Classifier Using Pontine Radial Diffusivity and Symptom Duration Accurately Predicts Recurrence of Trigeminal Neuralgia After Microvascular Decompression: A Pilot Study and Algorithm Description

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BACKGROUND: Preprocedure diffusion tensor magnetic resonance imaging (MRI) may predict the response of trigeminal neuralgia (TN) patients to Gamma Knife (Elekta AB) and microvascular decompression (MVD).

OBJECTIVE: To test this hypothesis using pontine-segment diffusion tensor MRI radial diffusivity (RD), a known biomarker for demyelination, to predict TN recurrence following MVD.

METHODS: RD from the pontine segment of the trigeminal tract was extracted in a semiautomated and blinded fashion and normalized to background pontine RD. Following validation against published results, the relationship of normalized RD to symptom duration (D_S) was measured. Both parameters were then introduced into machine-learning classifiers to group patient outcomes as TN remission or recurrence. Performance was evaluated in an observational study with leave-one-out cross-validation to calculate accuracy, sensitivity, specificity, and receiver operating characteristic curves.

RESULTS: The study population included 22 patients with TN type 1 (TN1). There was a negative correlation of normalized RD and preoperative symptom duration ($P = .035$, $R^2 = .20$). When pontine-segment RD and D_S were included as input variables, 2 classifiers predicted pain-free remission versus eventual recurrence with 85% accuracy, 83% sensitivity, and 86% specificity (leave-one-out cross-validation; $P = .029$) in a cohort of 13 patients undergoing MVD.

CONCLUSION: Pontine-segment RD and D_S accurately predict MVD outcomes in TN1 and provide further evidence that diffusion tensor MRI contains prognostic information. Use of a classifier may allow more accurate risk stratification for neurosurgeons and patients considering MVD as a treatment for TN1. These findings provide further insight into the relationship of pontine microstructure, represented by RD, and the pathophysiology of TN.

KEY WORDS: Trigeminal neuralgia, Facial pain, Diffusion tensor imaging

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Trigeminal neuralgia (TN) is a severe facial pain syndrome with severe lancinating pain that is readily treated with surgical intervention in well-selected patients.[1,2] The definitive surgical treatment has been microvascular decompression (MVD), which leads to a pain-free outcome in 76% of patients at mean follow-up of 1.7 yr.[3] However, the pain-free

ABBREVIATIONS: ANOVA, analysis of variance; **FPR,** false positive rate (1 – specificity); **LLSC,** linear least squares classifier; **MVD,** microvascular decompression; **RD,** radial diffusivity; **SVM,** support vector machine; **TN,** trigeminal neuralgia; **TN1,** trigeminal neuralgia type 1; **TN2,** trigeminal neuralgia type 2; **TPR,** true positive rate (sensitivity)

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cohort drops to 44% to 64% after 10 yr,[4-7] and operative decompression of the trigeminal root carries significant risk.[8] To stratify patient benefits from MVD, some have proposed preoperative scoring algorithms.[7,9,10] For example, Hardaway and colleagues[7] assign a score from 0 to 3 using pain type, presence of vascular compression, and compression severity, and find pain-free response rates of 36%, 43%, 56%, and 67% for groups 0, 1, 2, and 3, respectively.

Diffusion tensor magnetic resonance imaging (MRI) has proven useful in the evaluation of TN patients. Diffusion tensor imaging (DTI) studies reveal differences in anatomic microstructure between the affected and unaffected nerves,[11-18] and these differences can normalize after successful treatment.[19-22] Furthermore, the DTI measurement of radial diffusivity (RD) has also been shown to differ between trigeminal neuralgia subtypes 1 and 2 (TN1 and TN2), which respond differently to MVD.[23] Recently, Hung and colleagues[9] used DTI measurements to stratify patients undergoing Gamma Knife (Elekta AB; 21 patients) and MVD (10 patients) into responders and nonresponders. DTI measurements from the pontine segment and trigeminal root informed a linear discriminant analysis classifier to sort TN1 patients into responders and nonresponders at a statistically significant level and with 71% accuracy.[9]

This report aims to independently validate whether DTI measurements can predict remission (pain-free outcome) and recurrence in our cohort of TN1 patients undergoing MVD. We focus on RD, which represents the diffusion of water perpendicular to the direction of maximal diffusion, which is measured by axial diffusivity.[24] Increased RD—with constant axial diffusivity—is often related to demyelination.[25] Given the known role of demyelination in the pathophysiology of TN[26] and previous studies that suggest a link between RD and TN1 vs TN2,[23] we hypothesized that RD may contain prognostic information.

METHODS

Subject Selection and Classification

The study was approved by the University of Michigan Institutional Review Board (HUM00027829), and the requirement for informed consent was waived. Twenty-nine patients with TN1 without comorbid pain symptoms underwent high-resolution diffusion tensor MRI between 2007 and 2018. TN1 patients were defined as those in whom the episodic/lancinating pain occurred more often than constant pain (>50% episodic pain).[2] Five patients were excluded from the study for inadequate visualization of the trigeminal root entering the brainstem on imaging, and 2 patients lacked clinical details. The remaining 22 patients (15 females) comprised the TN1 group. Mean age ± the standard error was 60.1 ± 3.4 yr. To evaluate the novel semiautomated technique to calculate pontine-segment RD, the study group was compared to 6 patients with TN2 (all female, mean age 49.2 ± 6.6 yr) and 15 patients (controls; 13 females, mean age 57.5 ± 3.9 yr) imaged for non-TN conditions—headaches, fibromyalgia, migraines, rheumatologic disease, and myoclonus of tensor tympani/stapedius.

Of the 22 TN1 patients (8 females, mean age 58 ± 3.5 yr), 13 underwent MVD performed by the senior authors (P.G.P. and O.S.), 3 underwent radiofrequency ablation, 2 underwent glycerol injection, 2 were treated conservatively, 1 was treated elsewhere, and 1 was lost to follow-up. Patients were labeled as recurrent for any residual or recurrent pain, and as remission if completely pain-free. Although various pain scores exist, a strict pain-free requirement was used for those in remission (ie, Barrow Neurologic Institute pain score of 1)[9] to avoid confounding the analysis with subjective pain scores. In this observational study, routine patient follow-up occurred at 6 wk and 6 mo, and patients were also referred back to the neurosurgery clinic if pain recurred.

Measuring Normalized Pontine Trigeminal Radial Diffusivity

Diffusion tensor MRI was obtained on a 3T system (Achieva Quasar Dual, Philips, Andover, Massachusetts) with maximum gradient amplitude = 80 mT/m, rise time = 0.80 ms, and slew rate = 100 T/m/s. DTI protocol included an echo planar single-shot technique, repetition time = 4956 ms, echo time = 62 ms, flip angle = 90°, 16 motion probing gradient orientations, and b = 800 s/mm^2 using 2× image averaging. Two-millimeter axial slices were obtained with a parallel imaging technique (sensitivity encoding [SENSE]). A 112 × 112 matrix with isotropic voxels recorded measurements.

MRI images were loaded first into Analyze software (AnalyzeDirect Inc, Overland Park, Kansas), and the axial slice with the best view of the trigeminal root entering the brainstem was manually selected. This axial slice was then transferred to MATLAB (MathWorks, Natick, Massachusetts; Figure 1A). A MATLAB subroutine was created to allow the user to place a parameterized line on the dark ridge at the pontine edge (Figure 1B). The centrally myelinated portion of the root is defined as the portion of the root between where it enters the brainstem and the distal point where the central myelination transitions to peripheral myelination.[27] Since our analysis was performed only on fibers within the brainstem, we denote this region as the pontine segment. Furthermore, to ensure analysis of pontine-segment fibers that enter with the trigeminal root, patients without a well-visualized root entering the brainstem were excluded. To control for potential patient-to-patient variations in measurement, the peak value of RD along this parameterized line was then selected and normalized by the mean background level of the pons (Figure 1C). This normalized peak RD value, denoted P_{RD}, was used in the remaining analysis. The protocol described in this section (summarized in Figure 1D) allowed for a semiautomated method for extracting P_{RD} to reduce the variability caused by human measurement.

Analysis and Statistics

We compared P_{RD} for the 22 TN1, 6 TN2, and 15 control patients to verify that P_{RD} was elevated in the TN1 group compared to TN2 and control patients, as previously reported.[23] P_{RD} ipsilateral to the pain was also compared with P_{RD} contralateral to the pain to verify that ipsilateral was greater than contralateral P_{RD}.

To assess whether preoperative P_{RD} predicts treatment response, a linear least squares classifier (LLSC) and support vector machine (SVM) classifier were used to group patients into remission or recurrence. Since P_{RD} was found to be correlated with duration of symptoms (D_S), both P_{RD} and D_S were input into each classifier. The LLSC can be calculated with a closed-form expression and is equivalent to the linear discriminant analysis classifier (used by Hung and colleagues[9]) when there are only 2 classes with equal numbers of patients.[28] To ensure that

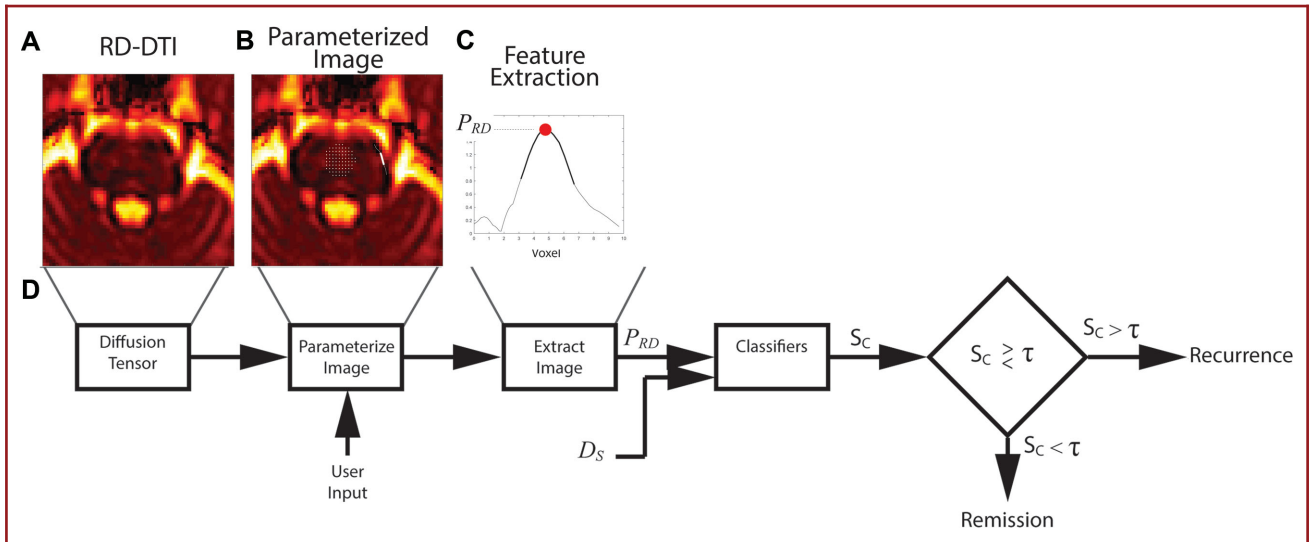

FIGURE 1. *Workflow for calculating P_{RD} and predicting response.* **A**, *Raw radial diffusivity image from diffusion tensor MRI.* **B**, *Raw radial diffusivity MRI depicting how the image was parameterized. The solid white thin line indicates a spline fit curve that estimates the position of the dark ridge at the edge of the pons. The solid white thick line indicates the gap between the dark ridge where the trigeminal fibers likely enter. The fine white dots in the pons indicate the voxels used to calculate the average radial diffusivity in the pons.* **C**, *The radial diffusivity measured within the solid white thick line was normalized by the pontine background level. The normalized peak radial diffusivity value, P_{RD}, is indicated by the red dot.* **D**, *The flow chart illustrates the workflow for extracting the value of P_{RD}, using a classifier to convert this to a score, S_C, comparing S_C to a threshold, τ, to make a prediction of either "Remission" or "Recurrence."*

performance was not entirely dependent on the choice of classifier, 2 classifiers were used. The analysis was conducted in Python using the LinearRegression subroutine in the sklearn.linear_model toolbox and the SVM subroutine from sklearn toolkit. To avoid testing classifiers on data used to train the classifiers, leave-one-out cross-validation was used.

Statistical significance ($P < .05$) between TN1, TN2, and control groups was conducted with one-way analysis of variance (ANOVA), and homoscedasticity was verified with Bartlett's test. Post hoc comparisons between groups were conducted with Tukey's honestly significant difference test. Statistical differences between the ipsilateral and contralateral pontine segments in TN1 patients were evaluated with a paired, 2-tailed *t*-test. The statistical significance of the classifiers was evaluated with Fisher's exact test. The following Python functions were used: statsmodels.stats.multicomp.tukeyhsd, scipy.stats.f_oneway, scipy.stats.bartlett, stats.linregress, stats.ttest_ind, and the gls function in the statsmodels.formula.api toolbox, and the roc_curve and auc subroutines in the sklearn.metrics toolbox. **Supplemental Digital Content, Document**, contains detailed analysis methods.

RESULTS

Surgical Outcomes for TN1 Patients

Of 13 TN1 patients undergoing MVD, 6 were in remission (46%) and 7 had recurrent pain (54%). Mean recurrence time was 1.7 yr and maximum recurrence time was 8 yr. Two patients with recurrent pain had venous instead of arterial compression during surgery, which may have predisposed them to pain recurrence. For comparison, previously reported 10-yr success rates are reported to vary from 44% to 67%, depending on patient selection.[6,7] Patient and outcome demographics are given in Table. There were no statistically significant differences in a post hoc comparison between patients in remission and recurrence groups with respect to gender ($P = .27$), age ($P = .08$), or symptom duration ($P = .23$).

Updated P_{RD} Calculation Differentiates TN1, TN2, and Pain-Free Controls

Previous work found differences in RD between TN1 and TN2 patients.[23] To ensure that our method for extracting RD allowed differentiation between TN1 and TN2, P_{RD} was compared for all TN1, TN2, and control patients to validate this method for calculating P_{RD} (Figure 2A). P_{RD} differed between groups (1-way ANOVA, $P < .001$). The post hoc analysis revealed P_{RD} for TN1 (1.57 ± 0.09) was greater than for TN2 (1.11 ± 0.14, $P = .008$) and for controls (1.05 ± 0.06, $P = .001$). The receiver operating characteristic (ROC) curve to differentiate TN1 from controls is given in Figure 2B. To serve as an internal control, P_{RD} was also compared ipsilateral and contralateral to the TN pain. P_{RD} ipsilateral to the pain (1.53 ± 0.09) was greater than contralateral to the pain (1.21 ± 0.08; $P = .010$, *t*-test). For a detailed discussion of the implications of RD differences between TN1 and TN2, see Willsey et al.[23]

RD Was Correlated With Symptom Duration

Given the relationship between RD and demyelination,[25] the effect of symptom duration on P_{RD} was examined to explore

TABLE. Outcome Demographics

Patient	Group	Sex	Age (yr)	Pain distribution	Pain duration (yr)	Recurrence onset (yr)
1	Remission	F	72	V1/2/3	4	–
2	Remission	F	45	V1	1	–
3	Remission	F	67	V2/3	0.5	–
4	Remission	M	76	V1/2/3	6.5	–
5	Remission	F	66	V2/3	7	–
6	Remission	F	62	V2/3	7.5	–
7	Recurrence	M	37	V1/2	3	0.1
8	Recurrence	F	51	V2/3	2	0.1
9	Recurrence	M	63	V1/2	10	6
10	Recurrence	F	67	V2/3	12.5	4
11	Recurrence	F	49	V2/3	11	0.8
12	Recurrence	M	62	V1	1.5	2
13	Recurrence	M	38	V1/2/3	10	0.1

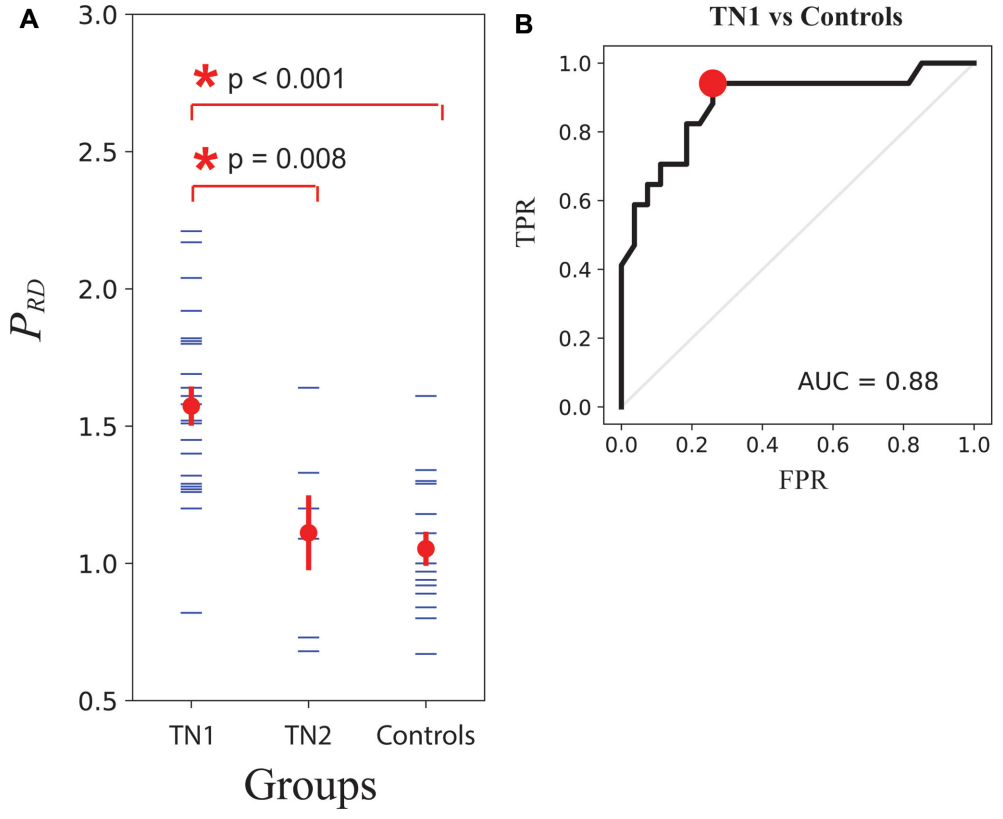

FIGURE 2. *Comparing P_{RD} in TN1 and TN2 plus controls.* **A**, *Illustrates the values of P_{RD} for the TN1, TN2, and control groups (n = 22, 6, and 15, respectively). The horizontal blue ticks indicate the value of P_{RD} for an individual patient. The red dot and error bars indicate the mean and standard error of the mean for the group, respectively. The asterisk denotes statistical significance. P-values are given in the table using 2-sample, 2-sided t-test. Two control patients had the same value of 0.94 for P_{RD}.* **B**, *The receiver operating characteristic curve describing the classification of TN1 versus controls. AUC = area under the curve; FPR = false positive rate (1 – specificity); P_{RD} = peak radial diffusivity; TN1 = type 1 trigeminal neuralgia; TN2 = type 2 trigeminal neuralgia; TPR = true positive rate (sensitivity).*

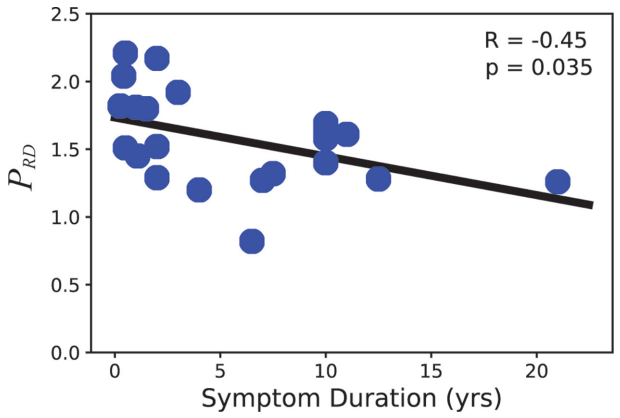

FIGURE 3. *P_{RD} correlated with symptom duration. The blue dots represent the P_{RD} for each of the 22 patients. The black line is the calculated linear regression line. R is the correlation coefficient, and p denotes the P-value for the linear regression.*

the potential role of demyelination in the pontine segment. P_{RD} was negatively correlated with symptom duration among the 22 patients with TN1 (P = .035; Figure 3). The calculated slope was −0.029/yr, and the y-intercept was 1.7. An R^2 value of .20 indicates that linear regression with symptom duration captures only about 20% of the variance in peak P_{RD}. There were no statistically significant associations between age (P = .21; R^2 = .04) and gender (P = .72). Furthermore, P_{RD} of the contralateral side was not correlated with symptom duration (P = .22; R^2 = .08).

RD and Symptom Duration Predict Response to MVD

Since RD differs between TN1 and TN2, which are known to respond differently to MVD,[23] P_{RD} was hypothesized to predict MVD outcome. To evaluate this hypothesis, both preoperative symptom duration and preoperative P_{RD} (found to correlate with symptom duration) were used to predict patient outcome. Both the LLSC and SVM were used to classify patients into remission and recurrence. The boundary between predicted remission and recurrence for each of the 2 classifier types is overlaid on the patient outcome data in Figure 4A. Each classifier separates most outcomes correctly into remission and recurrence groups. A complete evaluation, with cross-validation, for each classifier is shown using the ROC curves in Figure 4B. Evaluating each classifier on this data set with leave-one-out cross-validation produces percent correct of 85% for linear regression (P = .029) and 85% for SVM (P = .029). Both LLSC and SVM operate with a sensitivity of 83% and a specificity of 86%. The sensitivity/specificity operating point for each classifier is indicated by the color-coded dot in Figure 4B. In a post hoc analysis of the complete data, regressing recurrence outcomes over P_{RD} and symptom duration were statistically significant (P = .02, adjusted R^2 = .44) and revealed statistical significance and a relatively equal predictive contribution of P_{RD} (t = 2.96; P = .014) and symptom duration (t = 2.92; P = .015). Thus, both variables contained independent information improving the classifier accuracy, as can be qualitatively observed in Figure 4A.

DISCUSSION

Given the previous reports of the prognostic value of DTI in TN,[9] this study independently evaluated whether RD

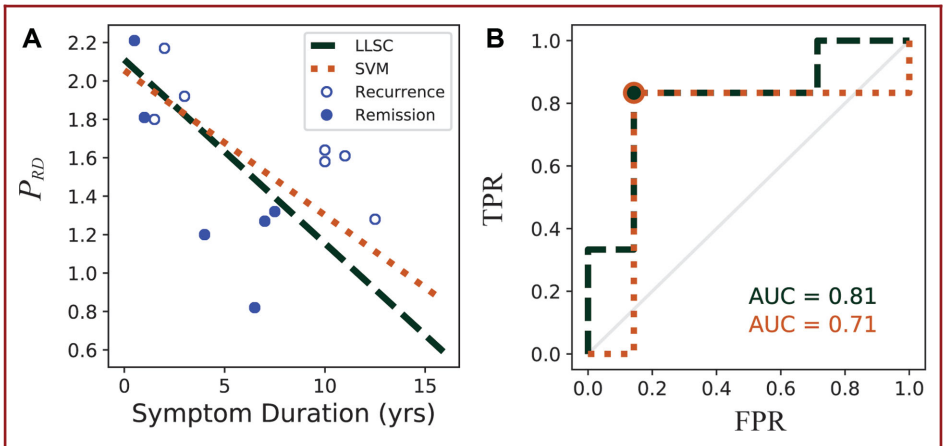

FIGURE 4. *P_{RD} and symptom duration predict outcome.* **A**, *The classifiers are shown separating remission and recurrence based on symptom duration and P_{RD}. Linear least squares classifier (LLSC) is in dark green and support vector machine classifier (SVM) is in orange. Open blue dots indicate recurrence, and solid blue dots indicate remission after intervention.* **B**, *Receiver operating characteristic curves are given for each classifier in* **A**. *The area under the curve (AUC) for each classifier is color coded as in* **A** *and given in the bottom right corner. FPR = false positive rate (1 – specificity); TPR = true positive rate (sensitivity).*

predicts MVD outcome. RD may be an especially useful DTI measurement given its relationship to demyelination and the role of demyelination in TN. Herein, we have demonstrated that (1) symptom duration, D_S, is negatively correlated with peak radial diffusivity, P_{RD}, and (2) D_S and P_{RD} can be inputs to a machine-learning classifier that correctly predicts long-term response with 85% accuracy and a sensitivity of 83% and a specificity of 86%. Collectively, this and Hung et al[9] suggest in a combined group of 23 patients undergoing MVD that DTI measurements may be very helpful in stratifying patients who will have a durable response even after 10 yr where pain-free outcomes range from 44% to 64%.[4-7]

DTI Abnormalities in the Pontine Segment of the Trigeminal Tract

While there are multiple DTI studies of the trigeminal root including its centrally myelinated portion,[11,12,15-18,29-32] few examine DTI parameters in the pontine segment of the trigeminal tract,[9,23,33] likely because of the sophisticated methods needed to differentiate between crossing fibers in the brainstem.[34] However, in this and previous work,[23] extracting DTI measurements adjacent to the entering trigeminal root may select for trigeminal fibers without requiring sophisticated tractography algorithms. In particular, by using this semiautomated method to calculate P_{RD} from the region of the pons adjacent to the root (Figure 1A and 1B), the P_{RD} may be specific for fibers originating from the chief sensory nucleus of V[33] and may account for the improved ability to use DTI to differentiate between TN1 and controls in this work compared to previous work.[23]

Studies that have not found correlations between DTI changes in TN for symptom duration did not include DTI measurements of the pontine segment.[13,15] Herein, we find that the increase in RD is negatively correlated with symptom duration. Since RD is a noninvasive marker of demyelination,[25] the negative correlation may be explained by an initial insult to the trigeminal root, which leads to demyelination that progressively remyelinates with time. Remyelination is known to occur where the trigeminal root enters the pons.[35] Regardless, more studies are needed to understand the time evolution of DTI changes in the pontine segment of the trigeminal tract.

Predicting Response to Intervention With Preoperative DTI Measurements

Two groups have used DTI measurements in TN patients to predict responses to treatment. Tohyama and colleagues[36] showed that *postprocedure* fractional anisotropy, when measured after Gamma-Knife radiosurgery (Elekta AB), predicts a long-term response (12 mo). Hung and colleagues[9] retrospectively compared *preprocedure* DTI measurements of 14 responders and 17 nonresponders to either MVD or Gamma-Knife radiosurgery. While no individual DTI measurement alone classified responders and nonresponders better than chance, linear combinations of DTI measurements from both the pontine segment and trigeminal root (determined by linear discriminant analysis) correctly classified responders and nonresponders with 71% accuracy when using leave-one-out cross-validation.

In this study, we used *preoperative* P_{RD} and D_S to inform LLSC and SVM that correctly classified 85% of MVD patients with a sensitivity of 83% and a specificity of 87%. Previous studies support prognostic information in both symptom duration and radial diffusivity. Hung et al[9] found that the majority of the predictive power was derived from the pontine segment, with RD being the most important DTI measurement. Second, in a recent meta-analysis, preoperative symptom duration was found to predict response to treatment.[3] Thus, our success in classifying patients into remission and recurrence groups may result from optimal combinations of RD and symptom duration. Furthermore, adding additional clinical variables to the machine-learning algorithms may provide for further improvements in classifier accuracy and needs testing in future studies.

Limitations

The limitations of this study are the relatively small number of patients treated, the number of patients lost to inadequate visualization of the pontine segment of the trigeminal tract, and the variable follow-up for patients. However, these findings independently validate the previous hypothesis that preoperative DTI measurements contain prognostic information. Furthermore, even with the small sample size, a strong effect was found using these methods. Definite validation is needed through a prospective, multicenter study with defined inclusion and exclusion criteria and follow-up time periods.

CONCLUSION

A statistically significant negative correlation between RD and preoperative symptom duration was found and then used to predict remission and recurrence with 85% accuracy in an MVD-only cohort. These results help independently validate the use of MR-DTI for predicting treatment response and can be used to select patients for MVD who are likely to have sustained pain relief. Furthermore, the insights gained suggest a role for demyelination of the pontine segment in the disease pathophysiology, since RD with constant axial diffusivity is often considered a noninvasive surrogate for demyelination.[25]

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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