Observational Study

Subtle Sensory Abnormalities Detected by Quantitative Sensory Testing in Patients with Trigeminal Neuralgia

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Background: Trigeminal neuralgia (TN) is characterized by paroxysmal pain attacks affecting the somatosensory distributions of the trigeminal nerve. It is thought to be associated with a neurovascular conflict most frequently, but pathomechanisms have not been fully elucidated. In general, no sensory deficit is found in routine clinical examination. There is limited data available, however, showing subtle subclinical sensory deficits upon extensive testing.

Objective: We used quantitative sensory testing (QST) to detect abnormalities in sensory processing in patients with TN by comparing the affected and non-affected nerve branches with their contralateral counterparts and by comparing the results of the patients with those of controls.

Study Design: Observational study.

Setting: University Hospital, Departments of Neurosurgery, Institute for Cognitive and Clinical Neuroscience.

Methods: QST was conducted on 48 patients with idiopathic TN and 27 controls matched for age and gender using the standardized protocol of the German Neuropathic Pain Network. Stimulations were performed bilaterally in the distribution of the trigeminal branches. The patients had no prior invasive treatment, and medications at the time of examination were noted.

Results: In patients with TN deficits in warm and cold sensory detection thresholds in the affected and also the non-affected nerve branches were found. Tactile sensation thresholds were elevated in the involved nerve branches compared to the contralateral side.

Limitations: More data are needed on the correlation of such findings with the length of history of TN and with changes of the morphology of the trigeminal nerve.

Conclusions: QST shows subtle sensory abnormalities in patients with TN despite not being detected in routine clinical examination. Our data may provide a basis for further research on the development of TN and also on improvement after treatment.

Key words: Quantitative sensory testing, trigeminal neuralgia, facial pain, neuropathic pain, microvascular decompression, cranial nerve

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Trigeminal neuralgia (TN) is a facial pain syndrome characterized by paroxysmal, lancinating pain attacks along the somatosensory distribution of one or more divisions of the trigeminal nerve. The pain attacks are predominantly unilateral, last from a fraction of a second to several minutes and are precipitated by innocuous stimuli to the affected side of the face. The diagnosis of idiopathic TN is based on the description of these pain characteristics by the patient. Magnetic resonance imaging (MRI) is usually

performed to rule out symptomatic causes such as tumors, vascular malformations of the cerebellopontine angle, inflammation, or demyelinization of the trigeminal nerve and its pathways.

The pathogenesis of TN, in general, is thought to be related to a neurovascular conflict at the trigeminal nerve root entry-zone in the prepontine cistern. There is mounting evidence, however, that additional neurophysiological mechanisms play a role (1). Clinical neurological examination of the trigeminal nerve usually reveals no somatosensory deficits (1-6).

Quantitative sensory testing (QST) describes a standardized examination of the different types of nerve fibers to detect abnormal responses to non-painful and painful sensory stimulation (7-12). This includes the testing of temperature sensation in thinly myelinated Aδ- and unmyelinated C-fibers as well as testing of touch and vibration eliciting activity in large myelinated Aβ-fibers (13). QST has been applied in patients with diabetic polyneuropathy, postherpetic neuralgia, posttraumatic incomplete nerve injury, radicular pain syndromes, chronic regional pain syndrome, central pain, and orofacial pain (14-32).

QST was investigated in only few previous studies in patients with TN (19-21,26-33). Higher thresholds for temperature and touch sensation of the involved nerve branches compared to the non-affected side in patients with TN were detected, although conclusions were limited due to methodological problems.

To extend previous observations and clarify the role of QST as a potentially valuable component of pain assessment in TN, we compared patients with TN to age- and gender-matched controls. The involved and non-involved nerve branches of the pain side and the unaffected contralateral side were examined according to the comprehensive standardized QST protocol of the German Neuropathic Pain Network (11).

Methods

Patients

The profile of sensory changes was investigated in 48 patients with classical idiopathic TN (22 women and 26 men) with a mean age of 59.2 years (SD = 10.18; range 34 – 76) and 27 controls (16 women, 11 men) with a mean age of 58.9 years (SD = 9.25; range 44 – 76). The groups were matched for age and gender and there were no significant differences between groups in either variable ($t_{(58.46)} = -0.12$, $P = .905$; $Chi^2_{(1)} = 1.25$, $P = 0.264$). Idiopathic TN was diagnosed according to the criteria of the second edition of the International Classification of Headache Disorders (Headache Classification Committee of the International Headache Society, 2004). Patients with TN had been suffering from pain for a mean of 7.1 years (SD = 7.06; range 0.5 – 26). In all cases, high resolution MRI of the cerebellopontine angle and trigeminal nerve was performed to rule out symptomatic causes such as multiple sclerosis, vascular malformations, or a tumor. The identification of a neurovascular conflict was not required as a confirmatory criterion. All patients had been treated pharmacologically and no invasive procedures at the Gasserian ganglion or trigeminal nerve had been performed prior to the first contact in the outpatient clinics of the Departments of Neurosurgery at the Heidelberg and Mannheim campuses of the University of Heidelberg or the Department of Clinical and Cognitive Neuroscience at the Central Institute of Mental Health, Mannheim. In 32 cases TN affected the right and in 16 cases the left trigeminal nerve. Patients with bilateral TN were excluded from the study. In all controls the clinical neurological examination revealed no central nervous deficit and they were all free from centrally acting medication. They had no operations of the nasal or paranasal cavities, and no dental treatment 2 weeks prior to the examination. Table 1 shows the demographic and clinical characteristics of the 2 groups. When the QST was administered, the majority of the patients were on carbamazepine (31 patients, 200 up to 1600 mg/d) or on gabapentin (11 patients, 100 to 1800 mg/d). The study protocol was approved by the ethics committees of both medical schools (Heidelberg and Mannheim Campus) of the University of Heidelberg and complied with the Declaration of Helsinki. All patients and controls were informed in detail about the QST procedure and the study and gave written informed consent.

Quantitative Sensory Testing

The standard examination protocol for QST of the German Research Network on Neuropathic Pain (11) was used. Quantitative testing of sensory nerve functions with tactile-static and tactile-dynamic sensation, pin-prick sensation, and cold/warm and cold/heat pain sensation in the distribution of the 3 trigeminal nerve branches was applied. The participant rested in a relaxed position with slight elevation of the upper part of the body. The room temperature was 18°C and measurements were performed after a habituation time of 30 – 45 minutes. The examination was well tolerated by all patients and no side effects or complications were

Table 1. *Demographic data of 48 patients with trigeminal neuralgia and 27 controls, as well as clinical data and pain-related characteristics.*

	Patients	Range	Controls	Range
N (male/female)	26 / 22		11 / 16	
Age in years, mean (SD)	59.2 (10.2)	34-76	58.9 (9.25)	44-76
Pain duration in years, mean (SD)	7.1 (7.06)	0.5-26		
Affected trigeminal branch	Right (n=32)	Left (n=16)		
V1	7	2		
V2	29	13		
V3	25	8		
One branch affected	7	11		
2 branches affected	24	4		
3 branches affected	1	1		

noted with the modified QST-protocol for the face. A commercially available set of von Frey filaments (Fruhstorfer, Optihair, Marstock Nervtest, Marburg, Germany) with doubling applying forces of 0.25 up to 256 mN and a set of 6 pin-prick needle stimulators (MRC Systems, Heidelberg, Germany) with doubling defined forces of 8 up to 256 mN were used. No neuralgic pain attacks were noted or triggered during the testing procedure. The local testing area was defined as the supraorbital region for the first trigeminal nerve branch, the nasolabial sulcus and medial cheek for the second, and the region around the mental foramen for the third nerve branch.

The QST examination protocol was divided into 6 parts.

A) *Thermal detection and pain thresholds:* The thresholds for cold, warm, thermal sensory limen (TSL) of alternating warm and cold stimuli, cold pain, and heat pain were determined 3 times with the arithmetic mean of these measures calculated as the final threshold (13). A thermal sensory analyzer (TSA-II, Medoc Advanced Medical Systems, Ramat Yishai, Israel, and Minneapolis, Minnesota, USA) and a thermode (Peltier element) with a contact area of 1.6 x 1.6 cm2 were used. The baseline temperature was 32°C, temperature change was 1°C per second and the cut-off limits 0°C and 50°C.

B) *Mechanical detection threshold:* A set of von Frey filaments (Fruhstorfer, Optihair2, Marstock Nervtest, Marburg, Germany) was employed with force intensities ranging from 0.25 to 256 mN. Threshold determinations were performed during 5 series of ascending and descending stimulus intensities using the "method of limits." If the lowest filament (0.25 mN) was recognized on the facial skin, the documented hypothetical subliminal intensity was the half force (0.125 mN). The final threshold was the geometric mean of these 10 series (34,35).

C) *Mechanical pain threshold:* Using a specially designed set of 7 pin-prick stimuli with a tip diameter of 0.2 mm and force intensities ranging from 8 to 256 mN, 5 series with increasing and decreasing stimulus intensities were performed. If pain was indicated even at 8 mN, the documented hypothetical subliminal intensity was the half force (4 mN). The final threshold was the geometric mean of these series.

D) *Mechanical pain sensitivity:* Mechanical pain sensitivity to pin-prick stimuli and dynamic mechanical allodynia using stroking light touch stimulators were determined. In this examination pin-prick stimuli of different intensities (8 – 256 mN) and usually non-painful light touch stimuli (cotton wisp, cotton wool tip, soft brush) were applied in a balanced order to obtain S/R-functions for the perceived pain intensities. The participants were asked to give a pain rating for each stimulus on a 0 – 100 numerical rating scale (NRS; "0" indicating "no pain," and "100" indicating "most intense pain imaginable"). Mechanical pain sensitivity was calculated as the arithmetic mean of the ratings across all pin-prick stimuli. Dynamic mechanical allodynia was found in less than 7% of the patients and in the controls and therefore it was dropped from analysis.

E) *Vibration detection threshold:* The sensitivity to vibratory stimuli was tested by using a Rydel-Seiffer tuning fork (64 Hz, 8/8 scale) over bony parts of both sides of the face (supraorbital region, os zygomaticum or infraorbital region, os maxillaris,

and os mandibularis at the chin). The geometric mean of the vibration detection threshold was calculated out of a series of 3 single tests.

F) *Pressure pain threshold:* This test was performed using a pressure gauge device (FDN200, Wagner Instruments, USA) with a probe area of 1 cm2 (probe diameter of 1.1 cm) that exerts pressure up to 20 kg/cm2 / ~200 N/cm2 / ~2000 kPa. The test area was the center of the masseter muscle, i.e., only the mandibular branches of the trigeminal nerves were included. The pressure pain threshold was determined with 3 series of ascending stimulus intensities. Each series was performed as a slightly increasing ramp of 50 kPa/s (~0.5 kg/cm2 * s). Data are reported in kg/cm². The arithmetic mean of the pressure pain threshold was calculated out of a series of 3 single tests.

All affected nerve branches and their contralateral counterparts in the TN patients as well as all nerve branches in the controls were examined. Non-affected nerve branches and their contralateral counterparts in TN patients were examined with a reduced protocol including cold and warm detection thresholds, tactile detection thresholds, and mechanical pain thresholds. The reduced duration of the examination yielded a better acceptance and compliance of the patients.

The examination time of a QST session with one affected nerve branch was ~1.5 hours. For 2 affected nerve branches and their corresponding control areas 2 – 2.5 hours were needed. The affected nerve branches were defined by the patient's pain location and the presence of trigger points for neuralgic pain attacks. Painful divisions will be termed affected, divisions contralateral to the painful branches unaffected separately for the maxillary and mandibular branches of the trigeminal nerve. There were not enough data for the ophthalmic branches to allow for separate analysis. Non-affected divisions on the same side as the affected divisions will be termed ipsilateral, non-affected divisions on the contralateral side contralateral separately for the ophthalmic and mandibular branches of the trigeminal nerve.

Statistical Analysis

As affected and unaffected sides were not equally distributed between left and right, a yoked control procedure was used that assigned the right or the left side as affected versus unaffected and ipsi- versus contralateral in a random procedure to the controls, stratified by the percentages of right and left affected sides in the patients. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS® 12.0.1, SPSS Inc., Chicago, IL, USA). Repeated measures analyses of variance were used with group as between- and affected versus unaffected or ipsi- versus contralateral as within-subjects factor. Analyses with affected versus unaffected as within-subjects factor were conducted separately for the maxillary and mandibular branches, analyses with ipsi- versus contralateral as within-subjects factor were conducted separately for the ophthalmic and mandibular branches, resulting in 4 comparisons per somatosensory perception or pain threshold. Due to the small number of patients with the first nerve branch affected (n = 9) and with the second nerve branch unaffected (n = 7) statistical analysis was not performed for the supraorbital nerve for the factor affected vs. unaffected or the factor ipsi- vs. contralateral, and only descriptive results are reported here.

All variables were tested for normal distribution using the Kolmogorov-Smirnov test. The data were controlled for extremes (values more than 3 box lengths from the upper or lower edge of the box where the box length corresponds to the interquartile distance). If normality could not be reached with this procedure, log-transformations were applied in a Box-Cox-transformation routine. If normality could not be reached by transformation, the data (tactile detection thresholds) were analyzed using Mann-Whitney-U tests and Wilcoxon matched pair tests where appropriate. Four planned post-hoc t-test comparisons were conducted each in case of significant results in the analyses of variance. The affected and the unaffected side as well as the ipsi- and the contralateral side were compared separately for patients and healthy controls (within group comparisons). In addition, the patients and controls were compared for the affected and unaffected or ipsi- and contralateral sides between-group comparisons.

For the comparison of the patients' QST data profiles with the group mean of the age- and gender-matched controls the data were z-transformed for each single parameter as follows: z-score = (Xsingle patient – Meancontrols)/SDcontrols (12,18). After this transformation z-values above "0" indicate a higher sensitivity to the tested stimuli compared with controls (hyperalgesia, allodynia, hyperpathia), z-scores below "0" indicate a lower sensitivity of the patients (small and large fiber dysfunctions). A z-score of zero indicates a similar

sensitivity of both groups in the tested stimuli. All levels of significance were set at $P = .05$.

Results

The QST results of the affected and unaffected nerve branches of the patient group as compared to the control group are shown in Tables 2 and 3, and in Fig. 1.

Thermal Detection and Pain Thresholds

For the maxillary branch, the interaction affected vs. unaffected x group was significant ($F(1,62) = 9.61$, $P = .003$) for cold detection thresholds. Post-hoc comparisons revealed significantly higher thresholds for patients than for controls for the affected side ($t(59.74) = 2.43$, $P = .02$), and significantly higher thresholds on the affected side than on the unaffected side in patients ($t(36) = -2.63$, $P = .01$). In the mandibular branch,

Table 2. *Descriptive results of QST in the patient with TN and the control group.*

	Ipsilateral						Contralateral					
	Patients			Control			Patients			Control		
	n	*mean*	*SD*	*n*	*mean*	*SD*	*n*	*mean*	*SD*	*n*	*mean*	*SD*
Ophthalmic branch (V1)												
CDT (°C)	9	29.33	2.28	27	30.10	1.26	10	30.21	0.99	27	29.74	1.73
WDT (°C)	9	35.71	1.02	27	37.76	4.34	10	35.88	2.21	27	35.79	2.11
CPT (°C)	8	13.13	9.57				8	19.89	9.64			
HPT (°C)	8	44.01	4.17				8	43.72	4.39			
TSL (°C)	8	6.63	3.93				8	4.97	2.25			
MDT (mN)	9	0.93	1.80	27	0.21	0.03	9	0.82	1.81	27	0.28	0.38
MPT (mN)	9	45.20	79.96	27	95.14	96.37	9	54.78	98.46	27	86.85	88.74
VDT (1/8)	6	6.47	1.00				6	6.78	0.74			
Maxillary branch (V2)												
CDT (°C)	37	29.62	1.74	27	30.46	1.02	37	30.22	1.01	27	30.00	1.55
WDT (°C)	37	34.70	1.37	27	34.04	1.25	37	34.43	1.04	27	34.10	1.17
CPT (°C)	35	13.32	10.47	27	11.95	9.35	35	12.00	10.13	27	11.64	8.54
HPT (°C)	35	42.92	5.38	27	43.05	4.33	35	43.38	5.41	27	43.86	4.08
TSL (°C)	35	5.50	3.54	27	4.24	3.23	35	4.42	2.60	27	4.21	2.65
MDT (mN)	40	0.39	0.92	27	0.18	0.01	40	0.32	0.87	27	0.19	0.01
MPT (mN)	40	33.93	33.50	27	80.75	97.92	40	45.42	58.66	26	78.40	89.10
VDT (1/8)	37	8.30	14.21	26	2.79	4.07	37	6.45	8.88	27	2.23	3.36
Mandibular branch (V3)												
CDT (°C)	22	29.21	2.29	27	30.53	0.85	22	29.54	2.20	27	30.64	0.62
WDT (°C)	22	36.81	2.71	27	35.12	1.93	22	34.99	1.57	27	34.65	1.23
CPT (°C)	22	10.68	10.30	27	10.21	9.98	22	10.66	10.87	27	11.66	9.45
HPT (°C)	22	45.87	3.98	27	44.84	3.72	22	45.86	4.57	27	45.08	3.85
TSL (°C)	25	6.95	4.06	27	4.11	2.21	22	5.15	2.66	27	3.75	2.16
MDT (mN)	26	0.20	0.02	27	0.19	0.02	25	0.18	0.01	27	0.19	0.03
MPT (mN)	23	40.53	60.04	27	96.96	108.39	26	56.42	77.89	27	100.02	108.05
VDT (1/8)	26	9.32	10.45	27	2.25	3.96	23	5.73	5.66	27	2.04	2.91
PPT (kPa)	27	7.48	0.69	27	7.72	0.40	26	7.46	0.64	27	7.80	0.27

(CDT = cold detection threshold, WDT = warm detection threshold, CPT = cold pain threshold, HPT = heat pain threshold, TSL = thermal sensory limen, MDT = mechanical detection threshold, MPT = mechanical pain threshold, VDT = vibration detection threshold, PPT = pressure pain threshold, °C= degrees Celsius; mN= milli-Newton; kPa= Kilo-Pascal; SD = standard deviation)

Table 3. *Z-transformed data for each single parameter, calculated as follows: z-score = ($X_{single\ patient} - Mean_{controls}$) / $SD_{controls}$.*

	Maxillary Branch		Mandibular Branch	
Z-Values	**Affected Side**	**Unaffected Side**	**Affected Side**	**Unaffected Side**
Cold Detection Threshold	-0.824	0.142	-1.734	-1.544
Warm Detection Threshold	0.528	0.282	1.231	0.085
Thermal Sensory Limen	0.390	0.079	1.285	0.648
Cold Pain Threshold	0.147	0.042	0.047	-0.106
Heat Pain Threshold	-0.030	-0.118	0.277	0.203
Mechanical Pain Threshold	-0.478	-0.370	-0.531	-0.405
Mechanical Pain Sensitivity	1.354	1.256	1.785	1.268
Wind Up Ratio	-0.110	-0.345	-0.492	-0.447
Vibration Detection Threshold	-0.620	-0.884	-0.600	-1.259
Pressure Pain Threshold			0.234	-0.117

patients showed significantly higher cold detection thresholds than controls, in general, (significant main effect of the factor group with $F_{(1,47)} = 10.44$, $P = .002$), with significant values for both the affected ($t_{(25.10)} = -2.68$, $P = .01$), and the unaffected side ($t_{(24.30)} = -2.16$, $P = .04$). A significant main effect of the factor ipsi- vs. contralateral was present for the mandibular branch ($F_{(1,39)} = 4.24$, $P = .046$) with higher cold detection thresholds on the ipsilateral – i.e., the unaffected branch on the affected side.

There were no significant effects for warm detection thresholds on the affected vs. unaffected side for the maxillary branch ($F_{(1,62)} = 3.22$, n.s.), but only for the main factor group. For the mandibular branch affected vs. unaffected side ($F_{(1,47)} = 8.59$, $P = .005$) and group ($F_{(1,47)} = 7.81$, $P = .007$) were significant. Post-hoc comparisons revealed higher warm detection thresholds for patients compared to controls on the affected ($t_{(31.94)} = 2.94$, $P = .006$), but not on the unaffected side ($t_{(47)} = 0.30$, n.s.). Warm detection thresholds were higher on the affected than on the unaffected side in patients ($t_{(21)} = 3.05$, $P = .006$), but not in controls ($t_{(26)} = 0.14$, $P = .888$). When ipsi- and contralateral sides were compared, a significant main effect for side evolved for the ophthalmic branch (ipsi versus contralateral: $F_{(1,55)} = 11.31$, $P = .001$). Interestingly, thresholds were higher on the ipsilateral side in both groups (patients: $t_{(29)} = 2.07$, $P = .048$; controls ($t_{(26)} = 2.86$, $P = .008$).

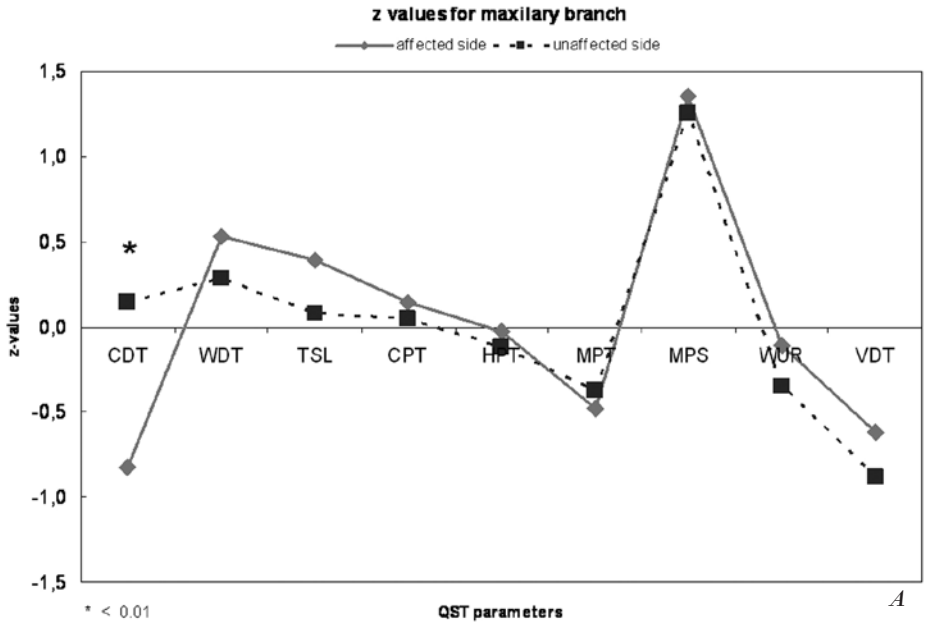
When thermal sensory limen were analyzed, only the mandibular branch showed significant results for side (affected vs. unaffected: $F(1,47) = 5.75$, $P = .021$) and group ($F_{(1,47)} = 10.078$, $P = .003$). Patients showed significantly higher thermal sensory limen than controls on the affected side ($t_{(30.86)} = 2.95$, $P = .006$). For cold and heat pain thresholds no significant effects were found for the maxillary or the mandibular nerve branches (all $F < 1.78$, all $P > .17$).

Mechanical Detection and Pain Thresholds

In the patients, significantly elevated mechanical detection thresholds were found on the affected compared to the unaffected side of the mandibular nerve branches ($Z = -2.74$; $n = 25$; $P = .006$). Mechanical detection thresholds on the ipsi- compared to the contralateral sides of the ophthalmic branches ($Z = -2.32$; $n = 34$; $P = .021$) were also significantly higher in the patients. The comparison between patients and controls were significant for higher thresholds on the contralateral side in controls (Mann-Whitney $U = 318.5$; $n1 = 34$, $n2 = 27$; $P = .024$).

For the mechanical pain thresholds on the affected and unaffected sides, the factor group was significant for both the maxillary ($F_{(1,65)} = 5.71$, $P = .020$) and mandibular ($F_{(1,51)} = 5.80$, $P = .020$) nerve branches. Patients always showed lower mechanical pain thresholds than controls, but planned comparisons were only significant on the affected sides (maxillary / affected side: $t_{(65)} = -2.42$, $P = .02$; maxillary / unaffected side: $t(65) = -2.16$, $P = .04$; mandibular / affected side: $t_{(51)} = -2.80$, $P = .007$; mandibular / unaffected side: $t_{(51)} = -1.81$, $P = .08$).

For the comparison between ipsi- and contralateral unaffected sides, the same pattern was present in both branches, but was only significant for the mandibular branch ($F_{(1,41)} = 11.14$, $P = .002$). As above, the patients had lower mechanical pain thresholds than controls (comparisons between groups: ipsilateral unaffected side: $t_{(41)} = -3.62$, $P = .001$; contralateral unaffected side: $t_{(41)} = -2.98$, $P = .005$).



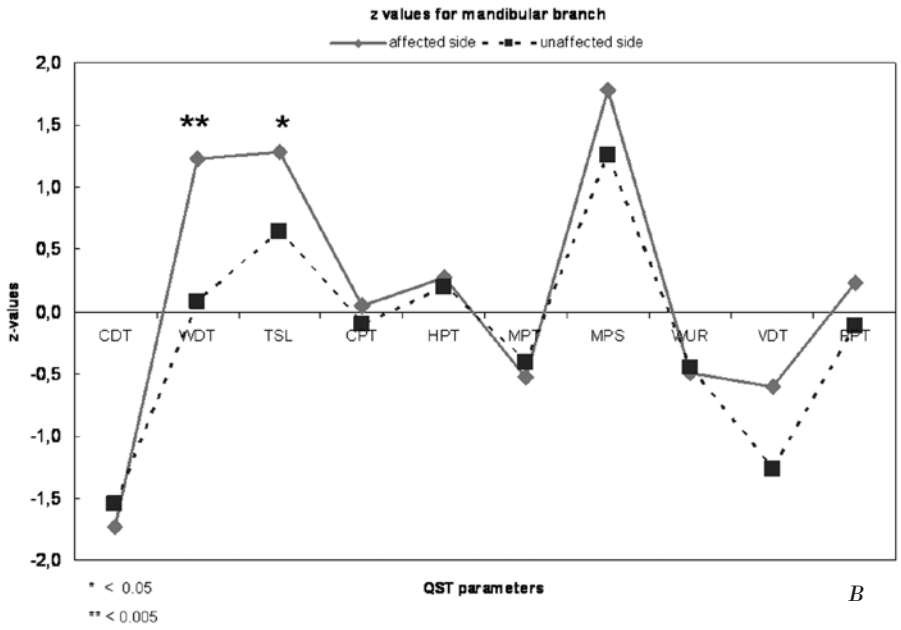


Fig. 1. *A. Quantitative sensory testing z values for the maxillary branch of the trigeminal nerve. z-transformed data for each single parameter e, calculated as follows: z-score = (Xsingle patient – Meancontrols)/SDcontrols. (CDT = cold detection threshold, WDT = warm detection threshold, TSL = thermal sensory limen, CPT = cold pain threshold, HPT = heat pain threshold, MPT = mechanical pain threshold, MPS = mechanical pain sensitivity, MDT = mechanical detection threshold, WUR = wind up ratio, VDT = vibration detection threshold; gray = affected side, dashed line = unaffected side). B. Quantitative sensory testing z values for the mandibular branch of the trigeminal nerve. z-transformed data for each single parameter, calculated as follows: z-score = (Xsingle patient – Meancontrols)/SDcontrols. (CDT = cold detection threshold, WDT = warm detection threshold, TSL = thermal sensory limen, CPT = cold pain threshold, HPT = heat pain threshold, MPT = mechanical pain threshold, MPS = mechanical pain sensitivity, MDT = mechanical detection threshold, WUR = wind up ratio, VDT = vibration detection threshold; gray = affected side, dashed line = unaffected side).*

Mechanical Pain Sensitivity

The same pattern was found for the mean pinprick ratings with a significant main effect of the factor group for both the maxillary ($F_{(1,60)}$ = 4.92, P = .030) and mandibular nerve branches ($F_{(1,47)}$ = 16.17, P < . 001). The mean ratings of the patients were always higher than the mean ratings of the controls, and in most cases the planned comparisons were significant (maxillary / affected side: $t_{(60)}$ = 2.18, P = .03; maxillary / unaffected side: t(60) = 2.35, P =.02; mandibular / affected side: $t_{(47)}$ = 3.83, P < .001; mandibular / unaffected side: $t_{(47)}$ = 4.08, P < .001).

Pressure Pain Thresholds

As the test area was the center of the masseter muscle, only the mandibular branches of the trigeminal nerves were included. Statistical analyses of the pressure pain thresholds revealed no significant difference between the affected and unaffected side neither for the patients (affected vs. unaffected: $F_{(1,52)}$ = 0.76, P = .39; group: $F_{(1,52)}$ = 0.09, P = .77), nor for the controls (ipsi- vs. contralateral: $F_{(1,42)}$ = 1.99, P = .17; group: F(1,42) = 0.02, P = .88).

Vibration Detection Thresholds

The maxillary as well as the mandibular nerve branch showed a significant main effect of the factor group (maxillary: $F_{(1,61)}$ = 7.14, P = .010; mandibular: $F_{(1,51)}$ = 5.15, P = .027). On average, controls were more sensitive to vibration than patients. Interestingly, the planned comparisons showed significant group differences for the unaffected, but not for the affected sides (results of the comparisons between groups: maxillary / affected side: $t_{(61)}$ = -2.14, P = .04 [n.s.]; maxillary / unaffected side: $t_{(61)}$ = -2.83, P = .006; mandibular / affected side: $t_{(51)}$ = -1.58, P = .12 [n.s.]; mandibular / unaffected side: $t_{(51)}$ = -2.75, P = .01). Vibration was not tested in the ipsilateral and contralateral unaffected sides.

Discussion

Our study documents subtle but distinct and specific deficits in sensory discrimination in patients with TN. In the affected nerve branches, the thresholds for cold and warm sensations were significantly higher. Even in non-affected nerve branches of the painful side a deficit of the warm detection threshold was demonstrated. Also, the touch sensation threshold of the mandibular nerve branch of the painful side was significantly increased as compared to the contralateral side. Statistical analyses revealed significant differences for the thresholds for heat pain, mechanical pain, and pin-prick rating of the affected and non-affected and the contralateral side.

Our study extends the knowledge obtained from previous investigations. Lindblom and Verillo (25) were among the first to report elevations of sensation thresholds for warm, cold, and touch in patients with chronic facial neuralgia. Nurmikko (26) detected significantly increased thresholds for touch and warm sensation of the affected in comparison with the healthy side in patients with TN. Also, the non-affected nerve branches of the painful side had significantly increased thresholds for warm and heat pain sensation and 2-point discrimination in comparison with the contralateral side. In addition, Bowsher and colleagues (27) demonstrated increased thresholds for touch and temperature sensation of the affected nerve branches. The limits for heat pain and mechanical pain sensation, however, were found unchanged. Furthermore, in non-affected nerve branches of the pain side an elevation of the tactile sensation threshold was detected. Similar results were found by Sinay and colleagues (30) who compared QST in 9 patients with idiopathic TN and 10 healthy persons. Their study also found changes of the non-affected nerve branches of the painful facial side, and significantly increased cold and heat pain thresholds as well as thermal hypoesthesia on the pain side. Another study reported elevated thresholds in the affected nerve branches for touch, warmth, and cold sensation in 19 patients with idiopathic TN, but no significant changes were detected for heat pain and pin-prick sensation thresholds (35). Interestingly, after microvascular decompression of the trigeminal nerve a significant deficit of pin-prick sensation was found, which had resolved one year later.

The influence of antiepileptic medication on QST is not well known. Recordings of somatosensory evoked potentials revealed an increase in latency and a decrease of the amplitude at high plasma levels of carbamazepine and phenytoin (36,37). However, this effect should have an influence on the nerve function in general and therefore bilateral changes would be expected.

It should be noted, that also changes in somatosensory evoked potentials and nerve conduction velocity of affected nerve branches were described earlier in TN (32,38-40). This could be due to a lesion of the peripheral thick myelinated (Aβ-) nerve fibers. Remarkably, after microvascular decompression or traumatic injury of the trigeminal nerve, regeneration of the nerve fibers

and "normalization" of the evoked potentials has been reported (32,40).

According to our data, TN patients have an incomplete deficit in the function of A-, Aδ-, and C-fibers (touch sensation and thermal sensation thresholds) on the affected painful side. Consistent with the findings of Bowsher and colleagues (27) and Miles and colleagues (33), a change of heat pain, as reported earlier (26,30) could not be reproduced in the present investigation.

Significantly elevated cold and warm sensation thresholds were demonstrated in affected nerve branches, compatible with dysfunction of Aδ- and C-fibers. Even in non-affected nerve branches on the painful side, a deficit of the tactile detection threshold was demonstrated, indicating a deficit of Aβ-fiber function. However, sensation threshold of vibration, also mediated by Aβ-fibers, was not altered. The fact that QST detected changes in clinically non-affected nerve branches of the painful side cannot solely be explained by peripheral nerve damage. The alterations of tactile sensation thresholds without changes of the thermal sensation most likely imply a central nervous mechanism (26,27,30). The results of the present study demonstrate mainly a deficit of thermal sensation transmitted by Aδ-fibers and C-fibers. A change in touch sensation may be secondary to a functional deficit of the myelinated Aβ-fibers. Contrary to this, vibratory sensibility, which is also a function of Aβ-fibers, was unaffected.

The occurrence of significant changes in cold/warm and touch sensation without being paralleled by changes of heat/cold pain, mechanical pain, and vibratory sensation may indicate a disturbance of pain transmission and/or pain sensation in the postganglionic pathway of the trigeminal nerve or changes along the central pathways. Our findings further revealed that different examinations of presumably the same nerve fibers resulted in incongruent findings (e.g., Aβ-fibers with significant differences in touch sensation but not in vibratory sensation). This may serve as support of the hypothesis that both peripheral and central nervous structures are involved in the pathogenesis of TN (26,30,35,41) similar as it has been suggested in other chronic pain syndromes (12,42-44).

We believe that a detailed analysis of QST data helps to further our knowledge of the underlying subtle sensory deficits in patients with idiopathic TN. More data are needed on the correlation of such findings with the length of the history of TN and also with changes in morphology of the trigeminal nerve in patients with a long history of pain attacks, such as deformation or atrophy (45,46). It would also be of interest to perform a comparative analysis with other trigeminal and facial pain syndromes.

Conclusions

In conclusion, standardized QST represents a valuable tool to quantify subtle sensory deficits in TN. These data may provide a basis for further research on the development of TN and also on its improvement after therapy. It could be worthwhile to investigate the time course of postoperative QST changes and to correlate such changes with improvement of pain after surgical treatment aiming to preserve trigeminal sensory function such as microvascular decompression.

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