Degree of distal trigeminal nerve atrophy predicts outcome after microvascular decompression for Type 1a trigeminal neuralgia

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OBJECT Trigeminal neuralgia is often associated with nerve atrophy, in addition to vascular compression. The authors evaluated whether cross-sectional areas of different portions of the trigeminal nerve on preoperative imaging could be used to predict outcome after microvascular decompression (MVD).

METHODS A total of 26 consecutive patients with unilateral Type 1a trigeminal neuralgia underwent high-resolution fast-field echo MRI of the cerebellopontine angle followed by MVD. Preoperative images were reconstructed and reviewed by 2 examiners blinded to the side of symptoms and clinical outcome. For each nerve, a computerized automatic segmentation algorithm was used to calculate the coronal cross-sectional area at the proximal nerve near the root entry zone and the distal nerve at the exit from the porus trigeminus. Findings were correlated with outcome at 12 months.

RESULTS After MVD, 17 patients were pain free and not taking medications compared with 9 with residual pain. Across all cases, the coronal cross-sectional area of the symptomatic trigeminal nerve was significantly smaller than the asymptomatic side in the proximal part of the nerve, which was correlated with degree of compression at surgery. Atrophy of the distal trigeminal nerve was more pronounced in patients who had residual pain than in those with excellent outcome. Among the 7 patients who had greater than 20% loss of nerve volume in the distal nerve, only 2 were pain free and not taking medications at long-term follow-up.

CONCLUSIONS Trigeminal neuralgia is associated with atrophy of the root entry zone of the affected nerve compared with the asymptomatic side, but volume loss in different segments of the nerve has very different prognostic implications. Proximal atrophy is associated with vascular compression and correlates with improved outcome following MVD. However, distal atrophy is associated with a significantly worse outcome after MVD.


KEY WORDS microvascular decompression; nerve atrophy; trigeminal neuralgia; pain

MICROVASCULAR decompression (MVD) has emerged as the most common surgical procedure for medically refractory trigeminal neuralgia (TN). While it can be curative for a majority of patients with typical TN symptoms, the response to MVD is sometimes incomplete and some patients do not respond at all. Risk factors for pain recurrence include lack of immediate relief, longer preoperative duration of symptoms, female sex, lack of vascular compression at surgery, and a significant component of constant, rather than episodic, pain. Nevertheless, some patients who otherwise appear to be excellent surgical candidates still experience suboptimal outcome.

Recent improvements in imaging technology have dramatically improved the ability to visualize neurovascular relationships in the vicinity of the trigeminal nerve, which has led to a number of investigations into potential preoperative tools for surgical planning and postoperative prognosis. Structural changes in the trigeminal nerve, leading to volume loss, have been well documented and a number of studies have demonstrated that nerve atrophy ipsilateral to the symptomatic side is visible on preoperative MRI. Recently, Leal et al. demonstrated that atrophy in the midcisternal region of the nerve is associated with more severe vascular compression, and these patients tend to exhibit greater clinical improvement following surgical decompression of the nerve. However, it is unclear whether the nerve atrophy is entirely due to physical compaction by the compressing vessel or whether it is due, in part, to irreversible structural changes. Distin-
guishing between these 2 processes may have important implications for long-term outcome. The purpose of this study was to evaluate whether preoperative evaluation of atrophy of different segments of the trigeminal nerve might be used to predict responses to MVD.

Methods

Patient Population and Surgical Treatment

Twenty-six consecutive patients with unilateral Bur- chiel Type 1a TN treated with MVD between 2009 and 2012 were enrolled in the study. All patients had triggerable pain, pain-free intervals, and a history of response to antiepileptic medication with decreased efficacy or worsening side effects. Patients were excluded from the study if they endorsed any significant component of constant background pain or sensory loss, if they had a history of multiple sclerosis, or if they had a history of surgical treat-

Imaging Protocol

MRI examinations were performed on a Philips Achieva 3-T MR scanner (Koninklijke Philips NV), and images were obtained using a dedicated, commercially available, 6-channel head coil with SENSE parallel processing capabil-

Postprocessing and Data Collection

Postprocessing was performed on an Apple Macin- tosh Power PC Laptop (Apple, Inc.) running OS 10.6.8 and OsiriX imaging software version 8.8.5 (32-bit ver-

Surgery

All patients underwent a retrosigmoid craniectomy fol-

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 17.0 (SPSS, Inc.). A 2-tailed Student t-test and 1-way ANOVA were used for parametric data, and a Fisher exact test was used for categorical data. A multivariate analysis was per-

Results

Patient Characteristics

Characteristics of the study patients are shown in Table

Nerve Atrophy

Clear visualization of the trigeminal nerve was possible in all cases. The results of comparison of nerve size ipsi-

Determination of atrophy of different segments was performed. The cross-sectional area of each trigeminal nerve at the point of entry into the pons was measured using OsiriX imaging software. Imaging was performed using a balanced fast-field echo technique centered on the pons in the region of the trigeminal nerve. Imaging characteristics were as follows: TR 5.8 msec, TE 2.4 msec, flip angle 45°, field of view 15 cm, and matrix 512 × 512. Slice thickness was 0.6 mm, with 0.3-mm³ voxels.

Postprocessing was performed on an Apple Macin-

tional to compare the relative contribution to surgical outcome (using the Barrow Neurological Institute Scale) of 8 predictors: age, sex, side of symptoms, duration of symp-

When proportional atrophy compared with the con-

Atrophy of the proximal trigeminal nerve was slig-

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Atrophy of the proximal trigeminal nerve was slig-

Atrophy of the proximal trigeminal nerve was slig-


dress a same day of symptoms, duration of symp-

ed as statistically significant. Bonferroni’s correction was used where appropriate. The study was reviewed and approved by our institutional review board.
of distal atrophy was found to be significant ($t(26) = 2.19$, $p < 0.05$). Univariate analysis demonstrated a significant relationship between outcome and degree of distal atrophy ($r = 0.45$, $p < 0.05$). There was no correlation between outcome and any other variable, and no correlation between either type of atrophy and duration of symptoms. Among the 7 patients who had greater than 20% loss of nerve volume in the distal nerve, 5 (71%) were not pain free at long-term follow-up ($p < 0.05$, Fisher exact test). Therefore, in our population, distal atrophy of greater than 20% was able to predict recurrence of pain with a sensitivity of 88% and a specificity of 56%.

Illustrative Cases

Figure 4 demonstrates measurements at the proximal and distal nerve for Patient 11, a 65-year-old woman with right V3 symptoms who was found to have Grade III arterial compression at surgery (artery displacing nerve) and who experienced excellent long-term outcome after MVD, with freedom from pain while not taking medications. Measurement of the proximal nerve demonstrated atrophy on the right near the point of arterial compression, but, distally, both trigeminal nerves were symmetric. Fig. 5 demonstrates measurements for Patient 20, a 41-year-old woman with right V2 and V3 symptoms who was found to have Grade I arterial compression at surgery (artery touching nerve but not indenting) and who experienced early recurrence of symptoms, ultimately requiring a trigeminal radiofrequency rhizolysis. Measurement of the distal nerve demonstrated atrophy on the right, but the proximal trigeminal nerves were symmetric.

Discussion

In this study, we examined cross-sectional areas of the proximal and distal trigeminal nerve in a series of 26 patients undergoing MVD for TN. We found a trend toward better surgical outcome in patients in whom preoperative MRI demonstrates significant atrophy of the proximal segment of the nerve due to direct compression by the offending vessel. Conversely, atrophy of the distal portion of the nerve (at Meckel’s cave) was associated with significantly worse clinical outcome and appeared to be a negative prognostic sign for MVD, suggesting that distal atrophy may indicate irreversible pathological changes within the nerve.

Improved imaging techniques have recently allowed superior characterization of the substrate of TN, including changes intrinsic to the nerve and its immediate environment. Numerous studies have assessed the pattern of neurovascular conflict (NVC) due to crowding of the cisternal space and the neurovascular structures that occupy that space and its association with symptoms of TN.5,17 Park and colleagues retrospectively reviewed MRI studies of 26 patients with unilateral TN treated with Gamma Knife radiosurgery.17 They found a significantly smaller cross-sectional area in the cerebello-pontine angle cistern in the symptomatic side compared with the asymptomatic side, as well as a shorter cisternal segment of the trigeminal nerve on the affected side. Both of these findings were felt.
to contribute to an increased opportunity for NVC, manifesting in symptoms of TN. Similarly, a study by Rasche and colleagues assessed 25 patients with unilateral, idiopathic TN who had not undergone an invasive procedure involving the gasserian ganglion or trigeminal nerve. High-resolution MRI studies obtained in these patients were compared with those acquired in 17 healthy, matched control subjects. The authors found a significantly smaller volume of the pontomesencephalic cistern on the affected side compared with the unaffected side in TN patients that was not seen in healthy control subjects. The diminished cisternal volume, due to a smaller Meckel's cave and a descending tentorium on the symptomatic side, was thought to result in a higher incidence of NVC in these patients.

In contrast, Horínek and colleagues evaluated 18 patients with unilateral TN and compared them radiographically to age- and sex-matched control subjects to investigate posterior fossa size, asymmetry of the pontomesencephalic cistern volume, and trigeminal nerve atrophy. Interestingly, the authors did not find a significant difference in posterior fossa size or asymmetry of the pontomesencephalic cistern volume. However, they did discover significant atrophy of the symptomatic trigeminal nerve compared with the contralateral asymptomatic side in subjects, which was not seen in control patients with a similar degree of NVC.

It is important to note that trigeminal nerve atrophy ipsilateral to TN symptoms has been documented by a number of investigators in previous studies, compared with the contralateral side and with asymptomatic indi-

### TABLE 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yrs), Sex</th>
<th>Side of Pain</th>
<th>Distribution of Pain</th>
<th>Duration of Symptoms (mos)</th>
<th>Op Findings*</th>
<th>Follow-Up (mos)</th>
<th>Outcome Grade†</th>
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<td>V2</td>
<td>168</td>
<td>2</td>
<td>12</td>
<td>I</td>
</tr>
</tbody>
</table>

* Intraoperative findings were graded as follows: 1 = arterial contact; 2 = arterial indentation; 3 = arterial nerve displacement.
† Outcome was graded as follows using the Barrow Neurological Institute Pain Intensity Scale: I = no pain, no medication; II = occasional pain, no medication; III = pain controlled by medication; IV = pain not controlled by medication but improved; V = no relief.

### TABLE 2. Relationship of clinical and surgical findings to long-term outcome

<table>
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<tr>
<th>Characteristic</th>
<th>Pain Free (n = 17)</th>
<th>Not Pain Free (n = 9)</th>
<th>p Value</th>
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<tr>
<td>Mean age (yrs)</td>
<td>67.5 ± 3.9</td>
<td>61.3 ± 4.7</td>
<td>0.27</td>
</tr>
<tr>
<td>Female sex, no. (%)</td>
<td>12 (71)</td>
<td>6 (67)</td>
<td>0.33</td>
</tr>
<tr>
<td>Rt-sided symptoms, no. (%)</td>
<td>10 (59)</td>
<td>7 (78)</td>
<td>0.22</td>
</tr>
<tr>
<td>Mean duration of symptoms (mos)</td>
<td>54 ± 16</td>
<td>80 ± 19</td>
<td>0.26</td>
</tr>
<tr>
<td>Arterial compression, no. (%)</td>
<td>15 (88)</td>
<td>7 (78)</td>
<td>0.33</td>
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</table>

* Mean values are presented ± SD.
In a retrospective study of 30 patients with idiopathic TN, Ha and colleagues demonstrated that, on preoperative FIESTA MRI, there was significantly more atrophy at the cisternal segment of the trigeminal nerve on the affected side than on the unaffected side compared with the affected and unaffected sides of age- and sex-matched control patients with hemifacial spasm. Of note, these authors also found a significant association between the sharpness of the trigeminal-pontine angle on the affected side compared with the unaffected side, which was not found in the control group. Likewise, a study by Erbay and colleagues looked at using MRI studies obtained in 36 patients with unilateral TN treated with Gamma Knife radiosurgery. The authors found that both the diameter and the cross-sectional area of the trigeminal nerve, measured 5 mm distal to its take off from the pons, were significantly smaller on the affected side than the asymptomatic side. Examination using diffusion tensor imaging has demonstrated that nerve atrophy is associated with a lower fraction of anisotropy and higher apparent diffusion coefficient. A prospective study of 62 subjects by Kress and colleagues found that nerve atrophy could be used not only to distinguish patients with TN but also to identify the side of symptoms.

While many studies have assessed the relationship between preoperative radiographic studies and clinical symptoms, relatively few studies have compared preoperative imaging findings with postoperative outcome following MVD. One study by Jo and colleagues retrospectively reviewed the cases of 141 patients with primary TN treated with MVD by a single surgeon and looked at preoperative images and intraoperative findings to predict outcomes. These investigators found preoperative documentation of severe conflict by a single vessel to be a good prognostic sign. Another recent study, by Leal and colleagues, evaluated 50 patients with unilateral idiopathic TN to determine if there is a relationship among the characteristics of symptoms, NVC, and clinical outcomes after MVD. They demonstrated that greater atrophy at the trigeminal root entry zone was associated with more severe vascular compression and significantly better clinical outcome, which is consistent with our observation that atrophy in the proximal nerve near the root entry zone is associated with a trend toward better outcome. However, that study did not evaluate the nerve along its entire course but only measured the midcisternal segment. Our data suggest that the story may be a bit more complex: Atrophy of the nerve in the cistern seems to be associated with better prognosis, possibly due to its correlation with vascular compression, but more distal atrophy (i.e., away from the site of vascular compression) might represent a poor prognosis, possibly due to intrinsic changes in the nerve. As such, we have been able to distinguish 2 types of trigeminal nerve atrophy with different implications for outcome after MVD.

The etiology of nerve atrophy in TN is not clear but is
Nerve atrophy in trigeminal neuralgia likely to involve some combination of physical nerve compaction due to extrinsic compression and intrinsic volume loss at the cellular level. Previous studies using MRI have demonstrated that neurovascular compression without atrophy is common even in asymptomatic individuals, but the presence of atrophy is much more likely to be associated with symptoms.1,15,18 Pathological analysis of nerve specimens obtained at surgery have demonstrated clear histological and ultrastructural changes in the symptomatic trigeminal nerve, including focal demyelination and axonal loss, which seem to be correlated with the severity of vascular compression.3,6,12 These changes might lead to alterations in conduction that lead to the development and progression of TN symptoms. Devor and colleagues found that, in segments of resected nerve that were the most severely damaged, very few axons remained, and those that did remain were almost all demyelinated.1 Interestingly, the region of nerve directly compressed by the offending vessel was relatively spared these changes. These pathological findings correlate well with our results, which suggest that TN may be associated with 2 distinct types of atrophy that have very different clinical implications. Atrophy of the proximal trigeminal nerve at the root entry zone is highly associated with vascular compression and, therefore, is a good prognostic sign. On the other hand, atrophy of the distal nerve is independent of compression and is associated with a much worse outcome, which implies that irreversible neuropathic structural changes might have occurred. This supports the concept that TN might be a progressive condition on the continuum of trigeminal neuropathic changes. Future studies involving evaluation of nerve atrophy in patients with constant pain (Type 2 symptoms) might help to confirm it.

Limitations of this study include its retrospective nature and heterogeneity of symptom duration, which varied from less than 1 year to more than 1 decade. Because we studied a homogeneous population (individuals with classic Type 1a trigeminal neuralgia who had not undergone previous treatment), the number of subjects is small compared with previous studies that included a more diverse set of patients. Also, since this population is known to do well after MVD, much of our analysis is based on the relatively small number of patients with suboptimal outcome, and our findings, therefore, should be interpreted with caution. Although follow-up was greater than 12 months for all patients, median follow-up was only 13 months, and it is possible that more relapses might have been seen if patients were observed over a longer time. Our use of an automatic technique for image segmentation was intended to allow objective analysis, but the interimage differences in signal intensity made it necessary to define the precise border of the nerve; other sequences, such as diffusion tractography, may provide more objective data and thus be a better measure of nerve injury. Identification of distal nerve atrophy does not appear sufficient for patient selec-

**Fig. 4.** MR images providing examples of nerve evaluation in a patient with proximal atrophy. This patient had right-sided symptoms, severe neurovascular compression at surgery (Grade III), and excellent long-term outcome. A: Axial image demonstrating location of measurement of the proximal nerves. B: Coronal reconstruction with segmentation (red) demonstrating proximal nerve atrophy on the symptomatic side (arrow) compared with the asymptomatic side (arrowhead). C: Axial image demonstrating location of measurement of the distal nerves. D: Coronal reconstruction with segmentation (red) demonstrating no proximal nerve atrophy of the symptomatic nerve (arrow) compared with the asymptomatic nerve (arrowhead). Figure is available in color online only.

**Fig. 5.** MR images providing examples of nerve evaluation in a patient with distal atrophy. This patient had right-sided symptoms, mild neurovascular compression at surgery (Grade I), and poor long-term outcome with early recurrence of pain. A: Axial image demonstrating location of measurement of the proximal nerves. B: Coronal reconstruction with segmentation (red) demonstrating no distal atrophy of the symptomatic nerve (arrow) compared with the asymptomatic nerve (arrowhead). Figure is available in color online only.
tion because some patients with severe distal atrophy were cured and one-half of the patients with residual pain did not have a significant degree of atrophy preoperatively. Finally, just as neurovascular compression was significantly more common and severe when proximal atrophy was seen, there was also a nonsignificant trend toward less neurovascular compression with distal atrophy, so distal atrophy may be more common in TN that occurs in the relative absence of neurovascular compression. In this context, it is not possible to distinguish whether degree of nerve atrophy or severity of vascular compression is more important for good long-term outcome. A prospective study of the effect of distal nerve atrophy will be necessary to confirm its utility as a clinical tool.

Conclusions

TN is frequently associated with atrophy of the root entry zone of the affected nerve. Proximal nerve atrophy is usually associated with significant vascular compression and tends to be correlated with an improved outcome following MVD. In contrast, distal atrophy is associated with a worse outcome after MVD, which might indicate that irreversible pathological changes have occurred independent of the severity of neurovascular compression. Future studies are necessary to determine the utility of this finding for patient selection.

References


Author Contributions
Conception and design: Miller, Duan, Sweet. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Miller, Duan, Sweet. Critically revising the article: Miller, Duan. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Miller. Administrative/technical/material support: Miller.

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