Track-density imaging: a new quantitative tool to identify cervical schwannoma’s nerve of origin?

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Authors: A. Attye, A. Kastler, L. Lamalle, O. Stephanov, F. Renard, A. Vigneron, B. Nicot, S. Grand, A. Krainik; Grenoble/FR
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Aims and objectives

Cervical schwannomas are benign Schwann cell neoplasm arising from cranial nerves, brachial and cervical plexus, or sympathetic chain. Twenty-five percent to 45% of extracranial schwannomas may be located in the head and neck area in the carotid or paravertebral cervical spaces (1) (2). They usually appear as fusiform mass’ growing eccentrically from the nerve. A delayed diagnosis is frequent due to nonspecific symptoms. Surgical resection is currently the best treatment option, however secondary postoperative nerve paralysis may have a major impact on quality of life as transecting cranial nerves such as hypoglossal or vagal nerve may lead to tongue paralysis and cord paralysis respectively (3). Magnetic resonance imaging (MRI) with contrast media injection is the modality of choice to explore such diseases, yet allow inconstantly identify either the schwannoma or its involved nerve (2) (4). Moreover, a reliable identification of the nerve of origin (NOO) could be useful to propose a conservative surgical approach, i.e a nerve-sparing technique using meticulous microsurgical dissection and intraoperative nerve monitoring. An imaging modality that directly highlights the NOO would also allow better preoperative patient information regarding potential risks and morbidity after surgical intervention.

Diffusion Tensor Imaging, based on tractography, has been shown to be useful in animal models to monitor peripheral nerve degeneration (5) or in the assessment of peripheral nerve infiltration by malignant tumors in human beings (6). Yet, DTI is known to potentially yield misleading information regarding the actual pathways of white matter in the brain (7). The Constrained Spherical Deconvolution method (CSD) allows the estimation of fibre orientation distribution, directly from diffusion-weighted MRI data, without the need for prior assumptions regarding the number of fibre populations present (8,9). This model has produced super-resolution tractography with the so-called track density imaging (TDI) (10) providing high anatomical contrast, by incorporating additional information from diffusion tractography modeling. In TDI, intensity of the image is proportional to the number of total streamlines entering each voxel.

In this prospective work, we hypothesized that TDI may reveal the NOO in cervical schwannoma by a higher quantitative value on TDI map in comparison with contralateral nerve. To achieve this goal, we conducted a clinical and radiological study.
Methods and materials

Patients and data acquisition

The study protocol was approved by our institutional review board. Patients aged 18 years or over were included in this study if they had (a) a history of cervical neck tumor, requiring surgical management between December 2013 and December 2014 and (b) had undergone MR scans with diffusion acquisition and post-processing track density imaging. However, patients who had no surgical treatment and those with no MR diffusion acquisition data at admission or cases that experienced diffusion sequence analysis difficulties, secondary to movement artifacts, were not included in this study. Two surgeons (AV and BN) managed the patients who required surgery. We performed the scan on a 3T MR imaging Philips ACHIEVA® 3.0T TX with a 32 channel head coil. The MR scan included pre- and postcontrast transverse T1-weighted spin-echo and transverse T2-weighted fast spin-echo MR images, 3D Balanced Fast Field Echo (bFFE) imaging and 3D Phase-contrast imaging. The parameters of the diffusion sequence were: b value of 1000 s/mm$^2$, 32 directions, acquired voxel size: 2 mm isotropic, field of view of 220 mm, single-shot spin-echo sequence, and scan duration time: 9'31''.

Pre-processing

We corrected motion and eddy-currents with Philips proprietary software Fibertrack® (11). A visual analysis of the raw image data was performed before proceeding to subsequent steps to ensure the quality of the acquisition. The pre-processing steps were performed using MRtrix package software (J-D Tournier, Brain Research Institute, Melbourne, Australia, http://www.brain.org.au/software/) (12). In the next paragraphs, values are specified as entered to the MRtrix software. Because of low Signal to Noise Ratio (SNR) in the studied area, all negative tensors were excluded during the estimation of DTI. Then the FA map was calculated. Furthermore, for CSD map generation, the number of spherical harmonic terms was set to 6 (8).

Post-processing

Using the CSD map, we generated TDI on the whole neck volume with iterative reconstructions of 5.000.000 fibers, a minimum of FA set to 0.3 and an isotropic voxel size of 300 µm. TDI maps were performed to produce an image of the count of fibres through each voxel. After the NOO identification, we manually drew seed masks on it before performing iterative reconstructions of 1000 fibres with a probabilistic algorithm (tractography processing). The post-processing lasted around 10 minutes for CSD map
generation and 20 minutes for TDI using a computer with a multi-core processor (Intel Core® i7, 3 GHz, Intel Corporation®, USA).

**Quantitative data and statistical analysis**

We calculated TDI values and fractional anisotropy (FA) of the NOO in comparison with contralateral nerve, using FA map as a template for the latter. A Student’s t-test was performed to assess the differences in FA and TDI arithmetic mean between the NOO and contralateral nerve among patients.

Besides the mean value statistical analysis, a two-sample Kolmogorov-Smirnov test for each patient was performed to compare the streamlines in all voxels along NOO and contralateral nerve on histograms. We considered p-values of <0.05 as significant.

Two radiologists (A.A. and A.Ka, neuroradiologists with a certificate of Added Qualification) performed evaluations of MRI tractography data including TDI and tractography reconstructions. Inter-rater agreement on detecting NOO was estimated using Cohen's kappa coefficient. Continuous statistical data were analyzed using SPSS software v22.0 (IBM, Inc., Armonk, New York, USA).

**Surgical confirmation of MR findings**

The relevant surgical teams used cervical parapharyngeal approaches for the schwannoma resection, trying to preserve the majority of the nerve fibers. An excision of the tumors with the division of NOO and intracapsular enucleation of tumors was practiced. The histological diagnoses were confirmed on paraffin-embedded sections. The surgeons were blinded to the tractography reconstructions in order no to infer with the reference standard.
Results

Patients

Six patients were included in this study (mean age: 48.2 years, 2 female) with a probable neck schwannoma on both clinical characteristics and MRI morphological sequences. They all referred with an enlarging asymptomatic neck mass. All tumors were encapsulated and NOOs were not seen on anatomical sequence. During surgical procedure, the NOO of schwannomas were: Vagal nerve (n=3), Cervical plexus nerve (n=2), Brachial plexus nerve (n=1). (Figures 1, 2 and 3).

Track density imaging

TDI maps allowed identifying each schwannoma NOO in comparison with surgeon findings (figure 2). In all cases, NOOs were hyperintense in comparison with other nerves and directly linked to the tumor. Inter-rater agreement on detecting NOO was estimated as being 1.0 on 2D and 3D reconstructions, implying that both radiologists were able to systematically detect NOOs among the 6 patients (kappa test).

The mean FA value of the NOOs was calculated as being 0.34 and the mean FA value of the contralateral nerve as being 0.32. There was no significant difference between the two sides (t test, p<0.05). The mean TDI value of the NOOs was calculated as being 106.72 streamlines per voxel and the mean TDI value of the contralateral nerves as 42.50 on the other side. There was a significant difference between the two sides (t test, p<0.01).

For each patient, the histogram analysis showed a narrower distribution of streamlines number per voxel on healthy nerve than on NOO and the change in the distribution was significant (p<0.01) for all patients (Figure 4 and Table 1).
Fig. 1: Figure 1: Steps of Whole Neck Track Density Imaging with MRtrix in an example of right vagal nerve schwannoma of the carotid space TDI map (B and D) were overlaid onto anatomic sequences (A and D, in this case Axial T2 Spin Echo acquisition) to analyze Whole Neck TDI (C and F). A and D/ Extensive mass (white star) involving the right carotid space, lying between carotid and jugular vessels. NOO was not seen at the jugular foramen level (A) as well as lower level (D) B and C/ Right vagal nerve "White Aspect" (white arrow) highlighting the schwannoma NOO. White aspect was explained by a most important number of streamlines per voxel along the NOO in comparison with contralateral vagal nerve (white arrowhead on B picture)

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Fig. 2: Example of schwannoma arising from Schwann cells of cervical plexus. The schwannoma location (white star) might lead to wrong NOO estimation if only analyzing the morphological sequence (A). After TDI overlaying process, the NOO appeared as a hypersignal (white arrow) in the right vertebral foramen. Surgical resection confirmed TDI data (C).

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Fig. 3: Figure 3: Example of brachial plexus schwannoma (white star) Axial Whole Neck TDI (A, B and C) and coronal scans (D) allowed to distinguish NOO (right C6 root, white arrow) from other C7 brachial root (black arrowheads) and left C6 (white arrowhead). Quantitative analysis of voxel intensity along the right C6 root confirmed a significant difference compared with contralateral nerve root.

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Fig. 4: Figure 4: Analysis of the voxel intensity along the nerves Direct nerve visualization allowed an accurate seed ROI tractography process. The tracks were sampled so as to present the same number of samples (1000), spaced at constant intervals. Histograms of intensities from both NOO (white arrow) and contralateral nerve (white arrowhead) were generated.

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Table 1: Histograms of number of streamlines per voxel along NOO (blue) and contralateral nerve (green) for each patient. There is a wider distribution of streamlines per voxel and a more important number of streamlines per voxel on NOO, supporting TDI findings of an abnormal presence of tracks connecting to these nerves in cases with schwannoma.

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Conclusion

This study is the first work to assess the feasibility and reliability of cervical schwannoma's nerve of origin identification using magnetic resonance diffusion imaging correlated with in vivo data. We successfully identified NOO and its relation to the schwannoma, in 6 patients using track-weighted imaging.

In the recently proposed track-density imaging, the nervous pathways can be combined with an anatomical reference map to facilitate pre-operative planning. Whilst seed based tractography is generally user-dependent, requiring in-depth structural neuroanatomical knowledge, a whole cervical fiber tracking approach offers a user-independent method and allows extracting visual information from the tractogram itself. The "white" aspect of NOO was of great help to identify this nerve among others in the whole-cervical volume. Since the voxel intensity value in the TDI map is determined by the count of tracks traversing a voxel, the NOO hyperintensity may be explained either by a microstructural abnormality of the nerve or an abnormal presence of tracks connecting to that nerve (13). Previous work suggested that the TDI contrast is unsuitable for quantitative comparisons (14,15). The contrast in TDI is dependent on the total number of fibre tracks and imaging noise. While imaging noise is quite problematic in brain area, the study of the cervical region is less prone to artifacts secondary to dental material. Moreover, we normalized our quantitative data by comparison with the contralateral nerve using a reliable number of generated fibers in the whole volume. This method was useful to avoid reproducibility problems.

We raise the hypothesis that diffusion biomarkers such as fractional anisotropy was normal in comparison with contralateral side due to the time of growing process as well as the asymptomatic characteristic of these lesions. Thus, NOO abnormal signal on TDI map may probably be explained by a higher presence of tracks connecting to the nerve of origin.

A limitation of this study is the number of inclusion. However, cervical schwannomas are rather rare lesions and these results require further assessment in diagnostic studies. It could be interesting to test TDI with intracranial schwannomas, requiring robust correction of susceptibility magnetic artifacts.

To conclude, these preliminary results are promising for surgical management of cervical schwannomas.
Personal information

Arnaud ATTYE, MD, MSc

Department of Neuroradiology and MRI, Grenoble University Hospital - SFR RMN Neurosciences, Grenoble - France; Inserm, US 17, Grenoble - France; Université Joseph Fourier, Grenoble Institute of Neurosciences UMR-S836 UMS IRMaGe, Grenoble - France

aattye@chu-grenoble.fr

Adrian KASTLER, MD, PhD

Department of Neuroradiology and MRI, Grenoble University Hospital - SFR RMN Neurosciences, Grenoble - France; Inserm, US 17, Grenoble - France; Université Joseph Fourier, Grenoble Institute of Neurosciences UMR-S836 UMS IRMaGe, Grenoble - France

akastler@chu-grenoble.fr

Felix RENARD, PhD

Department of Neuroradiology and MRI, Grenoble University Hospital - Université Joseph Fourier, Grenoble Institute of Neurosciences UMR-S836 UMS IRMaGe, Grenoble - France

felixrenard@gmail.com

Laurent LAMALLE, PhD
Laurent.lamalle@ujf-grenoble.fr

Olivier STEPHANOV, MD

Department of Pathology, Grenoble University Hospital, Grenoble - France
ostephanov@chu-grenoble.fr

Aurélie VIGNERON, MD

Department of Maxillofacial surgery, Grenoble University Hospital, Grenoble - France
avigneron@chu-grenoble.fr

Benjamin NICOT, MD

Department of Neurosurgery, Grenoble University Hospital, Grenoble - France
bnicot@chu-grenoble.fr

Sylvie GRAND, MD, MSc

Department of Neuroradiology and MRI, Grenoble University Hospital - SFR RMN Neurosciences, Grenoble - France; Inserm, US 17, Grenoble - France; Université Joseph Fourier, Grenoble Institute of Neurosciences UMR-S836UMS IRMaGe, Grenoble - France
Alexandre KRAINIK, MD, PhD

Department of Neuroradiology and MRI, Grenoble University Hospital - SFR RMN Neurosciences, Grenoble - France; Inserm, US 17, Grenoble - France; Université Joseph Fourier, Grenoble Institute of Neurosciences UMR-S836 UMS IRMaGe, Grenoble - France

akrainik@chu-grenoble.fr
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