Hypertrophic olivary degeneration in a child following midbrain tumor resection: longitudinal diffusion tensor imaging studies

Case report

GUNES ORMAN, M.D.,1 THANGAMADHANBOSEMANI, M.D.,1 GEORGE I. JALLO, M.D.,2 THIERRY A. G. M. HUISMAN, M.D.,1 AND ANDREA PORETTI, M.D.1

1Section of Pediatric Neuroradiology, Division of Pediatric Radiology, Russell H. Morgan Department of Radiology and Radiological Science; and 2Division of Pediatric Neurosurgery, The Johns Hopkins School of Medicine, Baltimore, Maryland

Hypertrophic olivary degeneration (HOD) is a dynamic process caused by disruptive lesions affecting components of the Guillain-Mollaret triangle (GMT). The authors applied diffusion tensor imaging (DTI) to investigate longitudinal changes of the GMT components in a child with HOD after neurosurgery for a midbrain tumor. Diffusion tensor imaging data were acquired on a 1.5-T MRI scanner using a balanced pair of diffusion gradients along 20 noncollinear directions 1 day and 3, 6, and 9 months after surgery. Measurements from regions of interest (ROIs) were sampled in the affected inferior olivary nucleus, ipsilateral red nucleus, and contralateral superior and inferior cerebellar peduncles and dentate nucleus. For each ROI, fractional anisotropy and the mean, axial, and radial diffusivities were calculated. In the affected inferior olivary nucleus, the authors found a decrease in fractional anisotropy and an increase in mean, axial, and radial diffusivities 3 months after surgery, while 3 months later fractional anisotropy increased and diffusivities decreased. For all other GMT components, changes in DTI scalars were less pronounced, and fractional anisotropy mildly decreased over time. A detailed analysis of longitudinal DTI scalars in the various GMT components may shed light on a better understanding of the dynamic complex histopathological processes occurring in pediatric HOD over time.

KEY WORDS • diffusion tensor imaging • magnetic resonance imaging • children • hypertrophic olivary degeneration • inferior olivary nucleus • Guillain-Mollaret triangle

Abbreviations used in this paper: DTI = diffusion tensor imaging; GMT = Guillain-Mollaret triangle; HOD = hypertrophic olivary degeneration; ROI = region of interest.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
Diffusion tensor imaging in hypertrophic olivary degeneration

Case Report

Presentation. This 14-year-old boy presented with new-onset subtle intention tremor and dysdiadochokinesia of the left hand and bilateral horizontal gaze-evoked nystagmus 3 months after resection of a midbrain pilocytic astrocytoma. Additionally, neurological examination revealed truncal ataxia, dysarthria, and increased muscle tone in the right upper and lower extremities that became apparent shortly after neurosurgery. Palatal myoclonus was not present.

Conventional MRI and DTI. The MRI studies were acquired on a 1.5-T clinical MR scanner (Avanto, Siemens) using a standard 8-channel head coil. The standard departmental protocols included multiplanar T1- and T2-weighted images, an axial FLAIR sequence, multiplanar T1-weighted images obtained after intravenous injection of a Gd-based contrast agent and a single-shot spin echo, and an echo planar axial DTI sequence with diffusion gradients along 20 noncollinear directions. An effective high b-value of 1000 sec/mm² was used for each of the 20 diffusion-encoding directions. We performed an additional measurement without diffusion weighting (b = 0 sec/mm²). For the acquisition of the DTI data, the following parameters were used: TR 7100 msec, TE 84 msec, slice thickness 2.5 mm, FOV 240 × 240 mm, and matrix size 192 × 192. Parallel imaging iPAT factor 2 (Siemens) with GRAPPA (generalized auto-calibrating partial parallel acquisition reconstruction) was used. The acquisition was repeated twice to enhance the signal-to-noise ratio.

Diffusion tensor imaging data were acquired 1 day and 3, 6, and 9 months after neurosurgery of a neoplasm affecting the left GMT.

Quantitative DTI Analysis. Diffusion tensor imaging data of the patient were transferred to an offline workstation for further postprocessing. Dtistudio, DiffeoMap, and RoiEditor software (available at www.MriStudio.org) were used. After correcting for eddy currents and motion artifacts, all images were coregistered to one another using a 12-mode affine transformation. Subsequently, the following maps were generated: fractional anisotropy, vector, color-coded fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. After rigid transformation for adjustment of position and rotation of images, regions of interest (ROIs) were drawn manually using the color-coded fractional anisotropy maps and the T2-weighted images, which have been coregistered to the DT images. Regions of interest were positioned within the inferior olivary nucleus, the ipsilateral red nucleus, contralateral inferior cerebellar peduncle, dentate nucleus, and superior cerebellar peduncle. For each ROI, fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity values were extracted.

Imaging Findings. Conventional MRI showed a CSF-filled postsurgical defect involving the medial portion of the left midbrain with residual tumor that was stable in size over time (Fig. 1). A mild T2 hyperintense signal and enlargement of the left inferior olivary nucleus was first seen 3 months after surgery and suggested left HOD (Fig. 2). T2 hyperintensity and enlargement of the left inferior olivary nucleus were noted 3 months later, confirming left HOD. The last follow-up MRI study obtained 9 months after surgery revealed no interval changes in T2 hyperintensity and degree of enlargement of the left inferior olivary nucleus. Contrast enhancement in the left inferior olivary nucleus was absent on all studies.

Absolute values of DTI scalars derived from the GMT components are shown in Table 1, and their changes over time are illustrated in Fig. 3. In the inferior olivary nucleus, fractional anisotropy prominently decreased at 3 months postsurgery, increased without achieving the initial value 3 months later, and remained stable at 9 months after surgery. The mean diffusivity, axial diffusivity, and radial diffusivity had an opposite course from that of fractional anisotropy. Compared with the left inferior olivary nucleus, fractional anisotropy values in the other GMT components were less prominently altered.

Discussion

Hypertrophic olivary degeneration is an intriguing
phenomenon affecting the inferior olivary nucleus. It is caused by disruptive lesions of the afferent GMT components (dentatorubral tract and central tegmental tract) resulting in a transsynaptic deafferentation of the inferior olivary nucleus. In children, disruptive lesions of the GMT may include low- and high-grade tumors and vascular malformations. Neurophysiologically, this causes the removal of inhibition of the electrotonic gap junctions in the inferior olivary nucleus. On histopathology, disinhibition and deafferentation of the inferior olivary nucleus result in vacuolar degeneration and enlargement of neurons and an increase in glial cells and hypertrophy of astrocytes. Hypertrophic olivary degeneration is not static, but it is a reactive, dynamic, and progressive process.

**TABLE 1: Diffusion tensor imaging scalars derived from the left GMT components on 4 postsurgical follow-up studies**

<table>
<thead>
<tr>
<th>GMT Component</th>
<th>Time Since Op</th>
<th>FA</th>
<th>MD†</th>
<th>AD†</th>
<th>RD†</th>
</tr>
</thead>
<tbody>
<tr>
<td>ION</td>
<td>1 day</td>
<td>0.253</td>
<td>1.154</td>
<td>1.459</td>
<td>1.001</td>
</tr>
<tr>
<td></td>
<td>3 mos</td>
<td>0.111</td>
<td>1.325</td>
<td>1.483</td>
<td>1.246</td>
</tr>
<tr>
<td></td>
<td>6 mos</td>
<td>0.202</td>
<td>0.929</td>
<td>1.124</td>
<td>0.831</td>
</tr>
<tr>
<td></td>
<td>9 mos</td>
<td>0.201</td>
<td>1.034</td>
<td>1.220</td>
<td>0.941</td>
</tr>
<tr>
<td>ICP</td>
<td>1 day</td>
<td>0.634</td>
<td>0.936</td>
<td>1.725</td>
<td>0.541</td>
</tr>
<tr>
<td></td>
<td>3 mos</td>
<td>0.577</td>
<td>0.975</td>
<td>1.677</td>
<td>0.624</td>
</tr>
<tr>
<td></td>
<td>6 mos</td>
<td>0.538</td>
<td>1.016</td>
<td>1.708</td>
<td>0.670</td>
</tr>
<tr>
<td></td>
<td>9 mos</td>
<td>0.532</td>
<td>1.025</td>
<td>1.714</td>
<td>0.680</td>
</tr>
<tr>
<td>DN</td>
<td>1 day</td>
<td>0.188</td>
<td>1.051</td>
<td>1.262</td>
<td>0.945</td>
</tr>
<tr>
<td></td>
<td>3 mos</td>
<td>0.175</td>
<td>1.117</td>
<td>1.309</td>
<td>1.021</td>
</tr>
<tr>
<td></td>
<td>6 mos</td>
<td>0.182</td>
<td>1.013</td>
<td>1.317</td>
<td>0.861</td>
</tr>
<tr>
<td></td>
<td>9 mos</td>
<td>0.172</td>
<td>1.009</td>
<td>1.330</td>
<td>0.848</td>
</tr>
<tr>
<td>SCP</td>
<td>1 day</td>
<td>0.711</td>
<td>0.880</td>
<td>1.763</td>
<td>0.439</td>
</tr>
<tr>
<td></td>
<td>3 mos</td>
<td>0.712</td>
<td>0.973</td>
<td>2.037</td>
<td>0.442</td>
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<tr>
<td></td>
<td>6 mos</td>
<td>0.709</td>
<td>0.986</td>
<td>1.941</td>
<td>0.508</td>
</tr>
<tr>
<td></td>
<td>9 mos</td>
<td>0.671</td>
<td>0.978</td>
<td>1.893</td>
<td>0.521</td>
</tr>
<tr>
<td>RN</td>
<td>1 day</td>
<td>0.293</td>
<td>0.984</td>
<td>1.306</td>
<td>0.824</td>
</tr>
<tr>
<td></td>
<td>3 mos</td>
<td>0.245</td>
<td>1.004</td>
<td>1.343</td>
<td>0.834</td>
</tr>
<tr>
<td></td>
<td>6 mos</td>
<td>0.236</td>
<td>1.436</td>
<td>1.766</td>
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<tr>
<td></td>
<td>9 mos</td>
<td>0.234</td>
<td>1.464</td>
<td>1.812</td>
<td>1.291</td>
</tr>
</tbody>
</table>

* AD = axial diffusivity; DN = dentate nucleus; FA = fractional anisotropy; ICP = inferior cerebellar peduncle; ION = inferior olivary nucleus; MD = mean diffusivity; RD = radial diffusivity; RN = red nucleus; SCP = superior cerebellar peduncle.
† Values are $\times 10^{-3}$ mm$^2$/sec.
and evolving process that may take months to years to progress. Goto et al. classified the pathological changes in HOD into 6 phases: 1) no olivary changes, observed within 24 hours after onset; 2) degeneration of the olivary amiculum (the capsule of white matter composing the periphery of the oliva) at 2 to 7 days or more; 3) olivary hypertrophy (the stage of mild olivary enlargement with neuronal hypertrophy and no glial reaction) at about 3 weeks; 4) culminating olivary enlargement (the stage of hypertrophy of both neurons and astrocytes) at about 8.5 months; 5) olivary pseudohypertrophy (the stage of neuronal dissolution with gemistocytic astrocytes) at about 9.5 months and later; and 6) olivary atrophy (the stage of neuronal disappearance with olivary atrophy and prominent degeneration of the amiculum olivae) after a few years.

Neuroimaging is necessary for diagnosis and confirmation of HOD and allows for study of the pathobiology of HOD in vivo. Conventional neuroimaging is mandatory for the diagnosis of HOD. Hypertrophic olivary degeneration is characterized by enlargement and increased T2 hyperintense signal of the inferior olivary nucleus. On postcontrast T1-weighted images, hypertrophic inferior olivary nuclei are typically not enhancing. Familiarity with HOD and its neuroimaging appearance in pediatric patients will help to avoid potential misdiagnosis of HOD as tumor recurrence, or, in high-grade primary tumors, for example, medulloblastomas, as metastatic lesions.

Conventional neuroimaging allows only a limited understanding of the pathobiology of HOD. In our patient, a mild enlargement and T2 hyperintensity of the left inferior olivary nucleus was visible 3 months after surgery, which subsequently increased 6 months after surgery. On conventional MRI, 3 distinct stages with specific time intervals have been described: 1) T2 hyperintense signal of the inferior olivary nucleus without hypertrophy within the first 6 months after the disruptive event, 2) T2 hyperintense signal and hypertrophy of the inferior olivary nucleus up to 3–4 years after HOD onset, and 3) T2 hyperintense signal with progressive resolution of inferior olivary nucleus hypertrophy. These stages take into account the dynamic course of HOD and match macroscopic changes of the inferior olivary nucleus in HOD, such as increased content of water as part of vacuolar degeneration and gliosis (both are depicted by a hyperintense signal on T2-weighted images). Conventional MRI, however, does not provide detailed information about the microscopic structural change in the inferior olivary nucleus and involvement of the other GMT components. As in the studied patient, the other components of the GMT appear unremarkable on conventional MRI except for the component directly affected by the primary lesion or neurosurgical procedure. However, the involvement of the other GMT components plays an important role in the manifestation of HOD symptoms. Secondary damage of the olivary-dentate tract may cause over-excitation of the dentate nucleus and result in functional impairment of the patient’s ability to estimate the direction of gravity as recently demonstrated in a patient with HOD.

Diffusion tensor imaging was shown to shed light on the pathobiology of HOD and microstructural changes occurring in the GMT components. At the mean postsurgical time of 20 months, Dinçer et al. demonstrated an increase in radial diffusivity, mean diffusivity, and axial diffusivity and a decrease in fractional anisotropy in all anatomical components of the GMT in 10 adults with HOD. A decrease in fractional anisotropy and an increase in radial diffusivity most likely represent demyelination in the late phase of HOD. Eight months after surgery, Meoded et al. found higher fractional anisotropy and axial diffusivity values of the inferior olivary nuclei and lower fractional anisotropy but higher radial diffusivity values of all other GMT components in a child with
bilateral HOD compared with age-matched controls.\textsuperscript{12} An increase in fractional anisotropy in the inferior olivary nuclei may reflect rearrangement of regenerating axons and shrunken neurons. Decreased fractional anisotropy and increased radial diffusivity in the other GMT components most likely reflect the demyelination process associated with axonal degeneration in accordance with histopathological studies. In this article, we applied DTI to investigate dynamic changes of the different GMT components in a child with HOD. In the left inferior olivary nucleus, fractional anisotropy had a variable course and decreased at 3 months after surgery. A decrease in fractional anisotropy, an increase in radial diffusivity and mean diffusivity, and an almost unchanged axial diffusivity may reflect transsynaptic deafferentation at an early stage of HOD with only mild olivary enlargement, which was depicted on conventional MRI. Six months after surgery, fractional anisotropy mildly increased and mean diffusivity, axial diffusivity, and radial diffusivity decreased. At this time, culminating olivary enlargement secondary to hypertrophy of both neurons and astrocytes was achieved.\textsuperscript{6} Olivary hypertrophy is expected to increase fractional anisotropy, while astrocytic proliferation or gliosis is expected to reduce it. Because fractional anisotropy increased in our patient 6 months after surgery, it is arguable that neuronal hypertrophy may play a preponderant role in comparison with gliosis. Nine months after surgery, fractional anisotropy remained stable, but mean diffusivity, axial diffusivity, and radial diffusivity increased. The lack of further increase in fractional anisotropy may represent a modified balance between neuronal hypertrophy and astrocytic proliferation. At about 9 months and later after surgery, neuronal dissolution and gemistocytic astrocytes represent the prominent histological findings.\textsuperscript{8} In the other GMT components, changes in DTI scalars present but are less pronounced than in the inferior olivary nucleus. A decrease in fractional anisotropy and an increase in radial diffusivity (particularly in the inferior cerebellar peduncle and superior cerebellar peduncle) most likely reflect secondary demyelination associated with axonal degeneration, which occurs in transneuronal degeneration. This finding is in accordance with histopathological studies and previous DTI studies.\textsuperscript{4,12}\textsuperscript{4,12} In the red nucleus, however, changes in DTI scalars over time are more prominent, particularly the increase in mean diffusivity, axial diffusivity, and radial diffusivity. The marked, global increase of the diffusivity in the red nucleus is likely due to the primary lesion and postsurgical changes with resolution of necrotic tissue and formation of cystic spaces.

Neurological symptoms in patients with HOD include palatal myoclonus, truncal and limb ataxia, and ocular movement disorders. These symptoms may be severe, have a major impact on activities of daily living, and consequently decrease the patient’s quality of life significantly. In adults with HOD, symptomatic therapeutic approaches using, for example, benzodiazepines or antiepileptic drugs have been attempted with varying results.\textsuperscript{9} A more detailed understanding of the pathobiology of HOD and its dynamic changes over time using noninvasive techniques such as DTI may allow the development of more causative treatments. Additionally, longitudinal, quantitative DTI studies may monitor therapeutic results in patients with HOD.

Preoperative DTI and fiber tractography allow the study of the integrity and course of the GMT as well as the study of the GMT’s anatomical relationship to the mass lesion, and these modalities determine children at risk for HOD. In a similar approach, DTI and fiber tractography are used to assess the risk of superior quadriangular field deficits by injury of the Meyer’s loop in temporal lobe resection.\textsuperscript{22–23} Integration of GMT fiber tractography into stereo-navigational systems together with T1-weighted anatomical images may reduce the risk of HOD due to GMT injury by neurosurgery. The feasibility of integration of GMT fiber tractography into stereonavigational systems for patients with brainstem lesions as well as its capability to prevent occurrence of HOD has to be addressed by future prospective studies.

We are aware of some limitations in our report, including the study of only 1 child with HOD, the retrospective nature of the study and the ROI-based analysis, which is investigator dependent.

Conclusions

Our study shows that longitudinal detailed DTI analysis of the various components of GMT may shed light on the dynamic complex histopathological processes occurring in pediatric HOD over time. Future studies with a larger number of subjects and dedicated high angular DTI study of the brainstem may better address this issue.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Poretti, Huismans. Acquisition of data: all authors. Analysis and interpretation of data: Poretti, Orman, Bosemani. Drafting the article: Orman. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Poretti. Study supervision: Poretti.

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