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Diffusion Tensor Imaging in a Child with Hypertrophic Olivary Degeneration

Avner Meoded,

Division of Pediatric Radiology, Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Andrea Poretti,

Division of Pediatric Radiology, Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

A. Turan Ilica,

Division of Neuroradiology, Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Phipps B-126-B, Baltimore, MD 21287-0842, USA

Randall Perez,

Division of Neurology, Dr. R.A. Calderon Guardia Hospital, University of Costa Rica, San Jose, Costa Rica

George Jallo,

Department of Neurosurgery, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Peter C. Burger,

Division of Neuropathology, Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Thierry A. G. M. Huisman, and

Division of Pediatric Radiology, Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Izlem Izbudak

Division of Neuroradiology, Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Phipps B-126-B, Baltimore, MD 21287-0842, USA

Izlem Izbudak: iizbuda1@jhmi.edu

Abstract

Hypertrophic olivary degeneration (HOD) is caused by disruptive lesions affecting components of the Guillain–Mollaret triangle (GMT). We present conventional magnetic resonance and diffusion tensor imaging (DTI) findings in a 6-year-old girl with HOD after surgery for a midbrain pilocytic

Correspondence to: Izlem Izbudak, iizbuda1@jhmi.edu.

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astrocytoma. To our knowledge, this is the first dedicated DTI analysis of GMT in a child with HOD in the literature. In our patient, we found higher fractional anisotropy (FA) and axial diffusivity values of the inferior olivary nucleus (ION) and lower FA, but higher radial diffusivity (RD) values of all other GMT components compared to age-matched controls. Increased FA values of the ION may be explained by increased packing of white matter fibers. However, associated hyperintense T2 signal is contradictory and the association between increased FA values and hyperintense T2 signal remains unclear. Low FA and high RD values of the other GMT components likely reflect demyelination with axonal degeneration and correlate well with histopathological findings.

Keywords

Guillain–Mollaret triangle; Hypertrophic olivary degeneration; Magnetic resonance imaging; Diffusion tensor imaging

Introduction

The Guillain–Mollaret triangle (GMT) or dentato-rubro-olivary pathway is a functional brain stem neurological circuit. The triangle consists of (1) olivary-dentato fibers from the hilum of one inferior olivary nucleus (ION) crossing the midline and traversing the inferior cerebellar peduncle (ICP) of the contralateral side to reach the contralateral dentate nucleus; (2) dentatorubral fibers arising from the contralateral dentate nucleus, entering their own superior cerebellar peduncle (SCP) and decussating within the midbrain to reach the opposite red nucleus; and (3) the ipsilateral central tegmental tract (CTT) or rubro-olivary tract descending from the red nucleus to the original ION [1].

Every part of the triangle may be affected by a variety of insults including ischemic, hemorrhagic, traumatic (including surgery), neoplastic, metastatic, or vascular lesions. Independently of the etiology, lesions that disrupt the afferent pathways to the ION are likely to result in hypertrophic olivary degeneration (HOD). Conventional magnetic resonance imaging (MRI) findings in HOD include increased size and T2 signal intensity changes of the affected ION [2]. However, there is no abnormal signal or size change in the other components of the GMT. MRI findings of HOD have been reported several times in adults, but only few single pediatric cases have been reported so far [3–5].

Diffusion tensor imaging (DTI) is an advanced MRI technique that allows the in vivo investigation of white matter organization, microstructure, and integrity [6, 7]. Therefore, DTI is a suitable MR tool to study the abnormal GMT non-invasively and may give insights into the pathogenesis of HOD. We are aware of only two reports about DTI findings in HOD [8, 9]. Both articles studied adult patients.

We report on conventional MRI and DTI findings in a child with HOD after surgery for a midbrain pilocytic astrocytoma.

Case Report

Clinical Findings

A 6-year-old girl presented with a subtle intention tremor of the left hand 3 months after neurosurgical resection of a midbrain pilocytic astrocytoma. A palatal myoclonus, nystagmus, and truncal ataxia were not present.

Conventional MRI

Conventional brain MRI was performed 3 months after neurosurgery on a 1.5-T scanner (Avanto, Siemens Medical Systems, Erlangen, Germany) using a standard eight-channel head coil. MRI demonstrated a postsurgical disruptive lesion involving the lower midbrain in the midline (right more than left) with residual tumor extending into the suprasellar cistern with abutment of the distal basilar artery and P1 segments of the posterior cerebral arteries (Fig. 1a). A T2 hyperintense signal was seen in both IONs (more pronounced on the right side) and the right ION was slightly enlarged suggesting bilateral HOD (Fig. 1b). Follow-up MRI 5 months later revealed increased T2 hyperintensity of both IONs and enlargement of the right ION (Fig. 1c).

Diffusion Tensor Imaging

A single-shot, spin-echo, echo-planar (EPI) DTI sequence was acquired. Balanced pairs of diffusion gradients were applied along 21 directions using b values of 0 and 1,000 s/mm², TR=8,200 ms, TE=84 ms, slice thickness 2.5 mm, field of view 240×240 mm, and matrix 192×192.

DTI post-processing was performed off-line using MRI Studio software (H. Jiang and S. Mori, Johns Hopkins University, available at www.MriStudio.org). After correction for eddy currents and motion artifacts, all images were co-registered to one another using a 12-mode affine transformation. Subsequently, fractional anisotropy (FA)-, color-coded FA- (Fig. 2), mean diffusivity (MD)-, axial diffusivity (AD)-, and radial diffusivity (RD) maps were generated. Regions of interest (ROIs) were manually positioned by an experienced neuroradiologist (A.M.) using the color-coded FA maps and the T2-weighted images, which have been co-registered to the DTI images. ROIs were positioned bilaterally within the ION, ICP, dentate nucleus, SCP, and red nucleus. For every ROI, FA, MD, AD, and RD values were calculated.

For the purpose of statistical analysis, we selected three age-matched children who had normal neurological exam and normal brain MRI. In these children, MRI of the head was performed for clinical indication because of lesions outside of the brain. Percentual differences of DTI parameters derived from GMT components between patient and three age-matched controls are shown on Table 1. Compared to the controls, FA values of our patient were increased in both ION but decreased in all the other components of the GMT. MD, AD, and RD values of the patient were higher compared to controls in all GMT components except for AD and MD of the right red nucleus and AD of the right SCP. The most significant difference between patient and controls was found in FA of the right red

nucleus. For all GMT components except ION, differences of RD values were more significant than MD and AD (Fig. 3).

Discussion

The dentato-rubro-olivary pathway or GMT is a functional neurological circuit connecting brain stem and contralateral cerebellum. HOD is the morphological correlate of disruptive lesions of the GMT. In children, reported HOD etiologies include low- and high-grade tumors and vascular malformations [3–5]. Symptomatic oculopalatal tremor is considered the hallmark symptom of HOD and consists of approximately synchronized movements of the palate and acquired pendular nystagmus [10]. However, some patients with HOD may not have oculopalatal tremor including our patient [11]. Tremor of additional muscles such as the facial muscles, pharynx, neck, trunk, and extremities as well as progressive ataxia may be additional clinical findings in patients with HOD.

HOD is characterized by enlargement and T2 hyperintense signal abnormality of the ION on conventional MRI [2]. The other components of GMT do not show any T2 or T1 signal abnormality or size change. Almost all HOD cases are unilateral and were reported in adults. Bilateral and pediatric HOD are exceptional [3–5]. Occurrence of bilateral HOD depends mostly on the location of the disruptive lesion. In our patient, the postsurgical lesion is midline and affects both red nuclei leading to bilateral HOD. Familiarity with this condition and its imaging appearance in pediatric patients will help to avoid potential misdiagnosis of HOD as tumor recurrence, or, in high-grade primary tumors, e.g., medulloblastomas, as metastatic lesions.

HOD is caused by lesions affecting the afferent components of GMT (dentatorubral tract and CTT). This results in interruption of the inhibition of the IONs by the deep cerebellar nuclei. Lesions affecting the olivary-dentato tract (efferent component) do not cause HOD. Indeed, the olivary deafferentation due to transneuronal degeneration is believed to be the main pathomechanism leading to HOD.

HOD is not static and residual but a reactive, dynamic, and continuing process that may take months to years of evolution. Histopathologically, HOD is characterized by vacuolation of neurons, glial proliferation, demyelination, and shrunken neurons [12, 13] and six consecutive morphological stages have been reported [14].

On conventional MRI, three distinct stages with specific time intervals have been described: (1) T2 hyperintense signal of the ION without hypertrophy within the first 6 months after the disruptive event, (2) T2 hyperintense signal and hypertrophy of the ION up to 3–4 years after HOD onset, and (3) T2 hyperintense signal with progressive resolution of ION hypertrophy [2]. The MR changes at the level of the IONs in our patient are matching these stages and time intervals. Additionally, the olivary-dentato pathway appears to be important for normal cerebellar trophism and its disruption may lead to cerebellar atrophy [10].

Conventional MRI reflects gross morphological changes of ION in HOD. The other components of GMT appear unremarkable on conventional MRI unless they are affected by the primary lesion or surgery. DTI, however, allows the investigation of white matter

organization and microstructure. FA maps spatially localize the degree of anisotropic diffusion, which is believed to be related to the degree of white matter tract packing, myelination, and fiber integrity. Increased MD values are related to an increased diffusivity of water molecules in the extracellular space and may be observed in chronic injury. Decreased FA values are seen in areas of white matter injury with loss of anisotropic diffusion resulting from disorganized or disrupted myelin sheaths. The analysis of the eigenvectors (λ_1 , λ_2 , λ_3) allows a more detailed study of the local tissue integrity by calculating AD and RD. AD, defined as the eigenvalue of the primary eigenvector is predominantly modified by acute axonal damage (decreased axial diffusivity). RD, defined as the mean of the eigenvalues of the second and third eigenvectors, may reflect selective myelin injury. Hence, these markers may detect and differentiate axon and myelin damage [15].

Compared to controls, in our child, FA and AD are higher in both IONs, while increase of RD values is less significant. Increase in FA was unexpected and may reflect peculiar arrangement of regenerating axons and shrunken neurons although the mechanism of which remains unclear. Glial proliferation has been described in HOD at about 8 months after onset [14], and in our patient, the DTI study was performed 8 months after surgery. Increased T2 signal is typically found in HOD and is likely due to astrocyte proliferation which is expected to reduce, not increase FA values. Therefore, the simultaneous increase in T2 signal and FA appears to be contradictory and both changes may not be explained by a single underlying pathomechanism. A possible explanation may be related to the manual ROI analysis. We used T2-weighted images to guide the positioning of ROIs and this may result in the inclusion of some pixels of surrounding tissue.

In their cohort of adult patients with HOD, Dincer et al. found decreased FA and significantly increased RD values in ION compared to controls [8]. Decrease in FA and increase in RD may represent demyelination in the late phase of HOD. Therefore, the results of the studies may represent histopathological changes in ION in two different phases of HOD. For all other GMT components, in our patient, FA was lower and RD higher compared to controls, while AD differences were variable and less significant. These results are similar to findings of Dincer et al. [8]. Increased RD and decreased FA values most likely reflect the demyelination process associated with axonal degeneration, which occurs in transneuronal degeneration in accordance with histopathological studies [14, 16].

In conclusion, we showed that a detailed DTI analysis of the various components of GMT in pediatric HOD might shed light on the underlying complex histopathological process and reveal unexpected findings. The selective evaluation of AD and RD may help to differentiate between the various components of myelin and axonal degeneration in HOD. Future studies with higher number of subjects and dedicated DTI study of the brain stem may address this issue to a better extent.

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Fig. 1.

a Axial T2-weighted images at the level of the midbrain and **b** at the level of the lower medulla 3 months after neurosurgery show a postsurgical disruptive lesion involving the lower midbrain in the midline right more than left (**a**), T2 hyperintense areas in both IONs (right more than left; *black arrow* and *arrowhead* on **b** show the right and left ION, respectively), and mild enlargement of the right ION (*black arrow* on **b**). **c** Follow-up axial T2-weighted image 8 months after neurosurgery revealed increasing T2 hyperintense signal abnormality of both IONs (*black arrow* and *arrowhead* on **c**) and enlargement of the right ION

Fig. 2.
a–l Axial color-coded FA maps of the patient (**a–d**) and healthy subject (**e–h**) show the components of the GMT. Due to HOD, demyelination, and axonal degeneration at the level of the other GMT components and postsurgical changes, GMT structures appear distorted and their signal is attenuated compared to healthy controls. **i–l** Mid-sagittal T1-weighted images of healthy subject show the positioning of the axial color-coded FA maps in relation to the brain stem. *DN* dentate nucleus, *ICP* inferior cerebellar peduncle, *ION* inferior olivary nucleus, *RN* red nucleus, *SCP* superior cerebellar peduncle

Fig. 3.

a, b Raw values and mean values with standard deviation for the patient and controls, respectively, of the DTI metrics for the different component of the right (**a**) and left (**b**) GMT. *AD* axial diffusivity, *Ct* control, *DN* dentate nucleus, *FA* fractional anisotropy, *GMT* Guillain–Mollaret triangle, *ICP* inferior cerebellar peduncle, *ION* inferior olivary nucleus, *MD* mean diffusivity, *Pt* patient, *RD* radial diffusivity, *RN* red nucleus, *SCP* superior cerebellar peduncle

Table 1

Percentual differences of DTI parameters derived from GMT components between patient and three age-matched controls

GMT	GMT component	FA (mean±SD)	MD (mean±SD)	RD (mean±SD)	AD (mean±SD)
Right GMT	Right red nucleus	-48±14	9±2.5	22±7	-5±1
	Left SCP	-42±8	27±1.9	55±6	3±0.4
	Left dentate nucleus	-31±6	23±1.7	32±3	12±0.5
	Left ICP	-25±3	18±1.5	34±5	4±0.4
Left GMT	Right ION	25±4	15±0.3	11±0.4	22±0.2
	Left red nucleus	-36±5	14±1.1	27±1	1±0.1
	Right SCP	-25±4	-5±1.6	2±1	-11±2.6
	Right dentate nucleus	-29±3	15±1.3	22±2	5±0.5
Right ION	Right ICP	-28±5	16±1.2	32±3	2±0.4
	Left ION	30±4	7±0.5	5±0.3	11±0.8

AD axial diffusivity, DTI diffusion tensor imaging, FA fractional anisotropy, GMT Guillain-Mollaret triangle, ICP inferior olivary nucleus, MD mean diffusivity, RD radial diffusivity, SCP superior cerebellar peduncle, SD standard deviation