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# The cervical spinal cord in neuromyelitis optica patients: A comparative study with multiple sclerosis using diffusion tensor imaging

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ABSTRACT

*Introduction:* This study aims to evaluate "in vivo" the integrity of the normal-appearing spinal cord in patients with neuromyelitis optica (NMO), using diffusion tensor MR imaging, comparing to controls and patients with multiple sclerosis (MS).
*Materials and methods:* We studied 8 patients with NMO and 17 without any neurologic disorder. Also, 32 MS patients were selected. Fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD) were calculated within regions of interest at C2 and C7 levels in the four columns of the spinal cord.
*Results:* At C2, the FA value was decreased in NMO patients compared to MS and controls in the anterior column. Also in this column, RD value showed increase in NMO compared to MS and to controls. The FA value of the posterior column was decreased in NMO in comparison to controls. At C7, AD value was higher in NMO than in MS in the right column. At the same column, MD values were increased in NMO compared to MS and to controls.
*Conclusions:* There is extensive NASC damage in NMO patients, including peripheral areas of the cervical spinal cord, affecting the white matter, mainly caused by demyelination. This suggests a new spinal cord lesion pattern in NMO in comparison to MS.



## 1. Introduction

Neuromyelitis optica (NMO) is a demyelinating autoimmune disease that affects the optic nerve and the spinal cord, causing blindness and paralysis. Recently, it was described in patients with NMO an auto-antibody anti-aquaporin 4 (AQP4) water channel (anti-NMO), which targets the blood–brain-barrier aquaporin-4 water channel [1]. This channel is mainly expressed on the plasma membrane of astrocytes, facing the endothelial basal membranes [3], thus around the ventricles, the hypothalamus, the central canal of the spinal cord and the optic nerves [2,4]. Lesion locations are usually correlated with AQP4 sites, which can be detected on the conventional magnetic resonance imaging (MRI) sequences. Optic nerve and spinal cord involvement is currently expressed as high signal intensity on T2-weighted images (WI) and contrast enhancement in the acute phase [6]. Atrophy is a common pattern latter during disease course [7]. MRI findings are so important in the evaluation of these patients that are considered supportive criteria. The finding of a large spinal cord lesion (≥3 vertebral bodies) and the presence of brain lesions that do not fulfill the Barkhof's criteria for multiple sclerosis (MS) are supporting criteria for the diagnosis of NMO, as suggested by Wingerchuk et al. [5]. Although there is an established pattern of lesion seen on conventional MRI, the true extension of damage is not quite understood.

Recent studies including histopathological analysis have shown that the cord damage is more extensive than the macroscopic lesions seen on conventional MRI [8], remitting to the concept of normal appearing spinal cord (NASC) [9]. NASC is an area of microscopic damage that has normal signal intensity on conventional MRI sequences. Such areas are better evaluated with advanced MRI techniques, such as the diffusion tensor imaging (DTI). This

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technique allows the analysis of tissues at a cellular level, once the microstructural architecture preservation of the white matter tracts are evaluated by water molecular diffusion along the axon fibers [10,11].

The DTI consists of three *eigenvectors* and to each one there is a corresponding diffusion axis that reports to the direction of diffusive water motion. Each *eigenvector* has a concerning *eigenvalue* that gives the magnitude of diffusive water. DTI-derived indices can be obtained by combining the three *eigenvalues*: the fractional anisotropy (FA), which measures the directionality of water molecular diffusion; the 'axial diffusivity' (AD), which is the main *eigenvalue* ($\epsilon_1$); the 'radial diffusivity' (RD), obtained by the average of the second ($\epsilon_2$) and third ($\epsilon_3$) *eigenvalues* of the DTI; and 'mean diffusivity' (MD), which represents the average among the three *eigenvalues*, reflecting the amount of water diffusion regardless of its preferential directionality. AD represents the water diffusion parallel to the axon bundle, usually related to axonal damage, while the RD represents the water diffusion perpendicular to this direction, commonly associated with demyelination [12].

This study aims to evaluate "in vivo" the integrity of the normal-appearing spinal cord in patients with NMO, using diffusion tensor MR imaging, comparing to controls and patients with multiple sclerosis (MS). We hypothesize that NMO patients will present lower FA values in the spinal cord compared with controls and MS patients. Also, this FA reduction is probably mainly caused by RD alteration, reflecting the demyelination process. Also, we will correlate the DTI metrics with clinically observed disability for NMO patients.

## 2. Materials and methods

### 2.1. Population

This study included eight patients with NMO (7 females, mean age 47.6 years-old, range from 35 to 66) and 32 patients with relapsing-remising MS (20 females, mean age 39.3 years-old, range from 16 to 57) selected from the clinical demyelinating disease database of our University Hospital. All NMO patients fulfilled the revised Wingerchuck criteria of 2006, and all MS patients fulfilled the McDonald criteria from 2005 [16]. In addition, we selected 17 healthy controls (13 females, mean age of 40 years-old, range from 21 to 69) without any known spinal cord disease or neurologic disorder. All subjects signed informed consent and the Institutional Review Board of our University Hospital approved the study.

Before MRI acquisition, the NMO patients were clinically assessed by an experienced neurologist, who performed the Expanded Disability Status Scale (EDSS), in order to standardize their neurological condition. The average scale value was 4.3, ranging from 1 to 9.

### 2.2. MR imaging

All patients underwent MR imaging on a 1.5-T Scanner (Avanto, Siemens, Erlangen, Germany), using an eight-channel phased-array headMatrix coil attached to neckMatrix coil in order to have higher signal-to-noise ratio at the cervical region. The conventional MRI protocol included: sagittal STIR images (repetition time [TR]: 4170 ms; echo time [TE]: 87 ms; field of view [FOV]: 250 mm; matrix: 256 × 320; with a 10% gap), axial T2* (TR: 606 ms; TE: 18 ms; FOV: 200 mm; matrix: 192 × 320; 30 slices with 3 mm thickness and 30% gap) and sagittal T1 (TR: 500 ms; TE: 9 ms; FOV: 220 mm; matrix: 320 × 240; 12 slices with 3 mm thickness and 30% gap) after administration of contrast medium (dimeglumine gadolinium, 0.1 mmol/kg; Schering AG, Berlin, Germany). In addition, diffusion-weighted single-shot echo-planar imaging was acquired with bipolar diffusion gradients applied along 20 noncollinear directions in the sagittal plan ($b0 = 0$, $b = 400$ and $b = 800$ s/mm$^2$, TR: 2800 ms; TE: 88 ms; FOV: 260 mm; matrix: 128 × 128; 16 slices with 3 mm thickness and 10% gap; 1 average).

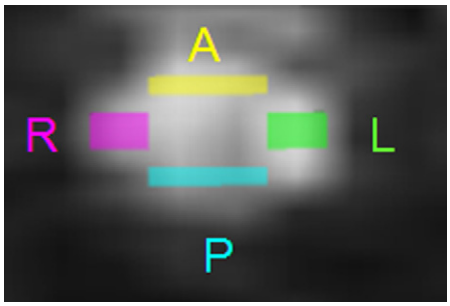


**Fig. 1.** The ROIs placement in the axial reformatted DTI images for each cervical spinal cord column at C2 and C7 levels. A—anterior; R – right lateral; P – posterior; L – left lateral.

### 2.3. DTI processing

Four regions of interest (ROIs) were drawn based on the anatomic landmarks of the reformatted axial b0 image at C2 and C7 level in the NASC, using VB15 (Siemens, Erlangen, Germany). In the workstation we used NEURO 3D, Software DTI Evaluation, version 1.0 for reconstruction (Siemens, Erlangen, Germany). They were located around the spinal cord in the anterior and posterior columns (ROI size: 6 voxels (20.42 mm$^3$)) and in the left and right lateral columns (ROI size: 4 voxels (13.62 mm$^3$)), as shown in Fig. 1, based on previous published data [18]. Lesions location were evaluated by an experienced neuroradiologist, and mapped across the whole spinal cord. ROIs that included at least one lesion at any of these columns at the level of C2 or C7 detected on conventional MRI were excluded from the analysis. The total number of ROIs considered for analysis at each level and each column was described at Tables 1 and 2.

FA, RD, AD and MD values were automatically generated from each ROI, and the average of each parameter was calculated for each column and for each spinal cord level for NMO and MS patients and also for controls.

### 2.4. Statistical analysis

The statistical analyses were performed with the Statistical Package for the Social Sciences version 17.0 (SPSS, Chicago, IL, USA). The Kolmogorov–Smirnov test was used to evaluate the normal distribution of the values. All variables were normally distributed and two-tailed paired Student's *t*-test was used for the comparison of DTI parameters for each region separately. The average value of each DTI parameter at C2 and C7 cervical spinal cord level of NMO patients was compared with MS patients (Table 1). Also, a comparison between NMO patients and controls group was performed (Table 2). A *p*-value of 0.05 was considered statistically significant.

To investigate the association between statistical significant FA alteration and the values of RD and AD values in NMO patients, we applied Pearson correlation.

Pearson test was also used to evaluate the correlation between altered DTI parameters in NMO patients and the clinical data available using EDSS.

## 3. Results

At C2 level, the FA value was decreased in NMO patients compared to MS patients (0.46 vs. 0.58, $p = 0.04$) and to controls (0.46 vs. 0.63, $p = 0.02$) in the anterior column. Also in this column, RD

**Table 1**
Comparison between DTI parameters in multiple sclerosis (MS) and neuromyelitis optica (NMO) patients in the four columns of the spinal cord (Right, Left, Ant – anterior, Post – posterior) at C2 and C7 levels. The number ($n$) of included regions of interest (ROIs) are represented in the corresponding column.

| MS vs. NMO | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Right | | | | | Left | | | | | Ant | | | | | Post | | | | |
| | | FA | AD | RD | MD | | FA | AD | RD | MD | | FA | AD | RD | MD | | FA | AD | RD | MD |
| C2 | | | | | | | | | | | | | | | | | | | | |
| MS – average ± SD | $n=23$ | 0.62 ± 0.20 | 2.15 ± 0.50 | 0.73 ± 0.54 | 1.27 ± 0.48 | $n=28$ | 0.69 ± 0.22 | 2.39 ± 0.37 | 0.72 ± 0.61 | 1.29 ± 0.47 | $n=30$ | 0.58 ± 0.07 | 2.29 ± 0.39 | 0.76 ± 0.27 | 1.33 ± 0.33 | $n=26$ | 0.71 ± 0.19 | 2.26 ± 0.25 | 0.61 ± 0.50 | 1.19 ± 0.43 |
| NMO – average ± SD | $n=7$ | 0.59 ± 0.19 | 2.12 ± 0.44 | 0.99 ± 0.57 | 1.26 ± 0.49 | $n=7$ | 0.57 ± 0.22 | 2.29 ± 0.93 | 1.08 ± 0.99 | 1.46 ± 0.92 | $n=8$ | 0.46 ± 0.15 | 2.41 ± 0.86 | 1.03 ± 0.38 | 1.53 ± 0.51 | $n=8$ | 0.55 ± 0.16 | 2.22 ± 0.15 | 0.74 ± 0.29 | 1.32 ± 0.18 |
| $p$-Value | | 0.83 | 0.90 | 0.13 | 0.95 | | 0.37 | 0.79 | 0.46 | 0.67 | | **0.04** | 0.76 | **0.03** | 0.42 | | 0.17 | 0.45 | 0.57 | 0.51 |
| C7 | | | | | | | | | | | | | | | | | | | | |
| MS – average ± SD | $n=29$ | 1.48 ± 0.40 | 2.12 ± 0.68 | 0.74 ± 0.68 | 1.19 ± 0.67 | $n=32$ | 0.61 ± 0.13 | 2.19 ± 0.40 | 0.75 ± 0.29 | 1.23 ± 0.28 | $n=32$ | 0.54 ± 0.11 | 2.29 ± 0.39 | 0.80 ± 0.27 | 1.31 ± 0.32 | $n=31$ | 0.54 ± 0.11 | 2.38 ± 0.58 | 1.01 ± 0.47 | 1.46 ± 0.49 |
| NMO – average ± SD | $n=7$ | 0.56 ± 0.12 | 2.34 ± 0.33 | 0.93 ± 0.34 | 1.40 ± 0.27 | $n=8$ | 0.57 ± 0.19 | 1.94 ± 0.49 | 0.80 ± 0.37 | 1.18 ± 0.38 | $n=7$ | 0.62 ± 0.09 | 2.23 ± 0.62 | 1.04 ± 0.33 | 1.42 ± 0.13 | $n=7$ | 0.62 ± 0.09 | 2.08 ± 0.49 | 0.74 ± 0.30 | 1.19 ± 0.35 |
| $p$-Value | | 0.30 | **0.02** | 0.24 | **0.04** | | 0.62 | 0.34 | 0.73 | 0.78 | | 0.20 | 0.83 | 0.12 | 0.66 | | 0.18 | 0.38 | 0.23 | 0.29 |

The significance of bold values is a $p$-value less than or equal to 0.05 was considered statistically significant.

**Table 2**
Comparison between DTI parameters in neuromyelitis optica (NMO) patients and controls.

| NMO vs. controls | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Right | | | | | Left | | | | | Ant | | | | | Post | | | | |
| | | FA | AD | RD | MD | | FA | AD | RD | MD | | FA | AD | RD | MD | | FA | AD | RD | MD |
| C2 | | | | | | | | | | | | | | | | | | | | |
| NMO – average ± SD | $n=7$ | 0.59 ± 0.19 | 2.12 ± 0.44 | 0.82 ± 0.57 | 1.25 ± 0.49 | $n=7$ | 0.57 ± 0.22 | 2.29 ± 0.93 | 1.08 ± 0.99 | 1.49 ± 0.96 | $n=8$ | 0.46 ± 0.15 | 2.41 ± 0.86 | 1.03 ± 0.38 | 1.54 ± 0.51 | $n=8$ | 0.55 ± 0.16 | 2.22 ± 0.16 | 0.74 ± 0.30 | 1.32 ± 0.18 |
| CONT – average ± SD | $n=17$ | 0.69 ± 0.15 | 2.65 ± 1.15 | 0.60 ± 0.29 | 1.19 ± 0.39 | $n=17$ | 0.74 ± 0.15 | 2.16 ± 0.35 | 0.54 ± 0.40 | 1.08 ± 0.37 | $n=17$ | 0.63 ± 0.05 | 2.02 ± 0.47 | 0.66 ± 0.23 | 8.74 ± 0.33 | $n=17$ | 0.79 ± 0.12 | 2.39 ± 0.69 | 0.6 0± 0.43 | 1.27 ± 0.44 |
| $p$-Value | | 0.23 | 0.35 | 0.33 | 0.79 | | 0.09 | 0.67 | 0.19 | 0.28 | | **0.02** | 0.19 | **0.008** | 0.36 | | **0.04** | 0.49 | 0.74 | 0.76 |
| C7 | | | | | | | | | | | | | | | | | | | | |
| NMO – average ± SD | $n=7$ | 0.56 ± 0.12 | 2.35 ± 0.33 | 0.92 ± 0.34 | 1.41 ± 0.27 | $n=8$ | 0.58 ± 0.19 | 1.93 ± 0.49 | 0.80 ± 0.37 | 1.18 ± 0.39 | $n=7$ | 0.62 ± 0.09 | 2.23 ± 0.62 | 1.04 ± 0.33 | 1.42 ± 0.43 | $n=7$ | 0.62 ± 0.09 | 2.06 ± 0.49 | 0.74 ± 0.30 | 1.19 ± 0.85 |
| CONT – average ± SD | $n=17$ | 0.66 ± 0.12 | 2.15 ± 0.30 | 0.75 ± 0.62 | 1.02 ± 0.23 | $n=17$ | 0.64 ± 0.08 | 2.14 ± 0.39 | 0.92 ± 0.58 | 1.33 ± 0.39 | $n=17$ | 0.56 ± 0.12 | 1.98 ± 0.79 | 0.85 ± 0.67 | 1.23 ± 0.71 | $n=17$ | 0.56 ± 0.18 | 2.44 ± 0.47 | 0.99 ± 0.52 | 1.48 ± 0.47 |
| $p$-Value | | 0.15 | 0.14 | 0.54 | **0.02** | | 0.32 | 0.47 | 0.67 | 0.50 | | 0.24 | 0.53 | 0.54 | 0.57 | | 0.47 | 0.3 | 0.31 | 0.29 |

The significance of bold values is a p-value less than or equal to 0.05 was considered statistically significant.

value showed significant increase in NMO patients compared to MS patients ($1.03 \times 10^{-3}$ mm$^2$/s vs. $0.76 \times 10^{-3}$ mm$^2$/s, $p = 0.03$) and to controls ($1.03 \times 10^{-3}$ mm$^2$/s vs. $0.66 \times 10^{-3}$ mm$^2$/s, $p = 0.008$). The FA value of the posterior column was decreased in NMO in comparison to controls (0.55 vs. 0.79, $p = 0.04$).

At C7 level, AD value was significantly higher in NMO than in MS patients ($2.34 \times 10^{-3}$ mm$^2$/s vs. $2.12 \times 10^{-3}$ mm$^2$/s, $p = 0.02$) in the right column. At the same column, MD values were increased in NMO compared to MS ($1.40 \times 10^{-3}$ mm$^2$/s vs. $1.19 \times 10^{-3}$ mm$^2$/s, $p = 0.04$) and to controls ($1.40 \times 10^{-3}$ mm$^2$/s vs. $1.00 \times 10^{-3}$ mm$^2$/s, $p = 0.02$).

The Pearson correlation ($r$ value) performed in the posterior column at the C2 level demonstrated inverse strong correlation between FA and RD values ($r = -0.988$, $p = 0.0001$), whereas no correlation was found between FA and AD ($r = 0.585$, $p = 0.128$). In the anterior column at the C2 level, the results showed no significant correlation between FA and RD ($r = 0.056$, $p = 0.896$) or AD ($r = 0.583$, $p = 0.129$).

The clinical correlation performed in altered DTI data and EDSS average values using Pearson coefficient showed significant inverse correlation between FA value of the posterior column in C2 and EDSS ($r = -0.800$, $p = 0.017$).

## 4. Discussion

In this study, we aimed to quantitatively assess the normal appearing spinal cord damage in the four columns of the cervical spinal cord in NMO patients compared to MS patients and controls using DTI parameters. Our results demonstrated that DTI derived indices are distinct between NMO and MS patients, as well as in comparison to controls. There is extensive NASC damage of NMO patients, notably in the white matter spinal cord.

Qian et al. used DTI to study the spinal cord of 10 NMO patients and 12 controls and detected white matter NASC damage, mainly affecting the lateral and dorsal column, characterized by decreased FA and increased MD and RD values [13]. Our results also showed reduced FA values and increased RD values in NMO patients when compared to controls, but affecting the anterior and posterior columns at C2 level. The Pearson correlation performed between DTI parameters in the posterior column elucidated a strong correlation between FA and RD values, reflecting the predominance of demyelination as the most relevant pathological mechanism. The report of white matter damage in such pathology was usually correlated with Wallerian degeneration, but now the possibility of microscopical demyelination should be considered. Ciccarelli et al. had already demonstrated the importance of RD to detect tissue damage that influences clinical recovery in MS patients [18].

Also, the difference found at the anterior column between NMO and MS patients is quite revealing. NMO patients showed lower FA and higher RD values when compared to MS ones, reflecting more microscopical lesions in the first group. This difference may be justified by genetic studies recently performed in order to explain the distinct lesion distribution pattern between these demyelinating diseases [14]. Blanco et al. recruited a cohort of 22 NMO patients, 228 MS patients and 225 healthy controls in order to analyze genetic aspects in Caucasians NMO patients. They concluded that Caucasian patients with NMO and MS have a different HLA-DRB1 allelic distribution throughout central nervous system [15], which may reflect histopathologic distinct damage pattern verified in NMO and MS.

Previous studies also evaluated cervical spinal cord in both demyelinating diseases. Benedetti et al. assessed the ability of diffusion tensor MRI to grade cervical cord damage comparing 10 NMO patients, 10 MS ones, and 10 healthy controls. They showed that cervical spinal cord MD values of patients with NMO are markedly increased compared to both patients with RRMS and healthy subjects [13]. Our results at the right column in the C7 level support this idea, as higher MD values were found in NMO compared to MS patients and to controls. This alteration may be explained by the presence of severe demyelination, cavitation, and necrosis of both gray and white matter in the spinal cord of patients with NMO, increasing permeability of tissue barrier to water molecular motion [15,17].

There are some limitations of this study. The DTI has several technical limitations, mainly related to low signal-to-noise ratio and movement artifacts associated to breath and pulsation [9]. The choice of ROI placement was dependant on the observer, whereas it would be preferable to make the choice based on consistent, well defined criteria [19,20]. In addition, the tensor model may tend to underestimate or overestimate FA values in areas where fibers cross. Finally, in clinical aspects, the diverse treatments such drug use for MS and NMO were not evaluated. Beyond, only relapsing-remising multiple sclerosis subtype was considered for analyses, which does not permit to infer our findings in its entirely.

## 5. Conclusions

We conclude that there is extensive NASC damage in NMO patients, including peripheral areas of the cervical spinal cord, affecting the white matter, mainly caused by demyelination. This suggests a new spinal cord lesion pattern in NMO in comparison to MS patients. Continuing studies investigating larger cohorts of patients with repeated clinical assessments and DTI measurements correlating with autoimmune mechanism are needed to understand the histopathological process behind such disease as well as to test the potential use of DTI as a clinical and prognostic marker.

## Conflict of interest statement

The authors' institutions have no conflicts of interest, such as financial or personal relationships.

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