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Predictive value of MRI for identifying symptomatic neurovascular compressions in classical trigeminal neuralgia: a PRISMA-compliant meta-analysis

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Abstract

Background Patients with trigeminal neuralgia frequently undergo magnetic resonance imaging (MRI) prior to surgery. In patients without the signs and symptoms of face discomfort, MRI has shown the presence of neurovascular contact (NVC) in humans. Therefore, its capacity to accurately exclude NVC of the trigeminal nerve is not properly understood. A meta-analysis of the literature satisfied the criteria to further explore the value of MRI for the diagnosis of classical trigeminal neuralgia (CTN).

Study design The association between the symptomatic and asymptomatic trigeminal nerves, NVC, root entry zone (REZ), non-REZ, and anatomical variation was measured by a comprehensive review and meta-analysis of 13 observational studies using MRI for CTN neurovascular compression diagnosis.

Objectives This study aimed to evaluate the effectiveness of MRI in detecting the neurovascular compression that causes symptoms in individuals with classic trigeminal neuralgia.

Setting This study was conducted at the Department of Neurosurgery, Yantai Yuhuangding Hospital, Qingdao University.

Methods Digital searches of PubMed, Embase, and the Cochrane Library were performed to identify studies published until December 31, 2023. The following were evaluated: (1) MRI evidence of NVC in symptomatic and asymptomatic trigeminal nerves; (2) MRI indication of NVC at the REZ in symptomatic and asymptomatic trigeminal nerves; (3) MRI substantiation of non-REZ neurovascular contact in patients with CTN; and (4) asymptomatic and symptomatic anatomical changes at the NVC site of the trigeminal nerves. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the fixed effects models.

Results We identified 13 observational studies (1 prospective and 12 retrospective studies) with data collected from 1770 nerves (728 symptomatic and 1042 asymptomatic) were meta-analyzed. First, MRI of 649/728 (88.2%) symptomatic versus 378/1042 (36.3%) asymptomatic trigeminal nerves revealed marked differences in NVC in the REZ ($OR = 16.3$; CI 95%=12.2–21.8; $p < 0.00001$). Second, pooled data showed that REZ NVC was detected in 206/262

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(78.6%) symptomatic and in 129/340 (37.9%) asymptomatic nerves (*OR* = 5.0; *CI* 95% = 3.4–7.3; $p < 0.00001$); Third, no significant differences were detected between 44/267 (16.5%) symptomatic and 23/189 (12.1%) asymptomatic nerves on MRI examination of NVC in the NON-REZ (*OR* = 0.9; *CI* 95% 0.5–1.6) ($p = 0.77$); Finally, MRI revealed marked differences in 302/567 (53.2%) symptomatic and 73/919 (7.9%) asymptomatic anatomic changes (atrophy, dislocation, distorsion, flattening or indentation) at the NVC site of the trigeminal segments (*OR* = 11.9; *CI* 95% = 8.8–16.2; $p < 0.00001$).

Limitations Despite the systematic evaluation of 13 observational studies, large-scale randomized controlled trials should be conducted, focusing on the specificity of MRI for the diagnosis of trigeminal neuralgia and evaluating the specificity of the imaging findings and the impact of the patient's postoperative treatment.

Conclusions A previous meta-analysis showed that patients with CTN were more likely to have NVC-specific anatomical changes. MRI of patients with CTN can detect anatomical changes in the REZ NVC with higher sensitivity.

Keywords Trigeminal neuralgia, Neurovascular contact, Magnetic resonance imaging, Root entry zone, Classical trigeminal neuralgia, Microvascular decompression, Odds ratio, Meta-analysis

Background

Trigeminal neuralgia is a recurrent neuropathic pain including the trigeminal system and is characterized by spontaneous and provoked paroxysms of electric shock-like or stabbing pain in the facial region. The symptoms of trigeminal neuralgia are identical across all recognized causes, including classical, secondary, and idiopathic trigeminal neuralgia [1]. The most prevalent is the classical type.

In the 1920s, Dandy proposed that the vascular compression principle may have accounted for the pathogenesis of classical trigeminal neuralgia (CTN) [2]. However, interpretations solely based on the vascular compression of anatomical structures of the trigeminal nerve may not be applicable to the pathogenesis of this disease. Nevertheless, several studies have evaluated the potential of intracranial microvascular surgery for treating trigeminal neuralgia. Currently, regardless of the lack of high-level evidence-based data, microvascular decompression (MVD) is well known as the sole etiological surgical remedy for refractory CTN [3–6].

In patients with trigeminal neuralgia, neuroimaging, particularly magnetic resonance imaging (MRI), is currently the most commonly used preoperative imaging modality. MRI is used not only to identify the potential presence of secondary causes of trigeminal neuralgia, such as tumors, multiple sclerosis, or vascular malformations, but also to further evaluate neurovascular contact (NVC) and estimate the degree of vascular compression at the root entry zone at the pons [7, 8].

MRI of the trigeminal nerve has revealed that NVC occurs often in humans in addition to signs and symptoms of facial pain. Moreover, excluding patients with MVD based strictly on preoperative MRI outcomes may prevent patients from experiencing the best possible therapeutic benefit [9]. Therefore, its capacity to accurately exclude NVC associated with trigeminal nerve is not properly understood.

In this meta-analysis, literature assembly was carried out using exceptional criteria, aimed at evaluating the sensitivity and specificity of MRI in predicting symptomatic NVC in patients who received MVD, Gamma Knife Surgery (GKS), or medical treatment. Preoperative MVD imaging in patients with trigeminal neuralgia offers a practical reference.

Methods

This systematic review was conducted and reported according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement (PRISMA) checklist [10]. Ethics committee approval was not essential for this review, as only de-identified pooled statistics from individual studies were analyzed.

Search strategy

All relevant studies published in English were included. To pool the literature, a digital search including PubMed, Embase, and the Cochrane Library was performed. The literature search was performed from the inception of the database until December 31, 2023. Predefined search terms, including CTN, neurovascular contact or compression, and MRI, were used as the core keywords, either alone or in combination. Although most of the previous literature was obtained via literature searches, to avoid the omission of eligible research data, we carried out a manual search of reference lists from the original and review articles.

Inclusion and exclusion criteria

Studies were searched and pooled to satisfy the following criteria: (a) all studies were consecutive observational studies with identical CTN diagnostic criteria, (b) all studies used MRI detection of NVC in symptomatic and asymptomatic trigeminal nerves, (c) blinded case-control studies of all published articles, and (d) sample size larger than 20 patients. The exclusion criteria were as follows:

(a) case reports/series and other stylistic features that did not provide complete information for the trials, (b) retrospective studies without a case-control or non-blinded trial, and (c) articles not written in English.

Study selection and quality assessment

Three authors selected the studies to be included in the review and extracted data for the meta-analysis, resolving any disagreements through discussion. The titles, abstracts, and full texts were independently reviewed after excluding duplicates. Full-text articles were reviewed if they met the inclusion criteria. Two authors performed quality assessments of the studies using the Newcastle-Ottawa Scale (NOS). The NOS is based on selection (four items), comparability (one item), and outcome (three items). A complete score of <4 indicated low quality, 4–6 moderate, and ≥ 7 indicated high quality [11].

Data extraction

Two authors independently extracted the applicable records using a standardized information extraction form, including the name of the first author and the publishing year, patient count (men/women), study design, country, interventions, MRI characteristics (machinery and sequences), the number of nerves in cases and controls, and the assessment of the diagnostic precision of radiological findings in identifying symptomatic nerves that revealed the degrees of sensitivity and specificity, including NVC in general, root entry zone (REZ) contact, and nerve anatomical changes at the contact site.

Statistical analysis

The Cochrane RevMan version 5.1 software was used to generate applicable data for the meta-analysis (Cochrane Collaboration, Oxford, UK) [10, 12]. The meticulous *ORs* and 95% *CIs* have been used in the pooled evaluation for the following:1) MRI evidence of NVC in symptomatic and asymptomatic trigeminal nerves; 2) MRI indication of NVC at the REZ in symptomatic and asymptomatic trigeminal nerves; 3) MRI confirmation of non-REZ neurovascular contact in CTN patients; and 4) MRI evidence of trigeminal nerve REZ NVC in CTN patients., in every team the use of fixed-effects models [13]. A fixed-effects model (Mantel-Haenszel method) was used for data with $I^2<50\%$. Otherwise, a random-effects model (DerSimonian and Laird method) was used. An I^2 value $>50\%$ or P values <0.05 was indicative of significant heterogeneity [12, 14].

Variable definition

The clinical criteria for CTN has been endorsed by both the International Headache Society (IHS) and International Association for the Study of Pain (IASP) [15–17].

The term "neurovascular contact" refers to the vessel touching nerve without cerebrospinal fluid intervention.

According to the numerous investigations, "nerve anatomical alterations" include nerve atrophy, distortion, flattening, or indentation.

The trigeminal REZ accounts for one-quarter of the cisternal part of the nerve, and is generally thought to be a tract extending from the nerve's point of entry into the brainstem to the point of transition from the central and peripheral myelin sheaths. The average length reported in the literature is approximately 6 mm [18, 19].

Results

Search results

The PRISMA flow diagram of the study selection process is presented in Fig. 1. Initially, 1102 articles were identified from three databases, PubMed, Embase, and the Cochrane Library. After screening and excluding studies based on the exclusion criteria ($n=522$) and duplicate studies ($n=567$), 13 articles were reviewed. The 522 articles excluded from the review consisted of irrelevant studies (430), unblinded case-control data (45), case series [29], and studies with continuous date [18]. Therefore, 13 studies were included in this meta-analysis.

Characteristics of included studies

Table 1 shows the characteristics of each study, and Table 2 summarizes the Newcastle-Ottawa Scale for Study Quality in Meta-Analysis. A total of 13 studies were included [20–32]. All articles were available in the database until December 31, 2023. A total of 728 "symptomatic" nerves were included, which refer specifically to the patient's trigeminal nerve involved in trigeminal neuralgia. The "asymptomatic" nerves included 728 nerves on the contralateral side of patients with trigeminal neuralgia and 314 from healthy controls. One study was prospective, and the remaining 12 were retrospective. One study was conducted each in Denmark, Korea, Belgium, Italy, and Argentina. Three and five studies were conducted in the United States and China, respectively. The interventions reported in the 13 studies were: two studies with GKS, two with medicinal therapy, and nine with MVD. On 3.0-T (Tesla) MRI scanners. The latter four studies used 1.5-T MRI machines [20, 22, 25, 29].

Systematic review and meta-analysis

The final analysis included 13 articles that satisfied the inclusion criteria, from which 728 nerves from patients with trigeminal neuralgia and 157 from healthy controls were included. Therefore, 728 symptomatic nerves and 1042 asymptomatic nerves were included. We amassed and collated data on the frequency of NVC in symptomatic and asymptomatic trigeminal nerves in 13 studies, REZ NVC in symptomatic and asymptomatic patients

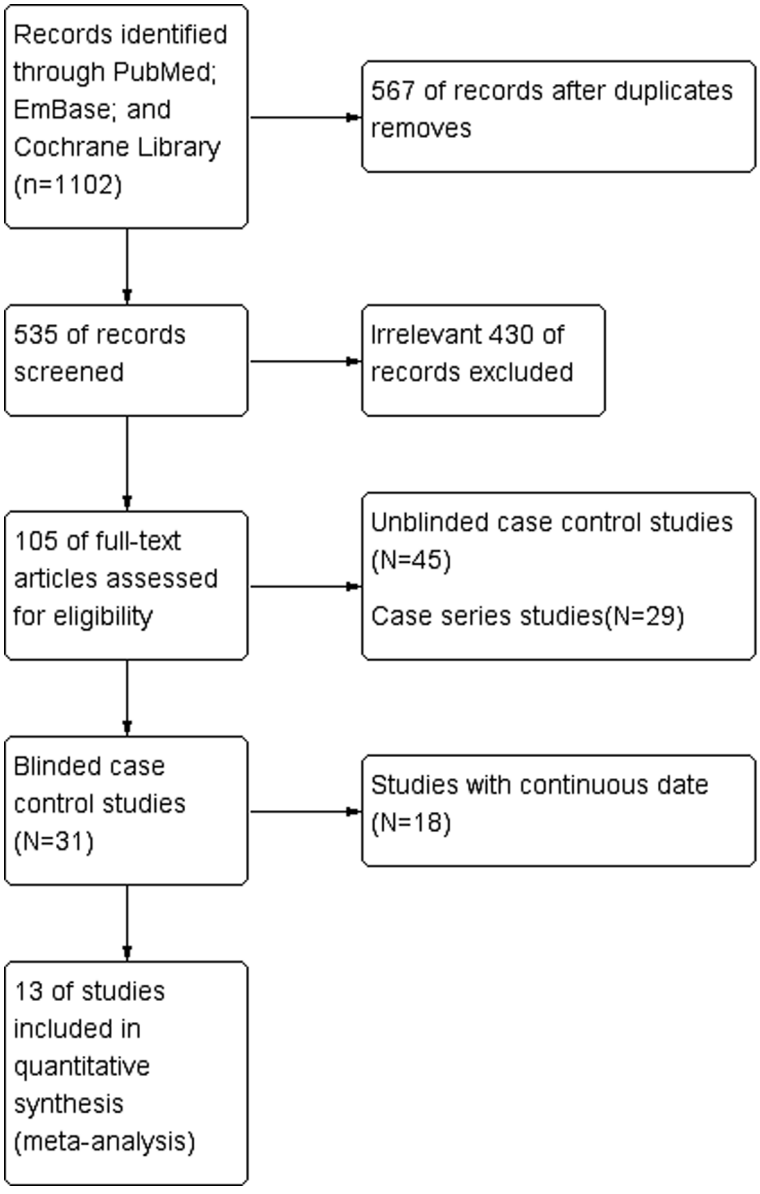

Fig. 1 Eligibility of studies for inclusion in meta-analysis

in five studies, non-REZ NVC in CTN in three studies, and asymptomatic and symptomatic anatomic changes at the NVC site of the trigeminal nerves in 11 studies. The assessment of the diagnostic accuracy of the radiological findings in detecting symptomatic nerves confirmed that sensitivity and specificity levels were, respectively, 0.75–0.97 and 0.26–0.86 for NVC in general, 0.66–0.88 and 0.29–0.90 for REZ NVC, 0.08–0.30 and 0.68–0.92 for non-REZ NVC, and 0.20–0.74 and 0.79–1 for nerve anatomical changes in the site of contact (Table 1). First, MRI of 649/728 (88.2%) symptomatic versus 378/1042 (36.3%) asymptomatic trigeminal nerves revealed marked differences in NVC in the REZ (OR=16.3; CI 95%=12.2–21.8; $p<0.00001$) (Fig. 2). Second, pooled five studies showed that REZ NVC was detected in 206/262 (78.6%) symptomatic and in 129/340 (37.9%) asymptomatic nerves (OR=5.0; CI 95%=3.4–7.3; $p<0.00001$) (Fig. 3). Third, no significant differences were detected between 44/267 (16.5%) symptomatic and 23/189 (12.1%) asymptomatic nerves on MRI examination of NVC in the non-REZ (OR=0.9; CI 95%= 0.5–1.6) ($p=0.77$) (Fig. 4); Finally, MRI revealed marked differences in 302/567 (53.2%) symptomatic and 73/919 (7.9%) asymptomatic anatomic changes (atrophy, dislocation, distortion, flattening or indentation) at the NVC site of the trigeminal segments (OR=11.9; CI 95%=8.8–16.2; $p<0.00001$) (Fig. 5), from 11 studies.

Table 1 Characteristics of the studies included in the meta-analysis

Study	M/F	Type of cohort study	Country	Intervention	MR Tesla/ MRI sequence	Cases/ controls	NVC in general	REZ NVC	NON-REZ NVC	Nerve anatomic changes*
							Sensit /Specif	Sensit /Specif	Sensit /Specif	Sensit / Specif
Erbay 2006	21/19	Retrospective	United States	GKS	1.5T/CISS	40/40	0.75/0.75	0.75/0.75	-	-
Lorenzoni 2008	50/39	Retrospective	Belgium	GKS	1.5T/ MRI	89/89	0.92/0.45	-	-	0.20/1.00
Miller 2009	13/17	Retrospective	United States	MVD	3.0-T/BFFE	30/60	0.90/0.55	0.73/0.87	0.17/0.68	0.43/0.85
Chun-Cheng 2009	25/20	Retrospective	China	MVD	3.0-T/SPGR, MRA	45/117	0.89/0.62	-	-	0.53/0.92
Ni 2009	14/19	Retrospective	China	MVD	3.0-T/FPGRI, MRA	33/33	0.88/0.27	0.88/0.73	-	0.61/0.91
Hanbing 2010	73/94	Retrospective	China	MVD	1.5-T/FPGRI, MRA	167/167	0.86/0.86	-	-	-
Zhou 2011	21/16	Retrospective	China	MVD	3.0-T/MRA	37/37	0.95/0.68	-	-	0.54/0.89
Cha 2011	29/37	Retrospective	Korea	MVD	3.0-T/MPR, MRA	66/66	0.95/0.26	-	-	0.74/0.79
Zeng 2013	21/16	Retrospective	China	MVD	3.0-T/FIESTA, MRA	37/101	0.94/0.69	-	-	0.56/0.96
Antonini 2014	11/13	Retrospective	Italy	Medical	1.5-T/CISS, MRA	24/72	0.87/0.73	0.66/0.90	0.30/0.78	0.66/0.94
Docampo 2015	11/19	Prospective	Argentina	MVD	3.0-T/FIESTA, MRA	30/130	0.83/0.72	-	-	0.36/0.99
Maarbjerg 2015	53/82	Retrospective	Denmark	Medical	3.0-T/BFFE, MRA	135/135	0.80/0.66	0.80/0.29	0.08/0.92	0.52/0.86
Hughes 2019	34/45	Retrospective	United States	MVD	3.0-T/SSFP	79/79	0.97/0.36	-	-	0.59/0.91

* Nerves with atrophy, dislocation, distortion, flattening or indentation; GKS: gamma knife surgery; CISS: constructive interference in steady state; BFFE: balanced fast-field echo; SPGRI: spoiled gradient-recalled imaging; MRA: magnetic resonance angiography; MPR: multiplanar reconstructions; FIESTA: fast imaging employing steady-state acquisition; SSFP: steady-state free precession

Discussion

Trigeminal neuralgia, also known as tic douloureux, is a painful neurological condition that significantly impairs the quality of life. In 1934, Walter Dandy observed via a craniotomy in a person affected with trigeminal neuralgia that the presence of vascular compression of the trigeminal nerve was responsible for TN [2]. MVD was developed by Jannetta et al. based on the neurovascular compression hypothesis [33], which is now known as the Jannette procedure. It relieves trigeminal neuralgia after surgery by separating only the nerves and blood vessels that are under stress from one another. Currently, the first treatment option for CTN is MVD [8]. For the etiological subclassification of clinically diagnosed trigeminal neuralgia into either primary trigeminal neuralgia or secondary trigeminal neuralgia, neuroimaging, particularly MRI, is crucial [34]. Therefore, the diagnostic and prognostic value of preoperative MRI for identifying CTN candidates for surgery is increasingly being investigated.

In addition, NVC of the trigeminal nerve frequently occurs in individuals who do not exhibit facial pain, and many have argued that the MRI findings of blood

Table 2 Results of quality assessment using the Newcastle-Ottawa Scale for case-control studies

Study	Selection				Comparability Control for important factor	Exposurer			Scores
	Adequate definition of cases	Representat-iveness of the cases	Selection of controls	Definition of controls		Ascertainment of exposure	Same method of ascertainment cases and controls	Nonresponse rate	
Erbay 2006	★	★	☆	★	★☆	★	★	★	7
Lorenzoni 2008	★	★	☆	★	★★	★	★	★	8
Miller 2009	★	★	★	★	★★	★	★	★	9
Chun-Cheng 2009	★	★	★	★	★★	★	★	★	9
Ni 2009	★	★	☆	★	★☆	★	★	★	7
Han-bing 2010	★	★	☆	★	★☆	★	★	★	7
Zhou 2011	★	★	☆	★	★☆	★	★	★	7
Cha 2011	★	★	☆	★	★★	★	★	★	8
Zeng 2013	★	★	★	★	★☆	★	★	★	8
Antonini 2014	★	★	★	★	★★	★	★	★	9
Docampo 2015	★	★	★	★	★☆	★	★	★	8
Maarbjerg 2015	★	★	☆	★	★★	★	★	★	8
Hughes 2019	★	★	☆	★	★★	★	★	★	8

★ Black stars indicate one point; ☆ white stars indicate non-point

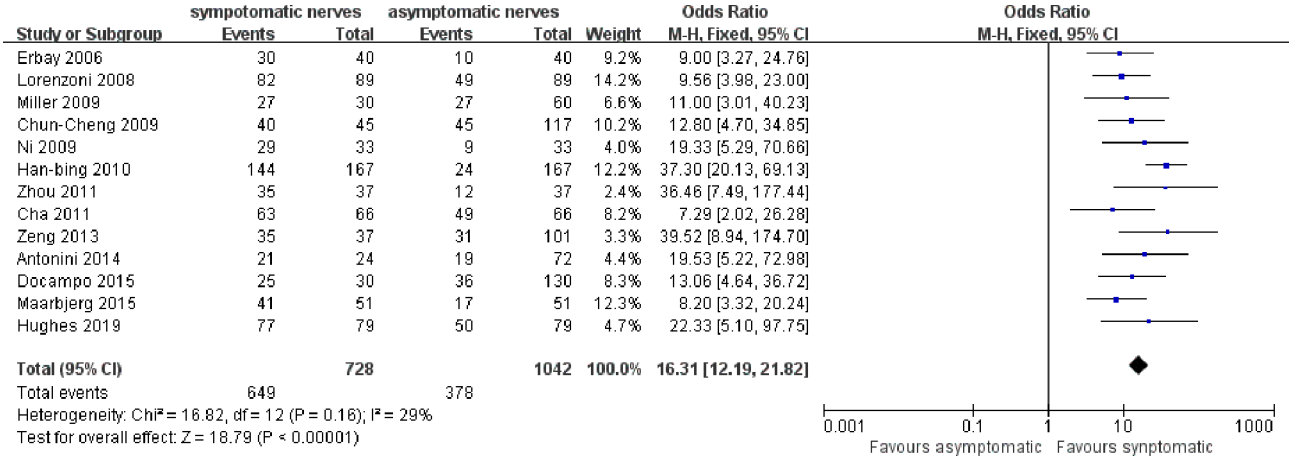

Fig. 2 OR of MRI evidence of NVC in patients with cTN, as reported in 13 blinded case-control studies

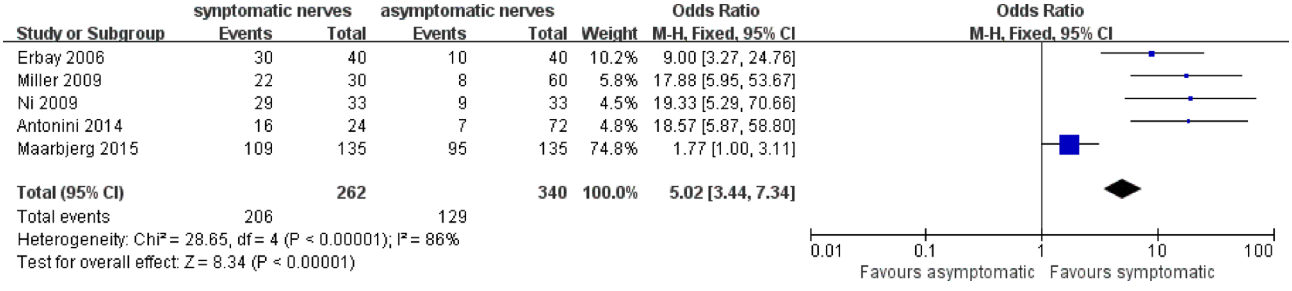

Fig. 3 OR of MRI evidence of trigeminal nerve REZ neurovascular contact in patients with cTN as reported in five blinded case-control studies

vessel contact with the trigeminal nerve are not necessarily pathological [35]. With the creation of functional MRI in recent years, diffusion tensor imaging and tractography have been used to reveal not only localized edema and demyelinating changes, but also microstructural changes in nerve compression sites [36, 37]. Approximately 3.3% of patients with trigeminal neuralgia do not experience vascular compression on the symptomatic side [38], while approximately 87.5% of the healthy population have vascular compression [39]. To assess the neurovascular relationship of MRI sequences and determine whether they should be utilized as a

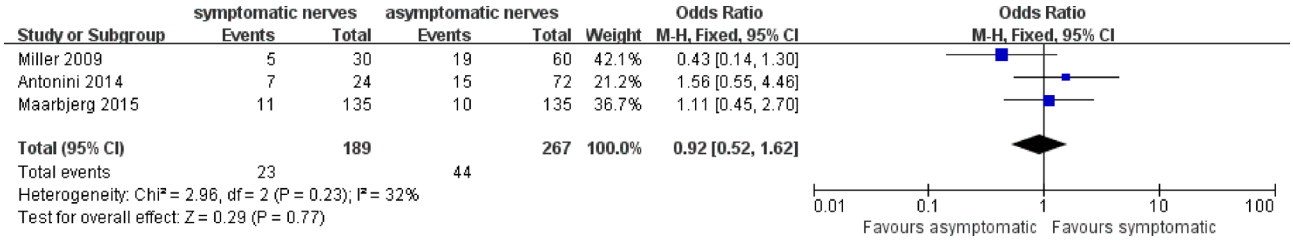

Fig. 4 OR of MRI evidence of non-REZ neurovascular contact in patients with cTN as reported in three blinded case-control study

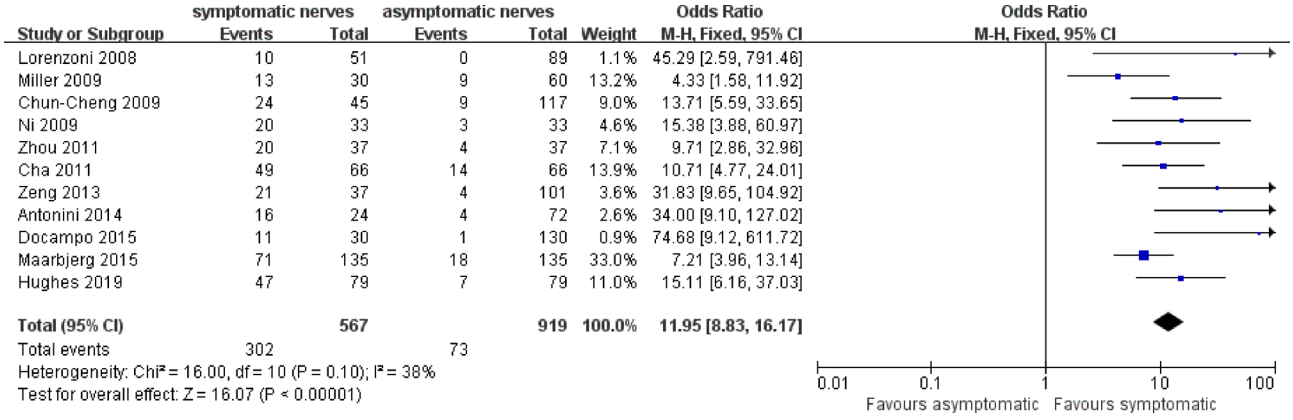

Fig. 5 OR of MRI evidence of anatomical changes of trigeminal nerve in the site of neurovascular contact in patients with cTN, as reported in 11 blinded case-control studies

reference for the clinical remission of trigeminal neuralgia by MVD in patients, we conducted a literature search and gathered a sizable number of investigators.

A systematic review and meta-analysis of 13 blinded case-control trials yielded strong evidence that MRI detection of trigeminal NVC is more frequent in nerves affected by CTN than in those that are asymptomatic. MRI findings suggest that the sensitivity of diagnosing symptomatic nerve is 0.75–0.97. NVC were found in 89.1% of symptomatic nerves in patients with CTN. In contrast, only 36.7% of the asymptomatic trigeminal nerves showed NVC. This difference was statistically significant ($p<0.05$). Although not all searched articles (only five) were included in the meta-analysis, the comparison was statistically significant ($p<0.05$) in terms of MRI-detected regions of the REZ NVC [20, 22, 24, 29, 31]. Among patients with CTN, 78.6% had symptomatic trigeminal nerves according to MRI results, which demonstrated a sensitivity of 0.66–0.88 for the diagnosis of symptomatic in the REZ NVC. REZ NVC was present in only 37.9% of the control trigeminal nerves. The results of the three investigations showed that non-REZ NVC was found in 12.2% of PTN patients and 16.5% of controls [22, 29, 31], with no statistically significant difference ($p>0.05$). Anatomical nerve changes (atrophy, dislocation, distortion, flattening, or indentation) and REZ NVC at the contact site are independently associated with CTN [29, 31]. The assessment of anatomical nerve changes on MRI in detecting symptomatic nerves published a sensitivity 0.20–0.74 and specificity 0.79–1. Anatomical changes were detected in 53.3% of the symptomatic trigeminal nerves in CTN compared with 7.9% in the control nerves, with a statistically significant difference ($p<0.05$). Thus, neurovascular relationships observed on MRI are valuable in the diagnosis of CTN. Furthermore, imaging assessments prior to MVD are important. MRI alone cannot precisely diagnose CTN when one of the markers such as NVC, REZ, NVC, or anatomical nerve changes is detected. When MRI reveals REZ NVC related to anatomical nerve changes, symptomatic neurovascular compression is more likely to be recommended. This is consistent with surgical findings in sufferers with CTN, where the responsible artery used to be greater often discovered in the REZ NVC place, and the neuroanatomical variability was higher in patients undergoing MVD [29, 34]. In 2019, Bendtsen reported that 68–88% of patients with CTN achieved satisfactory remission at 1–2 years after MVD, and 61–80% of patients remained in pain comfort after 4–5 years [8]. Despite the lack of high-level evidence-based data, many investigators agree that cautious preoperative MRI screening to eliminate sufferers who are not candidates for surgical treatment not only reduces the pain and risks related to surgery but also increases the effectiveness and success rate after surgery. A meta-analysis of the studies we collected also yielded a conclusion supporting

the investigator's hypothesis that MRI is highly likely to detect anatomical nerve changes in the REZ in symptomatic trigeminal nerves; however, we should also note from the results obtained by the analysis that MRI does not completely exclude CTN in the absence of NVC on the symptomatic trigeminal nerves. Similarly, MRI findings of each REZ NVC and anatomic changes indicate that both are more likely to be present on the painful side of the trigeminal nerve. However, this does not negate the fact that the asymptomatic side of the trigeminal nerve does not exhibit comparable changes; however, only a significantly lower frequency, and the differences are of clinical significance. Overall, 3.0 T or 1.5 T MRI offers an excellent way to evaluate anatomical changes in vascular compression nerves in CTN.

Although we searched as extensively as possible for a comprehensive literature report, there were some limitations to our study. First, we established consistency with the literature but used small CTN sample sizes. It is well established that large pattern sizes can enhance test effectiveness. Second, all reported outcomes were calculated using raw data, and adjusted results were not available. This may have a significant impact on the treatment effects in patients with CTN and the ability to diagnose trigeminal neuralgia using magnetic resonance imaging. Third, the duration of CTN, patient physical status, severity, surgical specificity, and other subjective and objective factors of CTN vary, and randomized double-blind groups cannot be generated in clinical studies. Consequently, a prospective study of this type would need to be designed. Last, individual data were not accessible, and the analysis used pooled data, limiting a more in-depth relevant analysis that would have allowed us to achieve more thorough conclusions.

Conclusions

In summary, the results of this meta-analysis suggest that patients with CTN are more likely to have symptomatic NVC when MRI shows REZ NVC related to anatomical nerve changes, which include nerve atrophy, dislocation, indentation, or flattening. CTN is indispensable for clinical diagnosis using MRI. MRI screening of the artery compressing the trigeminal nerve prior to microvascular decompression can be beneficial when the patient does not respond to medical remedies or when the side effects are severe. Similarly, additional sophisticated, intelligent, and revolutionary imaging technologies have been developed and are undergoing clinical exploration to enhance the sensitivity and accuracy of MRI for the prognosis of neurovascular compression in CTN.

Abbreviations

CTN	Classical trigeminal neuralgia
MVD	Microvascular decompression
GKS	Gamma Knife Surgery
MRI	Magnetic resonance imaging
NVC	Neurovascular contact
REZ	Root entry zone
ORs	Odds ratio
CIs	Confidence intervals

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None.

Author contributions
A and B contributed to the conception of the study and wrote the manuscript; C and D contributed significantly to the analysis and manuscript preparation; E and C helped perform the analysis with constructive discussions; and F directed the discussion, wrote, reviewed, and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.The authors A and B contributed equally to this paper.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
This study was conducted in accordance with the guidelines of the Declaration of Helsinki and all experimental protocol were approved by the Yantai Yuhuangding Hospital ethics committee.

Competing interests
The authors declare no competing interests.

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