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


Department of Neurological Surgery, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, WA, USA
Department of Radiation Oncology, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, WA, USA
Department of Neurology, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, WA, USA
Department of Hematology-Oncology, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, WA, USA
Department of Neurological Surgery, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, WA, USA

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 pyramidal 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.

© 2010 Elsevier Inc. All rights reserved.

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; Bovillas 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; IVG, 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).

doi:10.1016/j.neuroimage.2010.03.079
for any given pathological entities. Moreover, demyelinating disorders such as acute disseminated encephalomyelitis (ADEM) (Hyson 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 on serial imaging and in the clinical course can be helpful in

2005). Schwartz et al. (2006) showed that if the MRI abnormality

rami

obtaining standard IRB approval for a retrospective study review. Of

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/mm², 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 corticospinal 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
papilloma (Fig. 1A). He underwent preoperative MRI of the brain with DTI technique. The DTI fiber tracking of the cortico-spinal tracts showed a very accurate representation of the pyramidal tracts that run compactly through the brainstem without any distortion (Fig. 1B and C). The FA was calculated in the pons and in the medulla oblongata showing respectively a value of 0.72 and 0.39.

Demyelination (Cases 1–3)

Case 1 is a 17-year-old girl who presented to another hospital with a three week history of double vision, right cranial nerve six palsy and rapidly progressing left-side sensory symptoms. A CT-scan was reported as normal and CSF analysis for oligoclonal bands was negative for a demyelinating disease. Once transferred to our hospital, she underwent an MRI of the brain that showed a pontine lesion which was initially concerning for a brainstem tumor: the MRI showed a patchy increased T2 signal in the pons and cephalad portion of medulla with some associated decreased T1 signal and scant linear enhancement in the pons. The lesion measured 2 cm transverse, 2.2 cm anterior–posterior, and 2.6 cm craniocaudal (Fig. 2A). No gadolinium enhancement was present. No DTI technique was applied. Because of persistent diagnostic uncertainty, a second lumbar puncture was performed after a new evaluation at the tumor board. The CSF returned positive for oligoclonal bands. Visual evoked potentials did show normal response in the left eye, but the right eye showed a borderline high latency and decreased
amplitude. At that point the lesion was treated as a demyelinating disease. Along with steroids, she received IVIG with a rapid partial resolution of her symptoms. Even if no DTI fiber tracking technique was applied, this case is presented to underline how frequently potentially catastrophic misdiagnosis can occur in the scenario of brainstem pathology with an acute/subacute clinical presentation and equivocal imaging findings.

Case 2 is a 19-year-old girl who presented with a 4 months history of progressing weakness of the right side of the face, dizziness, vomiting and lack of gag reflex associated with weight loss. At admission she had progressed to developing left sided weakness.

She underwent, at an outside hospital, a lumbar CSF analysis that was normal. The patient was transferred to our ICU for the development of respiratory failure that necessitated intubation. A high dose steroid treatment was started. An MRI of the brain showed a cervico-medullary lesion which was initially concerning for a brain tumor: the exam showed a mild enlargement of the medulla with non-enhancing abnormal patchy regions of hyperintense T2/FLAIR signal involving also the upper cervical spine (Fig. 2B). DTI technique was applied. Because the clinical and radiological data were not unequivocally consistent with a diagnosis of brainstem glioma, a second lumbar puncture was performed. The CSF returned positive for oligoclonal bands. She subsequently started to improve clinically and radiographically.

The DTI fiber tracking showed a severe decrease of the corticospinal tracts representation along brainstem with an amputation of their medial component without any sign of distortion (Fig. 2B). The FA was calculated in the pons and in the medulla showing extremely low values (respectively 0.12 and 0.17), under the software cut-off for tracking.

Case 3 is an 8-year-old female with 4 days of progressively worsening headache, diplopia upon extreme upward, downward and leftward gaze, and dizziness. Four days prior to admission, she complained of headache and severe nasal congestion as well as a dry cough that were treated as a viral illness. At the time of admission to our hospital she presented with a multidirectional nystagmus, a left facial numbness, a left ptosis, cerebellar ataxia and dysmetria with a positive Romberg sign.

An MRI of the brain showed multifocal findings (Fig. 2C). The FLAIR sequences demonstrated an enlarged pons (2.6 × 3.6 cm in maximum axial dimensions) with a mild mass effect on the anterior aspect of the fourth ventricle as well as slight effacement of the inferior aspect of the basal cisterns. The pons showed a heterogeneous, patchy abnormal high T2 signal intensity with no enhancement after gadolinium. Supratentorial gray matter also showed multilobar ill-defined patches of abnormal high FLAIR signal intensity with no associated enhancement. Abnormalities of the thoracic spine were observed with abnormal high T2 signal intensity within the spinal cord at T3-T4, apparently affecting the central portion of the cord, with no definite associated abnormal enhancement. No gadolinium enhancement was present. Though the multifocal appearance suggested a more diffuse process, the imaging features were suggestive of either a pontine glioma or acute disseminated encephalomyelitis and thus non-conclusive.

The CSF findings (elevated IgG and no oligoclonal bands) were not definitely suggestive for a demyelinating disease. Further evaluation included a renal ultrasound and ophthalmologic exam to exclude Tuberous Sclerosis. The patient underwent empirically a 2 week high dose steroids treatment that determined a rapid improvement of the symptoms as well as a radiological improvement. The clinical and radiological course after the high dose steroids therapy was consistent with an ADEM.

The DTI fiber tracking showed a severe decrease of the corticospinal tracts representation along brainstem with an amputation of their medial and left components without any sign of distortion of the fibers (Fig. 2C). The FA was calculated in the pons and in the medulla oblongata showing higher values in comparison to the previous case (respectively 0.44 and 0.5).

Pontine glioma (Cases 4–6)

Case 4 is an 11-year-old boy with a two months history of worsening headache nausea and vomiting with strabismus and diplopia. His exam was consistent with an internuclear ophthalmoplegia associated with bilateral hypoacusia, severe balance problems as well as a dysarthria. The patient presented with an asymmetric hyperreactivity of his deep tendon reflexes.

The MRI of the brain showed the presence of an expansive lesion centered in the pons with a heterogeneous low T1 signal, and an elevated T2/FLAIR signal. The high T2/FLAIR signal extended from the pons to the left brachium pontes, and superiorly to the dorsal midbrain and tectum. A cystic area with high T2 signal was present in the posterior left pons. Postcontrast images demonstrated minimal contrast enhancement along the periphery of the cystic region (Fig. 3A). These MRI features were consistent with a pontine glioma. The severe clinical and radiological progression confirmed the oncological nature of the disease.

The DTI fiber tracking showed a mild decrease of the representation of the tracts that at the level of the pons were split in the coronal plane and bent posteriorly by the tumor in the sagittal plane (Fig. 3A). The FA was calculated in the pons and in the medulla oblongata showing low values very closed to the cut-off (respectively 0.27 and 0.24).

Case 5 is an 11-year-old boy with a 5 day history of occipital headache and progressive weakness of his left side associated to gait and balance problems. The MRI of the brain showed the presence of an expansive lesion centered in the pons with abnormal T2/FLAIR signal involving the mesencephalic structures and the upper part of the medulla. The lesion in the pons measured 4 cm by 3 cm. Post-contrast images demonstrated a ring-like enhancement of the pons (Fig. 3B). These MRI features were consistent with a pontine glioma. The severe clinical and radiological progression confirmed the oncological nature of the disease.

The DTI fiber tracking showed a strong representation of the tracts that at the level of the pons were split in the coronal plane and were distorted posteriorly by the tumor in the sagittal plane (Fig. 3B). The FA was calculated in the pons and in the medulla oblongata showing values close to the normal subject (respectively 0.67 and 0.52).

Case 6 is a 5-year-old girl with a 1 week history of worsening drooling, choking, slurred speech and gait imbalance, right side weakness and urinary retention. She underwent an MRI of the brain that showed a brainstem lesion with a high T2/FLAIR signal. The mass measured approximately 4.8 × 3.0 × 3.8 cm and was involving the adjacent left cerebellar peduncle measuring. On sagittal T1 post contrast imaging, there was a small focus of enhancement apparently within the central portion of the lesion at the level of the fourth ventricle. There was a mass effect and a deformation of the fourth ventricle (Fig. 3C). The MRI findings and the clinical history were consistent with a diffuse brainstem glioma. The severe clinical and radiological progression confirmed the oncological nature of the disease.

The DTI fiber tracking showed a mild decrease of the representation of the tracts that at the level of the pons were split in the coronal plane with an amputation on the left side. The tracts appeared bent posteriorly by the tumor in the sagittal plane (Fig. 3C). The FA was calculated in the pons and in the medulla (respectively 0.43 and 0.39).

Discussion

Summary of the DTI fiber tracking data

Comparing the DTI fiber tracking data of the pyramidal fibers of the control subject to the cases of diffuse brainstem tumors and the
demyelinating disease, two different patterns of fiber representation are recognizable.

The patients with demyelinating diseases show an extreme paucity of the pyramidal fibers that can be truncated. However, the fibers are located in their normal anatomical position and are not distorted. The FA values in these patients can be extremely low, under the cut-off value.

The patients with diffuse brainstem gliomas show a slight decrease in the representation of the pyramidal fibers. The fibers are always distorted by the tumor mass in both the sagittal and coronal views. The pyramidal tracts are in fact bent posteriorly by the tumors in the sagittal view and are split and pushed laterally in the coronal view. The FA values in these patients can be close to normal or low without typically being under the cut-off value.

Discussion of the clinical and radiological data

A differential diagnosis between a diffuse brainstem tumor and a demyelination process localized in the brainstem carries important therapeutic and prognostic implications.

In fact patients with diffuse brainstem gliomas die of the disease within 18 months of diagnosis, despite contemporary radiation therapy and chemotherapy (Barkovich, 2000; Jallo et al., 2003). Demyelinating diseases, such as MS, ADEM and transverse myelitis, can affect the same category of patients but their prognosis, if recognized promptly, can be favorable due to currently available therapies, even in the presence of an extremely severe clinical presentation. The current diagnosis for diffuse brainstem tumors is made clinically and by MR imaging due to the risks associated with stereotactic biopsy (Jallo et al., 2003; Cartmill and Punt, 1999; Boviatsis et al., 2001; Wagner et al., 2006). Unfortunately, demyelinating diseases purely involving the brainstem can present with similar clinical and radiological features as diffuse brainstem tumors.

The similarity seen on imaging can delay treatment and the potential for inappropriate treatment due to misdiagnosis is also a concern. In the three recent cases referred to our pediatric oncologic service the clinical and MRI appearance was sufficiently worrisome for brainstem tumor that these patients were considered for radiotherapy while waiting for follow up imaging recommended because of uncertainty in the diagnosis.

The recognition of a demyelination process depends on an awareness of this as a diagnostic possibility (Love, 2006). From a clinical point of view, demyelinating diseases affecting the brainstem can mimic a diffuse glioma presenting with a polyhedric neurologic scenario due to the complex neuroanatomical and neurophysiological architecture of the brainstem. A suggested difference between the two pathologic entities is the timing of the development of the symptoms: patients with demyelinating diseases typically present with a clinical history that is shorter (days to few weeks) than diffuse brainstem tumors (several weeks to months). Nevertheless, the present series of patients confutes this opinion: in fact, two brainstem tumor patients presented clinical histories of 5 days (case 5) and, in the other, 1 week duration (case 6) and two demyelinating patients presented with longer clinical histories – one 3 weeks (case 1) and one of 4 month duration (case 2).

CSF analysis has been reported to be sometimes inaccurate to establish a diagnosis of demyelinating diseases (Link and Huang, 2006; Selviaridis et al., 2007; Brinar, 2004; Schwartz and McCormick, 2000). The present series confirms these findings. In fact in two cases of demyelinating disease the first CSF analysis was negative initially orienting the tumor board team to a diagnosis of brainstem tumor.

In the present study, the pattern of representation of the fibers in the demyelinating diseases can be interpreted as the effect of the
demyleination on the water molecules diffusivity that is decreased in the context of the disruption the myelinated fibers. This decrease of the diffusivity negatively affects the DTI fiber tracking technique. It is important to emphasize that the meaning of this phenomenon is that the pyramid tracts fibers may still be in their normal location but the DTI technique cannot detect them. In fact, the results of the application of the DTI fiber tracking technique are a function of the cut-off value of the FA. The cut-off value of the FA is the result of a compromise between the capability to detect as much fibers as possible and to obtain a consistent fiber tracking rendering. The absence of a bundle in the tracking technique rendering does not imply that the tract is anatomically destroyed. Nevertheless, using the same FA value, the presence of different DTI fiber tracking patterns in two pathological entities is a function of how the pathological process affects the fibers. The effect of demyleination on the water molecules diffusion determines in our study a specific DTI fiber tracking pattern at an established FA cut-off value that, if confirmed by larger numbers, could be a pathognomonic radiological data for demyleinating diseases in comparison to intrinsic glioma and vice versa. Unfortunately, in the present series of demyleinating diseases only the third case showed in the conventional FLAIR images an enlarged pons with just a mild mass effect on the anterior aspect of the fourth ventricle and a slight effacement of the inferior aspect of the basal cisterns. For this reason it is not possible to infer the eventual DTI fiber tracking pattern of a demyleinating disease with an important tumefactive aspect: paucity/truncation of the fibers versus their displacement as in brainstem glioma.

On the other hand, the pattern of representation of the fibers in the diffuse brainstem tumors can be explained by the mass effect that the tumor exercises on the fibers. Besides the distortion of the fibers, the tumor produces a decrease of the fibers representation due to a decrease of the diffusivity. In fact a feature of glioma cells is to invade the normal tissue by migrating along the white matter fibers (Bello et al., 2004). This mechanism of tumor invasion can affect the diffusivity of the water molecules determining the mild decrease of the pyramidal fibers represented by the DTI technique.

Limits of the present study

The current study uses DTI/tractography to distinguish demyleinating disease from a diffuse brainstem tumor in a pediatric population that is prone to both pathologic entities. The two different patterns of the DTI fiber tracking of pyramidal tracts representation for diffuse brainstem tumors and demyleinating diseases, even if quite appealing and explainable from a physiopathologic standpoint, need to be further validated by a larger series study.

In fact, the major limit of this study is the small number of cases that prevent a consistent generalization of the results in the clinical-radiological work-up of brainstem lesions of uncertain nature in the pediatric population. The present series suggests advantages to the development of DTI fiber tracking as a diagnostic tool in the scenario of potential confusion between a demyleinating disease and an intrinsic brainstem tumor.

The other limit of this study is technical. DTI fiber tracking is software and operator dependent. This is a retrospective study of available clinical data and, as such, based on the routine clinical DTI scans (some of them as short as 2 min) with only 10 diffusion directions, not necessarily optimized for evaluation of a particular region. These were not intended to perform complete, rigorous tractography studies (e.g. trace cortico-spinal tracts from the spinal cord to the cortex). It would be useful to confirm these results with a larger number of patients and by using different DTI software and parameters to eventually establish a standard MRI/DTI protocol in clinical scenario similar to those presented here.

Conclusion

MRI is a vital tool in identifying CNS abnormalities in children with new onset focal neurologic deficits. However, in many cases the differential diagnosis includes neoplastic and demyleinating diseases, and the evaluation process can be problematic when the abnormality is in the brainstem, and biopsy is felt unsafe. In this setting radiographic inference of a specific diagnosis without confirmative biopsy can lead to chemotherapy and radiation that may be inappropriate.

DTI fiber tracking of the pyramidal pathways through the brainstem shows in the present study a different pattern of representation of the tracts that are postero-laterally dislocated in case of diffuse glioma and are less represented or even amputated in the case of demyleinating diseases.

When conventional MRI findings are equivocal for these two entities, we demonstrate that evaluating the DTI fiber tracking of the pyramidal tract can help to differentiate between diffuse brainstem glioma and demyleinating lesion. After a confirmation of these data with a larger study, this distinction could guide the clinical decision making, potentially limit the need for diagnostic biopsy in this situation and more accurately determine the appropriate course of therapy.

References


