NeuroImage 52 (2010) 217–223

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

DTI fiber tracking to differentiate demyelinating diseases from diffuse brain stem glioma

Carlo Giussani [a], Andrew Poliakov [a,b], Raymond T. Ferri [c], Lauren L. Plawner [c], Samuel R. Browd [a], Dennis W.W. Shaw [a,b], Tanya Z. Filardi [a], Corrine Hoeppner [d], J. Russell Geyer [d], James M. Olson [d], James G. Douglas [e], Elisabeth H. Villavicencio [d], Richard G. Ellenbogen [a], Jeffrey G. Ojemann [a,*]

[a] Department of Neurological Surgery, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, WA, USA
[b] Department of Radiology, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, WA, USA
[c] Department of Neurology, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, WA, USA
[d] Department of Hematology-Oncology, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, WA, USA
[e] Department of Radiation Oncology, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, WA, USA

ARTICLE INFO

Article history:
Received 28 December 2009
Revised 20 March 2010
Accepted 29 March 2010
Available online 2 April 2010

Keywords:
DTI fiber tracking
Diffuse brainstem glioma
Demyelinating diseases

ABSTRACT

Object: Intrinsic diffuse brainstem tumors and demyelinating diseases primarily affecting the brainstem can share common clinical and radiological features, sometimes making the diagnosis difficult especially at the time of first clinical presentation. To explore the potential usefulness of new MRI sequences in particular diffusion tensor imaging fiber tracking in differentiating these two pathological entities, we review a series of brainstem tumors and demyelinating diseases treated at our institution.

Material and methods: The clinical history including signs and symptoms and MRI findings of three consecutive demyelinating diseases involving the brainstem that presented with diagnostic uncertainty and three diffuse intrinsic brainstem tumors were reviewed, along with a child with a supratentorial tumor for comparison. Fiber tracking of the pyramidal tracts was performed for each patient using a DTI study at the time of presentation. Additionally Fractional Anisotropy values were calculated for each patient in the pons and the medulla oblongata.

Results: Routine MR imaging was unhelpful in differentiating between intrinsic tumor and demyelination. In contrast, retrospective DTI fiber tracking clearly differentiated the pathology showing deflection of the pyramidal tracts posteriorly and laterally in the case of intrinsic brainstem tumors and, in the case of demyelinating disease, poorly represented and truncated fibers. Regionalized FA values were variable and of themselves were not predictive either pathology.

Conclusion: DTI fiber tracking of the pyramid tracts in patients with suspected intrinsic brainstem tumor or demyelinating disease presents two clearly different patterns that may help in differentiating between these two pathologies when conventional MRI and clinical data are inconclusive.

Introduction

Pediatric brainstem tumors remain a major challenge in neuro-oncological practice, accounting for the 10–20% of pediatric brain tumors (Barkovich, 2000). The majority of brainstem gliomas show an infiltrative characteristic along the pons white matter fibers and are classified as intrinsic diffuse glioma (mainly localized in the ventral pons) in comparison to the more localized pattern of growth seen with exophytic brainstem gliomas (Reddy, and Mapstone, 1994). Currently, intrinsic glioma are considered inoperable while a subset of exophytic brainstem lesions are amenable to surgical resection and carry a better prognosis (Fisher et al., 2000). The deep localization and the pattern of growth of intrinsic diffuse brainstem glioma, interweaving between normal axons, render this group of tumors unfavorable to surgery (Epstein and Constantini, 1996; Lesniak et al., 2003) leading to upfront conventional radiotherapy and/or chemotherapy without tissue biopsy (Albright et al., 1993; Cartmill and Punt, 1999; Boviatsis et al., 2001; Wagner et al., 2006; Jallo et al., 2003). Controversy occasionally arises when differentiating between an intrinsic brainstem glioma and a demyelinating process as the treatment modalities for these entities are totally counter to one another. In our experience, diagnostic difficulty potentially arises when the clinical course is monophasic and develops over days to weeks rather than acutely and with variable neurological presentation

Abbreviations: ADEM, acute disseminated encephalomyelitis; DTI, diffusion tensor imaging; CSF, cerebral spinal fluid; FA, fractional anisotropy; FLAIR, fluid attenuation inversion recovery; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; PPD, principal diffusion direction; WM, white matter.

* Corresponding author. Department of Neurological Surgery, 4800 Sand Point Way NE, Mailstop W-7729, Seattle, WA 98105, USA. Fax: +1 206 987 3925.
E-mail address: jeff.ojemann@seattlechildrens.org (J.G. Ojemann).

1053-8119/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2010.03.079

for any given pathological entities. Moreover, demyelinating disorders such as acute disseminated encephalomyelitis (ADEM) (Hynson et al., 2001) often have multifocal abnormalities on MRI, however isolated involvement has been demonstrated as exemplified by tumefactive multiple sclerosis (Sagar et al., 1982; McAdam et al., 2002) and variants such as Balo concentric sclerosis (Revel et al., 1993; Gharagozloo et al., 1994) which can have a single lesion that mimics a neoplastic process. Reliable radiological technique to differentiate between intrinsic tumor and demyelination is critical to offer the proper treatment, especially if a diagnostic biopsy is not obtained prior to treatment. These lesions can be large and often have edema and mass effect (Luchinetti et al., 2008). MRI techniques such as magnetization transfer imaging, and MR Spectroscopy have not been able to definitively distinguish between demyelination and tumor. Progression on serial imaging and in the clinical course can be helpful in making a diagnosis; however, a delay in treatment can have significant ramification when the lesion involves the brainstem (Enzinger et al., 2005). Schwartz et al. (2006) showed that if the MRI abnormality shows ring enhancement, the pattern of ring enhancement and T2 hypointensity can differentiate between neoplasms, demyelination, and abscesses, but the MR patterns frequently overlap (Schwartz et al., 2006). Moreover, lumbar puncture for spinal fluid analysis is not always conclusive or even practical at clinical presentation (Link and Huang, 2006; Joseph et al., 2009).

Diffusion tensor imaging (DTI) and white matter fiber tractography are promising techniques for estimating the course, extent, and connectivity patterns of the white matter (WM) structures in the brain (Chen et al., 2007; Engelbrecht et al., 2002). In particular, DTI fiber tracking technique has been shown in pediatric patients to be reliable in distinguishing the involvement of white matter fibers in diffuse pontine glioma and focal brain stem tumors (Helton et al., 2006; Helton et al., 2008; Phillips et al., 2005; Rollins, 2007; Chen et al., 2007). Furthermore, the DTI features of different disorders affecting central nervous structures with a high concentration of white matter fibers, as demyelinating diseases or traumatic diffuse axonal injury, have been recently described (Rollins, 2007; Rutgers et al., 2008; Schneider et al., 2003; Yu et al., 2006; Filippi et al., 2001; Engelbrecht et al., 2002).

In fact, the motion of water molecules can be altered by the presence of structural obstacles at a cellular or subcellular level. Pathologic processes that modify the tissue organization by decreasing or increasing the number of barriers to water molecular diffusion, or that alter the permeability of the barriers, cause abnormal water diffusivity with a consequent impact on the rendering of the DTI fiber tractography of the white matter bundles passing through that area.

The current study investigated the potential DTI fiber tracking pattern differences of diffuse pontine glioma and midbrain/brainstem demyelinating processes to understand a reliable role of this technique in differentiating these diseases once the clinical and radiological features are not conclusive especially at clinical presentation.

We present retrospectively three proven cases of pediatric brainstem demyelination, initially thought to represent intrinsic glioma showing the difficult differential diagnosis that can accompany these lesions. A comparison of standard MRI and DTI fiber tracking findings is made between two of these cases and three cases of intrinsic diffuse brainstem glioma. In the context of the current study, the recent literature regarding DTI and brain stem tumors in children is reviewed.

Material and methods

Patient population

The study was conducted at Seattle Children's Hospital after obtaining standard IRB approval for a retrospective study review. Of the approximate 80 brain tumors treated annually at our institution, only a few represent diffuse intrinsic brainstem gliomas. Our treatment strategy follows national standards whereby intrinsic brainstem lesions that appear typical on imaging studies proceed to adjuvant therapy without a diagnostic brain biopsy. Pertinent to the current study, three patients with multifaceted symptomatology and MRI findings atypical for the classic appearance of a diffuse brainstem tumor who were referred to our Hospital over a period of one year were evaluated. Given the atypical nature of the original MR imaging, adjuvant therapy was delayed and upon serial imaging, radiographic features changed consistent with what was a final clinical and laboratory diagnosis of demyelinating diseases.

To understand the potential role of MRI sequences, including DTI fiber tracking, in differentiating a demyelinating disease from an intrinsic diffuse brain stem tumor we retrospectively compared the MRI (three patients) and DTI fiber tracking (two patients) features of three cases of demyelinating disease involving the brainstem to three different cases of diffuse brainstem glioma with pathognomonic standard MRI features, and to a patient with a supratentorial tumor and a normal brainstem as a case control. We specifically analyzed the pyramidal tracts which are commonly involved in the clinical manifestation of both tumor progression and pontine demyelination.

DTI and fiber tracking techniques

All patients underwent standard MR imaging of the brain with and without contrast, our current protocols include diffusion tensor sequences. MRI data were acquired on a 3 T Siemens Trio scanner with a Siemens 8-channel head coil. The DTI parameters were TR/TE = 5800/96 ms, b = 1000 s/mm^2, 10 diffusion directions repeated 2–4 times, 1.8 × 1.8 mm in-plane resolution, 3 mm (skip 0.5 mm) slice thickness. Analysis of DTI data was performed using FSL/FDT software (FMRIB Image Analysis Group, University of Oxford, http://www.fmrib.ox.ac.uk/fsl/) and included Eddy current correction, fitting of diffusion tensors and estimation of diffusion parameters including Fractional Anisotropy (FA), Principal Diffusion Direction (PDD), Mean Diffusivity and others. FA has emerged as the *de facto* standard for measuring microstructural tissue organization in clinical practice (Basser, 1995). To visualize and evaluate the tracks, we also used images commonly referred to as *color FA* map, which shows color-coded principle diffusion direction modulated by FA values. With this approach different primary colors are used to represent the components of the orientation of the fibers (Jones, 2005). Using Color FA maps helps identify adjacent fiber tracts that may have similar FA values since they may have quite different direction. One can gain an impression of the trajectory and integrity of cortico-spinal tract by viewing the direction of this pathway and following it from one slice to the next. In fiber tracking or tractography, algorithms can be used to perform a similar task (Mori and van Zijl, 2002). Tractography was performed using MedINRIA software package (Asclepios Research Project, http://www-sop.inria.fr/asclepios/software/MedINRIA/). A minimum FA value of 0.2 was used as the fiber termination criterion, in agreement with generally accepted practice based on typical FA values observed in gray and white matter (Mori and van Zijl, 2002). It should be noted that although we used software developed for research purposes and off-line analysis, similar functionality is now available commercially as part software provided by vendors of MRI equipment.

Case illustrations

Normal brainstem

A 15-year-old boy with a history of complex seizures and normal motor exam was operated on for a left temporal choroid plexus