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Magnetic resonance imaging findings at the first episode of acute optic neuritis

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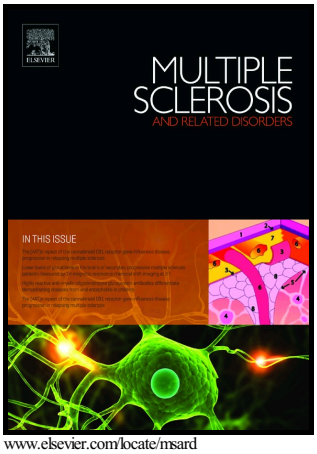

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Magnetic resonance imaging findings at the first episode of acute optic neuritis

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ABSTRACT

Background

Optic neuritis (ON) is a focal demyelinating event, which may evolve into multiple sclerosis (MS).

Objective

To study MRI characteristics in the acute phase of the first ON episode.

Methods

A prospective population-based study was performed on 31 patients with a first episode of acute ON with a one year follow-up. MRI, clinical evaluation, and detection of aquaporin-4 (AQP4)-IgG and myelin oligodendrocyte glycoprotein (MOG)-IgG was undertaken. For lesion characterization on MRI

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the optic nerves were divided into three segments: intra-orbital (IO), canalicular (CAN) and chiasmal (CHI).

Results

Lesions of the optic nerve were observed in 80.6 %(25/31), with IO location in 48 %(12/25), CAN in 8 % (2/25) and both IO and CAN in 44%(11/25). Patients who converted to MS had lesions located at IO in 77%(10/13), whereas the group with isolated ON had IO and CAN in 73% (8/11), p=0.003. Brain lesions were observed in 84 % (21/25) at onset of ON; 62%(13/25) progressed to MS with more frequent location in brainstem (p=0.030) and lesions in periventricular areas (p=0.015). Spinal cord lesions were detected only in patients who progressed to MS (p=0.002). MOG-IgG was detected in one patient with an optic nerve lesion located at IO and CAN. Serum AQP4-IgG was detected in none. Follow-up MRI showed progression in optic nerve lesions in 55% (11/20) patients.

Conclusions

Specific location of optic nerve and brain lesions and the presence of spinal cord lesions in the acute phase of the first ON episode facilitated an MS diagnosis. The extension of optic nerve lesions following ON suggests a long-term progressive degeneration as an important element of ON pathology.

Abbreviations

AQP4, aquaporin-4; AQP4-IgG, AQP4 specific IgG antibody; CAN, Canalicular; CHI, Chiasmal; CNS, Central nervous system; CSF, Cerebrospinal fluid; DIR, Double inversion recovery sequence; DWI, diffusion-weighted imaging; FLAIR, Fluid-attenuated inversion recovery; Gd, gadolinium; IDD, inflammatory demyelinating disease; IO, intra-orbital; MOG-IgG, Myelin oligodendrocyte glycoprotein specific IgG antibody, MRI, Magnetic resonance imaging; MS, Multiple Sclerosis;

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NMOSD, Neuromyelitis optica spectrum disorder; ON, Optic neuritis; SPIR, Spectral presaturation with inversion recovery; STIR, Short tau inversion recovery; VA, Visual acuity; WHO, World Health Organization; WM, White matter.

Keywords: Multiple sclerosis; Optic neuritis; MRI; myelin oligodendrocyte glycoprotein autoantibodies.

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Introduction

Optic neuritis (ON) is a common inflammatory demyelinating disorder (IDD) of the optic nerve that can be associated with multiple sclerosis (MS)(Petzold et al., 2014). ON causes acute, mostly monocular vision loss, often combined with retrobulbar pain (Petzold et al., 2014). It is normally a self-limiting event and recovery of visual acuity typically occurs within the first few weeks of symptom onset (Petzold et al., 2014). An initial rapid recovery is followed by a slow improvement that can continue for up to a year after onset (Kolappan et al., 2009), nonetheless some patients have persistent visual problems (Petzold et al., 2014). Magnetic resonance imaging (MRI) may facilitate diagnosis by helping detect optic nerve inflammation and exclude differential diagnoses(Petzold et al., 2014). Studies have investigated the predictive value of MRI for prognosis of visual impairment(Berg et al., 2015; Rocca et al., 2005), suggesting that long-segment inflammation of optic nerve is prognostic for loss of visual function(Kim et al., 2015). Differential MRI features of the optic nerve, including long lesions extending over half the optic nerve length, posterior nerve, and chiasmal involvement have been suggested to indicate antibody-mediated ON such as that occurring in neuromyelitis optica spectrum

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disorder (NMOSD)(Khanna et al., 2012; Ramanathan et al., 2016; Storoni et al., 2013). However, no significant differences have been observed distinguishing NMOSD from MS in the presence, degree or contrast enhancement of the optic nerve(Khanna et al., 2012; Storoni et al., 2013). Application of MRI to the assessment of optic nerve damage in a single episode of acute ON has been performed rarely. The aim of this study was to determine whether the specific location of optic nerve lesions was associated with risk of conversion to MS and acute or persistent visual impairment. Brain and spinal cord MRI were also examined, as simultaneous white-matter (WM) lesions (including the optic radiation), suggestive of demyelination, may contribute to visual outcome(Sinnecker et al., 2015) or risk for conversion to MS.

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Methods

Study design

As part of a population-based study reported in detail elsewhere (Soelberg et al., 2017) a clinical database for patients diagnosed with ON in the time period 2014-2016 in the Region of Southern Denmark was established. The study was a population-based prospective case series with a one year of follow-up (Soelberg et al., 2017). All referred patients with acute or subacute onset of symptoms compatible with ON were offered a clinical examination within one week after referral and an MRI within two months (median 21 days (range 3-55)). After one year all patients had clinical follow-up and 20 patients underwent follow-up MRI (median 268 days (range 100-498)). The diagnosis of ON was obtained by independent neurological and ophthalmological examination according to previously

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described (1991; Optic Neuritis Study, 2008). Exclusion criteria were ophthalmologic conditions not related to ON and patients were also excluded if they had been previously diagnosed with MS or NMOSD. Assignment of the MS diagnosis was based on the McDonald criteria 2010 (Polman et al., 2011; Soelberg et al., 2017).

Patient population

A total of 31 patients were obtained with the first episode of acute ON attack, who had complete MRI sequences for evaluation of the optic nerve sub-segments. All patients were Caucasian and the median age at onset was 40 years (range 17-66). The female:male ratio was 1.4:1. Twenty-nine patients had unilateral and two had bilateral ON symptoms.

Standard protocol approvals, registrations, and patient

The study was approved by the Committee on Biomedical Research Ethics for the Region of Southern Denmark (ref. nos. S-20130137) and by the Danish Data Protection Agency (ref. no. 14/26345). All patients provided verbal as well as written informed consent.

MRI technique

All patients underwent MRI of the brain and orbit, performed on a 1.5 Tesla scanner, in all but two cases in whom the follow-up MRI were performed using a 3.0 Tesla scanner.

MRI of the brain included sequences as T2 weighted, fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI). Orbits were imaged on 1.5 Tesla with 3D FLAIR, 2D FLAIR or 2D short tau inversion recovery (STIR). The two follow-up studies on 3.0 Tesla substituted a 3D DIR and SPIR sequence for the FLAIR. Most patients had a 3D FLAIR sequence performed with 1-mm

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slice thickness in sagittal plane and were reformatted to coronal and axial planes (to visualize the entire length of the optic nerve). STIR and/or T2-weighted sequences were primarily analyzed in spinal cord imaging.

Brain MRIs were reported as normal, nonspecific, or MS-like, i.e. meeting the Barkhof criteria for dissemination in space used in the McDonald criteria(Barkhof et al., 1997; Polman et al., 2011).

The MRI protocol was standard MS protocol (1.5 tesla) for all initial investigations, despite two cases at follow-up (3.0 tesla). Therefore, no adjustment for different MRI protocols was performed.

For lesion characterization, the optic nerves were divided into the following three segments: Intra-orbital (IO), canalicular (optic foramen to chiasm) (CAN) and chiasmal (chiasm ± optic tracts) (CHI), as depicted in Fig.1. One neuroradiologist (HPBS) re-evaluated all images, masked to the affected eye/eyes, clinical and serological information.

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Vision test

Visual acuity (VA) was measured at disease onset and at six and 12 months follow-up. In patients with bilateral ON, VA was measured in both eyes. The results were recorded as decimal equivalent (e.g. 6/6 =1.0, 6/9= 0.67, 1/60 = 0.02, finger counting=0.01, light perception =0.001, no light perception=0). Furthermore, the degree of visual loss was categorized semi-quantitatively into four groups; normal vision (≥0.8), reduced vision loss (≥0.25 to < 0.8), severe vision loss (≥0.05 to < 0.25) and blindness (<0.05), as specified by the World Health Organization (WHO). Visual recovery at re-examination was divided into four groups: group 1 with complete visual recovery (VA better than 0.8); group 2 with partial recovery (VA remaining less than 0.8), group 3 unchanged, group 4 aggravation.

Autoantibodies

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AQP4-IgG was determined with a immunofluorescence assay using transfected HEK293 cells as previously described(Asgari et al., 2011) and re-evaluated by means of an in-house cell based assay at the University of Heidelberg (Jarius et al., 2010). Antibody against myelin oligodendrocyte glycoprotein (MOG-IgG) was determined using two cell-based assays employing fixed and live HEK293 cells, respectively, transfected with full-length human MOG as previously described(Jarius et al., 2016a; Jarius et al., 2016b; Pache et al., 2016). Testing was performed in a masked fashion.

Statistical analysis

Statistical differences were tested using the Wilcoxon rank sum test for two-group comparisons and the Fisher exact test for group comparisons of categorical variables. P-values < 0.05 were considered significant. Due to the exploratory nature of the study no correction for multiple comparisons was made.

All analyses were carried out using STATA version 14.1 (Stata Corporation College Station, Texas, USA).(STATA [computer program]. Version 14.1)

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Results

Location of acute optic nerve lesions:

Signal abnormalities of the optic nerve were evaluated by 3D FLAIR, 2D FLAIR or 2D STIR and were demonstrated in 80.6 % (25/31) of the patients on the initial MRI. The optic nerve lesions had IO location in 48 % (12/25), CAN in 8 % (2/25) and combined IO and CAN in 44% (11/25). None of the patients had involvement of the chiasm on the initial MRI. Two female patients with unilateral symptoms had bilateral signal abnormalities, the lesions being longer on the clinically affected eye, in

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both cases IO+CAN, and IO in the fellow eye. Additionally, two patients had bilateral ON symptoms, only the optic nerve on the side with the most pronounced symptoms had MRI signal abnormalities (1 x IO, 1 x IO+CAN).

At the one-year clinical follow-up, isolated ON remained the diagnosis in 11/25 of the patients, one had MOG-IgG and 13/25 progressed to MS. In those diagnosed with MS(Soelberg et al., 2017) (eight at time of the acute ON, one at six months, and one at one year after onset of ON) the optic nerve lesion was located IO in 77% (10/13), in contrast to the patients with isolated ON where 73% (8/11) had signal abnormalities that involved both IO and the CAN segments (p=0.003). The single patient with MOG-IgG had a lesion located in both IO and CAN.

Progression of the optic nerve lesion at follow-up MRI

Follow-up MRI was available in 20/31 (MS=12, ON=8) patients and was performed with a median of 268 days (range 100-498 days) following onset of ON. A total of 18/20 patients had lesions of the optic nerve at the initial MRI and 19/20 patients had lesions at follow-up MRI on 3D FLAIR, 2D FLAIR or 2D STIR. Fifty five percent (11/20) had progression of the signal abnormalities (ON=3, MS=8). One patient who had a final diagnosis of isolated ON, initially had normal optic nerves and developed a lesion in two segments (IO and CAN). Optic nerve lesion progressed from isolated IO lesion to an additional segment in six patients (ON=0, MS=6), all into IO+CAN. In two patients (ON=0, MS=2) the lesion progressed from one segment (IO) to three segments with additional involvement of chiasma. Two patients (ON=2, MS=0) with IO+CAN on the initial MRI had progression to three segments (IO+CAN+CHI) (fig. 4). Of the remaining nine patients, eight had unchanged signal abnormality location and one optic nerve remained normal at follow-up MRI. Notably none of the patients with sign of ON on initial MRI normalized on follow-up MRI (fig. 2).

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Occurrence and location of brain lesions at the presentation of acute ON:

Initial brain MRI revealed lesions in 80.6% (25/31) patients (Fig 3). Fourteen had MS-like lesions at the initial MRI. Of those, 12 qualified for the diagnosis of MS(Soelberg et al., 2017), one remained as isolated ON and one was diagnosed with MOG-IgG-related encephalopathy. The remaining 11 /16 (62.5%) had non-specific WM brain lesions, nine remained as isolated ON and two developed MS(Soelberg et al., 2017). Significantly more patients who later developed MS had brain lesions compared to the group of patients who remained as isolated ON (p= 0.021). Simultaneous detection of brain and optic nerve lesion was observed in 13/14 (93%) patients, who progressed to MS.

Of the 25 patients with signal abnormalities of the optic nerve, 21 (84%) had brain lesions. The location of the brain lesions of the patients, who converted to MS and the isolated ON patients differed as follows: Brainstem involvement in 7/13 patients with MS, 1/12 patients with isolated ON (p=0.030), periventricular lesions in 13 and 7, respectively (p=0.015), cerebellar lesions 5 and 0, respectively (p=0.039), lesions in the centrum semiovale in 11 and 4, respectively (p=0.015), and corpus callosum lesions in 6 and 1, respectively (p=0.073) (fig. 5).

Of the 31 patients, 22 had spinal cord MRI at presentation of acute ON. Of those, 12 patients converted to MS and 10 remained as isolated ON. A total of eight patients had spinal cord lesions, all with an MS diagnosis (p=0.002), compared to patients with a final diagnosis of isolated ON at last follow-up.

Visual acuity

VA was measured at onset in 31 patients corresponding to 33 ON eyes with a median time after onset of 7 days (range 1-30 days), and again during follow-up in 30 (32 ON eyes) after six months and 29 (31 ON eyes) at the one-year follow-up. We compared VA in the two groups with either a normal optic

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nerve (n=8) versus a lesion (n=25) on MRI. There was no significant difference in VA (p=0.42, p=0.75 and p= 0.59, respectively). Furthermore, we did not find any difference in VA of patients with optic nerve involvement of one segment (IO or CAN) (14 optic nerves) compared to patients (11 optic nerves) with two-segment involvement (IO+CAN) (p=0.21, p=0.09 and p=0.50, respectively). At follow-up, there was no significant difference between VA in the eyes with or without progression in signal abnormality on MRI follow-up either of vision measured at onset (p= 0.98), at six months (p= 0.97) or at one-year follow-up (p=0.80). When VA was divided into four subgroups (unchanged, aggravation, partial recovery or complete recovery), no difference was observed with regard to localization or modification of lesions at follow-up.

The VA in patients with MS-like lesions were compared with the rest of the group at onset and at one-year follow-up. No differences were observed (p=0.47 and p=0.19, respectively). Additionally, we did not find any difference in VA in patients with and without spinal cord lesions at onset and at one-year follow-up (p=0.42 and p=0.77, respectively).

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Discussion

The visual system is susceptible to MS and antibody-mediated ON related damage (Jarius et al., 2016b). ON is an early inflammatory demyelinating event with acute focal damage of the anterior visual pathway, which can be visualized by MRI. The MRI features of the optic nerve lesion may allow discrimination between MS and other disease processes. This prospective study of 31 patients with the first episode of acute ON and with a one year clinical follow-up represents a population-based cohort with integration of clinical and laboratory findings. The main findings were that lesions of the optic nerve were detected significantly more often intra-orbitally in patients who later converted to MS and

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secondly that progression of optic nerve lesions with involvement of posterior segments was observed in a considerable proportion of ON patients at follow-up. Furthermore, WM lesions with specific locations, including brainstem, periventricular area, centrum semiovale, corpus callosum and spinal cord, occurred frequently at the time of the first single episode of acute ON in those patients who progressed to MS. Lastly, MOG-IgG was detected in one out of 17 patients with non-MS-related ON and was associated with an optic nerve lesion localizing to IO+CAN.

In the present study, a high frequency of optic nerve lesions abnormalities was observed (80.6%). All optic nerve abnormalities were located in the IO or CAN area at the initial MRI and no patients had involvement of the chiasm, characteristic of NMOSD (Ramanathan et al., 2016). As a novel finding, lesions of the optic nerve were predominantly located intra-orbitally in ON patients who subsequently developed MS. This finding supplements other studies (Khanna et al., 2012; Storoni et al., 2013), suggesting that MRI findings distinguish MS with short IO lesions from NMOSD and possible MOG encephalomyelitis(Jarius et al., 2016b) with long-segment lesions with posterior involvement. Additionally, simultaneous optic nerve and brain lesions were observed in 93% of patients progressing to MS. Previous MRI studies have reported that ON patients with no lesions at the time of ON have a 15–22% risk of MS compared to a 56–88% risk in patients with one or more brain lesions(Swanton et al., 2010). In the present study, the brain lesions included periventricular, centrum semiovale and infratentorial regions, which are regarded as characteristic for MS and occurred frequently in ON patients, who progressed to MS (Barkhof et al., 1997; Swanton et al., 2010; Tintore et al., 2010). The present data are in agreement with other studies of conversion of ON to MS, indicating that abnormal brain MRI at onset of ON is a predictor for development of MS(Ruet et al., 2011). Moreover, a considerable proportion of ON patients in our study had spinal cord lesions, remarkably

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occurring only in those who later converted to MS. This data supports a previous study (Sombekke et al., 2013) and is of considerable practical clinical importance. In conclusion, the demonstration of frequent IO location and specific brain lesions at the first single episode of acute ON has significant clinical implications, since those patients subsequently progressed to MS. It is potentially important to identify those patients who may convert to MS, as they may later be at greater risk of disability(Ramsaransing et al., 2001).

At follow-up MRI, we observed progression in the extension of optic nerve lesions in 55 % (11/20) with involvement of at least one more optic nerve segment. Abnormalities of the chiasm were seen in four patients who had MS-like brain lesions. Chiasmal involvement is regarded as typical for NMOSD(Kim et al., 2015; Ramanathan et al., 2016), but also has been described in MS as well as MOG encephalomyelitis(Jarius et al., 2016b; Kawasaki and Purvin, 2009; Lindenberg R, 1973). Progression of the optic nerve lesions in this present longitudinal MRI study represents an interesting finding, which may be related to pathogenicity of ON. After an attack of ON, there may be progressive damage to the optic radiations. Putatively, an anterograde trans-synaptic degeneration across the lateral geniculate nuclei has been suggested as the main mechanism for this continuing tissue damage(Jenkins et al., 2011; Tur et al., 2016). A limitation of this study was lack of quantitative imaging methods such as advanced MRI. However, our study based on conventional MRI longitudinally visualizes the consequences of ON,

In this study, the location of the optic nerve lesions, simultaneous brain and spinal cord lesions and progression of optic nerve lesions were not associated with acute or persistent worsening of visual

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impairment in the acute phase or at follow-up. An explanation could be the small size of the study and risk of a type II error. In addition, the MRIs were done without gadolinium (Gd) contrast, which may increase the sensitivity of MRI in detecting disease activity in ON. Previous retrospective studies, which used Gd, have revealed varying location of optic nerve lesions, varying association to VA and to visual recovery(Berg et al., 2015; Kupersmith et al., 2002; Youl et al., 1991). These discrepancies may result from lack of uniformity of survey methods, disease definitions and diagnostic criteria, complicating the conclusions and with a potential for selection bias. These inconsistencies emphasize the need for standardized and sensitive methods for assessment of both structure and function to more completely understand the pathophysiology underlying ON. Structural damage to the posterior visual pathways including optic radiation and visual cortex has also been reported by quantitative imaging methods in ON and MS and may be correlated to the level of visual impairment(Rocca et al., 2013). These data have been obtained by techniques such as functional MRI and diffusion tensor imaging which are useful to detect functional damage and to assess the quality of the remaining visual nerve fibers linking to recovery in patients with optic nerve damage. Further advanced MRI studies for imaging of ON lesions may be required to investigate underlying ON processes and assessment of structure and function.

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Strength of the study was that MRI scans were performed prospectively on acute ON patients in a population-based approach. Furthermore, the study involved a one year follow-up with the evaluation by both a neurologist and an ophthalmologist in the diagnostic algorithm. Finally, all the MRI scans were evaluated by the same neuroradiologist who was masked from all clinical information such as the ON eye, serological results, and final clinical diagnoses. Information was provided with integration of the imaging, clinical and laboratory findings.

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In conclusion, signal abnormalities of the optic nerve, brain and spinal cord occur frequently at presentation of a single ON event. Progression of optic nerve lesions with additional involvement of optic nerve segments was observed in a considerable proportion of patients at follow up. Patients who converted to MS typically had IO lesions of optic nerves and MS characteristic location of brain lesions. Notably, spinal cord lesions at the time of the first single episode of acute ON were associated with subsequent development of MS. These findings may facilitate identification of patients who progress to MS.

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KS: Study design, acquisition of data, statistical analysis, interpretation of results and writing of manuscript.

HPBS: Re-evaluation of MRI, acquisition of data, interpretation of results, revising manuscript and approving final version.

JG: Interpretation of results, revising manuscript and approving final version

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Figure legends

Figure 1, Acute optic neuritis signal change in the sub-segments of the optic nerve. MRI of optic nerves, reformatted images in the axial plane from 3D FLAIR sequences showing the segments of the optic nerve for lesion characterization: A) intra-orbital (white), B) canalicular, optic foramen to chiasm (yellow) and C) chiasmal, chiasm + optic tracts (red). This patient had an intra-orbital lesion of the right optic nerve and MS-like lesions in brain. MRI was performed 11 days after onset of symptoms.

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The patient was diagnosed with MS at the onset of optic neuritis. Figure 4 illustrates brain MRI scans from the same patient.

Figure 2, location of optic nerve lesion of the first episode of acute optic neuritis at baseline and follow up MRI. A flowchart illustrates location of optic nerve lesions on MRI at onset of the first episode of acute optic neuritis and at follow up. Remarkably, a posterior extension of the signal abnormalities of the optic nerve occurred in a considerable portion of patients with involvement of at least one more optic nerve segment at follow-up.

Abbreviations: IO=Intra-orbital, CAN=canalicular and CHI=chiasmal

Figure 3, occurrence of brain lesions at onset of first episode of acute optic neuritis Flowchart of the occurrence of brain lesions in the study population and the relation to the final diagnosis after one year of clinical follow up. A high frequency of brain abnormalities was observed at onset in the patients, who progressed to MS.

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Figure 4, progression of optic nerve lesion with chiasmal involvement at follow up MRI. A) Coronal 3D FLAIR sequence illustrating acute affection of the intra-orbital part of the right optic nerve with increased signal and size compared to the normal left optic nerve. B) MRI follow-up six months after onset shows still elevated signal with regression in size in the intra-orbital part of the right optic

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nerve and D) extension of lesion into the chiasm with increased signal on the right side compared to the normal chiasm at onset (C).

Figure 5, concurrent intra-orbital optic nerve lesions and MS-like brain lesions at the onset of first episode of acute optic neuritis. Coronal (A), sagittal (B and D) and axial (C) 3D FLAIR brain and orbital images from a patient with acute optic neuritis, who later was diagnosed with MS. A) Coronal image: Right optic nerve with signal abnormalities located intra-orbitally (yellow arrow). B) Sagittal image: Lesion in corpus callosum (red arrow). C) Axial image: Right optic nerve with intra-orbital signal abnormalities (yellow arrow) and peri-ventricular temporal lesions (red arrows). D) Parasagittal image showing multiple peri-ventricular lesions, some radiating from the ventricles, and a lesion in the cerebellar peduncle (red arrow).

Table 1 Demographics and characteristics of patients

Characteristics	
Subjects, n	31
Affected eyes (unilateral/bilateral)	29/2
Age [median (range)]	40 (17-66)
Gender, [F:M]	18:13
Ethnicity: Caucasian	31
Disease duration prior to acute MRI [days, median(range)]	21 (3-55)
Subjects follow-up MRI, n	20
Disease duration prior follow-up MRI [days, median (range)]	268 (100-498)

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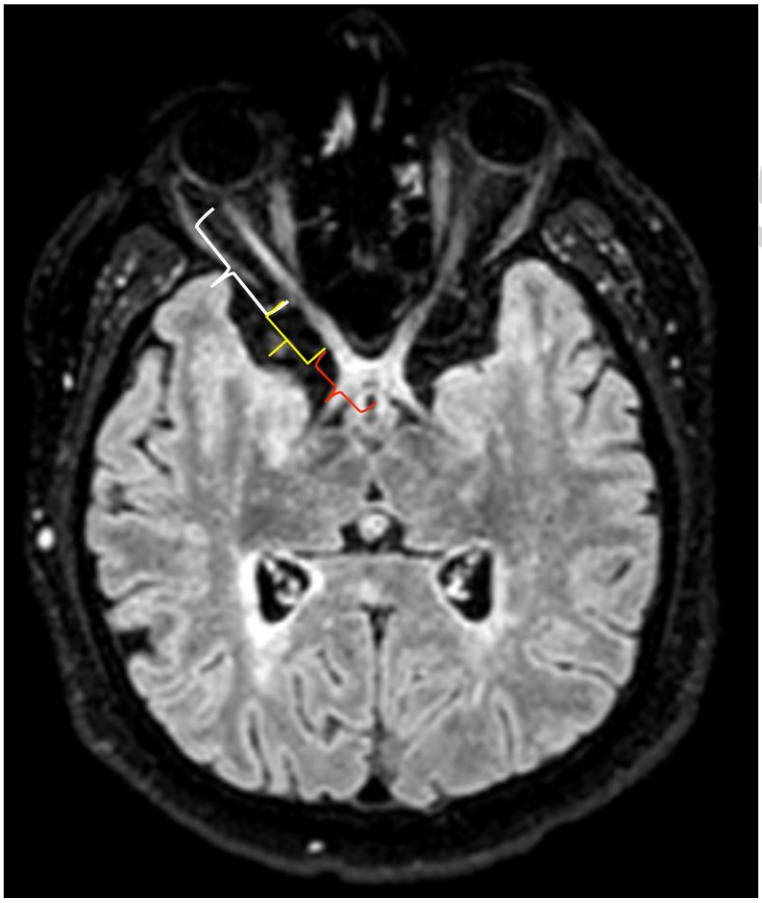
Highlights

- **Optic nerve lesions were detected frequently**
- **Lesions were located mainly intra-orbitally in patients who later converted to MS**
- **Progression of lesions was observed at follow-up**
- **Brainstem and spinal cord lesions occurred frequently in MS-ON patients**



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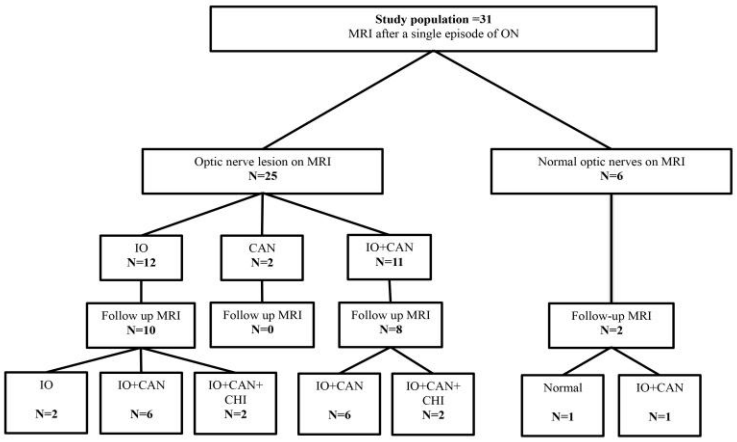

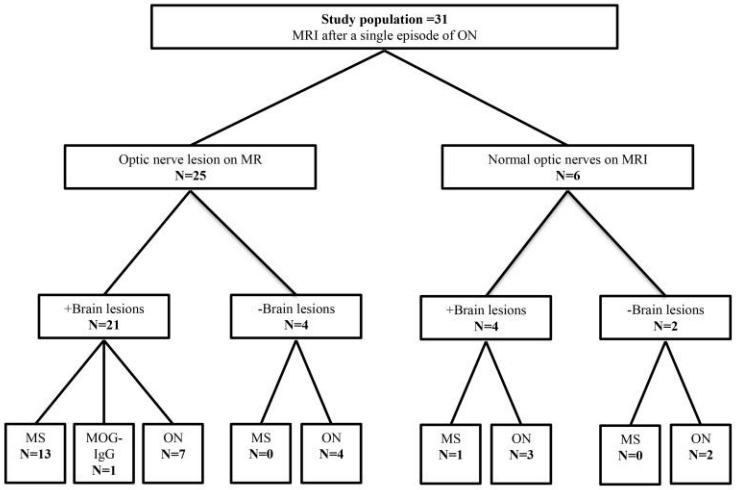

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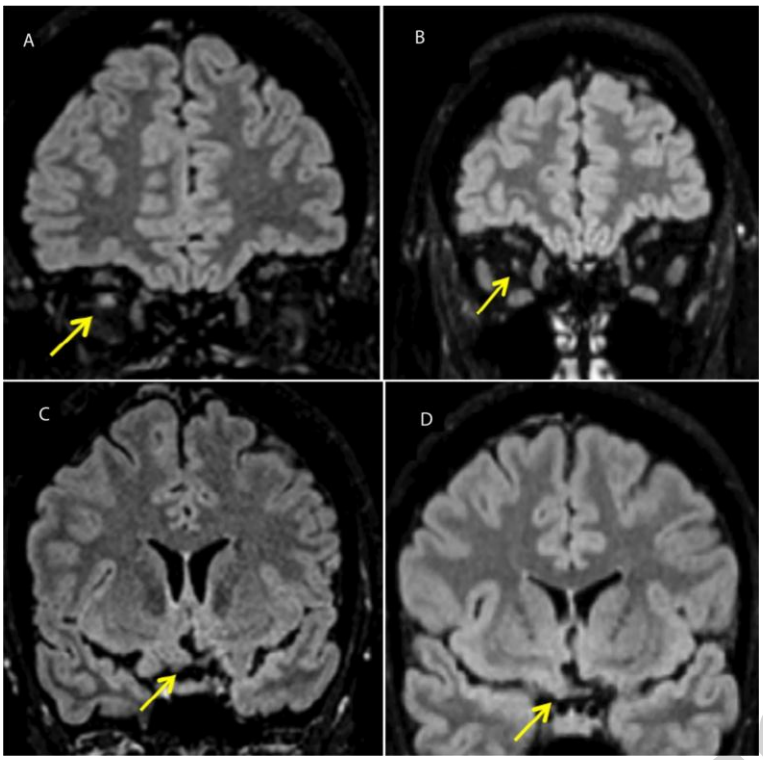

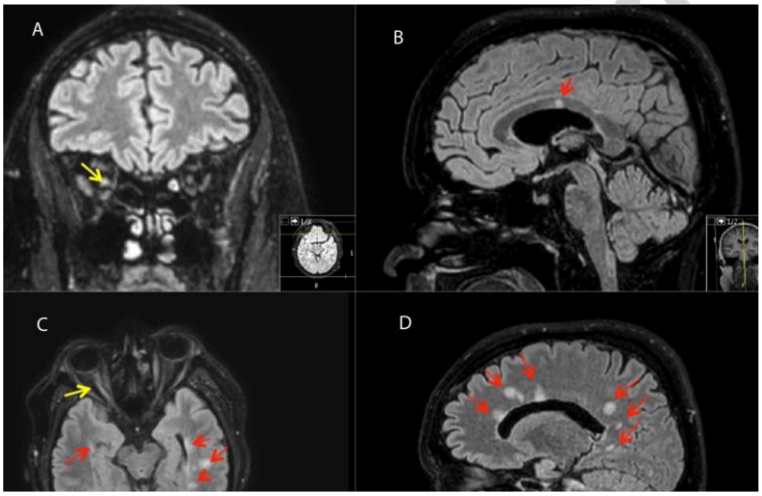

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