CyberKnife Stereotactic Radiosurgical Rhizotomy for Trigeminal Neuralgia: Anatomic and Morphological Considerations

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OBJECTIVE: To search for correlations between specific anatomic, geometric, and morphological properties of the trigeminal nerve and the success of radiosurgical treatment and elimination of facial hypesthesia as a complication.

METHODS: Forty-six patients with at least 6 months of follow-up after CyberKnife (Accuray, Inc., Sunnyvale, CA) rhizotomy were retrospectively reviewed. Patients treated after 2004 were entered into the study after congruity in treatment parameters was established. Anatomic variations regarding the length of each nerve segment and angle of trigeminal nerve takeoff from brainstem to Meckel's cave in the axial and sagittal planes were studied. Dose distribution to surrounding critical structures (brainstem and trigeminal ganglion) was measured. After spatial relationships of involved structures and dose distributions were recorded, their relationship to treatment success, failure, or complication (primarily facial numbness) was tabulated.

RESULTS: Forty-five patients (97.2%) experienced pain relief immediately or within weeks. Thirty-four patients maintained excellent outcome. Some degree of facial numbness developed in 18 patients (39.1%) and was mild in 11 of them (Grade II on the Barrow Neurological Institute scale). Patients with a sagittal-angle trigeminal nerve takeoff from the brainstem in the range of 150 to 170 degrees measured from the horizontal plane had a more favorable outcome ($P = 0.03$) than patients with less obtuse relationships to the proximal nerve origin. Patients who received higher doses of radiation to the brainstem/dorsal root entry zone of the trigeminal nerve experienced a higher rate of posttreatment facial anesthesia.

CONCLUSION: There may be important anatomic and geometric relationships between the treated trigeminal nerve and surrounding critical structures that warrant pretreatment target volume placement and dose distribution considerations.

KEY WORDS: Anatomy of trigeminal nerve, CyberKnife, Radiosurgery, Trigeminal neuralgia

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Trigeminal neuralgia (TN) afflicts 5 in 100 000 people. The pain is usually abrupt in onset with lancinating characteristics and is localized to 1 or more divisions of the trigeminal nerve, although it is described as "atypical" in a small percentage of treated patients (11). Anticonvulsants are often used as a front-line therapy for TN. Open surgical therapy for failed medical treatment includes microvascular decompression and a variety of "ablative" procedures.

ABBREVIATIONS: DBS, dose to brainstem; **DN**, dose to treated nerve segment; **MRI**, magnetic resonance imaging; **TN**, trigeminal neuralgia

Radiosurgical rhizotomy for TN was first introduced by Leksell (6) in 1951. Since the popularization of radiosurgical treatment for TN in the mid-1990s, there have been reports that gamma knife (Elekta AB, Stockholm, Sweden) radiosurgical treatment is effective in obtaining long-term pain relief in patients afflicted with TN (5, 10). CyberKnife (Accuray, Inc., Sunnyvale, CA) radiosurgical treatment of TN has a high rate of safety and efficacy, which parallels or supersedes results using other radiosurgical techniques (7, 13, 14). The frameless, noninvasive nature of the procedure is coveted by patients and their treating radiosurgeons. The success of the procedure and its ease of administration are factors in this increasingly used treatment modality.

Reports pertaining to individual characteristics of patients treated with stereotactic radiosurgery for TN from an anatomic and morphological standpoint are scarce (9). There are some references to the dose given to the treated trigeminal nerve and surrounding critical structures (1, 2, 14), yet there has been no mention of factors such as angular relationships between the treated trigeminal nerve and the brainstem, percentage of nerve treated to total length of nerve, or proximity of treated nerve segment to Meckel's cave and brainstem origin. Posttreatment facial anesthesia has been correlated with characteristics of the dose to the brainstem, but how this correlation applies to the proximal trigeminal nerve segment outside the target volume has not been reported.

Each patient is unique, with relevant variations in treatment anatomy. These diverse characteristics between patients can be objectively measured and accounted for in treatment planning. Ultimately, detailed analysis of each patient's local anatomy and morphology may contribute to better long-term outcomes and lower complication rates. This report attempts to correlate specific anatomic, geometric, and morphological attributes of the trigeminal nerve in individual patients treated with radiosurgery with the long-term alleviation of facial pain and avoidance of treatment-related facial hypesthesia.

PATIENTS AND METHODS

Patients treated for idiopathic TN from 2005 to 2007 were studied. Some patients had undergone previous failed microvascular decompression or other ablative procedures, and 2 patients in this study had undergone previous stereotactic radiosurgery. All patients had pretreatment facial pain of several years' duration, had tried and failed previous pharmacotherapy, and were deemed appropriate candidates for CyberKnife stereotactic radiosurgical rhizotomy of the trigeminal nerve. Only patients with available follow-up data for at least 6 months were included in this study. If patients had 2 or more CyberKnife treatments, only the first procedure was analyzed, as characteristics from this treatment session were most related to naïve anatomic and morphological variables. Forty-six patients in the total series qualified for the evaluation.

Radiosurgical trigeminal nerve rhizotomy was performed with the CyberKnife system using the technique described previously (14). Briefly, on fused pretreatment magnetic resonance imaging (MRI) and computed tomographic scans, segmentation tools were used to outline a 6-mm length of the retrogasserian trigeminal sensory root in the sagittal plane of the nerve, sparing the proximal 2 to 3 mm of dorsal root at the brainstem. Earlier patients in the cohort were treated with the 65-cm source to axis distance "trigeminal node set" providing a 6-mm collimator diameter. After the higher-output CyberKnife G4 model was installed at Stanford, patients were treated using a 5-mm collimator and an 80-cm source to axis distance. Four patients who experienced inadequate pain relief (3) or relapse (1) underwent repeat CyberKnife rhizotomy using the same protocol. The average length of treated nerve was 5.8 $\pm$ 0.7 mm (range, 4.0–8.0 mm). The maximum dose delivered to the treated nerve segment was 73.5 Gy (range, 71.4–86.2 Gy).

Clinical and anatomic characteristics of this patient population were taken into consideration. The treatment plan, the length of trigeminal nerve, trigeminal nerve relationships between the brainstem and trigeminal ganglion, angular takeoff from the brainstem of the trigeminal nerve, as well as length of nerve treated were studied. With regard to angle of takeoff, the axial angle was measured from the coronal plane, and the sagittal angle was measured from the axial plane. For each segment of length, the nerve from its brainstem exit to the center of the trigeminal nerve ganglion was divided as follows: a) from the center of the trigeminal ganglion to the distal end of the nerve, b) from the distal end of the nerve to the distal end of the treatment margin, c) from the distal treatment margin to the proximal treatment margin, and d) from the proximal treatment margin to the root exit at the brainstem (Fig. 1).

Response rates, pain control, recurrence, and incidence of hypesthesia were collected and correlated with anatomic variations of the trigeminal nerve and the dose to surrounding critical structures. Pain control was assessed using the Boulder-Stanford pain relief scale (8), on which

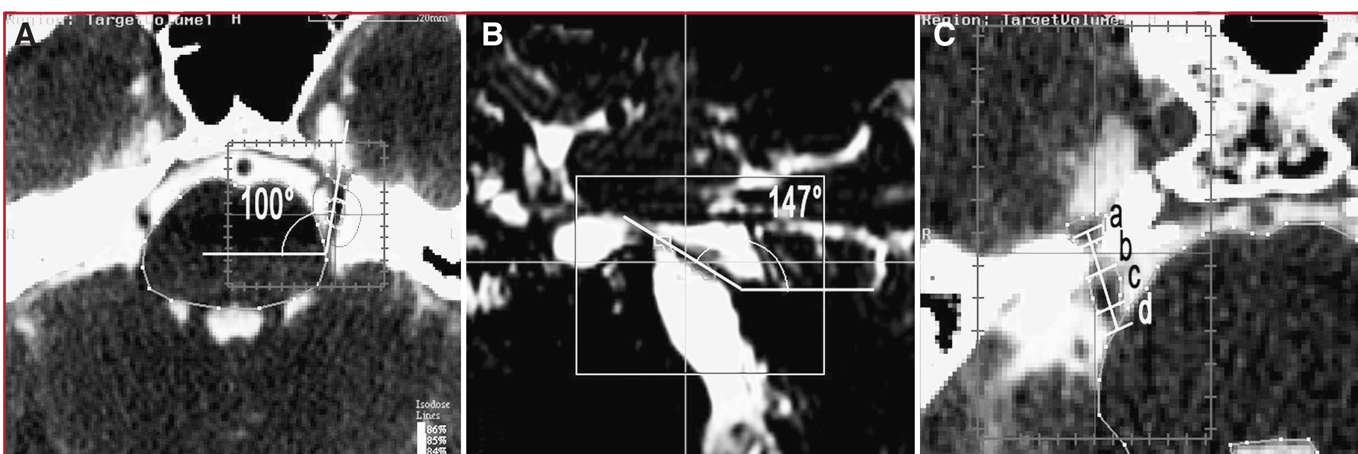

FIGURE 1. *Fused pretreatment magnetic resonance imaging and computed tomographic scans showing measurements of variations of anatomic features related to CyberKnife stereotactic radiosurgery for trigeminal neuralgia.* **A**, *the axial angle of the trigeminal nerve is measured from the coronal plane to the axis of the trigeminal nerve. It is 100 degrees in this case.* **B**, *the sagittal angle of the trigeminal nerve is measured from the horizontal plane. It is 147 degree in this case.* **C**, *measurements of distances (see text for detailed description). The length of the nerve is the sum of b, c, and d. the distance from the brainstem to the ganglion is the sum of a, b, c, and d.*

1 is excellent (>90% pain relief, completely off pain medications), 2 is moderate (>50% pain relief and <90% reduction in use of pain medications), 3 is mild (<50% relief, no change in use of pain medications), and 4 indicates no change in symptoms. Only excellent pain relief (i.e., patients off any pain medication for TN) was considered a successful treatment. Recurrences were defined as return of pain to the previous level or to at least 3 on the Boulder-Stanford pain relief scale.

The Barrow Neurological Institute facial hypesthesia scale and scoring system (12) was used to assess numbness. According to this scale, I indicates no facial numbness, II indicates mild facial numbness that is not bothersome, III indicates somewhat bothersome facial numbness, and IV indicates very bothersome facial numbness.

Logistic regression statistical analysis and Student's *t* test were performed to identify correlations among treatment parameters and clinical outcomes, durability of pain relief, and complications.

RESULTS

There were 29 women and 17 men in the series. The lateralization of pain was on the right in 29 patients and on the left in 17 patients. Eleven patients (24%) had failed previous surgical procedures; 14 had undergone microvascular decompression. A total of 10 patients had undergone a previous rhizotomy; open techniques were used in 3 patients, glycerol was used in 5 patients, and the gamma knife was used in 2 patients. The median age of the patients at the time of treatment was 73 years (range, 40–94 years). The mean follow-up time was 12.4 months (minimum, 6.2 months; maximum, 31.6 months), with a median of 10.5 months; no patients were lost to follow-up. Findings concerning anatomic variations of the trigeminal nerve and related structures are summarized in Table 1.

After CyberKnife radiosurgery, 45 of 46 patients reported some initial relief of pain. The pain recurred during the follow-up period in 7 of 45 patients. The degree of pain relief at the last follow-up evaluation was as follows: excellent in 34 patients, moderate in 6 patients, and no change in 6 patients. Logistic regression analyses were performed to determine which of the anatomic variations were predictive of better pain relief. Better pain relief was achieved when the sagittal angle was in the range of 150 to 170 degrees (logistic regression analysis, $P = 0.03$) (Table 2).

Some degree of facial numbness was reported by 18 (39.1%) of the 46 patients. The majority of cases of facial sensory change after the procedure were not bothersome and were considered mild (Grade II in 13 cases). There was no correlation between individual patients' anatomic and morphological variations and posttreatment facial numbness. There was, however, a correlation between the maximum dose delivered to the brainstem and posttreatment facial numbness (logistic regression analysis, $P = 0.01$) (Table 3). A maximum point of division in dose between those patients who avoided or developed facial numbness seemed to be at 5200 cGy (χ^2 test, $P = 0.02$).

DISCUSSION

Although it is known that the trigeminal nerve traverses the cistern somewhat rostrally and laterally from the brainstem to

TABLE 1. Anatomic variations of trigeminal nerve (n = 46)[a]

Anatomic measurement	No.
Axial angle (degrees)	
Range	77–125
Mean ± SD	100 ± 10.9
Sagittal angle (degrees)	
Range	116–229
Mean ± SD	155 ± 18.8
Length of trigeminal nerve (mm)	
Range	7.37–15.00
Mean ± SD	10.18 ± 1.68
Length of treated nerve (mm)	
Range	4.04–7.97
Mean ± SD	5.78 ± 0.75
Distance from ganglion to brainstem (mm)	
Range	9.06–17.02
Mean ± SD	11.97 ± 1.89
Distance from distal treatment margin to ganglion (mm)	
Range	1.93–6.85
Mean ± SD	4.23 ± 1.39
Distance from proximal treatment margin to ganglion (mm)	
Range	6.42–14.38
Mean ± SD	9.77 ± 1.63
Distance from proximal treatment margin to brainstem (mm)	
Range	0.36–4.12
Mean ± SD	2.30 ± 0.77
Distance from distal treatment margin to brainstem (mm)	
Range	5.39–10.21
Mean ± SD	7.69 ± 1.14

[a] SD, standard deviation.

TABLE 2. Factors related to treatment outcome[a]

Factor and categorization	Significance	Odds ratio
Sagittal angle (degrees)		
1 (<150 or >170)	0.03	0.19[b]
2 (150–170)		
Axial angle (degrees)		
1 (<90 or >110)	0.75	0.78
2 (90–110)		
Ratio of nerve length[c]	0.25	114

[a] Logistic regression analysis, $P < 0.001$ for goodness of fit.
[b] Excellent outcome is labeled as 1, so an odds ratio of less than 1 means that a sagittal angle of between 150 and 170 degrees increases the odds of better outcome, with statistical significance (5.3 times, 1/0.19).
[c] Length of nerve treated/total length of nerve.

TABLE 3. Factors related to facial numbness[a]

Factor and categorization	Significance	Odds ratio
Sagittal angle (degrees)		
1 (<150 or >170)	0.91	1.053
2 (150–170)		
Axial angle (degrees)		
1 (<90 or >110)	0.82	1.135
2 (90–110)		
Ratio of nerve length[b]	0.99	4.319
Maximum dose (rad)	0.99	0.998
Maximum dose (rad) to brainstem	0.01	1.001[c]
Maximum dose (rad) to trigeminal ganglion	0.60	1.000

[a] Logistic regression analysis, $P < 0.001$ for goodness of fit.
[b] Length of nerve treated/total length of nerve.
[c] A change of 100 rads in maximum dose to ganglion increases the odds of getting facial numbness by about 10%, with statistical significance.

the petrous apex (4), there may be variations in course, as depicted in this series of patients treated with CyberKnife stereotactic trigeminal nerve rhizotomy. To elucidate more precisely the impact of anatomic variation on treatment results or complications, other variables, such as length of nerve treated and dose to the treated trigeminal nerve, were maintained in a tightly constant range (14).

Although the site of arterial compression of the trigeminal nerve and the ultimate clinical outcome have been referenced in the radiosurgical treatment of TN pathology (9), there have been no previous studies linking the impact of individual anatomic and morphological variations among treated patients and clinical success or complication rates. In this series, the more obtuse the angle of takeoff was between the treated nerve segment and the brainstem, the more likely the patient was to have a successful treatment outcome, when this variable was statistically separated from others. This finding may be a result of higher dose distribution to the treated nerve segment (DN) in relationship to the dose to the brainstem (DBS): DN/DBS >1.4. If the angle of takeoff were less obtuse, as seen in those cases with lower success rates, the doses to treated nerve segment and brainstem would be more equivalent (DN/DBS <1.4), i.e., the maximum dose to the brainstem would be higher. A higher maximum brainstem dose did not correlate with better clinical outcome, but it did correlate with a higher incidence of posttreatment facial numbness. Interestingly, no other variable was correlated with treatment success.

Treatment complications of facial hypesthesia were, however, correlated with higher maximum brainstem doses. Again, posttreatment facial numbness was not correlated with treatment success, a finding that brings to light the argument of causality of posttreatment facial numbness. Some authors believe that facial numbness occurs as a function of higher brainstem dose during stereotactic radiosurgical rhizotomy, whereas others believe it is the higher dose to Meckel's cave that is the culprit. The answer may lie somewhere between the two, anatomically and theoretically. Detailed pretreatment analysis of the distances ascribed in Table 1 of this article affords the radiosurgeon greater information about a particular patient, with the hope that this information will translate into a better treatment outcome with lower complications.

The concept of sagittal nerve angle takeoff from the brainstem as a prognosticator of treatment outcome has not been previously reported. Previous detailed radiographic evaluations of trigeminal nerve anatomy and morphology have focused on signs of neurovascular conflict in the cerebellopontine angle (1). Many studies have noted some correlation between neurovascular conflict that is identifiable on MRI scans and pain relief, but it is notable that an indication of neurovascular conflict on high-resolution MRI is not necessarily equivalent to anatomy that is observed intraoperatively (2). Therefore, in the search for reliable surrogate measures of neurovascular conflict, we posit that nerve angle, because of the observed statistical correlation to pain relief, may present an intriguing target.

Several clinical and dosimetric factors have been reported to correlate to pain relief in TN radiosurgery; favorable clinical prognosticators include no previous surgery and absence of atypical features. In the case of isocentric radiosurgery, favorable dosimetric prognosticators include higher dose of radiation and proximity of the isocenter on the nerve to the brainstem (3, 5). Compared with this body of literature, the stark lack of anatomic and morphological investigations underscores the need for further investigation of this topic. This is an area which may grow as advances in imaging, such as the use of 3-T MRI (4), allow for increasingly nuanced morphological features to be studied preoperatively.

The fact that patients who undergo CyberKnife stereotactic radiosurgical rhizotomy achieve trigeminal nerve facial pain alleviation days or weeks after the procedure points to the realization that some factor other than radiation injury is put into play after the procedure. This phenomenon may be some form of neuromodulation, the alteration in axonal function, without apoptotic or other forms of cell death. The posttreatment microvascular milieu may have been altered as well. Further studies using functional neuroimaging and treatments in other areas of the central nervous system may lead to answers to this fundamental question: is it possible to further advance the field of functional neurosurgery, as Leksell once envisioned, using stereotactic radiosurgery as a tool in the modicum of neuromodulatory methods? While frameless stereotactic radiosurgery for TN is helping a growing population of TN patients, it is also serving as an example in the quest to answer this important question. Further work along the lines of this report to modify or support the findings in this anatomic and morphological study is necessary, both in frame-based and frameless radiosurgical methods, to increase our understanding of this elusive pathology.

Disclosure

John R. Adler, Jr., M.D., is a shareholder and a member of the board of directors of Accuray, Inc., the manufacturer of the CyberKnife robotic radiosurgery system. The other authors have no personal financial or institutional interest in Accuray or the CyberKnife system and have received no financial support in conjunction with the generation of this article.

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