ORIGINAL ARTICLE

Trigeminal nerve asymmetry in classic trigeminal neuralgia – pretreatment volumetry and clinical evaluation in patients irradiated by Leksell Gamma Knife

Dusan Urgosik [1], Jiri Keller [2,3], Vojtech Svehlik [4], Mohan Pingle [2], Daniel Horinek [4,5,6]

1 Department of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital, Prague, Czech Republic
2 Department of Radiology, Na Homolce Hospital, Prague, Czech Republic
3 Department of Neurology, Charles University in Prague, Third Faculty of Medicine, Prague, Czech Republic
4 International Clinical Research Center, St. Anne's University Hospital, Brno, Czech Republic
5 Department of Neurosurgery, First Faculty of Medicine, Charles University in Prague, Military University Hospital, Prague, Czech Republic
6 Department of Neurosurgery, Masaryk Hospital, J.E. Purkinje University, Usti nad Labem, Czech Republic

Correspondence to: Dusan Urgosik, MD., PhD.
Department of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital, Roentgenova 2, 15030 Prague, Czech Republic.
TEL: +420-603-440-178; FAX: +420-257-272-972; E-MAIL: urgosik@gmail.com

Submitted: 2014-02-19 Accepted: 2014-03-11 Published online: 2014-07-15

Key words: **trigeminal neuralgia; trigeminal nerve; neuropathic pain; magnetic resonance imaging; volumetry; radiosurgery; Leksell Gamma Knife**

Neuroendocrinol Lett 2014; **35**(4):285–289 **PMID:** 25038607 NEL350414A09 © 2014 Neuroendocrinology Letters • **www.nel.edu**

Abstract

OBJECTIVES: The etiology of classic trigeminal neuralgia (CTN) is still under debate and, together with neurovascular compression (NVC), other anatomical abnormalities have been considered, including differences of trigeminal nerve (TN) volume.

DESIGN: We evaluated the volumes of affected and non-affected nerves and the presence and type of NVC in large group of 84 CTN subjects prior to gamma knife treatment (GKS) on MR images. Correlation between affected nerve volume and NVC, treatment outcome and demographic characteristics were explored.

RESULTS: NVC was detected in 71% of affected nerves, 52% of non-affected nerves, and in 31% of subjects bilaterally. Lower trigeminal nerve volume was detected on the affected side ($p<0.001$, affected mean 34.9 mm^3 ± 14.4 SD, non-affected mean 41.9 mm^3 ± 17.7 SD), however, no correlation between affected nerve volume and the presence and type NVC, treatment outcome or demographic data was detected.

CONCLUSION: Our results suggest that NVC may trigger CTN in susceptible subjects but is not a reliable disease marker. Lower trigeminal nerve volume appears to manifest independently of NVC, and may represent nerve asymmetry rather than atrophy. No correlation between volumetry and clinical data was detected including treatment outcome after GKS.

Abbreviations:

CTN	- Classic trigeminal neuralgia	CISS	- constructive interference in steady state
NVC	- neurovascular compression	ANOVA	- analysis of variance
GKS	- gamma knife surgery	TZ	- trigger zone

INTRODUCTION

Classic trigeminal neuralgia (CTN) is one of the most commonly treated facial pain syndromes, although the cause of the disease is still under debate. Various authors have attempted to explain the etiology of trigeminal pain by different anatomical abnormalities including the finding of nerve volume differences. It has been shown the volume of affected nerves in CTN is lower than non-affected nerves (Erbay *et al.* 2006; Kress *et al.* 2006; Ha *et al.* 2012). The lower volume of affected nerves is often considered to reflect atrophy (Erbay *et al.* 2006; Kress *et al.* 2006; Ha *et al.* 2012), the gross manifestation of demyelinization and axonal derangement, following NVC or other insult. However, no effort to correlate trigeminal nerve volume with other imaging or clinical data has been undertaken to date. Based on our previous pilot study (in press) with a smaller number of patients, we evaluated the volumes of affected and non-affected nerves in larger group of CTN subjects refractory to pharmacological treatment that were referred to our institution of gamma knife treatment. We further evaluated subjects for the presence of NVC, classifying the type of contact when present. Our aim was to determine whether trigeminal nerve volume correlates with the presence and type of NVC, as well as clinical parameters such as age, disease duration, pretreatment clinical manifestations and treatment outcome following gamma knife surgery (GKS).

MATERIALS AND METHODS

Subjects

A total of 84 subjects diagnosed with classic trigeminal neuralgia were included in the study (40 male, 44 female; age 45–91 years, mean 69.6±9.6 SD; disease duration 3–268 months, mean 69.8±61 SD months). All subjects suffered from typical, idiopathic trigeminal neuralgia with a spontaneous onset of episodic facial pain. No subjects had undergone any type of neurosurgical procedure (radiofrequency rhizotomy, glycerol rhizotomy, balloon microcompression, microvascular decompression or peripheral neuroectomy) prior to GKS. The study was approved by the Ethics committee of Na Homolce Hospital in Prague, and all subjects provided written, informed consent.

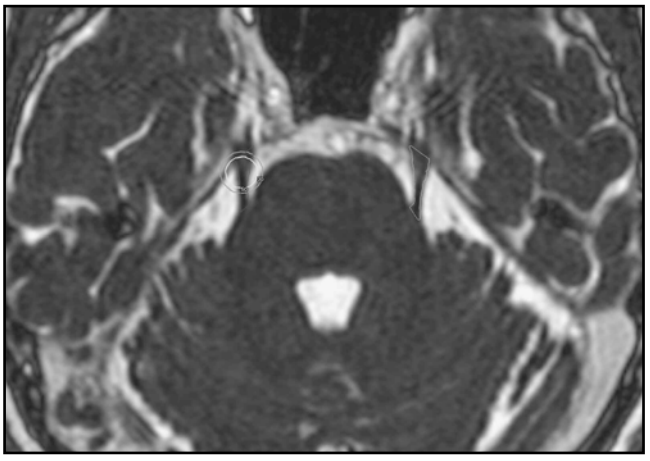

Fig. 1. 3D-CISS image used in volumetric evaluation. ROIs placed on the bilateral trigeminal nerves, circles placed on the side of neuralgia represent planned 50% and 30% isodoses delivered by gamma knife irradiation. CISS, constructive interference in steady state.

Clinical evaluation

All subjects were neurologically examined before the initiation of GKS treatment, 3 and 12 months after irradiation, and annually or biannually thereafter. The mean follow-up was 35.2 months±24.9 SD (range 12–96 months). Three subjects were lost to follow-up. In addition to neurological status, tactile and analgesic sensation (pin-prick test) were evaluated. Subjects classified the degree of pain relief following GKS using a percentile scale, with 0% representing pain free and 100% representing no change. The patients were divided into groups according to their perception of residual pain as follows: group I, excellent (0%); group II, good (1–50%); group III, poor (51–75%); group IV, failed (76–100%). Treatment was considered successful when the subject reached group I or group II and pain relief lasted a minimum of 6 months.

Radiosurgical technique

Radiosurgery was performed using a Leksell Gamma Knife model 4C and Perfexion (Elekta Instruments, Stockholm, Sweden). Planning was performed with the GammaPlan planning system (Elekta Instruments, Stockholm, Sweden). The trigeminal nerve along its course through the pontocerebellar cistern was targeted for irradiation such that a 20% to 30% isodose tangentially touched the surface of adjacent brainstem. A 4 mm collimator and a single shot with a maximal dose of 80 Gy were applied (Urgosik *et al.* 2000, Young *et al.* 2013).

Imaging protocol

All images were acquired after the administration of an IV contrast agent prior to GKS treatment. In addition to standard imaging sequences collected for clinical purposes, 3D constructive interference in steady state (CISS) images were obtained for volumetric evaluation. Thirty-nine subjects (18 male, 21 female; age 50–93 years, mean 70.1±9.8 SD; disease duration 3–268 months, mean 76.0±72.3 SD 3 months) were scanned on a 1.0 T Siemens Expert (Erlangen, Germany) scanner (3D-CISS; slice thickness 1.0 mm, in-plane resolution 0.98×0.98 mm, TE 8.08 ms, TR 16.7 ms, NEX=1), while fourty-five subjects (24 male, 21 female; age 54–86 years, mean 69.3±9.6 SD; disease duration 3–180 months, mean 64.3±49.8 SD months) were scanned at 1.5 T on a Siemens Avanto (Erlangen, Germany) scanner (3D-CISS; slice thickness 0.9 mm, inplane resolution 0.45×0.45 mm, TE 2.47 ms, TR 5.54 ms, NEX=2).

Copyright © 2014 Neuroendocrinology Letters ISSN 0172–780X • www.nel.edu

Postprocessing and ROI placement

Volumetry was evaluated in consistent grayscale using the auto-level mode in Leksell GammaPlan v.10.1 (Elekta Instruments, Stockholm, Sweden), by manually tracing the contours of trigeminal nerves between the brain stem and Meckel's cave (Figure 1). One investigator with 18 years experience in trigeminal nerve imaging performed all measurements, and repeat measurements were performed after a period of six months. NVC evaluation CISS and T1-weighted post-contrast MR images were used to detect and classify NVC based on localization and relation of the vessel to the nerve (Adamczyk *et al.* 2007). The presence or absence of NVC was evaluated, and the localization of NVC was recorded as root-entry zone or non-root-entry zone. The relation of the vessel to the nerve was further classified as u-shaped contact, parallel contact, crossing contact or nerve dislocation (Figure 2).

Statistical analyses

ROI data were processed in R (www.r-project.org). A paired t-test was used to evaluated differences between datasets from both scanners, including affected nerves and pooled data. As no differences were detected, the data were pooled in all further analyses. A paired t-test was additionally used to detect differences in trigeminal nerve volume on affected and non-affected sides, and a two-sample t-test was used to explore volume differences in affected nerves related to hypestesia, pain relief (complete versus other), recurrence, number of branches affected (1 versus 2), NVC type (REZ versus non-REZ), and the presence of a trigger zone. A one-way analysis of variance (ANOVA) test was used to examine potential volumes differences in subgroups of affected nerves classified according to type of NVC. A linear model was applied to investigate correlation between affected nerve volume and disease duration and patient age. Intra-rater variability was assessed using the single score intraclass correlation. The Bonferroni correction for multiple comparisons was applied to maintain an alpha level 0.05. All significant *p*-values reported are corrected.

RESULTS

Clinical results

The distribution of pain in trigeminal nerve branches was as following: 1 branch in 39 subjects (46%), two branches in 43 subjects (51%), and in 3 branches in 2 subjects (2%). Seventy of seventy-nine patients (89%) had a trigger zone (TZ). Initial, successful pain relief (group I and group II) occurred in 90% of patients. Fifty-four percent of patients were pain free (group I). In 10% of patients (group IV) treatment failed. No subjects were classified as group III. Pain relief appeared within the range of 1 day to 12 months (median 2 months). The recurrence of pain was noted in 22% of patients. Recurrence was defined as initial excellent or good response (group I or group II), later reclassified as poor or failed response (group III or group IV).

Adverse effects

Sensory examination was not performed in 8 patients. Facial sensory impairment was observed in 30 of 76 subjects (39%). Hypesthesia was of mild intensity and in many subjects was only revealed by detailed neurological examination. Sensory impairment manifested within 2 to 32 months (median 10 months).

NVC assessment

NVC was detected in 60 of 84 affected trigeminal nerves (71%), including 30 instances of kissing (u-shaped) contact (36%), 11 crossing contact (13%), 10 parallel contact (12%) and 9 instances of dislocation (11%).

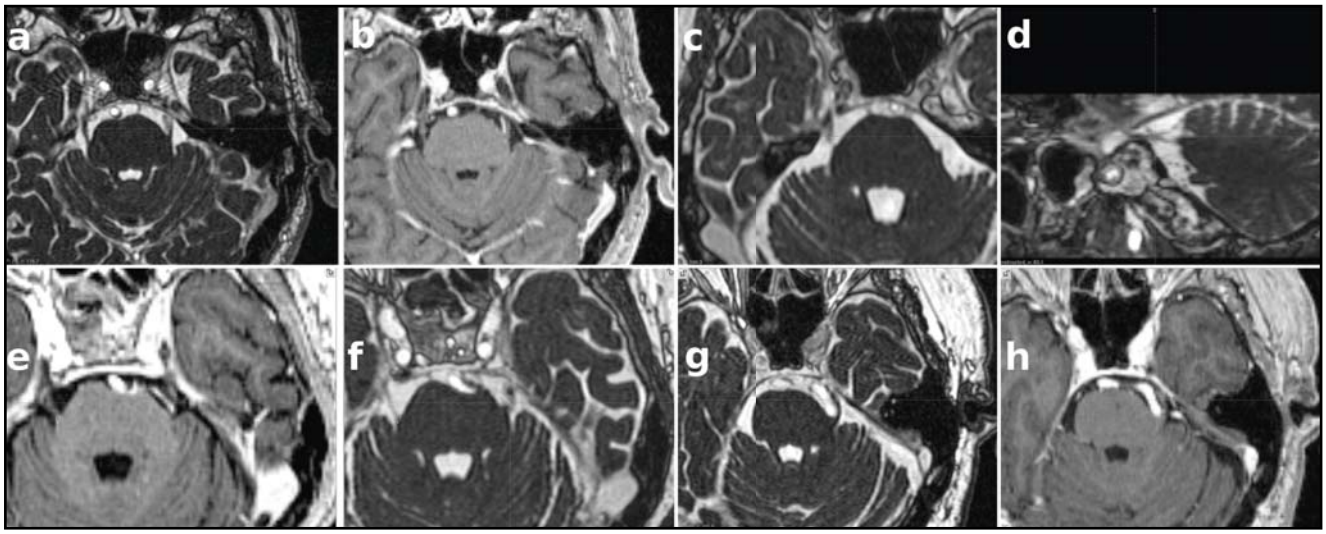

Fig. 2. Types of neurovascular conflict (all on the left side): Parallel contact on CISS (a) and contrast-enhanced T1WI (CE T1, b), u-shaped contact on CISS (c) and CE T1 (d), crossing fibers on CISS (e) and CE T1 (f), nerve dislocation by basilar artery on CISS (g) and CE T1 (h).

NVC within the REZ was observed in 23 (27%) affected nerves. In 44 (52%) subjects, NVC was detected on the non-affected side, including 16 (19%) instances within the REZ. NVC was detected bilaterally in 26 (31%) subjects.

Volumetric results

No differences were detected between datasets acquired at 1T and 1.5T with respect to pooled trigeminal nerve volume (p=0.52), affected trigeminal nerve volume (p=0.27) ,disease duration (p=0.42) and age (p=0.91). The two datasets were therefore pooled in volumetric analyses. Intra-rater agreement between two separate measurements was excellent (ICC=0.97) and the mean of these measurements was used in further tests. We detected lower group-wise trigeminal nerve volume in affected nerves versus non-affected nerves (p<0.001, affected mean 34.9 mm^3±14.4 SD, non-affected mean 41.9 mm^3±17.7 SD; Figure 3). No dependence on disease duration (p=0.27) or patient age (p=0.46) in affected nerves was detected. Additionally, no differences were detected in affected volumes between the various types of NVC ($F(4,79)$=0.49, p=0.74; Figure 4), between REZ and non-REZ contact (p=0.65), number of branches affected (1 versus 2, P=0.08), nor between subjects with and without the presence of a trigger zone (p=0.65). No volumetric differences in affected nerves were observed between subjects that experienced complete pain relief following GKS in comparison to other subjects (p=0.67) nor in those in which pain recurred (p=0.93), and no volumetric differences in affected nerves were observed between subjects with and without hypesthesia (p=0.18).

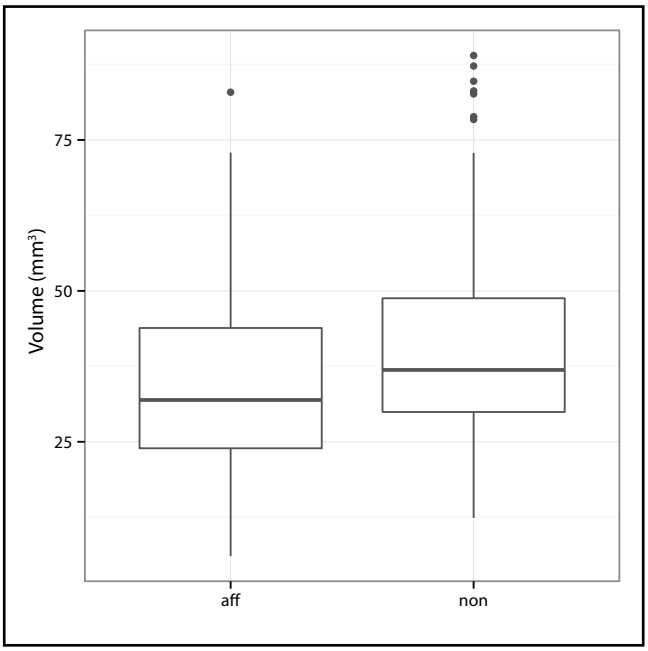

Fig. 3. Volumes of affected trigeminal nerves in CTN. CTN, classic trigeminal neuralgia; aff, affected side; non, non-affected side.

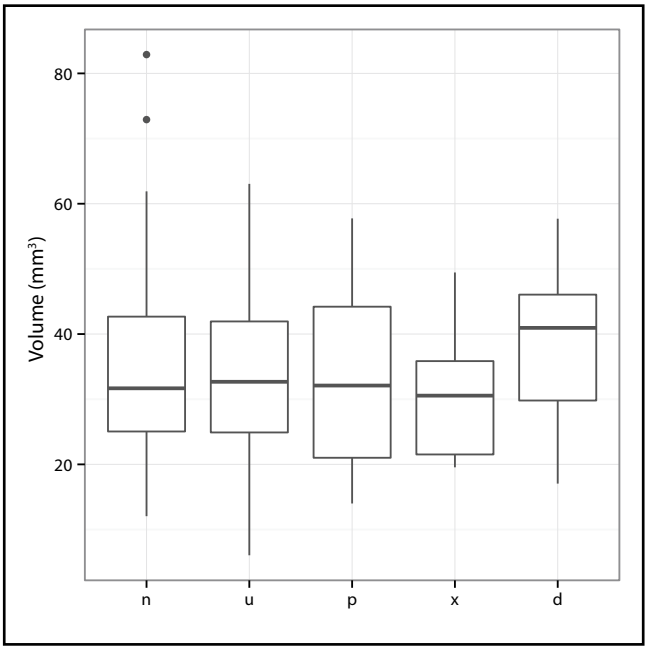

Fig. 4. Volumes of affected trigeminal nerves in CTN by type of NVC. The type of NVC classified as n for none, u for u-shaped contact, p for parallel contact, x for crossing contact and d for dislocation. CTN, classic trigeminal neuralgia; NVC, neurovascular compression.

DISCUSSION

In the present study, we evaluated clinical and MR imaging data in a large group of patients diagnosed with CTN that were referred to our institution for treatment by GKS. Nearly all patients presented with 1 or 2 branches affected in roughly equal proportion, while only 2 patients were affected in all 3 branches, and the majority of patients had a trigger zone. Following GKS, 90% of patients reported excellent or good pain relief (groups I and II), while treatment failed in 10% (group IV). Pain recurred in 22% of patients, and 39% developed hypesthesia.

NVC was detected on MR imaging in 71% of affected nerves, including 27% within the REZ. NVC was also detected in 52% of subjects on the non-affected side and in 31% bilaterally. This in agreement with previous studies (Haines *et al.* 1980; Magnaldi *et al.* 1992; Kress *et al.* 2006; Peker *et al.* 2009), suggesting that NVC may trigger CTN in susceptible subjects but is not a reliable disease marker.

In the evaluation of trigeminal nerve volume on MR images, we detected lower trigeminal nerve volume on the affected side in comparison to the non-affected side (Figure 2). Lower trigeminal nerve volume in CTN has been reported previously and has been posited to represent atrophy due to NVC (Erbay *et al.* 2006; Kress *et al.* 2006; Ha *et al.* 2012). However, previous studies have not explored potential correlation between nerve volume and other covariates such as the presence and type of NVC, disease duration or patient age. Although we detected lower nerve volume on the affected side in agreement with previous reports (Erbay *et al.* 2006;

Copyright © 2014 Neuroendocrinology Letters ISSN 0172–780X • www.nel.edu

Kress *et al.* 2006; Ha *et al.* 2012), we did not observe any correlation with other covariates in affected nerves. No differences in affected nerve volumes were detected in NVC positive and negative subjects, nor were any volume differences detected by number of branches affected, NVC classification (Figure 3) or the presence or absence or REZ contact. Additionally, no correlation was detected between affected trigeminal nerve volume and patient age, disease duration, successful treatment by GKS (pain relief, groups I and II) or the development of hypesthesia.

Histopathological studies in CTN have reported central demyelinization (Love *et al.* 1998; Marinkovic *et al.* 2009) as well as axonal changes (Marinkovic *et al.* 2009) in affected nerves. It is currently thought that CTN arrises in the presence of NVC due to pulsatile compression of demyelinated fibers, resulting in aberrant, ephaptically transmitted impulses (Love & Coakham, 2001), and the successful treatment of CTN by microsurgical decompression (Sindou *et al.* 2007) strongly supports the involvement of NVC in the pathogenesis. However, with regard to trigeminal nerve volume, our findings suggest that lower volume of affected nerves occurs independently of NVC. Lower trigeminal nerve volume is likely present prior to clinical onset and predisposes an individual to the development of CTN, rather than occurring as a consequence of NVC. This hypothesis is supported by the detection of NVC in non-affected nerves in the present study as well as in previous studies (Haines *et al.* 1980; Magnaldi *et al.* 1992; Kress *et al.* 2006; Peker *et al.* 2009) and also by the lack of correlation with disease duration and patient age at onset. We have no explanation for the lack of correlation between anatomical and clinical findings, including the results after GKS.

In conclusion, we observed NCV in 71% of affected nerves and 52% of non-affected nerves in CTN, suggesting that NVC may trigger CTN in susceptible subjects but is not a reliable disease marker. No dependence of affected trigeminal nerve volume on demographic factors or clinical outcome was observed. Additionally, no volume dependence on the presence or type of NVC was detected. Therefore, we recommend the term asymmetry be used to describe lower volume of affected trigeminal nerves in CTN, rather than atrophy.

ACKNOWLEDGMENTS

This work was supported by Grant IGA NT11328-4/2010**;** MH CZ - DRO (Nemocnice Na Homolce - NNH, 00023884) and Research Project Charles University in Prague PRVOUK P34 and P26/LF1/4.

REFERENCES

1 Adamczyk M, Bulski T, Sowiska J, Furmanek A, Bekiesiska-Figatowska M (2007). Trigeminal nerve – artery contact in people without trigeminal neuralgia – MR study. Med Sci Monit **13**(Suppl 1): 38–43.
2 Erbay S, Bhadelia R, O'Callaghan M, Gupta P, Riesenburger R, Krackov W, Polak J (2006). Nerve atrophy in severe trigeminal neuralgia: noninvasive confirmation at MR Imaging – initial experience. Radiology **238**: 689–692.
3 Ha SM, Kim SH, Yoo EH, Han IB, Shin DA, Cho KG, et al (2012). Patients with idiopathic trigeminal neuralgia have a sharper-than-normal trigeminal-pontine angle and trigeminal nerve atrophy. Acta Neurochir (Wien) **154**: 1627–1633.
4 Haines SJ, Jannetta PJ, Zorub DS (1980). Microvascular relations of the trigeminal nerve. An anatomical study with clinical correlation. J Neurosurg **52**: 381–386.
5 Kress B, Schindler M, Rasche D, Hhnel S, Tronnier V, Sartor K (2006). Trigeminal neuralgia: how often are trigeminal nerve-vessel contacts found by MRI in normal volunteers. Rofo **178**: 313–315.
6 Love S, Coakham HB (2001). Trigeminal neuralgia: pathology and pathogenesis. Brain **124**: 2347–2360.
7 Love S, Hilton DA, Coakham HB (1998). Central demyelination of the Vth nerve root in trigeminal neuralgia associated with vascular compression. Brain Pathology **8**: 1–11.
8 Magnaldi S, Cecconi P, Skrap M, Ricci C, Cova MA, Pozzi-Mucelli RS (1992). Magnetic resonance in trigeminal neuralgia. Radiol Med **83**: 700–705.
9 Marinkovic S, Gibo H, Todorovic V, Antic B, Kovacevic D, Milisavljevic M, Cetkovic M (2009). Ultrastructure and immunohistochemistry of the trigeminal peripheral myelinated axons in patients with neuralgia. Clin Neurol Neurosurg **111**: 795–800.
10 Peker S, Diner A, Necmettin Pamir M (2009): Vascular compression of the trigeminal nerve is a frequent finding in asymptomatic individuals: 3-T MR imaging of 200 trigeminal nerves using 3D CISS sequences. Acta Neurochir (Wien) **151**: 1081–1088.
11 R Development Core Team (2008): R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0.
12 Sindou M, Leston J, Decullier E, Chapuis F (2007): Microvascular decompression for primary trigeminal neuralgia: long-term effectiveness and prognostic factors in a series of 362 consecutive patients with clear-cut neurovascular conflicts who underwent pure decompression. J Neurosurg **107**: 1144–1153.
13 Urgosik D, Vymazal J,Vladyka V,Liscak R (2000): Treatment of postherpetic trigeminal neuralgia with the gamma knife. J Neurosurg **93**(Suppl 3): 165–168.
14 Young B, Shivazad A, Kryscio RJ, St Clair W, Bush HM (2013): Long-term outcome of high-dose knife surgery in treatment of trigeminal neuralgia. J Neurosurg **119**: 1166–1175.