Peripheral nerve field stimulation in medically refractory trigeminal neuralgia attributed to multiple sclerosis

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OBJECTIVE Case reports and small patient series have suggested peripheral nerve field stimulation (PNFS) as a treatment for refractory trigeminal neuralgia attributed to multiple sclerosis (MS). Here, the authors aimed to assess the effects of this technique on long-term pain severity.

METHODS Data were prospectively collected on patients with refractory trigeminal neuralgia attributed to MS who underwent PNFS between July 2013 and August 2017 at the authors' neurosurgical department. Patients were evaluated before and after the first treatment as well as at follow-up at least twice a year. Patients underwent assessment of their pain severity using the Barrow Neurological Institute (BNI) Scale before treatment and at follow-up and were questioned about adverse events following cranial MRI performed after implantation of a permanent PNFS system.

RESULTS Eight patients (3 women) underwent PNFS trials and their median age was 61 years (IQR 73.75 – 46.5 years). Seven patients proceeded to permanent implantation of the stimulation system. At a median follow-up of 33 months (IQR 42 – 24 months), pain severity decreased from baseline to the last follow-up (BNI score decrease from V [IQR V – V] to III [IQR V – III], $p = 0.054$). Four patients experienced long-lasting benefit (at 48, 33, 24, and 15 months' follow-up, respectively), while in 3 patients the treatment eventually failed after an initially successful period. One patient had an infection, requiring system removal and subsequent reimplantation. No other complications occurred. No adverse events were noted in the patients undergoing MRI postimplantation.

CONCLUSIONS This analysis indicates a possibly beneficial long-term effect of PNFS on refractory trigeminal neuralgia attributed to MS in some patients.

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KEYWORDS trigeminal neuralgia; facial pain; neuropathic pain; neuromodulation; stimulation

TRIGEMINAL neuropathic pain occurs more often in patients with multiple sclerosis (MS) than in the general population with reported incidence rates of 1.9%–6.3%.^{16,32,37} The symptoms can be indistinguishable from those in classic trigeminal neuralgia (CTN), with paroxysmal, short-lived, stabbing or sharp pain attacks in the distribution of one or more trigeminal nerve branches, which can be triggered by talking, chewing, or brushing teeth.⁴⁴ Yet, while CTN is caused by neurovascular contact, the most likely reason for trigeminal neuropathic pain in MS is demyelinating plaque in the trigeminal root entry zone or the intrapontine trigeminal primary afferents.¹⁰

The first-line symptomatic treatment for trigeminal

neuralgia in MS is the same as in CTN, with carbamazepine the initial drug of choice and oxcarbazepine, lamotrigine, gabapentin, and baclofen constituting second-line treatment.⁴⁴ While microvascular decompression is a viable and established surgical therapy with high success rates in medically refractory cases of CTN,⁴ such therapy is rendered controversial in trigeminal neuralgia attributed to MS given its different etiology, even if a neurovascular contact is additionally present.^{2,8,13} Other therapies are mostly destructive procedures, such as rhizotomy by radiofrequency or glycerol, radiosurgery, balloon compression, or open partial rhizotomy (Dandy procedure). These procedures can be effective; however, they are associated

ABBREVIATIONS BNI = Barrow Neurological Institute; CTN = classic trigeminal neuralgia; MS = multiple sclerosis; PNFS = peripheral nerve field stimulation; RRMS = relapsing-remitting MS.

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with potentially permanent complications such as hypoesthesia.^{5,7,25,28,39} Alternatively, spinal cord stimulation, motor cortex stimulation, and deep brain stimulation have been used for the treatment of refractory facial pain.^{6,33,40}

Peripheral nerve field stimulation (PNFS) is a simple surgical procedure in which one or more electrodes are implanted subcutaneously into the painful area and connected to an implantable stimulator. An electric current is then produced and applied via electrodes. Controlled research has shown the technique's efficacy in alleviating low-back pain^{21,27} as well as different headache syndromes.^{11,24,29,35} Neuropathic facial pain is among the conditions that seem amenable to PNFS,^{12,18,36} and interest in this procedure for patients suffering from refractory trigeminal neuropathic pain syndromes has been increasing.^{14,17,19} Patients with MS present particular challenges in the neuromodulatory treatment of trigeminal neuropathic pain, including their need for regular MRI, which can be disturbed by the stimulation device.

We aimed to identify a cohort of MS patients receiving PNFS for trigeminal neuralgia and assess the effects of stimulation on long-term pain severity as well as the impact on the tolerability of MRI.

Methods

Study Design and Population

After electrode implantation in our first 2 MS patients, we established prospective data collection for patients with trigeminal neuralgia attributed to MS. In the present retrospective analysis, we included only the patients who had undergone PNFS in the period between July 2013 and August 2017 in our neurosurgical department and were over the age of 18 years, had previously received specialist neurological and pain therapeutic treatment, and were considered to have medically refractory disease or had suffered from intolerable medication-related adverse effects such as severe gait ataxia, confusion, or hyponatremia. These patients were routinely informed about percutaneous methods as treatment options before consenting to a PNFS trial. The patients were followed up in our outpatient department. Additionally, their medical records were reviewed, and the data collection was completed with repeated telephone interviews.

Surgical Procedure

A trial stimulation was performed after preoperative marking of the painful area and the planned position of the electrode tip. Implantation of the electrode was performed in a sterile surgical fashion with the patient under either local anesthesia or general anesthesia, depending on their preference. If two trigeminal branches were affected, two electrodes were implanted. The lead was externalized and connected to an external pulse generator, which allowed the patient to adjust the stimulation amplitude and test the PNFS system at home. The trial was considered successful if at least a 50% improvement in self-reported pain intensity and/or frequency of attacks was achieved and both the patient and the physician explicitly favored definitive implantation. In these cases, a permanent system was implanted while the patient was under general

anesthesia. We have used Vectris SureScan MRI leads and PrimeAdvanced SureScan MRI impulse generators since 2015, and Pisces Quad Plus leads and PrimeAdvanced impulse generators were used in 2 patients before 2015 (all Medtronic). The impulse generators were programmed on the 1st day after surgery, and patients were trained in adjusting the amplitude according to their needs. The goal was to induce slight, pleasant paresthesia in the affected area. Patients were advised not to turn off the stimulation completely. The usual settings on first programming were 40–80 Hz, 450 μ sec, and very variable amplitudes depending on the individual patient's perception. All contacts were activated with alternating anode-cathode order with adjustments if required. If necessary, the settings were corrected during outpatient contacts. A more detailed description of the implantation procedure has been provided elsewhere.¹⁹

Evaluation of Patients

Routine follow-up controls were performed twice a year in the neurosurgical pain outpatient clinic. Pre- and postoperative pain characteristics, medication use, and adverse effects were evaluated. Additionally, patients were contacted by telephone by one of the authors (J.K.) to gather missing or updated information on pain perception, medication use, and possible adverse events. Self-reported pain intensity was rated according to the Barrow Neurological Institute (BNI) pain intensity score, a scale ranging from I (no pain, no medication) to V (severe pain, no relief).³⁴

Statistical Analysis

For statistical analysis of the BNI score, we applied a Wilcoxon signed-rank test in JASP version 0.9 (JASP Team). The line graph was created in Microsoft Excel 2010 (Microsoft Corp.).

Ethical Considerations

All patients gave written informed consent for the use and publication of their data. The study was approved by the ethics commission at the Technical University Dresden.

Results

Eight consecutive patients underwent PNFS testing for trigeminal neuralgia attributed to MS at our institution. The cohort comprised 5 men and 3 women, whose median age was 61 years (IQR 73.75 – 46.5 years) and median symptom duration of facial pain was 11 years (IQR 13.75 – 5 years). In 1 case, microvascular decompression had been performed without success. Two patients had received percutaneous treatment in the past without lasting relief.

All 8 patients, all of whom had undergone test stimulation, experienced a significant response with over 50% pain reduction and thus were considered for definitive implantation. A young man died of progressive multifocal leukoencephalopathy before implantation of the permanent PNFS system was scheduled; all remaining patients received the stimulation system. A total of 11 electrodes

TABLE 1. Overview of the patient cohort including outcome data

Dx	Area	MS Duration (yrs)	TN Duration (yrs)	Preop BNI Score	FU BNI Score	FU (mos)	Preop Analgesics (mg)	Last FU Analgesics (mg)	Preop MS Therapy	PNFS AEs
RRMS	Lt V3	18	13	V	I	48	PHT 300, BAC 62.5, CBZ 800, HYD 8	None	Interferon beta	None
SPMS	Lt V2+3	37	17	V	V	42	GBP 2400, OXC 1800	BAC 10, OXC 600, LTG 225, OXY 40	Fampridine	None
SPMS	Rt V2+3	29	5	V	III	33	GBP 2000, LTG 275, BAC 30	OXC when needed (once in 3–4 days)	Fampridine	Infection
RRMS	Lt V2+3	NA	2.5	V	IV	36	BAC 30, LTG 275, GBP 2000	CBZ 2100, LTG 100	Fingolimod	None
RRMS	Rt V3, Lt V2	13	11	V	V	28	BAC 50, GBP 1800, CBZ 600	BAC 75, GBP 2000, PHT 300	Dimethyl fumarate	None
SPMS	Lt V3	NA	NA	V	III	24	CBZ 600	OXC 1200	Siponimod or placebo (EXPAND trial)	None
SPMS	Rt V3	23	14	IV	III	15	OXC 1500	OXC 900, LTG 125	None	None

AE = adverse event; BAC = baclofen; CBZ = carbamazepine; Dx = diagnosis; FU = follow-up; GBP = gabapentin; HYD = hydromorphone; LTG = lamotrigine; NA = not available; OXC = oxcarbazepine; OXY = oxycodone; PHT = phenytoin; SPMS = secondary progressive MS; TN = trigeminal neuralgia.

were implanted in 7 patients (Table 1). The patients were scheduled for follow-up visits once every 6 months. Additional visits took place as needed. The median follow-up time was 33 months (IQR 42 – 24 months).

Shortly after implantation of the definitive system, all patients had marked self-reported improvement in their trigeminal neuropathic pain, and in 5 cases, medication could be reduced (Table 1). In the long term, symptom development was highly variable, with 4 patients experiencing some lasting improvement upon the latest follow-up and 3 patients suffering relapses of their trigeminal

neuralgia to a BNI score of IV or V, corresponding to treatment failure. The time to treatment failure was 16, 25, and 36 months, respectively. Pain severity decreased from baseline to the last follow-up (median BNI score decrease from V [IQR V – V] to III [IQR V – III], $p = 0.054$). Figure 1 provides a representation of symptom development from baseline to the last follow-up. Two patients later received high cervical spinal cord stimulation as a salvage procedure after experiencing no relief from PNFS—both, again, without lasting success. None of the patients received percutaneous treatment since implanta-

FIG. 1. Development of the BNI score in 7 patients with trigeminal neuralgia attributed to MS after the beginning of PNFS. The data are presented as individual BNI scores (y-axis) at different time points expressed in months (x-axis) following the implantation. Each line represents one patient, and the symbols mark the time points of the respective follow-up. Figure is available in color online only.

tion of the PNFS system either because a rhizotomy had already been attempted in the past or because the patients did not consent.

No patient experienced stimulation-dependent adverse effects. One patient suffered from an infection of the stimulation system, which had to be explanted and was reimplanted 3 months later. No pain at the stimulator site, electrode dislocation, or other mechanical complications arose.

At least 4 of the patients underwent MRI studies after implantation of the stimulation system, which were performed at 1.5 T without any special adjustments apart from possible reduction of the specific absorption rate at the radiologist's discretion. The stimulators were switched into the MRI mode or turned off for the time of the scan and turned back on afterward. The scans were uneventful, and the quality of the MR images was without artifacts. No patient reported heating of the electrodes or any dysfunction. In the 4 patients whose MR images are available to us, no changes in the MS lesions occurred during the study period.

Discussion

In our cohort, PNFS led to a long-term decrease in the pain level in 4 of 7 patients with refractory trigeminal neuralgia attributed to MS. Although this result may indicate a potentially beneficial effect of the procedure, our findings need to be interpreted with care given the lack of a control group.

We observed a high initial response, with all patients reporting a notable decrease in pain and most patients reducing their medication after implantation. One patient experienced remission and did not require any specific medication at the latest follow-up. In the long term, however, 3 of the 7 patients had a notable deterioration and did not seem to obtain any benefit from stimulation. These treatment failures occurred at 16, 25, and 36 months, respectively: an elderly man with secondary progressive MS and a 17-year history of neuropathic facial pain at the time of surgery, a middle-aged woman with relapsing-remitting MS (RRMS) and an 11-year history of neuropathic pain, and another middle-aged woman with RRMS who had had a 2.5-year history of pain. The treatment failures were not related to the progression or a relapse of the MS. While 5 of the 7 patients could cut down on their medication after system implantation, most of them needed to increase their drug intake after some time. These dynamics are not reflected by the BNI score because of relative imprecision: a score of III, meaning "some pain, adequately controlled with medication," allows for a broad spectrum of states including very little or a high amount of medication to achieve acceptable pain control.

One can only hypothesize about the reason for the apparent decline in the stimulation effect over time. Regarded skeptically, the initial response may be indicative of a placebo effect, which chronic pain patients are prone to.^{9,20} Yet, given our experience, including a relapse 2 years after system implantation, which entailed an emergency admission and turned out to be caused by a discharged implantable pulse generator in a patient not included in this

series (unpublished data), we believe that a placebo effect is unlikely to be the sole explanation for the clear improvement in our patients. Also, the effectiveness of subcutaneous stimulation has been demonstrated in other studies, including double-blind settings.¹¹ As for the reduction in the treatment effect, one possible reason is progress of the underlying pain syndrome. Moreover, placement of the electrodes and/or the stimulation itself may have led to the development of scarring in the surrounding subcutaneous tissue, which, in turn, may have impeded the distribution of electrical current toward small fiber nerve branches. It must be noted, however, that various treatments have shown a similar decline in effectiveness over time, underlining the difficulties in treating refractory trigeminal neuralgia in MS patients.^{22,31}

The usefulness of PNFS for patients with trigeminal neuralgia attributed to MS needs to be carefully evaluated. While our excitement about the initial success has been tempered by experience, our results indicate that 4 of 7 patients still had some benefit in the long term. At $p = 0.054$, the reduction in the BNI score bordered on statistical significance despite the small number of patients. Given the arduous nature of the pain syndrome and the multitude of failed therapies that led to the consideration of PNFS, this finding must be regarded as a notable result. Compared to that in our previous publication,¹⁹ we found a markedly reduced rate of adverse events. With only one infection and no other side effects, the risk profile seems to be favorable and to support the role of PNFS as a treatment option.

PNFS has been described as a treatment alternative for refractory facial pain in various case reports and case series including etiologies such as postherpetic^{12,15,17,18,38} and posttraumatic^{3,15,18,23,38} origins as well as CTN, MS-associated trigeminal neuralgia, and atypical facial pain or persistent idiopathic facial pain.^{15,18,19,26,43} Table 2 gives an overview of these cases. Most studies had a mean follow-up of less than 2 years, and not all gave sufficient detail about the conditions treated. In some cases, the pain syndromes were not even clearly defined.^{14,41,42} These shortcomings indicate a risk of bias. In our study, we found a high initial treatment response in all patients with significantly less success at the long-term follow-up. A shorter follow-up time could have falsely yielded more positive results.

As MRI controls are of paramount importance for the management of MS, the treatment should not interfere with the diagnostics. Thus, we chose Medtronic Vectris SureScan MRI leads—which were originally designed for epidural spinal cord stimulation—and since 2015, we have used Medtronic PrimeAdvanced SureScan MRI impulse generators, as these are eligible for full-body MRI. As no MRI-related complications arose, we are encouraged in referring patients with PNFS systems for MRI at 1.5 T despite being an off-label use.

Our study suffers from the limitations of an uncontrolled observational single-center study. Although we standardized outcome parameters (e.g., not considering the numeric rating scale, as we found it to be unreliable for neuropathic facial pain) and adhered to a regular follow-up routine, we cannot exclude recall bias and regression

TABLE 2. Overview of case series reporting on PNFS in patients with facial pain

Authors & Year	No. w/ IPG	Etiology	FU	Outcome	Complications
Duntzman, 2002	2	PH	3 yrs	Approximately 50% improvement	None
Johnson & Burchiel, 2004	10	PT, PH, AFP	2 yrs	70% of pts w/ >50% pain relief	3/10 (2 wound breakdown, 1 short extension cable)
Slavin & Wess, 2005	9	Not reported	35 mos	73% of pts w/ >50% pain relief	2/9 (1 loss of effect, 1 skin erosion)
Narouze & Kapural, 2007	1	CH	14 mos	Remission	None
Asensio-Samper et al., 2008	1	PT	4 yrs	VAS score reduction from 10 to 2	None
Amin et al., 2008	10	SN	30 wks	Average VAS score reduction from 7.5 to 3.5	3/10 (2 superficial infection, 1 wound breakdown)
Yakovlev & Resch, 2010	1	AFP	12 mos	Excellent	None
Stidd et al., 2012	3	PT, PH	Mean 18.7 mos (range 6–27)	Mean 87% pain relief (range 60%–100%)	1/3 (occasional HA)
Lenchig et al., 2012	1	PT	3 mos	>50% pain relief	None
Feletti et al., 2013	6	PIFP, PT, PS, PH	Mean 17 mos (range 0–32)	Mean pain score reduction from 10 to 2.7	2/6 (1 traumatic rupture, 1 infection)
Verrills et al., 2014	10	HA disorders	Average 12.9 mos	68% of pts w/ >50% pain relief	10/10 including occipital nerve stimulation (7 hardware erosion, 1 hardware failure, 1 lead migration, 1 short cable)
Ellis et al., 2015	15	HA, TNP, PH, TN, SN, TDP, TMJ disorders	Average 15 mos	73% of pts w/ improvement	12/15 including trial electrode implantations (7 electrode malfunction, 1 extension wire malfunction, 1 IPG pocket pain, 3 inadequate pain relief)
Klein et al., 2016	8	CTN, MS, PIFP	Mean 11.3 mos (range 5–28)	Mean 91% pain relief (range 57%–100%)	3/8 (1 electrode defect, 1 wound breakdown, 1 IPG dislocation)
Jakobs et al., 2016	6	PH, CTN	Average 15.2 mos	Mean 88% pain relief (range 75%–100%)	3/6 (1 infection, 2 muscle stimulation)
Weiner et al., 2017	10	Chronic craniofacial pain	4 wks	Mean 91% pain relief (range 47.7%–100%)	None
McMahon et al., 2019*	17	PIFP	Mean 10 mos	Mean 97% pain reduction†	7/17 (2 infection, 1 local pain, 1 wound dehiscence, 1 CSF leak, 1 local pain, 1 lead migration)

AFP = atypical facial pain; CH = cluster headache; HA = headache; IPG = implantable pulse generator; PH = postherpetic; PIFP = persistent idiopathic facial pain; PS = postsurgical; PT = posttraumatic; pts = patients; SN = supraorbital neuralgia; TDP = trigeminal deafferentation pain; TMJ = temporomandibular joint; TNP = trigeminal neuropathic pain; VAS = visual analog scale.

* PNFS and/or trigeminal ganglion stimulation.

† VAS score available in 13 patients.

toward the mean. However, at a median of 33 months, we report a comparatively long follow-up time with regular patient contact.

Although there have been several calls for randomized trials of PNFS in trigeminal neuralgia, a closer look at the reality of the situation bears little promise in achieving this goal. In the specific case of trigeminal neuralgia due to MS, the very low incidence of the disease is associated with major problems in terms of patient recruitment: in Northern Europe and North America, the incidence of MS has been reported to be anywhere between 7 and 20 cases per 100,000 persons. Given that only a minority of MS patients suffers from trigeminal neuralgia (1.9%–6.3%^{16,32,37}), this incidence translates to approximately 0.13–1.26 cases per 100,000 persons. Only a subgroup of these cases are refractory to medical treatment, and among those that are,

many receive other treatments. Even considering trigeminal neuropathic pain of various etiologies would yield only a small number of patients available for a clinical trial, as a large variety of treatment options can be considered. Furthermore, given the rarity of the condition, device manufacturers have little incentive to invest in a controlled trial.

Conclusions

PNFS has been in use in the management of facial pain for over a decade, yet the evidence still does not exceed case series with short follow-up times and is thus unsatisfactory. It remains one of the options, among other treatments, to be individually considered for MS patients with refractory facial pain, as highlighted by our cohort observation.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Klein. Acquisition of data: Klein. Analysis and interpretation of data: Klein. Drafting the article: Klein. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Klein. Statistical analysis: Klein. Study supervision: Klein.

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