Evidence of descending inhibition deficits in atypical but not classical trigeminal neuralgia

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Abstract

Trigeminal neuralgia (TN) is a rare neuropathic facial pain disorder. Two forms of TN, classical TN (CTN) and atypical TN (ATN), are reported and probably have different aetiologies. The aim of the present study was to evaluate the functional integrity of the diffuse noxious inhibitory controls (DNIC) in (1) a group of patients with classical trigeminal neuralgia (CTN), (2) a group of patients with atypical trigeminal neuralgia (ATN), and (3) a group of healthy controls in order to determine if a descending pain modulation deficit could participate in the pathophysiology of TN pain. DNIC responses of 14 CTN patients, 14 ATN patients and 14 healthy controls were obtained by comparing thermode-induced facial heat pain scores before and after activating DNIC. DNIC was triggered using a standard counter-irritation paradigm (i.e., immersion of the arm in painfully cold water). General sensitivity to pain was also evaluated by measuring mechanical pain thresholds over 18 points located outside the trigeminal territory. Healthy participants and CTN patients showed a 21% and 16% reduction in thermode-induced pain following the immersion, respectively (all p-values <.01), whereas ATN patients experienced no change (p=.57). ATN patients also had more tender points (mechanical pain thresholds < 4.0 kg) than CTN and healthy controls (all p-values < .05). Taken together, these results suggest that the underlying physiopathology differs between CTN and ATN and that a deficit in descending inhibition may further contribute to the pain experienced by patients with ATN.

Introduction

Trigeminal neuralgia (TN) is a rare neuropathic facial pain disorder affecting the fifth cranial nerve. Two forms of TN, classical TN (CTN) and atypical TN (ATN), are reported [55]. Patients with CTN experience sharp, paroxystic pain lasting from a few seconds to two minutes, whereas ATN patients report (in addition to these pain paroxysms) a more constant and diffuse type of pain which is, clinically, often more difficult to treat [55;56]. It should be noted that differentiation between CTN and ATN is based on symptom constellation (i.e. presence or absence of constant pain between paroxysms). This categorization should be distinguished from other commonly proposed classifications such as those which divide TN into idiopathic or symptomatic based simply on aetiology [8;16].

Even though TN was first described centuries ago, its underlying pathophysiology remains poorly understood [7;39]. Microvascular compression of the trigeminal nerve continues to be the most proposed cause of TN [31]. However, the latter cannot entirely explain TN as neuroimaging and post-mortem evidence demonstrate that: (1) microvascular compression is absent in many patients with TN [3;20;43], and (2) many people with a microvascular compression do not report facial pain [2;18;23].

Some authors have suggested that a deficit in the functional integrity of endogenous pain modulating responses could contribute to the pain experienced by TN patients [42]. Such a premise comes, for the most part, from the work of Fromm and colleagues [13] who showed, using animal models, that the anticonvulsant drugs that effectively treat TN (carbamazepine, baclofen, phenytoin) increased endogenous pain modulating responses, whereas anticonvulsants that were ineffective in treating TN

(phenobarbital) did not affect endogenous pain modulating responses. These observations gave rise to the hypothesis that a failure of inhibitory mechanisms may play an important role in the pathogenesis of TN, a hypothesis that has never been formerly tested.

Endogenous pain modulating deficits as a possible cause of chronic pain is not specific to TN and has in fact been postulated and validated in a variety of other painful disorders including fibromyalgia (FM), tension-type headache (TTH), migraine, and temporomandibular disorders (TMD)[21;25;30;40]. More specifically, these studies revealed that FM, TTH, migraine and TMD patients all showed a deficit of the diffuse noxious inhibitory controls (DNIC), a descending pain modulating mechanism originating in the brainstem and exerting a powerful and diffuse analgesic effect [27]. These findings clearly remind the clinician and the researcher that painful conditions should not only be seen as the end result of increased nociception but also, in some situations, as the product of impaired inhibitory processes [11].

The primary objective of this study was to evaluate the functional integrity of the DNIC system in a group of healthy controls, a group of CTN patients and a group of ATN patients. A second objective was to compare the strength of DNIC in the three groups. Finally, a third and last objective was to determine if CTN and ATN patients display evidence of increased tenderness in body regions not innervated by the fifth cranial nerve, thus testing the possibility that an eventual DNIC deficit would influence pain sensitivity beyond the trigeminal territory.

Methods

Participants

Thirty patients diagnosed with TN (15 CTN and 15 ATN) and 15 healthy controls participated in the study (all participants ≥ 40 years old). All TN patients were recruited among patients referred to the Gamma-knife surgery (GKS) clinic of the Sherbrooke University Hospital. Diagnosis of idiopathic TN was confirmed by a neurosurgeon (DM, JB or BK) using the International Classification of Headache Disorders criteria [19]. Patients with atypical facial pain (a distinct condition characterized by unexplained facial pain but without paroxysmal attacks [12;19]) were excluded from the present study. Patients with symptomatic TN (e.g. TN secondary to multiple sclerosis or with symptoms suggesting post-herpetic or deafferentation pain syndromes were also excluded. No patients showed evidence of tactile, thermal or pricking hypoesthesia. There was no sign of dysesthesia, hyperesthesia or allodynia. In addition to a conventional neurologic examination, every participant was examined with a magnetic resonance imaging (MRI) to rule out neuronal damage.

Differentiation between CTN and ATN was made by the experimenter (GL) and by the neurosurgeons (DM, JB and BK) before psychophysical testing using the criteria proposed by Zakrzewska [55]. Specifically, patients with painful paroxysms but who were pain free between the attacks were classified as CTN patients. In contrast, patients who reported painful paroxysms with the presence of a dull, burning, continuous background pain in between the attacks were classified as ATN patients. These differentiation criteria have been used previously both for clinical and experimental purposes [36;55;56].

Healthy controls were recruited through local ads and were all community-dwelling individuals. They all had good general health and none suffered from any painful conditions with the exception of three participants who reported minor osteoarthritic pain. An attempt was made to age and sex match healthy controls with patients. Every participant was asked to refrain from using short term analgesics two hours before testing and from drinking coffee and smoking cigarettes six hours before testing. TN patients were also asked to stop all pain medications for a period of 24 hours before their appointment. Patients' characteristics are listed in Table 1 and 2.

The experiment took place at the Clinical Research Centre of the Sherbrooke University Hospital (Sherbrooke, Quebec, Canada). The entire experimental session lasted about 120 minutes. The local Institutional Ethics Committee approved the study's procedures and each participant provided informed consent before participation.

Trigeminal thermode testing

Participants were seated comfortably in a reclining chair. A pre-testing session was first provided where three painful thermal stimulations (46, 47 and 48 degrees Celsius) were applied for 5 seconds (preceding ramp-up time of 15 seconds, interval between stimuli of 30 seconds) on the trigeminal affected area using a 1 cm^2 Peltier-type thermode (Medoc, Advanced Medical Systems, Minneapolis). This pre-testing session allowed our participants to become familiar with the experimental protocol and helped reduce stress and anxiety. When more than one trigeminal division was affected, the thermode was placed over the most affected division. This resulted in 2 patients being tested on the V1 territory, 18 patients on the V2 territory and 10 patients on the V3

territory. Healthy controls were also exposed to the same three thermal stimulations as those provided to TN patients and on regions which matched (in location and proportion) those of TN patients (9 healthy controls tested on the V2 territory and 6 healthy controls tested on the V3 territory).

Participants were then given a 5 minute rest period before the experimental test began. All participants were told that the stimulation used during testing would be similar to the ones experienced during pre-tests, and that they would have to evaluate the intensity of the pain using a 0 to 100 numerical rating scale (NRS) (0 = no pain, 100= intolerable pain) during the interval between stimuli. Testing then began using the same protocol (trigeminal distribution, temperatures, ramp-up time, interval between stimuli) employed during the pre-test. At all times during the pre-testing and testing sessions, great care was taken to avoid stimulation of TN trigger zones.

Arm Cold Pressor Test (DNIC activation)

Participants were then asked to immerse their right arm for 5 minutes in a bath of circulating cold water maintained at 10 degrees Celsius. This procedure, commonly known as the cold pressor test (CPT), was used to trigger descending inhibitory responses, with previous studies showing that it is a reliable and effective way of triggering such responses [45]. Every 30 seconds, patients rated their immersion-induced pain using the same numerical scale that was used during thermode testing (0= no pain; 100 = intolerable pain). Subjects were instructed to remove their arm if the stimulation became too painful or uncomfortable. Participants who were unable to tolerate the stimulation for more than 2 minutes were excluded from all analyses. This occurred in

only three participants (1 CTN, 1 ATN and 1 healthy control; n after exclusions = 42). Imposing a minimum of 2 minutes of immersion time ensured that the CPT was sufficiently painful to trigger inhibitory responses [45]. Most of the remaining participants tolerated the CPT for the entire 5 minutes (long immersion group) however 9 of them (3 CTN, 5 ATN and 1 healthy) removed their arm between 2 and 5 minutes of immersion time (short immersion group). A preliminary Kruskall-Wallis analysis conducted to ensure that long and short immersions produced similar DNIC effects showed that immersion time did not influence DNIC effects ($p=.21$), at least for situations where immersions lasted more than 2 minutes.

Immediately after the CPT, subjects were asked to remove their arm from the cold water and the thermode test was repeated one last time over the same region as the one previously tested. The percentage difference in thermode pain scores obtained prior to and following the immersion procedure constitutes the metric of the inhibitory response.

Mechanical pain thresholds

In order to evaluate pain sensitivity outside the territory of the trigeminal nerve, mechanical pain thresholds were determined using a standard pressure algometer (FGE-100X, Shimpo Instruments, Illinois). To ensure standardisation, and because we wanted to measure pain sensitivity over both upper and lower quadrants of the body, measures were taken over the 18 tender points used to diagnose FM according to the American College or Rheumatology [51]. Mechanical pain thresholds less than 4.0 kg were considered "positive" (abnormally sensitive), and the total number of positive points were summed for each participant. Importantly, mechanical pain thresholds were obtained

before thermode testing began, at the onset of the experiment, so that none of our experimental tests affected pressure values.

Statistical analysis

Because of the relatively small number of subjects included in this study and because visual inspection of the histograms did not allow us to assume that the data were normally distributed, non-parametric tests were used. Specifically, the Wilcoxon Signed-Rank Test (within-subject analysis) was used to compare thermode pain scores before and after CPT. This allowed us to evaluate the functional integrity of the DNIC system for each group (Objective 1). Alternately, between-subject analyses (Mann-Whitney Test and Kruskall-Wallis Test) were used to compare (i) the percentage change in pain scores before and after the CPT, and (ii) the number of tender points between the three different groups. This allowed us to meet our second and third objectives which were to determine (i) if there was a difference in the strength of DNIC between the three groups of participants, and (ii) if CTN and ATN patients showed evidence of increased tenderness in body regions not innervated by the fifth cranial nerve when compared with healthy participants. Differences were considered to be significant if $p < 0.05$ was obtained.

Results

Baseline thermode measures

Facial pain scores obtained prior to CPT for the different temperatures (46, 47 and 48º C) are reported in Table 3. As it can be seen from the table, higher thermode temperatures were rated as more painful than lower thermode temperatures in all three

groups. Table 3 also shows that the three groups of participants had comparable levels of baseline pain, although there was a slight tendency for both CTN and ATN patients to report higher scores than healthy controls. Between group differences reached statistical significance only for the 47º C stimulation condition, revealing higher pain scores for CTN and ATN patients than for healthy controls.

Immersion-induced pain

Every participant experienced the CPT as painful (all NRS ≥ 20). Kruskall-Wallis Test conducted to test for group differences in average CPT pain revealed a group effect (p=.02) , with Mann-Whitney post-hoc tests showing that both CTN and ATN patients had higher pain scores than healthy controls (CTN = 73 ± 25, ATN = 69 ± 27, healthy controls = 47 ± 25; all p-values < .05). There was no difference between the CTN and ATN group (p=.66).

Functional integrity of the DNIC system

In order to simplify data presentation and because statistical analyses showed no effect of thermode temperature on DNIC results, facial pain ratings obtained at each of the three stimulation levels (46, 47 and 48 degrees Celsius) were averaged and this average was used in all subsequent analyses. Average thermode pain scores obtained before and after CPT showed that DNIC efficacy varied among the three groups. Specifically, Wilcoxon Signed-Rank tests revealed that both healthy controls and CTN patients experienced a reduction in thermal pain following immersion in cold water (all

p-values <.01), whereas there was no change for patients with ATN (p=.57) (see Figure 1).

Strength of the DNIC effect

In order to directly test for group differences in DNIC efficacy, percentages of pain reductions were calculated for each group [pain reduction = (pain before CPT – pain after CPT)/ pain before CPT * 100] and compared using a Kruskall-Wallis Test. Healthy controls, CTN patients and ATN patients experienced a 21%, 16% and 1% reduction in pain following CPT, respectively, with the Kruskall-Wallis test showing a significant difference between the three groups. Mann-Whitney post-hoc tests revealed that there was a difference in terms of percentage of pain reduction between the ATN and CTN group (p=.02) and between the ATN and healthy control group (p=.03) but not between the CTN and healthy control group (p=.38). Differences between each group in terms of percentages of pain reductions are illustrated in Figure 2.

Additional analyses were performed to determine if thermode laterality (i.e. if the thermode was placed ipsilaterally or contralaterally to the arm used for CPT) affected the magnitude of the DNIC response. Mann Whitney Tests for all groups showed no effect of thermode placement on DNIC strength (all p-values >.22).

Mechanical pain thresholds

Because of time constraints, measures of mechanical pain thresholds could not be obtained from two participants (one CTN and one ATN patients). Results obtained from the remaining 40 participants revealed that there was a difference between the three

groups for the number of tender points (healthy controls = 4 ± 3, CTN patients = 6 ± 3, ATN patients = 10 ± 4; $p<.01$). Post-hoc analysis using Mann-Whitney Tests revealed that ATN ($p<.001$), but not CTN patients ($p=.09$) had more tender points than healthy control. Comparison between ATN and CTN patients was also significant, with ATN patients exhibiting a higher number of tender points ($p<.05$). Interestingly, when considering the criteria of the American College of Rheumatology (ACR) for a positive diagnosis of FM (i.e. tenderness at 11 or more sites [51]) 38% of the ATN patients would have met the criteria for FM compared with 15% for CTN patients and 0% for healthy participants.

Previous TN surgery

Because some of the patients tested had previous TN surgery, we performed exploratory analyses to determine whether there were any differences between patients with and without previous neurosurgical intervention. Mann-Whitney Tests for both CTN and ATN patients showed that there were no differences between patients with and without previous TN surgery for all dependent variables of interest (baseline facial pain ratings, DNIC strength, number of tender points, McGill Pain Questionnaire score; all p-values >.14).

Discussion

Main findings

In the present report, we sought to determine if TN could be associated with a deficit of the DNIC system. Our results showed that ATN, but not CTN patients, had a

reduced DNIC effect compared to healthy controls. Healthy participants and CTN patients showed a 21% and 16% reduction in pain following CPT, respectively, whereas ATN patients experienced only a 1% change. The idea that a deficit of the endogenous modulating system could contribute to the pain experienced by TN patients is not new and as been suggested by various authors [13;42]. Until today, however, this hypothesis was never formally tested, and so remained purely hypothetical. The present study provides, to our knowledge, the first evidence of a deficit of the endogenous pain modulating system in ATN patients.

Traditionally, evaluation of the DNIC system has been made by comparing a first set of nociceptive measures obtained at baseline with a second set of nociceptive measures obtained *during* a conditioning stimulus [26;35]. Alternatively, other studies have employed experimental paradigms in which DNIC evaluation was made by comparing nociceptive measures obtained before to nociceptive measures obtained *after* the conditioning stimulus [24;45]. Testing DNIC by applying the conditioning and test stimuli successively is possible because DNIC's analgesic effect persists beyond the application and removal of the conditioning stimulus [5;15;37;47;50]. Although simultaneous application of the test and conditioning stimuli probably yield higher DNIC effects than sequential paradigms (notably because DNIC effects fade with time) [37], the latter have the advantage of diminishing the potential for distraction-induced confounds. This is particularly relevant since a strong, painful conditioning stimulus likely has attention-grabbing properties.

Mechanical pain thresholds

Since DNIC effects are diffuse by nature, one could expect that the consequences of a DNIC deficit would not solely be restricted to the region of the face. The fact that ATN patients showed increased tenderness in body regions not innervated by the trigeminal nerve supports the hypothesis of a general and diffuse inhibitory deficit. It remains unclear, however, why ATN patients predominantly report clinical symptoms that are circumscribed to the trigeminal territory. A possible explanation might be that DNIC deficit will evolve through time to eventually produce pain across various regions of the body. In this manner, ATN patients, if assessed longitudinally, may eventually report painful symptoms not circumscribed to the face. It is also important to note that we did not explicitly (and comprehensively) assess pain complaints beyond the trigeminal territory.

This association between facial pain and widespread pain has been shown in previous studies[17;44;46]. For instance, Hagberg et al.[17] reported that the prevalence of musculoskeletal pain in various parts of the body was higher in women suffering from craniomandibular disorders than in women sampled from the general population. Similarly, Sipilä et al.[44] showed that, compared with control subjects, subjects with TMD and other undiagnosed facial pain disorders had significantly more pain outside the facial area and significantly more painful fibromyalgia points. Although we did not evaluate pain complaints outside the trigeminal territory, our findings of increased tender points in ATN patients are coherent with the results of Hagberg et al.[17] and Sipilä et al.[44].

Interestingly, the large number of positive tender points found in ATN patients suggests that a parallel can be drawn between ATN and FM. In fact, our results indicate that up to 38% of ATN patients would have met the ACR defined criteria for FM (compared with 15% for CTN patients and 0% for healthy participants). These observations are coherent with the results of other studies who have suggested some important overlap between facial pain conditions and FM [1;4;9;38]. They are also especially compelling if we consider that FM (like ATN) has been associated with a descending inhibitory deficit [21;25].

Perhaps another resemblance between ATN and FM is the limited success that appears to be obtained following conventional therapeutic interventions. For instance, several authors have shown that the efficacy of microvascular decompression (MVD) and GKS was decreased in ATN patients when compared with CTN patients [6;14;28;29;48]. This resistance to treatment can probably be explained by the fact that surgical interventions will have little to no effect on the functional integrity of descending inhibitory circuits. Additional therapeutic interventions aimed at rekindling inhibitory responses may yield more promising results than surgical management alone [33;34;49].

A recent study by Obermann et al. [36] found that ATN patients had larger pain-related evoked potentials (PREP) amplitudes following electrical stimulation of the trigeminal nerve than CTN patients. Because there was no difference between CTN and ATN patients for the nociceptive blink reflex, Obermann et al. [36] concluded that the increased PREP amplitudes probably reflected global supraspinal adaptation mechanisms associated with the development of chronic constant pain in the group of ATN patients. These adaptations could include increased activity of the excitatory mechanisms (e.g.

sensitization) and/ or decreased activity of the inhibitory mechanisms [34]. Without excluding the legitimacy of the former alternative, the present study suggests that the increased PREP amplitudes observed by Obermann et al. could be related to a deficient inhibitory endogenous pain modulating system.

Previous TN surgery

Our results also showed that, compared to ATN patients, a greater proportion of CTN patients had previously received TN surgery (see Table 2). This phenomenon is probably attributable to the fact that the efficacy of neurosurgical interventions is lower in ATN patients than CTN patients [6;14;28;29;48]. Nevertheless, for all our variables of interests, the analyses showed that there was no difference between patients with and without previous TN surgery.

Cause or consequence

At this point, it is difficult to know if the reduced DNIC observed in the ATN group represents a cause or a consequence of non-paroxystic pain episodes. Traditionally, it is assumed that deficient descending inhibitory circuits predate the development of chronic pain. Supporting this hypothesis are recent results from Yarnitsky and colleagues [53] who show that inter-individual variations in DNIC strength predict inter-individual differences in the development of chronic post-operative pain. Hence it is tempting to suggest that DNIC deficits may play a causal role in non-paroxystic pain episodes. However, it is also possible that long-lasting noxious insults deplete endogenous inhibitory resources. As a result, DNIC deficits may evolve from

prolonged pain [22]. Clearly, future research is essential to better understand the link that exists between chronic pain conditions and the functional integrity of pain modulating systems.

Increased CPT pain scores

A finding somewhat more unexpected was that CTN and ATN patients had higher pain scores during CPT than healthy controls. It is uncertain whether these differences are due to physiological or psychological factors. For example, increased CPT pain for ATN patients could be attributable to reduced descending inhibition. This explanation however falls short for the CTN group, in which a DNIC deficit was not observed. Future studies are necessary to examine this issue. Importantly however, these group differences in CPT pain scores do not jeopardize the conclusions regarding DNIC differences, since all participants (including ATN patients) experienced pain during the CPT (a prerequisite for the activation of DNIC).

Limitations

An important limitation of the present study concerns the relatively small number of participants tested. It is important to point out, however, that TN is a rare condition [41;54], making large sample size difficult to obtain. Moreover, and despite this relatively small sample size, our main statistical analyses had appreciable power ($1 - \beta = 69\%$) and reached statistical significance, a situation that can be attributable to the large effect size observed ($\eta^2 = .17$).

An additional limitation concerns the possible generalizability of our results. Because participants were recruited from the GKS clinic (which is usually reserved for patients who fail to respond to TN medication), one can wonder if the results obtained from this group of patients would also have been found in a more general TN population. Although we cannot completely rule out the possibility that our results are limited to patients who are unresponsive to medication, this appears unlikely since patients scheduled for GKS were not systematically unresponsive to medication. Indeed, many patients agreed to GKS because they wanted to decrease drug doses and their accompanying side-effects. Thus, our results are not limited to patients who fail to respond to TN medication.

Finally, the absence examiner blinding in this study constitutes a possible form of bias. Although enormous care was taken to prevent examiner-induced effects (e.g., use of identical methodology, standardized instructions and recording), one cannot completely exclude this possibility. Future studies should be wary of this potential confound.

Conclusion

In conclusion, our results show that ATN patients, but not CTN patients, have a reduced DNIC when compared to healthy controls. These differences suggest that the underlying pathophysiology likely differs between CTN and ATN and that a deficit of the DNIC system may further contribute to the constant and diffuse pain experienced by patients with ATN. The fact that ATN patients also showed the greatest degree of

sensitivity in body regions not innervated by the trigeminal nerve further supports the hypothesis of a global pain inhibitory deficit in this subgroup of patients.

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Figures

Figure 1. Comparisons of pain measures to thermal stimulation (mean of three stimulations) obtained before and after CPT. Unlike ATN patients, healthy participants and CTN patients showed a reduction in pain after the CPT (** p<.01).

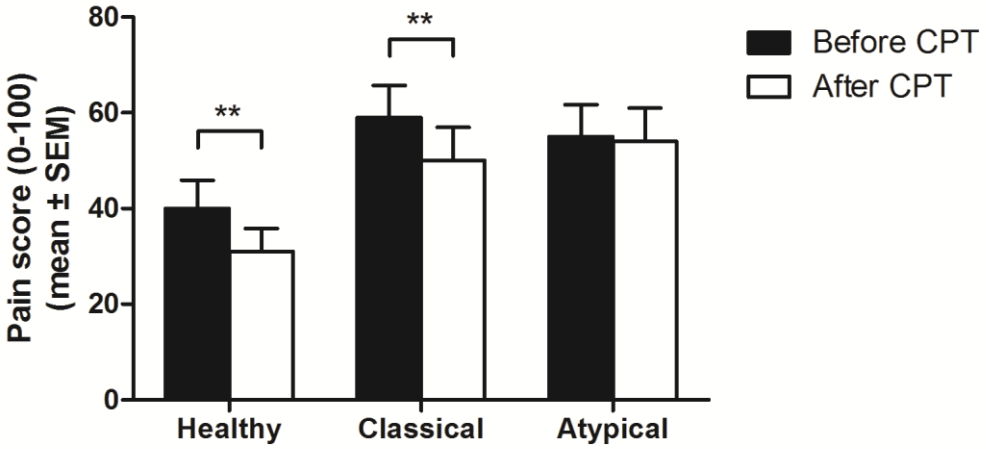

Figure 2. Percentage changes between thermal pain measures obtained before and after CPT. Healthy participants and CTN patients had a 21% and 16% reduction in thermal pain following CPT, respectively, whereas there was virtually no change for patients with ATN (1% decrease) (* p<.05).

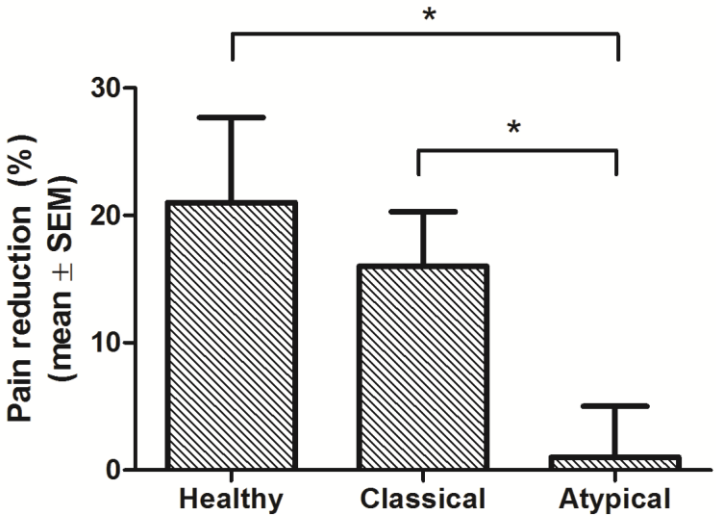

Table 1

Patient number	Age (yrs)/ gender	Classification	Affected side	Affected territory	Medications (daily doses)
1	85/ F	ATN	Right	V2, V3	Pregabalin 150 mg BID Celecoxib 100 mg BID Carbamazepine 200 mg BID
2	81/ F	ATN	Left	V2, V3	Oxcarbazepine 50 mg BID
6	53/ F	ATN	Left	V1, V2, V3	Pregabalin 75 mg BID
8	62/ M	ATN	Left	V2, V3	Oxcarbazepine 300 mg QID
13	39/ F	ATN	Left	V1	Tramadol/acetaminophen 75 / 650 mg QID Hydromorphone (controlled release) 3 mg BID
14	50/ M	ATN	Right	V2, V3	Oxcarbazepine 600 mg BID Amitriptyline 20 mg QD
15	72/ M	ATN	Right	V2, V3	Carbamazepine 200 mg TID Gabapentine 100 mg QID
18	71/ F	ATN	Left	V3	Gabapentine 600 mg TID
19	72/ M	ATN	Right	V3	Pregabalin 75 mg BID
20	72/ M	ATN	Right	V1, V2, V3	Prednisone 5 mg QD Carbamazepine CR 200 mg TID Acetylsalicylic acid 160 mg QD Acetaminophen 500 mg QID Oxycodone 5 mg QID PRN
21	53/ M	ATN	Left	V2	Gabapentine 300 mg TID
22	53/ M	ATN	Left	V1, V2	Topiramate 100 mg BID Baclofen 20 mg TID Methadone 5 mg QID Duloxetine 60 mg QD Quetiapine 200 mg QD
26	76/ M	ATN	Left	V3	Oxcarbazepine 600 mg BID Acetylsalicylic acid 325 mg QD Phenytoin 100 mg TID

Patient number	Age (yrs)/ gender	Classification	Affected side	Affected territory	Medications (daily doses)
27	76/ M	ATN	Left	V1, V2, V3	Carbamazepine 600 mg BID
3	67/ M	CTN	Left	V2	Gabapentine 1200 mg BID Pregabalin 300 mg BID Naproxen 500 mg PRN
4	69/ M	CTN	Right	V2, V3	Pregabalin 150 mg BID
5	64/ M	CTN	Left	V1	Gabapentine 400 mg TID Baclofen 10 mg QID Pramipexole 0.25 mg QD
7	78/ M	CTN	Left	V2	Oxcarbazepine 150 mg BID
9	57/ F	CTN	Right	V2, V3	Carbamazepine 200 mg BID
10	66/ M	CTN	Left	V2, V3	Gabapentine 300 mg QID Carbamazepine 200 mg TID Topiramate 100 mg TID
11	70/ F	CTN	Right	V1, V2	Oxcarbazepine 300 mg BID
12	59/ M	CTN	Right	V2	Carbamazepine 1200 mg TID Acetylsalicylic acid 325 mg QD
16	80/ F	CTN	Right	V3	Carbamazepine 300 mg TID Gabapentine 400 mg QD
17	58/ M	CTN	Right	V2	Carbamazepine 400 mg QID
23	65/ M	CTN	Left	V1	Oxcarbazepine 600 mg TID
24	59/ M	CTN	Right	V2, V3	Oxcarbazepine 900 mg BID Baclofen 20 mg TID
25	42/ F	CTN	Left	V2	Oxcarbazepine 300 mg TID
28	56/ F	CTN	Right	V1, V2	Carbamazepine 500 mg BID Amitriptyline 20 mg QD

Table 2

	Healthy (n=14)	*CTN (n=14)*	*ATN (n=14)*	***p-value***
Gender	7 males	9 males	9 males	.67
Age	64.6 ± 9.4	63.6 ± 9.6	65.4 ± 13.6	.78
Time since onset of symptoms (yrs)	-	6.1 ± 5.3	8.6 ± 7.5	.51
Side affected	-	6 left	9 left	.45
Territory affected	-	V1 = 2 V2 = 5 V3 = 1 V1, V2 = 2 V2, V3 = 4	V1 = 1 V2 = 1 V3 = 3 V1, V2 = 1 V2, V3 = 5 V1, V2, V3= 3	.19
Previous TN surgery	-	7	1	<.05
MPQ	-	44.2 ± 12.8	39.5 ± 18.3	.51

MPQ = McGill Pain Questionnaire (Pain Rating Index)[32]

Table 3

	Facial pain scores			
	46 ºC	***47 ºC***	***48 ºC***	***p-value***
CTN	47 ± 29	62 ± 25	66 ± 25	**<.001**
ATN	46 ± 25	56 ± 28	63 ± 28	**<.001**
Healthy	34 ± 21	38 ± 24	48 ± 25	**<.01**
p-value	**.26**	**.03**	**.11**	

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