

Prognostic Impact and Post-operative Evaluation of Volumetric Measurement of the Cerebellopontine Cistern in Trigeminal Neuralgia Using 3 Tesla Magnetic Resonance Imaging

Yoshiki OBATA,¹ Yoshihisa KAWANO,^{1,2} Yoji TANAKA,¹ and Taketoshi MAEHARA¹

¹Department of Neurosurgery, Tokyo Medical and Dental University, Tokyo, Japan;

²Department of Neurosurgery, JA Toride Medical Center, Toride, Ibaraki, Japan

Abstract

The aim of this study was to evaluate the importance of pre- and post-operative volumetric measurement of the cerebellopontine angle (CPA) using 3 Tesla (3T) magnetic resonance imaging (MRI). Between April 2012 and December 2015, a total of 87 consecutive patients underwent microvascular decompression (MVD) for trigeminal neuralgia (TN), of whom 51 with primary TN caused by arterial compression were enrolled in this study. Bilateral CPA cistern volume was evaluated using 3T MRI before and after surgery; the Cistern Deviation Index was used to represent the degree of deviation of the CPA cistern. The relationships between CPA cistern volume and the etiology of TN were assessed, and post-operative changes in anatomical parameters were examined to determine differences between recurrent and non-recurrent patients with TN. The mean volume of the CPA cistern on the affected side was significantly smaller than the unaffected side ($P < 0.001$). Five of 51 (10%) patients experienced TN recurrence. The recurrent cases demonstrated significantly lower pre-operative Cistern Deviation Index scores than non-recurrent cases ($P = 0.035$). On the unaffected side—but not the affected side—post-operative volume reduction was significantly greater in the recurrence group than in the non-recurrence group ($P = 0.004$). The pre-operative Cistern Deviation Index was a useful parameter to predict the recurrence of TN. In recurrent patients, post-operative inflammatory reaction may extend to not only the operated side but also the healthy side and reduce the volume of the CPA cistern.

Key words: trigeminal neuralgia, magnetic resonance imaging, cerebellopontine angle cistern, microvascular decompression

Introduction

Recent advances in magnetic resonance imaging (MRI) have enabled pre-operative visualization of neurovascular compression (NVC), which is widely accepted as a cause of trigeminal neuralgia (TN).^{1–3} Moreover, characteristic pre-operative MRI features in TN patients, such as trigeminal nerve atrophy,⁴ smaller volume of the pontomesencephalic,⁵ or the cerebellopontine angle (CPA) cistern of the affected side,⁶ may be factors involved in TN pathogenesis. Additionally, recent several studies have revealed that pre-operative assessment of NVC at 3-Tesla (3T) MRI has better anatomical conspicuity than 1.5T-MRI.^{7,8}

In a previous study,⁹ we calculated the volume of the CPA cistern using high-resolution 1.5T-MRI imaging and found significant differences in primary TN patients between the affected and unaffected sides, but no significant differences in healthy controls. We developed the Cistern Deviation Index to evaluate the degree of deviation of the CPA cistern and to analyze inter-individual variation between two groups (i.e., patients vs. controls, or recurrent vs. non-recurrent patients). The Cistern Deviation Index was statistically smaller in patients with TN than in controls without TN, and significantly larger in non-recurrent than recurrent patients. Finally, surgical procedure (transposition vs. interposition) and Cistern Deviation Index were found to be predictors of outcome in microvascular decompression (MVD).

Although we successfully evaluated the importance of pre-operative volumetric measurement of the CPA

Received July 10, 2017; Accepted August 27, 2017

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cistern, we did not analyze post-operative changes in the CPA cistern, which may extend our understanding of the underlying causes of recurrent TN. To investigate these possibilities, we calculated pre- and post-operative CPA cistern volume and the Cistern Deviation Index in primary TN patients using high-resolution 3T MRI, and compared volumetric parameters between patients with non-recurrent and recurrent TN after MVD.

Materials and Methods

Patient population

The present study was approved by the Institutional Ethics Committee of Tokyo Medical and Dental University (Tokyo, Japan). A total of 87 consecutive patients who underwent MVD for TN at the Institute between April 2012 and December 2015 were enrolled in the study. Informed consent was obtained from all patients, who fulfilled the following criteria: diagnosed with primary TN according to the *International Classification of Headache Disorders*;¹⁰ treated with pure MVD; followed-up for at least 1 year post-operatively; and available high-resolution MRI datasets, including three-dimensional (3D) time-of-flight magnetic resonance angiography and 3D fast imaging employing steady-state acquisition (FIESTA). Patient age at surgery, sex, affected side, topography of facial pain, compressing vessels, duration of follow-up, and serum C-reactive protein (CRP) level in the hospital were retrospectively reviewed from medical records. Fourteen patients, who previously underwent MVD, and 22 in whom the pathology was caused by veins or other etiology, were excluded from analysis, resulting in 51 patients with initial surgical intervention who were included in the final analysis.

Recurrence of TN was defined as cases taking medication (e.g., carbamazepine) or second surgery for ipsilateral pain. Except for patients continuing outpatient visits to the Institute, telephone interviews were conducted to assess pain status. The endpoint of follow-up in the non-recurrent patients was defined as the time of the last outpatient visit or telephone interview, whereas the endpoint for the recurrent patients was the time of pain recurrence.

Surgical procedure

All patients underwent MVD via a 2 cm to 3 cm diameter retrosigmoid craniotomy with one or two burr holes. Compressing vessels in contact with the trigeminal nerve were identified microsurgically and then transposed using a small piece of Teflon felt.

The operation records were reviewed to assess the compressing vessels.

Imaging

All of the patients were examined using a 3T MRI scanner (GE Signa HDxt; GE Healthcare, Waukesha, WI) before surgery, and two to five months after surgery. The parameters used in the 3D-FIESTA scan were as follows: repetition time, 8.2 ms; echo time, 2.6 ms; flip angle, 70°; field of view, 160 mm; matrix, 320 × 320; slice thickness, 0.4 mm or 0.6 mm; and acquisition time, from 6 min 54 s for 0.6 mm thickness, to 7 min 30 s for 0.4 mm thickness.

MRI image processing was performed using OsiriX open source software (version 8.0.2, Pixmeo, Geneva, Switzerland). The volume of the CPA cistern was then measured as described previously.^{4,9} Briefly, the CPA cistern was defined as the area between the anterior surface of the pons and cerebellum and the posterior surface of the petrous bone. The cerebellar flocculus was defined as the posterior limit, and the midline was defined as the anterior limit. The median line was identified by drawing a line between the anterior median fissure and the median sulcus of the floor of the fourth ventricle. The volume of the CPA cistern, with 1.2 mm thickness, was calculated from the cross-sectional measurement of the same sections passing through the trigeminal nerve root entry zone. Although the volume of the CPA cistern was previously calculated using 1.0 mm slices,⁹ the slice thickness used in the current study was 0.6 mm because the volume of the CPA cistern with 1.2 mm slice thickness was calculated. The volume of the CPA cistern was measured bilaterally. The volume measurement was performed blinded to the clinical data, such as the affected side of the TN, and no revision was possible after unblinding to the clinical data.

Cistern Deviation Index values were calculated to represent the degree of deviation of the CPA cistern, as previously described.⁹ Briefly, the index was the numerical value of the number obtained by dividing the volume of the affected side by the total volume of both sides, multiplied by 100.

Statistical analysis

χ^2 tests were used to test the significance of differences between groups for categorical data. Mann-Whitney *U*-tests were used to compare continuous data, and Wilcoxon signed-rank tests were used to assess the significance of CPA cistern volume differences between the affected and unaffected sides. All statistical analyses were performed

using JMP version 12.0.1 (SAS Institute Inc., Cary, NC, USA). The level of significance was set at $P < 0.05$.

Results

Patient characteristics

Patient characteristics are summarized in Table 1. Among the 51 patients enrolled in this study, the mean age was 61.94 ± 13.03 years; 25 were males and 26 were females. In this sample, 30 patients exhibited TN on the right, and 21 on the left. Thirty-four cases were caused by the superior cerebellar artery, and nine were caused by the anterior inferior cerebellar artery. The follow-up period among the 51 patients was 18.09 ± 8.20 months. The mean volume of the CPA cistern on the affected side was significantly smaller than the unaffected side ($215.57 \pm 54.57 \text{ mm}^3$ and $233.71 \pm 59.07 \text{ mm}^3$, respectively; $P < 0.001$).

Table 1 Characteristics of patients

	Total ($n = 51$)	
Age (years)	61.94 ± 13.03	
Sex		
Male	25	
Female	26	
Side		
Right	30	
Left	21	
Topography		
V1 or V1 + V2	5	
V2	9	
V3	8	
V2 + V3	29	
Compressing vessel		
SCA	34	
AICA	9	
SCA + AICA	2	
VA or BA	5	
PICA	1	
Period to the endpoint (months)	18.09 ± 8.20	
Volume of CPA cistern (mm^3)	Affected side	Unaffected side
	215.57 ± 54.59	$233.71 \pm 59.07^*$

AICA: anterior inferior cerebellar artery, BA: basilar artery, CPA: cerebellopontine angle, SCA: superior cerebellar artery, VA: vertebral artery, *Unaffected side was statistically larger than affected side ($P < 0.001$). P -values calculated using Pearson's chi-square tests for categorized data and Mann-Whitney-U tests for continuous data.

Comparison of various parameters between recurrent and non-recurrent patients

Among the 51 patients, recurrence of TN occurred in 5 (10%) patients. None of the patients underwent a second operation, even in cases with post-operative recurrence. There were no significant differences in age, sex, side, or topography of facial pain between the recurrence and non-recurrence group. The follow-up period of non-recurrent patients was 19.51 ± 7.17 months and the pain relief periods of recurrent patients were 4.96 ± 4.87 months. There was no significant difference in the period between MVD and post-operative MRI between the recurrence and non-recurrence groups (2.92 ± 0.81 months and 2.43 ± 0.44 months, respectively; $P = 0.155$). Moreover, there was no significant difference between the recurrent and non-recurrent patients in mean serum levels of CRP immediately after surgery ($0.11 \pm 0.10 \text{ mg/dl}$ vs. $0.22 \pm 0.38 \text{ mg/dl}$; $P = 0.280$), approximately one week after surgery ($0.94 \pm 0.38 \text{ mg/dl}$ vs. $0.94 \pm 0.70 \text{ mg/dl}$; $P = 0.639$), and the maximum value in the hospital ($5.42 \pm 1.63 \text{ mg/dl}$ vs. $4.76 \pm 3.19 \text{ mg/dl}$; $P = 0.289$) (Table 2).

Pre- and post-operative Cistern Deviation Index

Pre-operative Cistern Deviation Index scores in the recurrence group were significantly lower than those in the non-recurrence group (43.17 ± 5.09 and 48.49 ± 3.32 , respectively; $P = 0.035$). On the other hand, there was no significant difference in the post-operative Cistern Deviation Index between the recurrent and non-recurrent patients (41.54 ± 7.21 and 44.58 ± 5.53 ; $P = 0.295$; Table 3).

Pre- and post-operative change in the volume of CPA cistern

Overall pre-operative CPA cistern volume on the operated side was $214.66 \pm 55.56 \text{ mm}^3$ and was significantly reduced to $187.14 \pm 59.96 \text{ mm}^3$ after surgery ($P = 0.006$). On the unaffected side, pre-operative volume was $233.00 \pm 58.14 \text{ mm}^3$ and was similar ($230.04 \pm 56.71 \text{ mm}^3$) after surgery.

On the affected side, the post-operative volume of the CPA cistern in the recurrence group demonstrated a tendency toward smaller values compared with those of pre-operative volume ($147.04 \pm 20.80 \text{ mm}^3$ vs. $171.12 \pm 25.45 \text{ mm}^3$; $P = 0.189$). The same pattern was found in the non-recurrence group, and the difference was significant ($189.78 \pm 59.89 \text{ mm}^3$ vs. $220.26 \pm 54.84 \text{ mm}^3$; $P < 0.001$). Regarding pre- vs. post-operative volume reduction, there was no significant difference between the recurrence and non-recurrence groups ($24.08 \pm 27.10 \text{ mm}^3$ vs. $30.48 \pm 35.64 \text{ mm}^3$, respectively; $P = 0.84$) (Table 4).

Table 2 Univariate analysis of pre-operative clinical characteristics associated with outcome of MVD

	Recurrence (<i>n</i> = 5)	Non-recurrence (<i>n</i> = 46)	<i>P</i> -value
Age (years)	60.00 ± 12.40	62.15 ± 13.21	0.579
Sex (male/female)	4/1	21/25	0.145
Side (right/left)	3/2	27/19	0.955
Topography			0.888
V1 or V1 + V2	0	5	
V2	1	8	
V3	1	7	
V2 + V3	3	26	
Compressing vessel			0.597
SCA	5	29	
AICA	0	9	
SCA + AICA	0	2	
VA or BA	0	5	
PICA	0	1	
Period to the endpoint (months)	4.96 ± 4.87	19.51 ± 7.17	0.001
Period to the postoperative MRI (months)	2.92 ± 0.81	2.43 ± 0.44	0.155

AICA: anterior inferior cerebellar artery, BA: basilar artery, MRI: magnetic resonance imaging, MVD: microvascular decompression, SCA: superior cerebellar artery, VA: vertebral artery, *P*-values calculated using Pearson's chi-square tests for categorized data and Mann–Whitney-U tests for continuous data. Cistern Deviation Index defined as the value multiplied by 100 to the number obtained by dividing the volume of the affected side by the total volume of both sides.

Table 3 Pre- and post-operative Cistern Deviation Index associated with outcome of MVD

	Recurrence (<i>n</i> = 5)	Non-recurrence (<i>n</i> = 46)	<i>P</i> -value
Preoperative Cistern Deviation Index	43.17 ± 5.09	48.49 ± 3.32	0.035
Postoperative Cistern Deviation Index	41.54 ± 7.21	44.58 ± 5.53	0.295

MVD: microvascular decompression, *P*-values calculated using Mann–Whitney-U tests for continuous data. Cistern Deviation Index defined as the value multiplied by 100 to the number obtained by dividing the volume of the affected side by the total volume of both sides.

Table 4 The volume change of the CPA cistern before and after operation

	Affected side			Unaffected side		
	Recurrence	Non-recurrence	<i>P</i> -value	Recurrence	Non-recurrence	<i>P</i> -value
Preoperative	171.12 ± 25.45	220.26 ± 54.84	0.044	227.52 ± 47.64	234.13 ± 59.89	0.635
Postoperative	147.04 ± 20.80	189.78 ± 59.89	0.642	209.52 ± 40.59	231.49 ± 57.14	0.544
ΔV (pre-post)	24.08 ± 27.10	30.48 ± 35.64	0.840	18.00 ± 21.64	2.64 ± 51.36	0.004

CPA: cerebellopontine cistern, *P*-values calculated using Mann–Whitney-U tests.

The CPA cistern on the unaffected side of the recurrence group tended to have a smaller post-operative volume (pre-operative $227.52 \pm 47.64 \text{ mm}^3$; post-operative $209.52 \pm 40.59 \text{ mm}^3$; $P = 0.188$). On the unaffected side, the recurrence group exhibited a significantly greater post-operative volume reduction than the non-recurrence group ($18.00 \pm 21.64 \text{ mm}^3$ vs. $2.64 \pm 51.36 \text{ mm}^3$, respectively; $P = 0.004$) (Table 4). Figure 1 shows the pre- and post-operative CPA cistern volume reduction in a recurrent case.

Discussion

The concept of NVC is widely accepted as the etiology of TN. MRI using 3D-FIESTA and other high-resolution sequences is excellent for the detection of NVC.^{3,11,12} Anderson et al. reported that the offending vessel was correctly identified using this technique, comparing MRI findings with intraoperative observations (sensitivity, 76%; specificity, 75%).¹³ Moreover, several recent studies

have revealed that pre-operative assessment of NVC using 3T MRI, compared with 1.5T MRI, produced superior anatomical conspicuity, higher resolution, and greater sensitivity and specificity;^{7,8,14} therefore, we used high-resolution 3T MRI.

As previously reported, the volumetric measurement of anatomical features obtained from modern MRI, including the area or volume of the CPA cistern, the degree of the CPA, and the length or the volume of the trigeminal nerve, play an important role in determining the factors involved in TN pathogenesis.⁴⁻⁶ Park et al. evaluated the volume of the CPA cistern using cross-sectional measurement of the root entry zone and demonstrated that there was a significant difference in the MRI findings of the affected side compared with the unaffected side of the trigeminal nerve.⁴ Moreover, Parise et al. found that the cross-sectional area of the CPA cistern on the affected side was smaller than on the unaffected side, and concluded that the measurement of the CPA cistern was useful for surgical planning.⁶ These studies support the hypothesis that a smaller CPA cistern leads to a higher incidence of symptomatic NVC. In our study investigating volumetric measurement of the CPA cistern, these results were confirmed. Concerning volumetric measurement, to suppress variations in measurement, we measured the localized volume around the root entry zone (REZ). We believed that evaluation of the volumetric measurement with thickness would provide more accurate results as a pathogenic factor of TN than large volumetric measurement or the area of the CPA cistern.

MVD has been the standard treatment for TN since it was introduced by Jannetta in 1967.¹⁵ However, complete pain relief is not achieved in all patients with TN following MVD, and recurrence of trigeminal pain is observed in some patients after surgery. Barker et al. reported that immediate and complete post-operative pain relief occurs in approximately 80% of patients, and 75% experience pain relief 1 year after MVD.¹⁶ Sun et al. analyzed 61 TN patients with arterial compression and reported that 18% exhibited recurrence of TN.¹⁷ Burchiel et al. reported that 31% of patients experienced post-operative recurrence after decompression of the offending artery.¹⁸ Moreover, several studies have reported that >70% of patients experience pain relief for 5 to 20 years after MVD.¹⁹⁻²² The present study revealed that 5 of 51 (10%) patients exhibited recurrence of TN, with a mean follow-up period of 18.09 ± 8.20 months. Several predictive factors of recurrence have been reported in previous studies, including female sex,^{16,17} atypical symptoms,^{16,23} longer duration of symptoms,^{16,23,24}

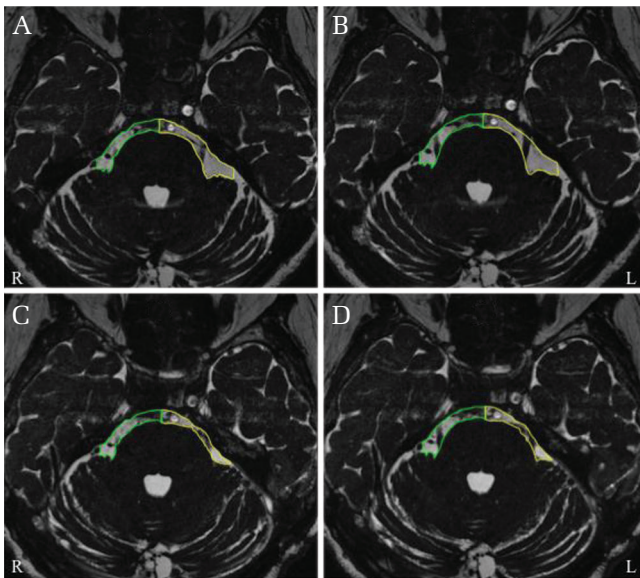


Fig. 1 Pre- (A, B) and post-operative (C, D) fast imaging employing steady-state acquisition (FIESTA) of a 67-year-old woman with recurrent left-sided trigeminal neuralgia exhibiting severe post-operative volume reduction in the affected cerebellopontine angle (CPA) cistern (yellow enclosed area), and mild reduction in the unaffected CPA cistern (green enclosed area). The CPA cistern volume of eight images was measured in this case. On the affected left side, pre-operative CPA cistern volume was 204.7 mm^3 , and post-operative volume was 153.1 mm^3 . On the unaffected right side, pre-operative CPA cistern volume was 232.3 mm^3 , and post-operative volume was 219.1 mm^3 .

severe compression of the trigeminal nerve,⁸⁾ and venous compression.^{16,24–26)} In this study, there was no statistical difference between recurrent patients and non-recurrent patients in many features previously reported as prognostic factors, including sex, age, and topography of facial pain.

In the current study, we examined the role of volumetric measurement of the CPA cistern as a potential predictive factor for post-operative recurrence. We developed the Cistern Deviation Index, and reported the availability of this index for the volumetric measurement of the CPA cistern in the analysis of inter-individual variation between recurrent and non-recurrent patients.⁹⁾ Cistern Deviation Index scores before surgery were significantly correlated with post-operative recurrence, and our current 3T MRI results are consistent with this previous finding.

Because pre-operative Cistern Deviation Index scores were a significant predictive factor for recurrence, we analyzed post-operative CPA cistern volume in more depth. We first focused on post-operative volumetric change on the affected side. We found that the CPA cistern on the affected side exhibited a volume reduction of $24.08 \pm 27.10 \text{ mm}^3$ after surgery in recurrent cases and $30.48 \pm 35.64 \text{ mm}^3$ in non-recurrent cases, with no statistical difference between recurrent and non-recurrent cases. In cases of MVD with small craniotomy, we found that the post-operative CPA cistern volume on the operated side was reduced. Because surgical intervention inevitably causes adhesion of cerebral tissues or the arachnoid membrane,²⁷⁾ the volume of the CPA cistern on the operated side is usually reduced. Furthermore, because the patients underwent the typical MVD procedure and experienced an inflammatory reaction, the same reactions occurred on the operative side. Therefore, post-operative CPA volume changes on the affected side do not serve as an associated factor for recurrence.

We then examined post-operative volume change on the healthy side. While there was no significant volume change in non-recurrent cases, recurrent cases exhibited significant volume reduction after surgery. One possible explanation for the reduction in cistern volume in recurrent cases is that a post-operative inflammatory reaction may extend to the healthy side and reduce the volume. Although we observed no cases with post-operative meningitis, the possibility of chemical meningitis or other conditions cannot be excluded. Most patients reported post-operative headache and also exhibited an increase in blood levels of CRP. If an inflammatory reaction is sufficiently strong to induce volume reduction on the unaffected side, an affected trigeminal nerve

with arterial compression in the narrow CPA cistern may be damaged, potentially leading to the recurrence of TN.

Thus, our current findings suggest that volume reduction on the healthy side reflects the degree of post-operative inflammatory reaction(s); consequently, there is a possibility that these inflammatory reactions contribute the post-operative recurrence of TN. Several previous studies have highlighted the importance of pre-operative volumetric measurement in TN patients. However, to our knowledge, no previous studies have evaluated the post-operative change in anatomical parameters using 3T MRI, and investigated differences between recurrent and non-recurrent patients with TN. Although we previously discussed that the widening of the CPA cistern may contribute to reducing the recurrence rate, we found this may not be the case. We need to prevent post-operative inflammatory reactions and/or adhesions so as not to spread the influence to the unaffected side. Future studies involving a larger number of cases and more comprehensive examination of inflammation are needed to test this possibility.

Conclusions

We examined the utility of CPA cistern volumetric measurement using high-resolution 3T MRI, and evaluated Cistern Deviation Index scores and changes in volumetric features pre- and post-operatively. The pre-operative Cistern Deviation Index was a useful parameter to predict the recurrence of TN. On the affected side, the post-operative CPA cistern volume was reduced in both recurrent and non-recurrent cases. In contrast, on the unaffected side, the degree of volume change before and after surgery of the CPA cistern was significantly different between recurrent and non-recurrent cases. Post-operative inflammatory reaction(s) in the CPA cistern may reduce its volume and play an important role in recurrence after MVD.

Conflicts of Interest Disclosure

The authors have no conflicts of interest to declare. All authors who are members of the Japan Neurosurgical Society (JNS) have registered online, self-reported COI Disclosure Statement forms through the *Journal's* website.

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Address reprint request to: Yoshiki Obata, MD, Department of Neurosurgery, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8519, Japan.
e-mail: obata-tmd@umin.ac.jp