

Predicting the therapeutic effect of carbamazepine in trigeminal neuralgia by analysis of neurovascular compression utilizing magnetic resonance cisternography

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Abstract. The aim of this study was to determine whether the evaluation of neurovascular compression (NVC) using new criteria on magnetic resonance (MR) cisternography improves the prediction of the curative effects of carbamazepine (CBZ) in trigeminal neuralgia (TN). In this study, a new analysis of NVC using MR cisternography was performed retrospectively for 280 patients with clinical signs and symptoms suggesting TN. The new analysis examined whether the site of the NVC was less than 3 mm from the edge of the exit point and within the first third of the root entry zone on MR cisternography. Prediction of the curative effects of CBZ using the new evaluation of distance to the NVC improved on the predictive ability of the previous method of calculating the NVC volume (Mantel–Haenszel coefficient, $P < 0.01$). In particular, initial treatment with CBZ 100 mg/day for 2 weeks appeared more effective for patients with NVC volumes of $\leq 5 \text{ mm}^3$ plus a distance to the NVC of $\leq 3 \text{ mm}$, than for those with NVC volumes $> 5 \text{ mm}^3$. The evaluation of NVC on MR cisternography using this new approach appears to be more useful than the previous method for predicting the initial treatment response in patients with TN.

Key words: trigeminal neuralgia; MR cisternography; pain; treatment; neurovascular compression.

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Trigeminal neuralgia (TN) is a disease that dentists commonly encounter. Patients affected with TN usually present with severe lancinating pain involving the oral and maxillofacial regions. Neurovascular compression (NVC) in the root entry zone (REZ) of the trigeminal nerve, which is in the cerebellopontine angle cistern, is among the most frequent causes of TN¹. Previous studies, including studies performed by the present authors, have reported the potential usefulness of magnetic resonance (MR) cisternography for identifying and analyzing NVC in the REZ of TN patients²⁻⁵. In addition, we have shown that the effects of carbamazepine (CBZ) therapy as an initial treatment for TN can be predicted by analyzing NVC volume on MR cisternography², although the effects of local anaesthetic block by tetracaine as additional therapy could not be predicted⁶.

It was recently suggested by Suzuki et al. that the distance from the trigeminal nerve to the blood vessel responsible should be considered when evaluating NVC in patients with TN⁷. Specifically, they suggested that TN symptoms occurred when the site of the NVC was less than 3 mm from the edge of the exit point and within the first third of the REZ on MR cisternography. This method of assessment may be very useful for the evaluation of TN patients in whom NVC of the trigeminal nerve is the cause, because the new approach to the evaluation of NVC should help provide a precise diagnosis of TN caused by NVC⁷. However, this analysis was only very recently reported⁷, and the relationships between NVC volume and CBZ and tetracaine therapies could not be determined in previous studies^{2,6}. Therefore, it was hypothesized that the curative effects of CBZ therapy as the initial treatment for TN could be better predicted with the use of this new analysis.

This study was performed to determine whether the new approach to the evaluation of NVC on MR cisternography is better than the previous method for the prediction of the curative effects of CBZ treatment in TN.

Materials and methods

Subjects

This retrospective study investigated the cases of 280 patients with TN (118 male, 162 female; mean age 61.8 years, range 22–93 years) attending Kyushu Dental University Hospital between July 1999 and March 2014, who underwent MR imaging². This

Table 1. Correlation between the region of clinical neuralgia and the site of neurovascular compression^a.

Correlation	Clinically affected regions of the branches of the trigeminal nerve						Total
	V1	V2	V3	V1 and V2	V2 and V3	V1, V2, and V3	
MRI (N = 259)							
Matched	13	74	103	19	31	5	245
Mismatched	2	7	5	0	0	0	14

V1: first branch area of the trigeminal nerve; V2: second branch area of the trigeminal nerve; V3: third branch area of the trigeminal nerve.

^a Values indicate the numbers of patients.

study was approved by the Institutional Review Board of Kyushu Dental University. The patients' informed consent was not required for this retrospective study.

Seven of the 280 patients were treated by microvascular decompression surgery at another hospital and 14 had a brain tumour invading the REZ of the trigeminal nerve²; these 21 patients were excluded from the present analysis². In addition, a further 14 patients who showed a mismatch between the region of the clinical neuralgia manifestations and the site of the NVC were also excluded (Table 1). The compression sites were evaluated based on the detailed anatomy of the intracranial portion of the trigeminal nerve, as reported by Gudmundsson et al.⁸, and found to correspond to each branch. The vessels responsible were not detected on MR cisternography in four patients, and these patients were also excluded from the study. The remaining patients were interviewed to gather information on their history, the nature of their pain (sites, typical paroxysms, refractory period, and trigger zone), and evidence of definite facial sensory loss or other cranial nerve dysfunction^{9,10}. A visual analogue scale (VAS) was used to categorize the degree of pain of the most intense episode on a scale from 0 to 100.

MR acquisition including MR cisternography sequences

Potential local causes of TN were routinely evaluated using T1-weighted images, T2-weighted images, and MR cisternography images with three-dimensional (3D) fast asymmetric spin-echo sequences (FASE). The presence of space-occupying lesions (such as brain tumours) and multiple sclerosis (such as cerebral infarction) was ruled out by examination of T1- and T2-weighted images.

A 1.5-T full-body MR system (EXCELART Vantage powered by Atlas, Toshiba, Tokyo, Japan; or VISART, Toshiba, Tokyo, Japan) equipped with a circularly polarized head coil was used to obtain all images. The parameters listed in Table 2 were used for MR cisternography with 3D-

FASE; images were acquired using the method of Tanaka et al.^{2,5}. Following the completion of data acquisition for 50 sections, a multi-planar reconstruction algorithm was used to create coronal and sagittal reformatted images. Furthermore, black and white were inverted for the MR cisternography images with 3D-FASE for the evaluation of NVC^{9,10}. A multi-planar reconstruction algorithm was also used to create two other reformatted images that were angled perpendicular and parallel to the trigeminal nerve at the REZ. All of the original transverse images and the four reformatted images were evaluated.

Measurements of NVC using MR cisternography

Detailed analyses of the MR cisternography images were performed to identify the presence of NVC, the site of NVC, and the NVC volume. The new analysis method of Suzuki et al. (Fig. 1) was used to evaluate the presence and the site of NVC on MR cisternography⁷, specifically whether the site of the NVC causing TN was less than 3 mm from the edge of the exit point and within the first third of the REZ.

NVC volume was assessed as described by Tanaka et al.² (Fig. 2). All digitized MR cisternography images were sent to a MacBook Pro workstation (Apple Inc., Cupertino, CA, USA). NVC volume was then measured using OsiriX imaging software (FDA cleared; Pixmeo SARL, Geneva, Switzerland). The measurement of NVC volume in a patient with TN using OsiriX imaging software is shown in Fig. 2. The NVC volume was automatically displayed on the MacBook Pro workstation based on all digitized MR cisternography images sent to the software (Fig. 2). If the NVC volume could not be measured because there was little or no contact, it was assigned a value of 0 mm³; therefore, NVC of 0 mm³ did not necessarily indicate the absence of compression between the trigeminal nerve and vessels, but that it could not be measured due to the limitations of the measurement systems.

Table 2. Imaging parameters.

	Sequence					
	MR cisternography		T1WI		T2WI	
	EXCELART Vantage	VISART	EXCELART Vantage	VISART	EXCELART Vantage	VISART
TR (ms)	6000	6000	580	500	4100	4000
TE (ms)	250	250	15	15	100	100
Flip angle (°)	90	90	70	90	90	90
FOV (mm)	150 × 150	150 × 150	220 × 220	220 × 220	220 × 220	220 × 220
Section thickness (mm)	1.0	1.0	6.0	6.0	6.0	6.0
Intersection gap (mm)	0	0	1.0	1.0	1.0	1.0
Slab thickness (mm)	50	50	119	119	119	119
Matrix (pixels)	512 × 512	192 × 192	320 × 320	256 × 256	304 × 304	256 × 256

MR, magnetic resonance; T1WI, T1-weighted image; T2WI, T2-weighted image; TR, repeat time; TE, echo time; FOV, field of view.

Two radiologists (T. T. and Y.M.) independently assessed the MR cisternography images with 3D-FASE and were blinded to the clinical findings. If the two radiologists disagreed, a final assessment was reached by consensus.

Analysis of NVC and treatment of the patients with TN

All patients were initially treated for 2 weeks with CBZ 100 mg/day. Following this, those who did not respond to the 100 mg/day

dosage were treated with dosages of up to 800 mg/day for their pain. The maximum permissible dosage per day for patients with TN was based on the information provided in the CBZ package insert.

A retrospective analysis of the efficacy of initial treatment for TN (100 mg/day) in the study hospital was performed for 231 patients (Fig. 3). A VAS was used to evaluate the therapeutic effect of initial treatment with CBZ. The therapeutic effect was considered 'improvement' when there was a decrease in the VAS score from baseline, while the

therapeutic effect was considered 'no improvement' when there was no change or an increase in the VAS from baseline.

The therapeutic effects of CBZ treatment were evaluated in three groups. In the first group, only the distance from the trigeminal nerve to the blood vessel responsible was examined, as determined using the new method of analysis. In the second group, only the volume was examined, as calculated using the previous method of analysis². In the third group, both the distance to the NVC and the NVC volume were evaluated,

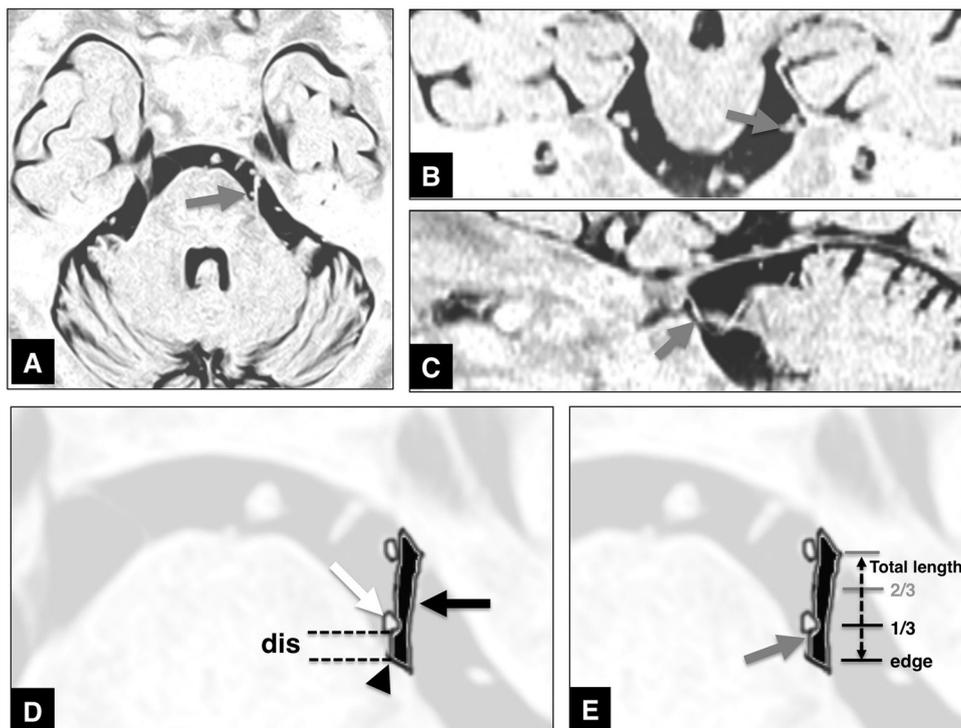


Fig. 1. Measurement methods for the new evaluation of neurovascular compression (NVC) on MR cisternography. Images for the diagnosis of NVC: (A) transverse image; (B) coronal image; (C) sagittal image (NVC is indicated with grey arrows). Images D and E are reformatted and enlarged schematic versions of image A, showing the blood vessel and the trigeminal nerve at the root entry zone. (D) Measurement of the shortest distance between the nerve root (black arrow head) and the blood vessel (white arrow) at the site of NVC, and evaluation of the site of NVC on multiple sides of the trigeminal nerve. When contact is seen on multiple sides of the trigeminal nerve (black arrow), the shorter one of the two distances is measured (dis). When contact is seen on only one side, the distance on the corresponding side is measured. (E) Determination of the site of the NVC causing trigeminal neuralgia: from the edge of the exit point to a point one-third into the root entry zone.

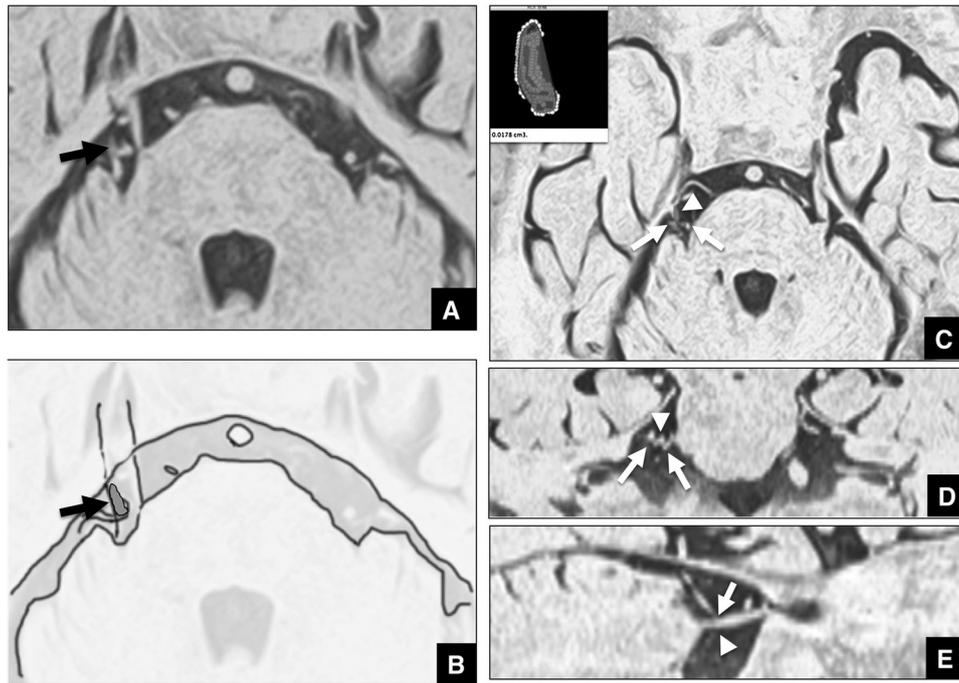


Fig. 2. Three-dimensional MR cisternography images used to measure neurovascular compression volume: (A) the contact area (black arrow) of the nerve and the blood vessel is delineated in each image ((B) schematic version of image A); the volume is then calculated three-dimensionally by the software. The trigeminal nerve (white arrowheads) is seen to be surrounded by a mesh of blood vessels (white arrows) on MR cisternography: (C) axial, (D) reformatted coronal, and (E) reformatted sagittal images.

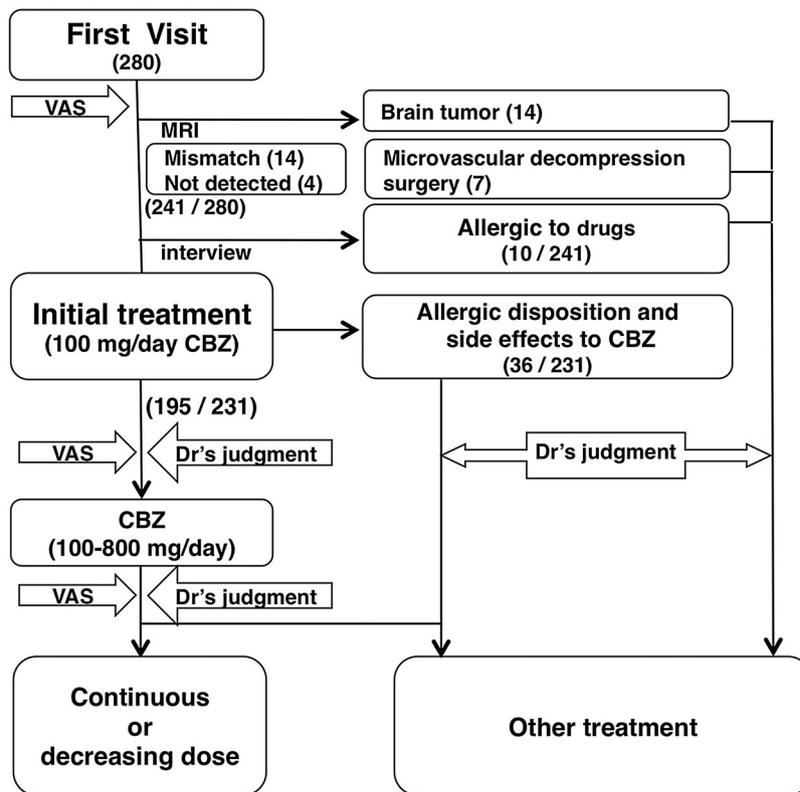


Fig. 3. Flow chart of the treatment of patients with trigeminal neuralgia included in the study. Carbamazepine could not be given to 10 of the 241 patients allocated to treatment because of a past history of allergy on medical interview. Therefore, carbamazepine 100 mg/day was given for 2 weeks to 231 patients as initial treatment. However, 36 of these 231 patients experienced side effects on this dosage of carbamazepine and could not be completely followed-up. Thus, 195 patients with trigeminal neuralgia were followed-up in the present study. After initial treatment with carbamazepine (100 mg/day) had been given for 2 weeks, it was left to the doctor's discretion to provide any further treatment with carbamazepine based on each patient's symptoms.

with the site of the NVC (between the edge of the exit point and a point one-third into the REZ) as the additional criterion². Spearman's correlation coefficient and Pearson's χ^2 test were used to assess the relationships between the change in pain after CBZ 100 mg/day and the distance, NVC volume, or both measured on MR cisternography, as well as the relationships between the therapeutic effect by CBZ dosage per day and the distance, NVC volume, or both. The Mantel-Haenszel test was used to assess the relationship between the change in pain after CBZ 100 mg/day for 2 weeks and the NVC volume plus the distance. *P*-values of <0.05 were considered significant.

Results

Relationship between the change in pain after CBZ administration and the distance to the NVC on MR cisternography according to the new analysis method, in patients with TN

One hundred and ninety-five patients with TN were included in this analysis. The relationship between the change in pain after CBZ 100 mg/day as initial treatment and the distance to the NVC measured with the new method of analysis, with the site data of NVC on MR cisternography as the additional criterion, is shown in Table 3. The shorter the distance was, the higher the rate of a therapeutic effect (Table 3). A significant correlation was found between the change in pain after CBZ 100 mg/day as initial treatment and the distance to NVC on MR cisternography in patients with TN (Spearman's correlation coefficient, $r = 0.31$, $P = 0.001$).

Next, the cases were divided into two groups based on the data acquired and the cut-off distance suggested by Suzuki et al.²: those with a distance of ≤ 3 mm and those with a distance > 3 mm. The distribution of the two groups by thera-

Table 4. Summary of the correlation between the effect of initial treatment and the distance to the site of neurovascular compression.

Distance ^a (mm)	Improvement ^b	No improvement ^c
0–3.0	122	38
≥ 3.1	14	21
Total	136	59

χ^2 test, $P < 0.01$.

^aDistance: distance to the site of neurovascular compression on magnetic resonance images.

^bImprovement: the VAS score for pain decreased after treatment with carbamazepine 100 mg/day.

^cNo improvement: the VAS score for pain did not decrease after treatment with carbamazepine 100 mg/day.

peutic effect after initial treatment is shown in Table 4. This analysis showed the relationship between the therapeutic effect of initial treatment and the distance more clearly than the analysis presented in Table 3. The therapeutic effect of initial treatment tended to increase in patients with a short distance (≤ 3 mm). Conversely, in patients with a long distance (> 3 mm), the therapeutic effect after initial treatment tended to be low. There was a significant difference in the therapeutic effect after CBZ 100 mg/day as initial treatment between patients with a short distance and patients with a long distance ($P < 0.01$). However, there was no significant correlation between the therapeutic effect according to the CBZ dosage per day administered to relieve the pain and the distance on MR cisternography (Spearman's correlation coefficient, $r = 0.14$, $P = 0.19$) (Table 5).

Relationship between the change in pain after CBZ administration and NVC volume on MR cisternography according to the previous analysis method, in patients with TN

The relationship between the change in pain after CBZ 100 mg/day as initial treatment and NVC volume on MR cisternography, without the data for the site of

NVC, in patients with TN, is shown in Table 6. The smaller the NVC volume was, the higher the rate of a therapeutic effect (Table 6). A significant correlation was found between the change in pain after CBZ 100 mg/day as initial treatment and NVC volume on MR cisternography in TN patients (Spearman's correlation coefficient, $r = 0.24$, $P = 0.01$).

Next, the cases were divided into two groups based on a cut-off volume determined in a previous study²: those with a volume of ≤ 5 mm³ and those with a volume > 5 mm³. Table 7 shows the distribution of the two groups by therapeutic effect after initial treatment. This analysis more clearly showed the relationship between the therapeutic effect of initial treatment and NVC volume than the analysis presented in Table 6. There was a tendency for the therapeutic effect of initial treatment to be greater in patients with a small NVC volume (≤ 5 mm³). There was a significant difference in the therapeutic effect after CBZ 100 mg/day as initial treatment between patients with a small NVC volume and those with a large volume ($P < 0.01$). However, there was no significant correlation between the therapeutic effect according to the dosage per

Table 3. Correlation between the effect of initial treatment and the distance to the site of neurovascular compression.

Distance ^a (mm)	Improvement ^b	No improvement ^c
0–1.0	70	16
1.1–2.0	35	10
2.1–3.0	17	12
3.1–4.0	9	8
4.1–5.0	2	2
≥ 5.1	3	11
Total	136	59

Spearman's correlation coefficient, $r = 0.31$, $P = 0.001$.

^aDistance: distance to the site of neurovascular compression on magnetic resonance images.

^bImprovement: the VAS score for pain decreased after treatment with carbamazepine 100 mg/day.

^cNo improvement: the VAS score for pain did not decrease after treatment with carbamazepine 100 mg/day.

Table 5. Correlation between the dosage of carbamazepine to control the pain and the distance to the site of neurovascular compression.

Distance ^a (mm)	Dosage of carbamazepine (mg/day)				
	≤ 100	200	300	400	500–800
0–1.0	70	6	7	2	1
1.1–2.0	35	5	2	1	2
2.1–3.0	17	5	4	2	1
3.1–4.0	9	3	3	1	1
4.1–5.0	2	2	0	0	0
≥ 5.1	3	3	3	3	2
Total	136	24	19	9	7

Spearman's correlation coefficient, $r = 0.14$, $P = 0.19$.

^aDistance: distance to the site of neurovascular compression on magnetic resonance images.

Table 6. Correlation between the effect of initial treatment and the volume of neurovascular compression.

Volume ^a (mm ³)	Improvement ^b	No improvement ^c
0	63	17
0.1–5.0	41	14
5.1–10.0	22	16
10.1–15.0	7	9
15.1–20.0	3	3
Total	136	59

Spearman’s correlation coefficient, $r = 0.24$, $P = 0.01$.

^aVolume: volume of neurovascular compression on magnetic resonance images.

^bImprovement: the VAS score for pain decreased after treatment with carbamazepine 100 mg/day.

^cNo improvement: the VAS score for pain did not decrease after treatment with carbamazepine 100 mg/day.

Table 7. Summary of the correlation between the effect of initial treatment and the volume of neurovascular compression.

Volume ^a (mm ³)	Improvement ^b	No improvement ^c
0–5.0	104	31
5.1–20.0	32	28
Total	136	59

χ^2 test, $P < 0.01$.

^aVolume: volume of neurovascular compression on magnetic resonance images.

^bImprovement: the VAS score for pain decreased after treatment with carbamazepine 100 mg/day.

^cNo improvement: the VAS score for pain did not decrease after treatment with carbamazepine 100 mg/day.

day of CBZ given to relieve the pain and NVC volume on MR cisternography (Spearman’s correlation coefficient, $r = 0.11$, $P = 0.14$) (Table 8).

Improvement of the correlation between the curative effect on pain of CBZ administration and NVC volume plus the distance using the new and previous analyses by MR cisternography, in patients with TN

The relationship between the change in pain after CBZ 100 mg/day for 2 weeks as initial treatment and the NVC volume plus the distance to the NVC is shown in Table 9. The patients were divided into two groups by NVC volume (≤ 5 mm³ and > 5 mm³) and then each group was further subdivided into two subgroups based on distance (≤ 3 mm and > 3 mm) (Table 9). There was a significant relationship between the change in pain after CBZ 100 mg/day for 2 weeks as initial treatment and the NVC volume plus the distance (Mantel–Haenszel test, $P < 0.01$). The therapeutic effect of initial treatment tended to increase in patients with a small NVC volume and a short distance to the NVC (Fig. 4). Conversely, in patients with a long distance plus a large NVC volume,

the therapeutic effect after initial treatment tended to be low.

Discussion

A new evaluation for NVC causing TN has recently been introduced, and this was shown by Suzuki et al.⁷ to improve the accuracy of TN diagnosis. In this new analysis, the shortest distance between the nerve root and the blood vessel at the site of NVC is measured. In particular, it is determined whether the site of the NVC causing TN is less than 3 mm from the edge of the exit point and within the first third of the REZ on MR cisternography⁷. The most interesting

Table 8. Correlation between the dosage of carbamazepine to control the pain and the volume of neurovascular compression.

Volume ^a (mm ³)	Dosage of carbamazepine (mg/day)				
	≤ 100	200	300	400	500–800
0	63	5	7	3	2
0.1–5.0	41	7	3	2	2
5.1–10.0	22	5	6	3	2
10.1–15.0	7	5	3	0	1
15.1–20.0	3	2	0	1	0
Total	136	24	19	9	7

Spearman’s correlation coefficient, $r = 0.11$, $P = 0.14$.

^aVolume: volume of neurovascular compression on magnetic resonance images.

result of the present study was that the prediction of the curative effect of CBZ in patients with TN was more accurate when the new analysis was added to the previous evaluation than with the previous approach alone^{2,7}. Therefore, it seems appropriate to evaluate the potential efficacy of treatment for patients with TN using the analysis of NVC on MR cisternography. Based on the results of this study, it appears that the analysis of NVC on MR cisternography would be useful to many radiologists and neurosurgeons.

A possible explanation for the clinical utility of the new analysis is that the trigeminal nerve from the edge of the exit point to a point one-third into the REZ is composed of an oligodendroglial myelin sheath without fibrous tissues. Therefore, the area is more likely to be affected by mechanical stress such as NVC than the subsequent two-thirds with fibrous tissues. Using the new analysis on MR cisternography improved the accuracy of diagnosis for patients with TN^{7,11} and could clearly result in a better prediction of the patient’s prognosis with initial CBZ treatment; patients likely to have no effect from initial treatment with CBZ could be better identified using

Table 9. Summary of the correlation between the effect of initial treatment and the volume of neurovascular compression plus the distance to the neurovascular compression.

Volume ^a (mm ³)	Distance ^b (mm)	Improvement ^c	No improvement ^d
0–5.0	0–3.0	100	31
	≥ 3.1	4	0
≥ 5.1	0–3.0	22	7
	≥ 3.1	10	21

Mantel–Haenszel coefficient, $P < 0.01$.

^aVolume: volume of neurovascular compression on magnetic resonance images.

^bDistance: distance to the site of neurovascular compression on magnetic resonance images.

^cImprovement: the VAS score for pain decreased after treatment with carbamazepine 100 mg/day.

^dNo improvement: the VAS score for pain did not decrease after treatment with carbamazepine 100 mg/day.

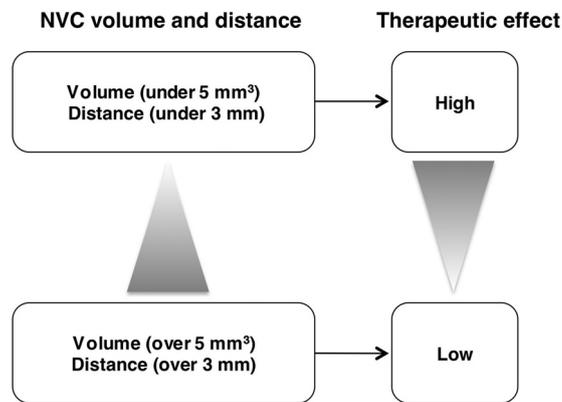


Fig. 4. Schematic diagram providing a simple explanation of the improved prediction of the therapeutic effect of carbamazepine in the treatment of trigeminal neuralgia through the use of the new evaluation of neurovascular compression by MR cisternography. The therapeutic effect of initial treatment tends to be highest in patients with a small NVC volume ($\leq 5 \text{ mm}^3$) and a short distance ($\leq 3 \text{ mm}$). Conversely, in patients with a long distance ($>3 \text{ mm}$) plus a large NVC volume ($>5 \text{ mm}^3$), the therapeutic effect after initial treatment tends to be low.

the new method than using previous methods.

Considering the results of Suzuki et al. and those of the present study, it appears that the new analysis using MR cisternography would be of benefit in improving the prediction of the curative effects of CBZ as treatment for TN with NVC^{2,5-7}. However, the pain caused by NVC may be related not only to the distance and/or amount of NVC of the trigeminal nerve, but also to other factors, including the patient's age and sex. In particular, the degree of pain in TN may depend greatly on the patient's sense of pain. Therefore, it appears difficult to evaluate the degree of pain.

The methods used in this study were relatively similar to those used in the previous study by this investigator group, because the purpose of this study was to determine whether using the new analysis on MR cisternography could improve the prediction of the curative effect of CBZ in patients with TN². Therefore, treatment with CBZ 100 mg/day for 2 weeks was selected as the initial treatment for patients with TN. In addition, if the curative effects were not apparent after initial treatment with CBZ at 100 mg/day, increased dosages of CBZ (from 100 mg/day to 800 mg/day) could be administered^{12,13}. Of note, patients in whom an adverse reaction to CBZ was anticipated were excluded from the present study, as was the case in the previous study.

To analyze the relationship between the new and previous analyses of NVC and the change in pain with CBZ treatment, 195 patients in whom the region of clinical neuralgia manifestations matched the NVC sites, who did not have space-occupying lesions and did not experience side effects of CBZ treatment, were selected as

subjects. Thirty-six patients had side effects after CBZ 100 mg/day and could not be completely followed-up. Therefore, these patients were excluded from the data analysis. It is believed that the sample size was sufficient to evaluate the efficacy of initial treatment with CBZ in patients with TN, as in the previous study².

Clinically, the effect of CBZ therapy as an initial treatment for TN is around 70%. Based on the study data, the analysis of NVC on MR cisternography represents a very appropriate method to judge whether the patient with TN should be treated with CBZ as the initial treatment in clinical practice, thereby avoiding invasive treatments. If the patient with TN has a small NVC ($< 5 \text{ mm}^3$) plus a short distance to the NVC ($\leq 3 \text{ mm}$), the doctor and/or dentist should preferentially choose CBZ treatment. However, in patients with a large NVC or long distance to the NVC, other treatments, such as local anaesthetic block with tetracaine should be selected instead of CBZ. Our next trial will seek to examine the relationship between the effectiveness of CBZ and the time interval from the first attack of TN.

Funding

None declared.

Competing interests

The authors declare that there is no conflict of interest.

Ethical approval

This study was approved by the Institutional Review Board of Kyushu Dental University (No. 13-74).

Patient consent

The patients' informed consent was not required for this retrospective study.

Conflict of interest

None.

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