Journal of Neuroimmunology 304 (2017) 81–85

Contents lists available at ScienceDirect

Journal of Neuroimmunology

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

"A new imaging modality to non-invasively assess multiple sclerosis pathology"

Anne H. Cross [a,*], Sheng-Kwei Song [b]

[a] Department of Neurology, Washington University School of Medicine, Campus Box 8111, 660 S. Euclid Avenue, St. Louis 63110, MO, USA
[b] Department of Radiology, Washington University School of Medicine, Campus Box 8225, 660 S. Euclid Avenue, St. Louis 63110, MO, USA

ARTICLE INFO

Article history:
Received 17 May 2016
Received in revised form 30 September 2016
Accepted 4 October 2016

Keywords:
Multiple sclerosis
Diffusion tensor imaging
Inflammation

ABSTRACT

We describe a novel imaging method to assess central nervous system pathology called "Diffusion Basis Spectrum Imaging" (DBSI). Diffusion tensor imaging (DTI) has been widely used to estimate axonpathology and demyelination. However, in the settings of acute inflammation and chronic tissue loss asare common in multiple sclerosis, DTI signals can lead to false interpretations. DBSI is a computationallynovel method that separates isotropic from anisotropic components in imaging voxels. Isotropicdiffusion is believed to reflect inflammatory components (cells, edema), as well as intrinsic cells andextracellular space. DBSI enables the measurement of axial and radial diffusivities within the anisotropiccomponents of imaging voxels, which reflect the integrity of axon fibers and myelin, respectively.

1. Introduction

Multiple sclerosis (MS) is a chronic disease of complex and heterogeneous pathology which involves inflammation, demyelination, remyelination and axon injury and loss. MS is common - about 2.5 million people worldwide have the disease. The pathology of MS varies between individuals and in the same individual patient over the time-course of the disease (Lucchinetti et al., 2000). The variability of the clinical course and neuropathology of MS has proven to be a barrier to the complete understanding of the disease. As biopsies of the central nervous system (CNS) are infrequent (and are usually done in atypical cases) and serial biopsies are even more rarely done, understanding of the underlying neuropathology of MS derives mainly from end-of-life autopsies and less invasive methods such as imaging and blood and cerebrospinal fluid (CSF) analyses. Methods providing a non-invasive window into the CNS to better understand the pathophysiology of progression are greatly needed.

Inflammatory demyelination of CNS white matter (WM) was formerly regarded as the main pathology of MS. Prior to the past two decades, gray matter (GM) involvement received less emphasis which is perhaps due to the difficulty to detect or measure it. However GM involvement in MS, including cortical GM damage, can be extensive and correlates better with disability measures than does WM damage (Fisher et al., 2008; Rudick et al., 2009). The primary substrate of disability is thought to be axon injury and loss (Kornek et al., 2001). Accurate measures of axon injury and loss in the CNS of MS patients are needed to better understand the pathology of MS over the course of the disease, to monitor responses to therapies, and to use as a surrogate marker in clinical trials, especially for progressive MS trials.

The advent of magnetic resonance imaging (MRI) revolutionized the diagnosis and has greatly improved the monitoring of MS. Gadolinium-enhanced MRI lesions serve as surrogate biomarkers of clinical MS relapses (Sormani et al., 2009). The latter has expedited research leading to approval of several of the thirteen disease modifying therapies (DMTs) for relapsing forms of MS. Current DMTs work best to reduce relapse rate, but do not completely eliminate relapses, and do not work in all patients. None of the present approved DMTs are highly effective at slowing disability progression and none yet repairs axons in the CNS. Novel imaging tools that can be used to identify responses to promising new therapies, such as remyelinating agents that are in early phases (Mi et al., 2013; Wootla et al., 2013) are also needed. This paper will discuss updates on diffusion MR methods to detect and quantitate axon loss, as well as demyelination, cellular inflammation and edema in the MS-affected CNS.

2. Diffusion magnetic resonance imaging

Diffusion-weighted MRI measures water apparent diffusion coefficient (ADC) through the application of a pair of diffusion weighting pulsed magnetic field gradients of altering magnitude, duration, and time interval of separation between gradients; the term "b-value" derived from a landmark study (Stejskal & Tanner, 1965) is used to control

Abbreviations: DBSI, diffusion basis spectrum imaging; DTI, diffusion tensor imaging; DMT, disease modifying therapy; ADC, apparent diffusion coefficient; PBH, persistent black hole; WM, white matter; GM, gray matter.

* Corresponding author.
E-mail address: crossa@neuro.wustl.edu (A.H. Cross).

http://dx.doi.org/10.1016/j.jneuroim.2016.10.002
0165-5728/

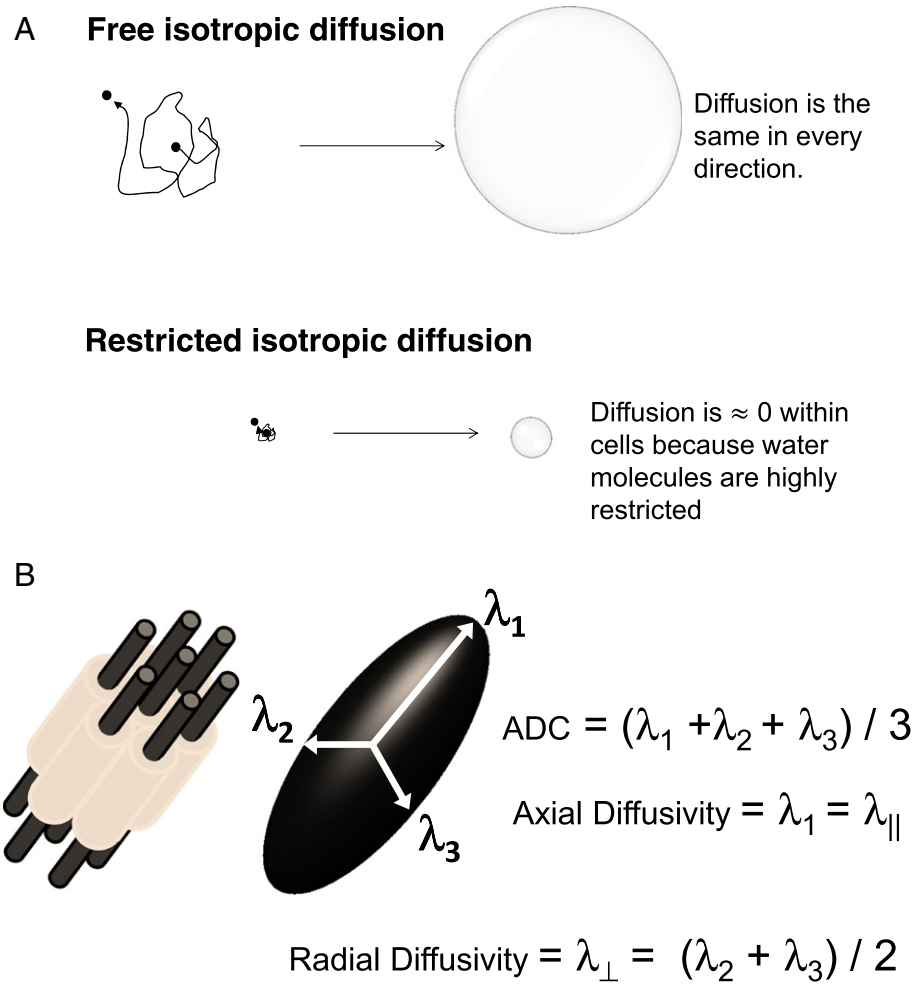

Fig. 1. Isotropic and Anisotropic diffusion depicted graphically. A) Free and restricted isotropic diffusion. B) Anisotropic diffusion.

the extent of signal loss for quantifying ADC. Diffusion tensor imaging (DTI) employs multiple directions of diffusion weighting to quantitatively describe water diffusion in tissues (Basser et al., 1994a,b). The displacement of cerebrospinal fluid (CSF) water molecules can be described as a sphere, i.e., isotropic diffusion. Water molecules in CSF move freely without hindrance. The ADC is the same in any direction it is measured; one-direction diffusion weighting is sufficient to describe isotropic diffusion (Fig. 1A). In contrast, the displacement of water molecules in WM tracts is described as an ellipsoid, i.e., anisotropic diffusion. For anisotropic diffusion, ADC varies depending on the direction of diffusion weighting gradients. A multiple-direction diffusion weighting is necessary to accurately describe water diffusion in most biological tissues (Fig. 1B).

3. Diffusion imaging in MS

Over a decade ago, we began to test if DTI-derived directional diffusivity might help understand the underlying pathology in MS. Our hypothesis was that reduced myelin would lead to an increase in radial diffusivity, i.e., the ADC perpendicular to axonal tracts, as measured by DTI. We set out to test this hypothesis by examining shiverer mice, that have a mutation in the gene encoding myelin basic protein and are therefore dysmyelinated, by DTI. These mice have normal axons. The expectation was that these mice would have increased radial diffusivity due to lack of normal myelin, but normal axial diffusivity (ADC parallel to axonal tracts) indicating normal axons. Indeed, the major WM tracts of shiverer mice had axial diffusivity that was similar to that of WT with approximately 30% increase in radial diffusivity (Song et al., 2002).

As part of a phase 2 trial of rituximab performed from 2002 to 2009 at Washington University, we also obtained DTI of the brains of relapsing MS patients in the study. Each enrolled patient underwent seven gadolinium-enhanced brain MRIs. We found that increased radial diffusivity at the time of a new gadolinium-enhancing lesion predicted the eventual development of a persistent black hole (PBH) (Naismith et al., 2010). As the latter is indicative of worse damage and more axon drop-out than a gadolinium-enhanced lesion that subsequently becomes isointense on T1w imaging, DTI appeared useful as an early indicator of pathology occurring at the time of lesion onset.

We also hypothesized that reduced axial diffusivity would indicate damage to the axon or even axonal transection. In another study using retinal ischemia to kill retinal ganglion cells leading to initial axon and subsequent myelin degeneration ("Wallerian degeneration"), this appeared to hold true (Sun et al., 2008). However, results obtained when applying DTI in human CNS did not always conform to expectations. In studies of transverse myelitis patients using DTI, although radial diffusivity was increased at the site of injury as expected, axial diffusivity also was increased above normal (Naismith et al., 2013). An explanation for the increased axial diffusivity, as well as a factor expected to contribute to increased radial diffusivity, was increased extracellular space, which would be expected in regions of significant axon loss (such as in PBH). Similarly, in acute lesions with enhancement, the blood brain barrier integrity is compromised and with the entry of more free water (vasogenic edema) an increase in radial diffusivity would also be expected.