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Significance of neurovascular contact in classical trigeminal neuralgia

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Neurovascular contact is considered a frequent cause of classical trigeminal neuralgia and microvascular decompression with transposition of a blood vessel is preferred over other surgical options in medically refractory patients with classical trigeminal neuralgia. However, the prevalence of neurovascular contact has not been investigated in a representative cohort of patients with classical trigeminal neuralgia based in a neurological setting and using high-quality neuroimaging and blinded evaluation. We aimed to investigate whether presence and degree of neurovascular contact are correlated to pain side in classical trigeminal neuralgia. Consecutive classical trigeminal neuralgia patients with unilateral symptoms were referred to 3.0 T magnetic resonance imaging and included in a cross-sectional study. Magnetic resonance imaging scans were evaluated blindly and graded according to presence and degree of neurovascular contact. Severe neurovascular contact was defined as displacement or atrophy of the trigeminal nerve. A total of 135 patients with classical trigeminal neuralgia were included. Average age of disease onset was 53.0 years (95% confidence interval mean 40.5–55.5) and current age was 60.1 years (95% % confidence interval mean 57.5–62.7). Eighty-two (61%, 95% confidence interval 52–69%) patients were female. Neurovascular contact was prevalent both on the symptomatic and asymptomatic side [89% versus 78%, $P = 0.014$, odds ratio = 2.4 (1.2–4.8), $P = 0.017$], while severe neurovascular contact was highly prevalent on the symptomatic compared to the asymptomatic side [53% versus 13%, $P < 0.001$, odds ratio = 11.6 (4.7–28.9), $P < 0.001$]. Severe neurovascular contact was caused by arteries in 98%. We conclude that neurovascular contact causing displacement or atrophy of the trigeminal nerve is highly associated with the symptomatic side in classical trigeminal neuralgia as opposed to neurovascular contact in general. Our findings demonstrate that severe neurovascular contact is involved in the aetiology of classical trigeminal neuralgia and that it is caused by arteries located in the root entry zone.

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Abbreviation: ICHD = International Classification of Headache Disorders

Introduction

Classical trigeminal neuralgia is one of the most painful diseases known to man. In the Second International Classification of Headache Disorders (ICHD-2) (Headache Classification Committee of the International Headache Society, 2004) published by the International Headache Society, classical trigeminal neuralgia is characterized by stereotyped attacks of paroxysmal pain lasting from a split second up to 2 minutes and located in the distribution

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of the trigeminal nerve. The pain is intense, of sharp or stabbing quality and can be provoked by trigger factors or trigger areas. It is widely accepted that a neurovascular contact in the cisternal segment of the trigeminal nerve is the primary cause of classical trigeminal neuralgia (Devor *et al.*, 2002). However, previous studies have cast doubt on this hypothesis because a neurovascular contact was reported to be prevalent on both the symptomatic and the asymptomatic side and therefore suggested that the severity of the neurovascular contact should be taken into account (Masur *et al.*, 1995; Anderson *et al.*, 2006; Miller *et al.*, 2009*a*). The previous studies were limited by small sample size, lack of blinding, MRI was done with low magnetic field strength or study populations were highly selected consisting only of patients from neurosurgical departments.

Understanding the importance of a neurovascular contact is crucial for classical trigeminal neuralgia aetiology. Moreover, it is important for clinical management because transposition of a blood vessel in microvascular decompression is generally considered first choice surgical treatment in medically refractory classical trigeminal neuralgia (Cruccu *et al.*, 2008). The present study is, to the best of our knowledge, the first systematic prospective study based in a neurological setting, with a large representative patient population, using high quality neuroimaging and a neuroradiologist blinded to symptom side.

According to the ignition hypothesis, a neurovascular contact is thought to damage the myelin sheath in the trigeminal nerve which renders the sensory afferents hyperexcitable by means of ectopic pacemaker sites and ephaptic cross-talk and crossed afterdischarge between axons (Rappaport and Devor, 1994; Devor *et al.*, 2002). Anatomical studies confirmed that the root entry zone or transition zone of the trigeminal nerve, where the myelination changes from peripheral Schwann cell myelination to central oligodendrocyte myelination, (Peker *et al.*, 2006) is a site of dysmyelination in patients with classical trigeminal neuralgia with a neurovascular contact (Rappaport *et al.*, 1997).

Our aim was to evaluate the presence, degree, localization and origin (arterial versus venous) of the neurovascular contact in classical trigeminal neuralgia. We hypothesized that severe neurovascular contact was associated with the pain side.

Materials and methods

We included consecutive patients seen at the Danish Headache Centre with the diagnosis of unilateral classical trigeminal neuralgia from April 2012 to November 2013. Exclusion criteria were bilateral classical trigeminal neuralgia, communication barriers, prior microvascular decompression or rhizotomia, symptomatic trigeminal neuralgia and MRI contraindicated due to claustrophobia or implanted magnetic devices.

The Danish Headache Centre is a tertiary medical treatment centre for facial pain and headache that receives patients from all over Denmark. Patients suspected to have classical trigeminal neuralgia are referred from general practitioners, private neurologists and other hospital departments. We have developed a seamless patient path so that all patients, also those referred to the Department of Neurosurgery at The National Hospital of Denmark, are first seen in the Danish Headache Centre for presurgical evaluation.

Diagnosis was based on the diagnostic criteria of the ICHD-2 and patients were diagnosed by neurologists with an expertise in headache and facial pain. The diagnostic criteria state that there should be no sensory abnormalities in classical trigeminal neuralgia and this is unchanged in the recently published beta-version of the 3rd edition of ICHD (Headache Classification Committee of the International Headache Society, 2013). Meanwhile, psychophysical data by Maier *et al.* (2010) and clinical experience demonstrated that some patients do have sensory abnormalities and that in some patients this is detectable at bedside neurological examination. Therefore in case of sensory abnormalities at clinical routine neurological examination for touch with cotton swab and pinprick with a pin in the three branches of the trigeminal nerve, we diagnosed classical trigeminal neuralgia if the other diagnostic criteria where fulfilled and a complete clinical history, neurological and clinical examination and a 3.0 T MRI did not raise any suspicion of another disease. We previously demonstrated that patients with classical trigeminal neuralgia with sensory abnormalities have a higher prevalence of concomitant persistent pain (Maarbjerg *et al.*, 2014*a*), but are otherwise not significantly different from patients without sensory abnormalities in terms of fulfilment of the other diagnostic criteria or regarding classical clinical features of classical trigeminal neuralgia (Maarbjerg *et al.*, 2014*b*), and argued that sensory abnormalities should be allowed if secondary causes of classical trigeminal neuralgia have been ruled out by MRI (Maarbjerg *et al.*, 2014*c*) in the final version of the 3rd edition of ICHD. All clinical data were obtained by experienced neurologists and recorded in semi-structured interview forms.

MRI protocol and definitions

All patients underwent an MRI scan within 2 months after the semi-structured interview was obtained. Imager was a 3.0 T Phillips Achieva imager (Phillips Medical Systems) equipped with a 32-channel head coil with Multi Transmit parallel RF transmission. The MRI protocol included sagittal T_2-weighted turbo-spin-echo sequence covering the whole brain, axial thin-section T_2-weighted GRASE (gradient and spin-echo) sequence encompassing the brainstem and the proximal and posterior fossa, 3D time of flight magnetic resonance angiography (s3DI MC HR) and 3D high spatial resolution heavily T_2-weighted sequence (3D balanced fast field echo, BFFE). Multiplanar reconstructions were performed of the cisternal part of the neurovascular contact strongly parallel to the trigeminal nerve in the axial and sagittal plane and perpendicular to the neurovascular contact in the coronal plane.

The MRI scans were all evaluated by the same experienced neuroradiologist (F.W.), who was blinded to symptom side. A neurovascular contact was defined as contact between a blood vessel and the trigeminal nerve without visible CSF between the two structures. If the neuroradiologist was uncertain whether there was a contact it was considered as 'no neurovascular contact'. It was evaluated for (i) degree of contact; (ii) localization; and (iii) type of blood vessel. Degree of contact was graded on a 3-point scale as simple contact (Fig. 2),

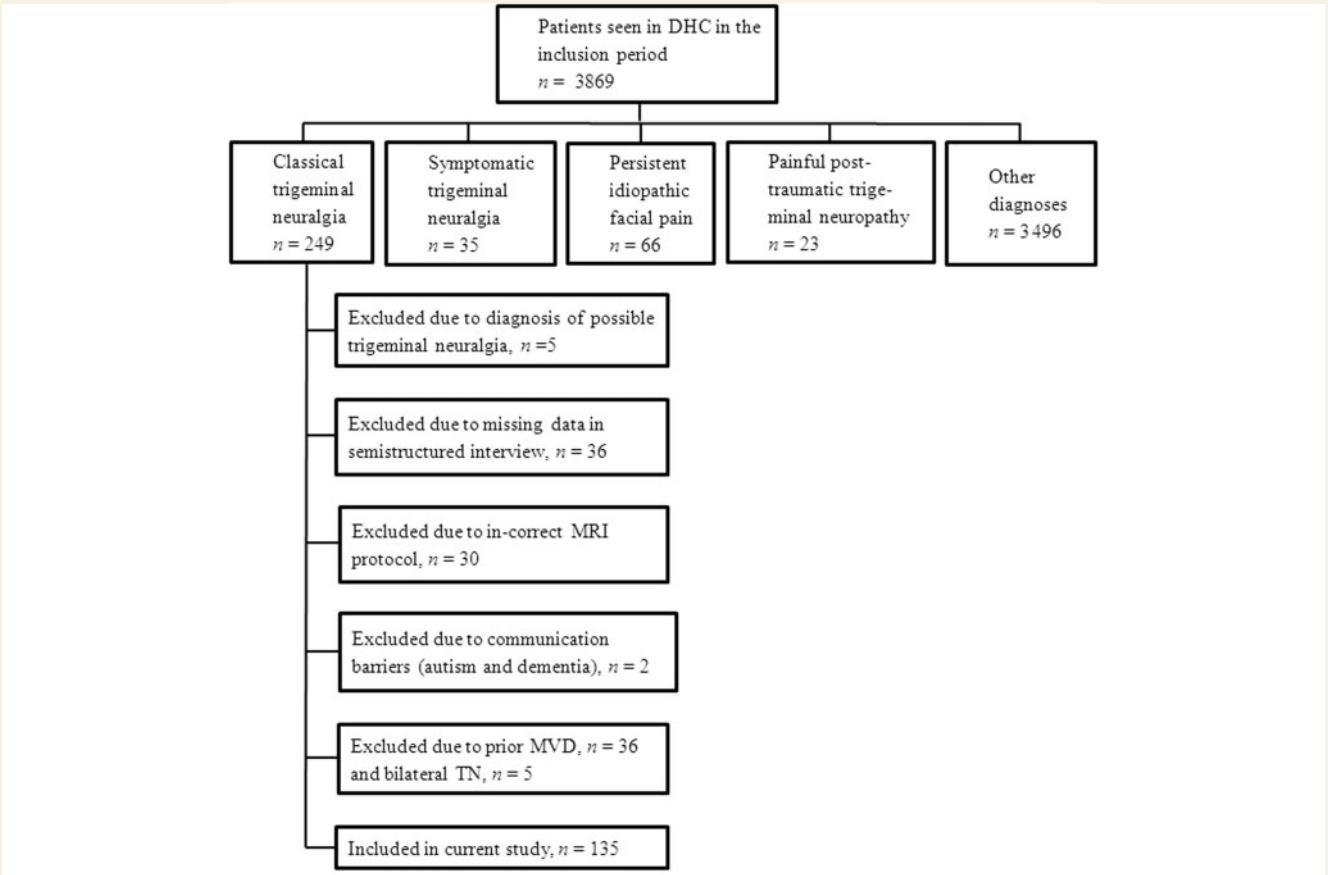

Figure 1 Flowchart of included patients. DHC = Danish Headache Centre; MVD = microvascular decompression; TN = classical trigeminal neuralgia.

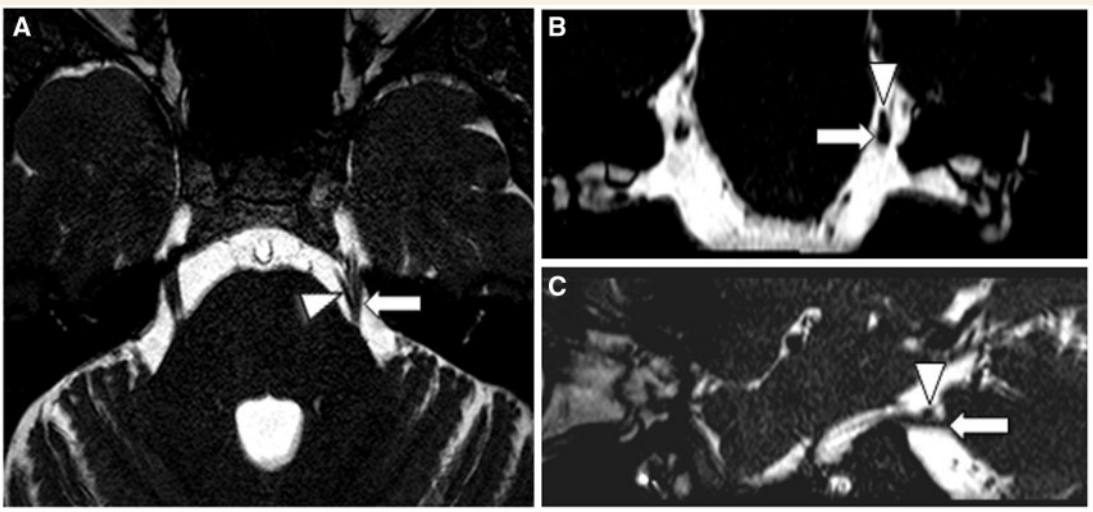

Figure 2 Simple neurovascular contact. MRI balanced fast field echo with axial (**A**), coronal (**B**) and sagittal (**C**) planes of the posterior fossa showing simple neurovascular contact between the left trigeminal nerve (arrows) and the left superior cerebellar artery (arrowheads) in the root entry zone. Patient suffers from left-sided trigeminal neuralgia.

displacement (Fig. 3) or atrophy (Fig. 4). Displacement was defined as displacement or distortion of the trigeminal nerve at the site of a neurovascular contact. Atrophy was defined as reduced volume of the trigeminal nerve at the site of a neurovascular contact. 'Severe neurovascular contact' was defined as a neurovascular contact with displacement or atrophy. Neurovascular contact was classified to be either at the root entry zone or peripheral. The root entry zone, i.e. the

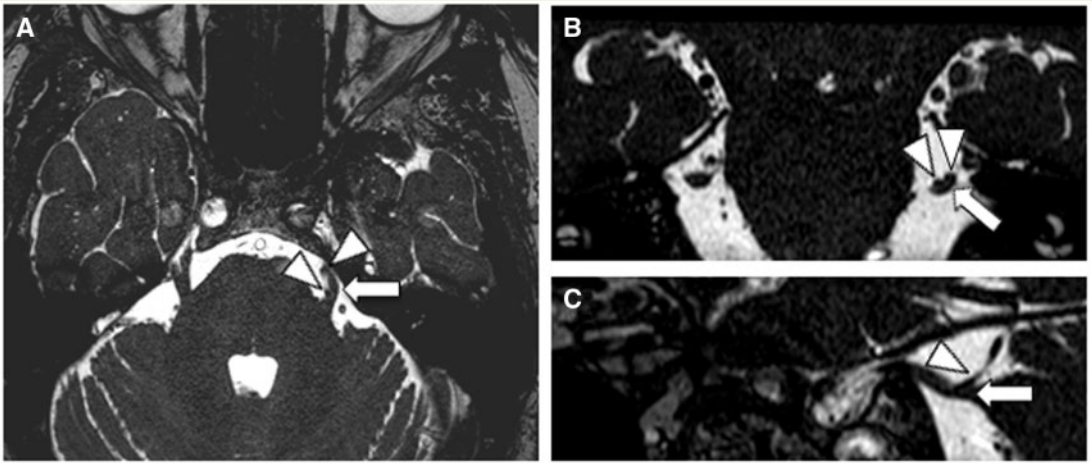

Figure 3 Neurovascular contact with displacement. MRI balanced fast field echo with axial (**A**), coronal (**B**) and sagittal (**C**) planes of the posterior fossa showing displacement of the left trigeminal nerve (arrows) caused by the left superior cerebellar artery (arrowheads) in the root entry zone. Patient suffers from left-sided trigeminal neuralgia.

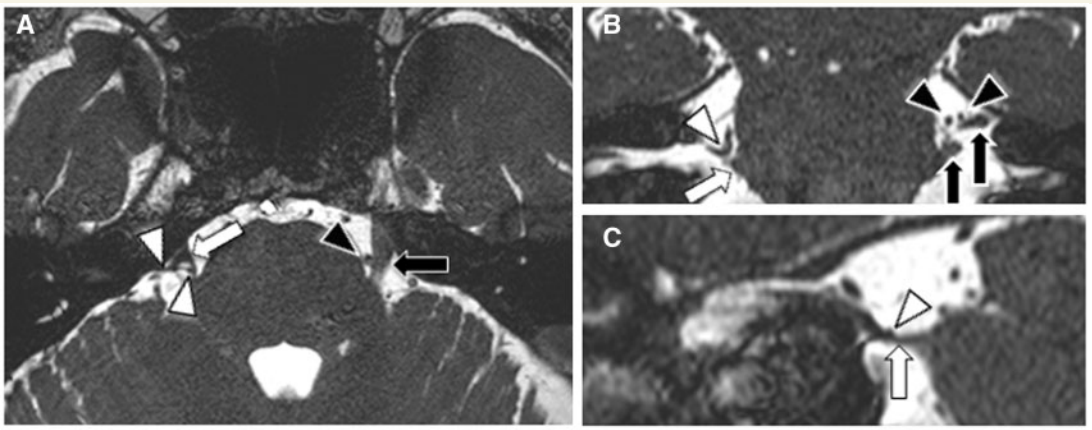

Figure 4 Neurovascular contact with atrophy. MRI balanced fast field echo with axial (**A**), coronal (**B**) and sagittal (**C**) planes of the posterior fossa showing an atrophic right trigeminal nerve (white arrows) caused by a loop of the right superior cerebellar artery (white arrowheads). Left trigeminal nerve has a simple neurovascular contact (black arrows) with the left superior cerebellar artery (black arrowheads). Patient suffers from right-sided trigeminal neuralgia.

zone where peripheral myelination transitions to central myelination, was defined as the area from the site of entry of the trigeminal nerve into the pons to 7 mm peripherally along the nerve (Peker *et al.*, 2006). We chose to use the term 'root entry zone' instead of 'transition zone' for historical reasons. Peripheral neurovascular contact was defined as neurovascular contact >7 mm from the site of entry of the trigeminal nerve into the pons. Neurovascular contact with one or more arteries involved was defined as an arterial contact and likewise a neurovascular contact with one or more venous contacts was defined as venous. When there was both a vein and an artery involved it was defined as a mixed contact. 'Artery involved' defines arterial or mixed neurovascular contacts. If there was more than one neurovascular contact, the one with the highest degree of contact was graded. If there were two neurovascular contacts with equal degree of contact on the same side, we favoured the one in the root entry zone.

Statistical analyses

Continuous data such as age were summarized by descriptive statistics. Categorical variables are presented with frequency distributions (N, %) and exact confidence limits. McNemar's test for paired and the Chi square test for unpaired proportions were used to assess associations of categorical variables. Univariate conditional logistic regression was used to estimate odds ratio (OR) of a neurovascular contact in predicting pain side. If >5% of the clinical data from the semi-structured interview form were missing, the patient was excluded from the analyses. We calculated the sensitivity and specificity of each of the characteristics of the neurovascular contact comparing the symptomatic (diseased) and asymptomatic side (healthy). Positive likelihood ratio (LR+) was calculated as [sensitivity/(1 − specificity)] and the negative likelihood ratio (LR−) was calculated as [1 − sensitivity)/specificity)].

Table 1 Demographics

	n (%)	95% CI mean
Age at pain onset, years	53.0	50.6–55.5
Current age, years	60.1	57.5–62.7
Female	82 (61)	52–69%
Right-sided[a]	72 (53)	45–62%

Values represent numbers of patients (%) unless otherwise indicated, $n = 135$.
[a]Bilateral cases were excluded.

P-values are reported as two-tailed with a level of significance of 5%. Analyses were carried out using SAS 9.3 (SAS Institute Inc).

Results

A total of 3869 patients were seen at the Danish Headache Centre in the inclusion period. Of these, 249 patients had classical trigeminal neuralgia. Thirty-six patients were excluded due to missing data in the semi-structured interview forms and two patients were excluded due to communication problems. Five patients were excluded due to a diagnosis of 'possible classical trigeminal neuralgia', which could not be clarified at the end of the inclusion period. Thirty-six patients were excluded due to previous microvascular decompression and five patients were excluded due to bilateral symptoms. The remaining 135 patients constitute the study population (Fig. 1). Table 1 outlines the demographics of the included patients. In three cases the evaluation of the neurovascular contact was uncertain on the symptomatic side and in five cases on the asymptomatic side. These cases were considered as no neurovascular contact.

Neurovascular contacts on the symptomatic and asymptomatic side

There was a high prevalence of neurovascular contacts on both sides but neurovascular contact was more prevalent on the symptomatic (89%) compared to the asymptomatic side (78%) ($P = 0.014$) (Table 2) and presence of neurovascular contact was significantly associated with the pain side (OR = 2.4 [95% confidence interval (CI) 1.2–4.8, $P = 0.017$)]. Considering presence of neurovascular contact on the symptomatic side as a diagnostic test for classical trigeminal neuralgia, sensitivity was 89% while specificity was 22%. Seventy per cent of patients had bilateral neurovascular contact. Prevalence of neurovascular contact in the root entry zone was similar on the symptomatic and asymptomatic side (81% versus 70%, $P = 0.100$), but neurovascular contact involving an artery was more prevalent on the symptomatic side (74% versus 56%, $P = 0.001$).

Severe neurovascular contact

Severe neurovascular contacts were considerably more prevalent on the symptomatic compared to the asymptomatic side [53% versus 13%, $P < 0.001$, OR = 11.6 (95% CI 4.7–28.9), $P < 0.001$] (Table 2). Sensitivity and specificity of a severe neurovascular contact were 53% and 87%, respectively. Nearly all severe neurovascular contacts on the symptomatic side involved one or more arteries as opposed to the simple neurovascular contacts on the symptomatic side. Just over half of these involved arteries (99% versus 58%, $P < 0.001$). Patients with severe neurovascular contact on the symptomatic side more frequently had neurovascular contact bilaterally compared to those without a severe neurovascular contact on the symptomatic side (80% versus 58%, $P = 0.005$).

Sensory abnormalities

Comparing patients with ($n = 47$) and without ($n = 86$) (missing data in two patients) sensory abnormalities at neurological examination as separate groups, there was no difference in the prevalence of neurovascular contact on the symptomatic side in patients with and without sensory abnormalities (96% versus 86%, $P = 0.137$). There were no differences between the two groups when comparing the prevalence of neurovascular contact on the asymptomatic side (77% versus 78%, $P = 1.000$), the prevalence of a severe neurovascular contact on the symptomatic side (60% versus 49%, $P = 0.278$) or involvement of an artery on the symptomatic side (81% versus 71%, $P = 0.210$).

Discussion

This is the first prospective, consecutive blinded 3.0 MRI study based in a neurological setting demonstrating that in a large cohort of patients with classical trigeminal neuralgia, the mere presence of any type of neurovascular contact was not specific for classical trigeminal neuralgia to a clinically useful degree as neurovascular contacts were highly prevalent on both the symptomatic and the asymptomatic side. A neurovascular contact is thus a common neuroanatomical variant at least in this patient population. In contrast, severe neurovascular contact was much more prevalent on the symptomatic side than on the asymptomatic side. Our findings have implications both for the understanding of classical trigeminal neuralgia aetiology, for evaluation of neuroimaging and probably also for clinical decision-making.

Previous studies reported highly varying prevalence of neurovascular contact on the symptomatic (56–95%) and the asymptomatic side (10–71%) (Masur *et al.*, 1995; Patel *et al.*, 2003; Kuncz *et al.*, 2005; Anderson *et al.*, 2006; Antonini *et al.*, 2014). The high variability was probably

Table 2 Prevalence and characteristics of neurovascular contacts

Characteristics of neurovascular contact	Symptomatic side		Asymptomatic side		*P*-value	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
	n (%)	95% CI mean	*n* (%)	95% CI mean					
No contact	15 (11)	6–18%	30 (22)	16–30%	**0.014**	11	78	0.5	1.1
Any type	120 (89)	82–94%	105 (78)	70–84%	**0.014**	89	22	1.1	0.5
Root entry zone[a]	109 (81)	73–87%	95 (70)	62–78%	0.100	81	30	1.2	0.7
Peripheral[b]	11 (8)	4–14%	10 (7)	4–13%	0.808	8	93	1.1	1.0
Simple	49 (36)	28–45%	87 (64)	56–72%	**<0.001**	36	36	0.6	1.8
Severe[c]	71 (53)	44–61%	18 (13)	8–20%	**<0.001**	53	87	3.9	0.6
Displacement	55 (41)	32–50	17 (13)	8–19%	**<0.001**	41	87	3.2	0.7
Atrophy	16 (12)	7–19%	1 (1)	0–4%	**<0.001**	12	99	16	0.9
Arterial[d]	76 (56)	48–65%	52 (38)	48–65%	**<0.001**	56	62	1.5	0.7
Mixed[e]	24 (18)	12–25%	24 (18)	12–25%	1.000	18	82	1.0	1.0
Artery involved[f]	100 (74)	66–81%	76 (56)	48–65%	**0.001**	74	44	1.3	0.6
Venous[g]	20 (15)	9–22%	29 (21)	15–29%	0.150	15	79	0.7	1.1

n = 135 patients with classical trigeminal neuralgia with 135 symptomatic sides and 135 asymptomatic sides. Test for significant difference = McNemar's test.
[a]Root entry zone defined as from the site of entry of the trigeminal nerve into the pons to maximum 7 mm peripherally along the nerve.
[b]Defined as >7 mm from the site of entry of the trigeminal nerve into the pons.
[c]Defined as displacement and/or atrophy.
[d]One or more arterial contacts.
[e]At least one artery and one venous contact.
[f]Either one or more arterial contacts or mixed contact.
[g]One or more venous contacts.

influenced by the quality of imager (Yamakami and Kobayashi, 2000; Kuncz *et al.*, 2005; Cruccu *et al.*, 2008), the experience of the neuroradiologist and by differences in study populations. One study also analysed asymptomatic nerves and nerves of healthy subjects mixed together (Antonini *et al.*, 2014). The guidelines from the American Academy of Neurology and the European Federation of Neurological Societies for classical trigeminal neuralgia management conclude that because of the inconsistency in the prevalence estimates there 'is insufficient evidence to support or refute the usefulness of MRI to identify a neurovascular contact' in classical trigeminal neuralgia (Cruccu *et al.*, 2008). There was also a variable prevalence of neurovascular contact in neuroimaging studies of healthy subjects (7–88%) (Hutchins *et al.*, 1990; Meaney *et al.*, 1994; Majoie *et al.*, 1997; Ueda *et al.*, 1999; Miller *et al.*, 2009*a*; Peker *et al.*, 2009) and in anatomical studies of cadavers without a history of classical trigeminal neuralgia (14–52%) (Hardy and Rhoton, 1978; Haines *et al.*, 1980; Klun and Prestor, 1980; Hamlyn, 1997; Ramesh and Premkumar, 2009). The largest study to date ($n = 100$) of normal material was performed by Peker *et al.* (2009) in a 3.0 T MRI study. Out of 200 trigeminal nerves, 87.5% had a neurovascular contact. The authors did not grade the neurovascular contact. Our demonstration of the importance of a severe neurovascular contact confirms results from previous smaller studies where displacement or atrophy at the site of a neurovascular contact was consistently rare in healthy subjects (0–1%) (Meaney *et al.*, 1994; Majoie *et al.*, 1997; Ueda *et al.*, 1999) and in cadavers (0–11%) (Haines *et al.*, 1980; Klun and Prestor, 1980; Hamlyn, 1997; Ramesh and Premkumar, 2009).

Importance of the neurovascular contact for the aetiology of trigeminal neuralgia

We demonstrate that a severe neurovascular contact is highly associated with the pain side in classical trigeminal neuralgia and is nearly always caused by an artery. While the final proof that a severe neurovascular contact caused classical trigeminal neuralgia in the individual patient would be freedom of pain after microvascular decompression, we conclude that, based on the strong association between a severe neurovascular contact and the symptomatic side, a severe neurovascular contact is a major aetiological factor in classical trigeminal neuralgia.

Only half of the patients had, however, a severe neurovascular contact on the symptomatic side and there was a high prevalence of neurovascular contact in general on both symptomatic and asymptomatic sides, as well as a high prevalence of bilateral neurovascular contacts. This suggests that in patients who have a non-severe neurovascular contact on the symptomatic side it is likely to be a normal anatomical variant which is not, or only to a small extent, a precipitating or perpetuating factor in the aetiology of classical trigeminal neuralgia. Other factors have to be present for the disease to evolve. Predisposing systemic factors such as hormonal levels and genetic disposition could be involved. Other aetiological factors must be

localized as bilateral pain is rare (Rasmussen, 1991; Maarbjerg *et al.*, 2014*b*).

Clinical implications in diagnosis and management of trigeminal neuralgia

The likelihood ratios listed in Table 2 indicate that presence, localization and type of blood vessel of the neurovascular contact perform very poorly as diagnostic tests for classical trigeminal neuralgia. Thus, while MRI is essential in ruling out symptomatic trigeminal neuralgia, it cannot be used to diagnose classical trigeminal neuralgia. Only an atrophic neurovascular contact had a favourable positive likelihood ratio implying that in case of an atrophic neurovascular contact, the likelihood of classical trigeminal neuralgia on that side is very high.

This and previous studies indicate that some neurovascular contacts on the symptomatic side are not involved or at most are only a contributing factor to the aetiology of classical trigeminal neuralgia. In such patients microvascular decompression might not be effective. Numerous studies reported a good to excellent outcome in the majority of patients with classical trigeminal neuralgia after microvascular decompression (74–92%) (Kuncz *et al.*, 2005; Miller *et al.*, 2009*b*; Degn and Brennum, 2012) but most studies have major methodological shortcomings (Zakrzewska and Lopez, 2003; Akram *et al.*, 2013) and the procedure can potentially cause severe disability and in rare cases, death (Barker *et al.*, 1996). According to our results it is most likely that the chance of a positive result of microvascular decompression is dependent on the grade of neurovascular contact. This should be tested in prospective controlled neurosurgical studies.

State-of-the-art neuroimaging in trigeminal neuralgia

We and others have shown that the majority of all neurovascular contacts are found in the root entry zone and involve an artery regardless of whether they are located on the symptomatic or the asymptomatic side. The present study, as well as previous studies using 3.0 T MRI (Miller *et al.*, 2009), as opposed to those using 1.0–1.5 T MRI (Masur *et al.*, 1995; Majoie *et al.*, 1997; Kuncz *et al.*, 2005), have demonstrated a high prevalence of neurovascular contacts. Our findings also demonstrate the great importance of grading the neurovascular contact. Thus, we suggest that neuroimaging in classical trigeminal neuralgia, in clinical practice, should be performed with 3.0 T MRI if possible. Moreover, we suggest concentrating on the presence and degree of neurovascular contact. Whether the neurovascular contact involves arteries versus veins or is located in the root entry zone versus peripherally is without importance in clinical practice. A proposed standardized scheme for evaluation of neurovascular contact in clinical practice is presented in Fig. 5.

	Side	
Presence and grade	Right	Left
No contact*		
Simple contact**		
Severe contact***		
Comments		

Preferably, the radiologist should be blinded to symptom side and evaluation bilaterally should be based on MRI axial, sagittal and coronal planes. If this is not feasible in the daily routine, evaluation of the symptomatic side should be based on axial, sagittal and coronal planes. The asymptomatic side is useful for comparison and the axial and coronal planes on the asymptomatic side are sufficient for clinical purposes.

In case of more than one neurovascular contact, the one with the highest degree of severity should be graded. Other neurovascular contacts should be described in 'Comments'.

*If evaluator is uncertain it should be rated as 'No'.

**Defined as contact between a blood vessel and the trigeminal nerve without visible cerebrospinal fluid between the two structures. No displacement, distortion or atrophy of the nerve.

***Defined as displacement, distortion and/or atrophy with reduced volume of the trigeminal nerve at the site of a neurovascular contact.

Figure 5 Proposed standardized scheme in classical trigeminal neuralgia for evaluation of presence and degree of neurovascular contact in the prepontine segment of the trigeminal nerve.

The definition of the root entry zone varies (3–7 mm) (Sindou *et al.*, 2002; Leal *et al.*, 2009; Miller *et al.*, 2009*a*; Antonini *et al.*, 2014), which might represent a problem when comparing results across studies. For research purposes, the root entry zone might better be defined by a proportion of the nerve relative to the total length of the nerve (Peker *et al.*, 2006) adjusted for medial or lateral localization. Studies showed that the extent of central myelination is shorter medially compared to laterally along the trigeminal nerve (McLaughlin *et al.*, 1999; Peker *et al.*, 2006), and that the length of the root entry zone (0.1–6.75 mm), as well as the total length of the cisternal segment of the nerve (8–15 mm), varies (Peker *et al.*, 2006).

Strengths and limitations

The present study was prospective, included a large representative population of patients with classical trigeminal neuralgia and blinded MRI evaluation. High quality MRI was performed according to a protocol designed for the trigeminal nerve.

There are some limitations of the study; we used only a single MRI evaluator, no healthy controls and could not correlate MRI findings to findings during or outcome after microvascular decompression. Detailed MRI evaluations of a large volume of patients with classical trigeminal neuralgia recruited from a neurological setting were prioritized in the design of the study to obtain a sample representative of the full disease spectrum. Such sample ensures that the findings are not biased toward a high prevalence of neurovascular contact on the symptomatic side, as generally only patients with neurovascular contact undergo microvascular decompression. We considered the asymptomatic side in patients with classical trigeminal neuralgia sensible to use as control in a case-control design as development of bilateral classical trigeminal neuralgia is extremely rare ((Rasmussen, 1991; Maarbjerg *et al.*, 2014*a*) and as some previous studies in healthy controls and +cadavers have demonstrated a high prevalence of neurovascular contact (Hardy and Rhoton, 1978; Miller *et al.*, 2009; Peker *et al.*, 2009; Ramesh and Premkumar, 2009). The proposed standardized scheme (Fig. 5) for evaluation of neurovascular contact should be tested in a prospective blinded study using two or more neuroradiologists.

Furthermore, the MRI evaluator was not blinded to diagnosis which could induce an expectation of only one neurovascular contact. Rather, we report a high number of bilateral neurovascular contacts and significant differences with respect to severity between the symptomatic and asymptomatic sides. Our finding of a relatively high prevalence of neurovascular contact regardless of side is likely due to the high imaging quality.

The sample size was determined by the number of patients in the inclusion period rather than based on sample size calculation. An explorative design was chosen because of the low number of previous studies based in a neurological setting and the highly variable prevalence estimates in previous studies.

Future perspectives

Prospective studies using independent assessors of how outcome of microvascular decompression is associated with the neuroanatomical abnormalities are warranted. The current patient cohort will be followed prospectively to evaluate treatment outcome after medical and surgical treatment. Diffusion tensor imaging could prove to be an useful non-invasive way of assessing damage of the nerve at the site of a neurovascular contact to estimate the importance a neurovascular contact preoperatively (Leal *et al.*, 2011; Desouza *et al.*, 2014).

As only half of the patients in the current study had severe neurovascular contact on the symptomatic side, future studies exploring other possible aetiological factors, such as hormonal levels and genetic disposition in classical trigeminal neuralgia, are crucial.

Conclusion

Grading the neurovascular contact in classical trigeminal neuralgia is scientifically and probably also clinically important. Our findings demonstrate that neurovascular contact is highly prevalent on both the symptomatic and asymptomatic sides. We demonstrate that severe neurovascular contact is involved in the aetiology of classical trigeminal neuralgia and that it is caused by arteries located in the root entry zone. Findings also indicate that in some patients with classical trigeminal neuralgia a neurovascular contact is not involved in the aetiology of the disease or may only be a contributing factor in combination with other unknown factors. The degree of neurovascular contact could thus be important when selecting patients for surgery.

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