain control after single or multiple thermorhizotomies. These authors claim they have done 'well' in all 17 of the patients they treated with 80% of their patients reporting as having achieved 'satisfactory' pain control at 5 years.

Gamma-knife radiosurgery has been effective in 80% of cases with 33% of the patients so-treated requiring multiple treatments.[37] Interestingly, the authors of this study have also reported that the mean onset of the beneficial effects is 13 days (range 1–61 days) which is a noticeably longer period of time when compared with our series, where the mean is 3 days. Even more telling, we believe, is the observation that their maximal effect on pain was obtained after a mean of 56 days while DBS, in our study, finds maximal pain relief as occurring just after stimulation is turned on.

However, it does need to be emphasized that all ablative procedures, including with radiosurgery, carry high risks of causing dysesthesia, facial numbness and neuro-ophthalmic adverse effects such as corneal reflex impairment, corneal anesthesia, keratitis and the so-called 'dry eye'.[20,45] The risks of neuro-ophthalmic adverse effects are even higher when the trigeminal pain involves the ophthalmic trigeminal branch. In this regard, it is worth mentioning that none of the patients in our series experienced any neuro-ophthalmic complications after DBS implantation.

Although they arise from different etiologies, TN and TACs involve the first trigeminal division and share the same painful territories such as orbital, forehead and eye. Posterior hypothalamic DBS was begun in the last decade to treat trigeminal autonomic cephalagias[21] when neuroimaging evidence displays an activation of the posterior–inferior nucleus of the hypothalamus during the cluster bouts in patients suffering from CCH.[26,27] For this reason, neurostimulating leads have been subsequently implanted in the posterior hypothalamus, ipsilaterally to the painful side[21] in CCH patients, and in a patients with a different type of TACs, the so-called SUNCT.[46] Both CCH

and SUNCT patients referred pain in the area surrounding the eye which is innervated by the first branch of the trigeminal nerve, but in both of these pathologies thermorhizotomy has been shown to be ineffective.[28,47]

Thermocoagulation of the posterior medial hypothalamus in the treatment of facial cancer pain was first applied by the Japanese neurosurgeon Sano[48] in 1977. Subsequent studies, using experimental models, have described the following: analgesia following the electrical stimulation of the hypothalamus;[49] a monosynaptic pathway connecting the hypothalamus and the trigeminal nucleus;[50] and a differential modulation by hypothalamic neurons on trigeminal nucleus caudalis nociceptors.[51] Interestingly, in 10 CCH patients whom have received beneficial effects by pHyp DBS, a recent PET study has investigated the potential differences in the cerebral metabolic activity when the stimulator was on or off.[52] These results reveal stimulator-induced activations in the ipsilateral pHyp (site of the DBS tip), ipsilateral thalamus, somatosensory cortex, praecuneus, anterior cingulate cortex, and the ipsilateral trigeminal nucleus and ganglion. They also reveal a reduced metabolism in the middle temporal gyrus, posterior cingulate cortex, bilateral inferior temporal gyrus, and contralateral anterior insula.[52] Excluding the possibility of a pure inhibition of hypothalamic activity these data may be suggesting that the efficacy of the DBS in TN may be secondary to a direct modulating effect by hypothalamic neurons on the complex neuronal networks mediating pain transmission as opposed to some kind of local effect.

Interestingly, the benefit of pHyp DBS in CCH patients has been found to occur gradually, over 42 days (range 1–86 days),[29] which is considerably longer than the rapid efficacy we report in our MS patients.

In conclusion, this study provides the first evidence of the efficacy of posterior hypothalamic DBS for the treatment of paroxysmal ophthalmic pain in MS. We therefore conclude that DBS may be a safe (avoiding potentially adverse effects on the eye) and efficacious option in the treatment of recurrent TN-MS when the pain is localized in the area innervated by the first trigeminal branch.

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