MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Optic nerve double inversion recovery hypersignal in patients with clinically isolated syndrome is associated with asymptomatic gadolinium-enhanced lesion

Multiple Sclerosis Journal
1–8
DOI: 10.1177/1352458518815797

Frédéric London, Hélène Zéphir, Nawal Hadhoum, Julien Lannoy, Patrick Vermersch, Jean-Pierre Pruvo, Jérôme Hodel, Xavier Leclerc and Olivier Outteryck

Abstract

Background: Optic nerve involvement is not considered in dissemination in space (DIS) or time (DIT) of multiple sclerosis (MS) lesions.

Objectives: To evaluate frequency of optic nerve involvement using three-dimensional (3D)-double inversion recovery (DIR) sequence in clinically isolated syndrome (CIS) and to measure its relationship with DIS and DIT (2010 and 2017 McDonald criteria).

Methods: From November 2013 to August 2016, 57 CIS patients underwent 3T-magnetic resonance imaging (3T-MRI) including 3D-DIR sequence and optical coherence tomography (OCT) at 3 months after CIS. We assessed signal abnormalities of the optic nerves on DIR sequence and collected data for DIS and DIT criteria according to 2010 and 2017 McDonald criteria.

Results: Among the 57 recruited patients, the presence of ≥ 1 DIR hypersignal in optic nerve was observed in 36 (63%; 48 optic nerves) including asymptomatic hypersignal in 22 (38.5%; 25 optic nerves). Optic nerve involvement was significantly associated with DIT ($p=0.006$) and MS according to 2010 criteria ($p=0.01$) but was not significantly associated with presence of DIS criteria according to 2010 and 2017 McDonald criteria. We identified a significant ($p<0.001$) temporal peripapillary retinal nerve fiber layer thinning on eyes with optic nerve involvement versus healthy controls.

Conclusions: Optic nerve involvement is very frequent at the earliest clinical stage of MS. It is associated with the presence of asymptomatic gadolinium-enhancement and retinal axonal loss and may reflect the inflammatory disease activity level.

Keywords: CIS, DIR, optic neuritis, MRI, multiple sclerosis

Date received: 8 August 2018; revised: 30 October 2018; accepted: 7 November 2018

Correspondence to:
O Outteryck
Department of Neuroradiology, Roger Salengro Hospital, CHU Lille, University of Lille, 59037 Lille, France.
olivier.outteryck@chru-lille.fr

Frédéric London
Nawal Hadhoum
Julien Lannoy
Department of Neurology, Roger Salengro Hospital, CHU Lille, University of Lille, Lille, France

Hélène Zéphir
Patrick Vermersch
Department of Neurology, Roger Salengro Hospital, CHU Lille, University of Lille, Lille, France/LIRIC UMR 995, CHU Lille, University of Lille, Lille, France

Jean-Pierre Pruvo
Jérôme Hodel
Xavier Leclerc
Department of Neuroradiology, Roger Salengro Hospital, CHU Lille, University of Lille, Lille, France/UMR 1171, CHU Lille, University of Lille, Lille, France

Olivier Outteryck
Department of Neurology, Roger Salengro Hospital, CHU Lille, University of Lille, Lille, France/Department of Neuroradiology, Roger Salengro Hospital, CHU Lille, University of Lille, Lille, France/UMR 1171, CHU Lille, University of Lille, Lille, France

Introduction

The diagnostic criteria of multiple sclerosis (MS) have changed considerably over time, especially due to the ability of magnetic resonance imaging (MRI) to predict conversion in clinically definite MS.[1] In 2016, the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) group proposed modifications of MRI criteria for the diagnosis of MS and notably the addition of optic nerve as a fifth typical location for dissemination in space (DIS).[2] However, although involvement of optic nerve is known to be frequent in MS patients,[3–5] evidence to support the introduction of optic nerve as a fifth anatomical location in the McDonald criteria are currently insufficient.[6,7] The absence of a validated and homogeneous assessment using MRI, neurophysiology, or optical coherence tomography (OCT) to detect optic nerve lesions is the main reason which motivated the 2017 Panel Membership not to include it in the 2017 revised MS criteria.[6] Consequently, there is an unmet need to provide a consensual, and reliable tool, easily applicable in clinical routine, to assess the involvement of optic nerve in the patients with clinically isolated syndrome (CIS).

Over the past years, double inversion recovery (DIR) sequence has been introduced as a novel technique that outperforms conventional MRI sequences for the detection of cortical lesions.[8,9] More recently, this sequence demonstrated its usefulness to detect spinal cord[10] and optic nerve inflammatory lesions.[11] By achieving adequate cerebrospinal fluid (CSF) and white matter suppression, the three-dimensional (3D)-DIR sequence improved the detection of optic nerve demyelinating lesions with a reported sensitivity and specificity of 95% and 94%, respectively, but this study only concerned patients with symptomatic optic neuritis (ON) and did not investigate optic nerve demyelination in visually asymptomatic CIS patients.[11] Intra- and inter-observer agreements have been previously reported as excellent.[11,12] Despite these promising results, the use of DIR imaging technique is not established for the diagnosis of MS in clinical routine, and there are only few data about the utility of this sequence in the evaluation of asymptomatic optic nerve demyelination.[12,13]

The aim of this study was to investigate in a cohort of CIS patients the frequency of optic nerve involvement (asymptomatic and symptomatic) on 3D-DIR sequence and its association with the DIS and dissemination in time (DIT) criteria for relapsing–remitting multiple sclerosis (RRMS) according to McDonald 2010 and 2017 criteria at baseline.

Materials and methods

CINOCIS study is a prospective follow-up (FU) study of CIS patients, including clinical and imaging (MRI, OCT) parameters. Its aim is to search new potential biomarkers which could have a prognostic value in MS. This study was approved by our local ethical committee of Lille University Hospital. All participants provided written consent. Between November 2013 and August 2016, we prospectively enrolled 57 patients who presented with a first symptomatic episode of central nervous system (CNS) demyelination. Inclusion criteria were age 18–65 years, a CIS in the 3 previous months, and the absence of previous history of neurological symptoms. CIS was defined as a monophasic, focal or multifocal, clinical episode of CNS demyelination, developing acutely or subacutely, with a duration of at least 24 hours, in the absence of fever or infection, and not attributable to other CNS diseases. All patients were followed at Lille MS center (France), had a diagnosis work-up including standard brain ± spinal cord MRI, lumbar puncture, and had a complete comprehensive work-up at onset to rule out mimickers of MS. CIS patients who developed clinically definite multiple sclerosis (CDMS) soon after their CIS and before inclusion period were excluded. Data on sex, age at CIS onset, type of onset, and presence of oligoclonal bands (OCBs) were collected.

MRI protocol

Each patient underwent both brain and spinal cord MRI at 3 months after CIS. In our analysis, we did not consider the previous standard brain ± spinal cord MRI performed during the diagnosis work-up. In our study, MRI examinations were performed on a 3-Tesla MR system (Achieva; Philips Medical Systems, Best, The Netherlands) and included 3D sequences (T1, fluid-attenuated inversion recovery (FLAIR), DIR, T1-gadolinium) on the brain and two-dimensional (2D) sagittal acquisitions (T1 and T2-SPAIR sequences) on spinal cord. MRI parameters of 3D-DIR were as follows: sagittal acquisition, voxel size (1.2 mm × 1.2 mm × 0.65 mm), TR 5500, TE 252, TI Dual 625/2600, NEX 2, fat suppression SPIR, matrix size 208 × 208, FOV 250 × 250 × 195, number of slices 300, and CS factor 2. During the 3D-DIR acquisition[11] (Figure 1), patients were asked to close their eyes and to avoid eye movements as much as possible.

Image analysis

MRI images were interpreted independently by two trained examiners (F.L. and O.O.); discordant results were reconsidered to reach a consensus. Within each patient, the presence/absence of T2-weighted lesions in each of the four anatomical areas for demyelinating MS lesions,[1,6] the presence/absence of gadolinium-enhancing lesions, and the presence/absence of uni- or bilateral optic nerve DIR hypersignal were recorded. Therefore, we investigated the frequency of optic nerve DIR hypersignal and also more specifically asymptomatic optic nerve DIR hypersignal at baseline and its association with DIS and DIT according to McDonald 2010 and 2017 criteria.

OCT

At the time of MRI, bilateral OCT scan (Spectralis; Heidelberg Engineering, Heidelberg, Germany) respecting OSCAR-IB quality criteria was performed.[14] We measured the peripapillary retinal nerve fiber layer (pRNFL) thickness in the temporal quadrant which is early[15] and more specifically affected in MS[16] (12°, 3.4-mm circular scan around the papilla with a minimum of 50 automatic real time). All CIS patients were matched (1:1) to healthy controls (HCs) extracted from our local OCT database according to age and sex.[16]

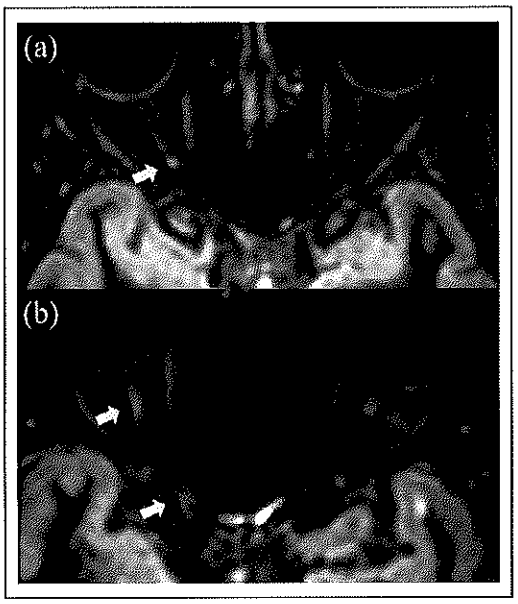

Figure 1. Optic nerve imaging with 3D-DIR sequence. (a) CIS patient presenting a spinal cord syndrome. 3D-DIR axial reconstruction showed an asymptomatic DIR hypersignal of the orbital portion of the right optic nerve (yellow arrow). (b) CIS patient presenting with a left clinical episode of ON. 3D-DIR axial reconstruction showed one symptomatic DIR hypersignal of the orbital portion of the left optic nerve (red arrow) and two asymptomatic DIR hypersignal of the orbital and prechiasmatic portions of the right optic nerve asymptomatic (yellow arrows). CIS: clinically isolated syndrome; 3D-DIR: 3-dimensional double inversion recovery.

Statistical analysis

The frequency distribution of variables was obtained using contingency tables. Chi-square test was used to evaluate the significance between the two proportions. Fisher's exact test was used when one of more of the cells had an expected frequency of 5 or less. Mann–Whitney *U* test was used to compare ranks distribution of quantitative values of two groups. All reported *p* values were two-sided and considered statistically significant if less than 0.05.

Results

Clinical findings

A total of 57 CIS patients were included. Of them, 40 (70%) were women. Mean age was 29.2 ± 7 years. At inclusion, no patient received any disease-modifying treatment (DMT). Of the 57 patients, 21 (36.8%) presented with clinical episode of ON, 10 (17.5%) with brainstem symptoms, 20 (35.1%) with spinal cord symptoms, and another 8 (14.0%) patients had a different presentation (hemispheric topography). Monofocal presentation was predominant (96.5%), two patients (3.5%) presented with a polyregional onset (ON + hemispheric and ON + spinal cord). Two patients (9.5%) had bilateral ON simultaneously; none had anti-MOG (myelin oligodendrocyte glycoprotein) or anti-aquaporin-4 antibodies. Of the 114 eyes, 1 was excluded because of right-sided eye agenesis.

Among all patients, one was lost during the 24 months FU from CIS because of moving. During the 24 months FU, 45 patients (80.4%) started a DMT and 11 did not. These 11 patients did not developed CDMS during FU. A majority of patients started a treatment before occurrence of CDMS ($n=32$; 57.1%) and were considered as "early treated." In all, 22 patients were early treated due to DIS and DIT observed on MRI at 3 months from CIS and 10 were treated later (9.4 ± 6.0 months) due to DIS and DIT observed on MRI FU. Among the 32 patients starting DMT before CDMS, half presented a clinical episode of ON ($n=16$) as CIS and two-thirds ($n=22$) presented a symptomatic or asymptomatic optic nerve involvement on MRI. In all, 23 patients developed a CDMS during the 24 months FU. Among patients developing a CDMS, a majority ($n=13$; 56.5%) were not treated at the time of the second clinical relapse. Among patients not developing CDMS ($n=33$), a majority ($n=22$; 66.7%) were early treated. Among "early treated" patients ($n=32$), one-third developed a CDMS ($n=10$; 31.3%), and among "not early treated" patients ($n=24$), more than half developed a CDMS ($n=13$; 54.2%).

MRI findings

Among the 57 patients, all had ⩾1 periventricular lesions, 44 (77%) had ⩾1 juxtacortical lesions, 39 (68%) had ⩾1 infratentorial lesions, 37 (65%) had ⩾1 spinal cord lesions, and 26 (46%) had ⩾1 gadolinium-enhancing lesions. All gadolinium-enhancing lesions were asymptomatic except for one patient who had both symptomatic and asymptomatic gadolinium-enhancing lesions.

MRI quality of 3D-DIR sequence allowed MRI analysis in good conditions.[11] The distribution of optic nerve lesions is reported in Figure 2. The presence of ⩾1 optic nerve DIR hypersignal was observed in 36 (63%) of the 57 patients (48 optic nerves among 113 eyes). All patients with clinical episode of ON ($n=21$, 37%; 23 optic nerves) had a symptomatic optic nerve DIR hypersignal, whereas 22 patients (38.6%; 25

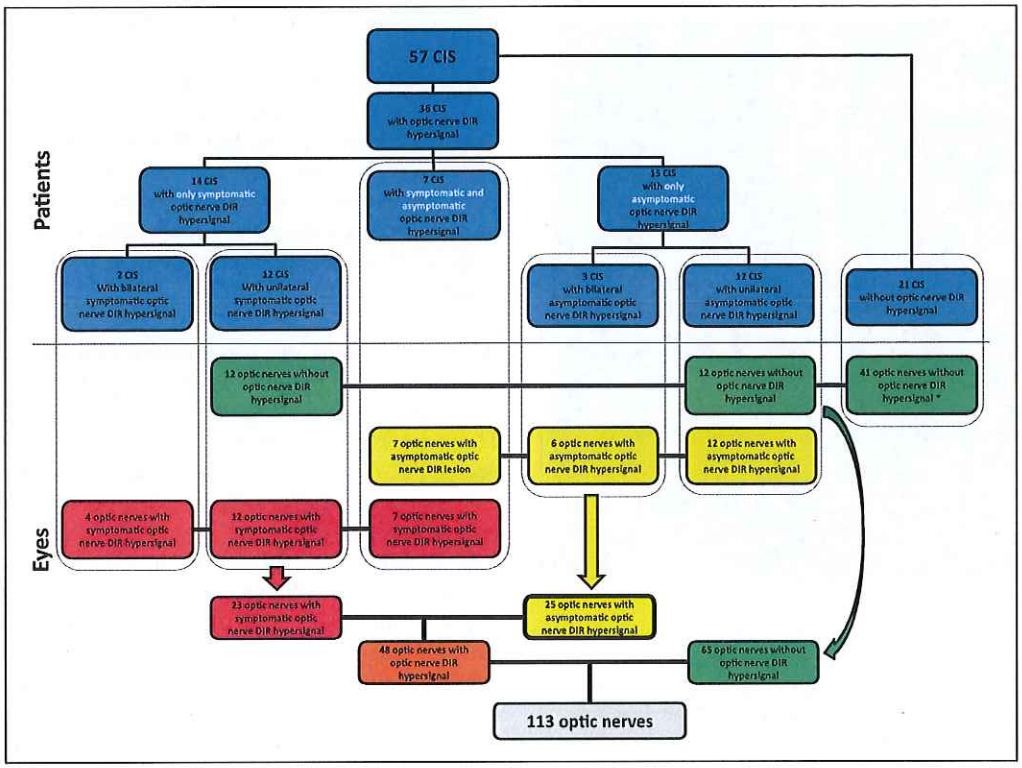

Figure 2. Flowchart describing the distribution of symptomatic and asymptomatic optic nerve DIR lesions in the 57 CIS patients and in the 113 optic nerves included in the prospective study. CIS: clinically isolated syndrome; DIR: double inversion recovery.
*One optic nerve was excluded because of eye agenesis.

optic nerves) had an asymptomatic optic nerve DIR hypersignal. Among these 22 patients, 7 had a clinical episode of ON in the opposite eye and 15 had only asymptomatic optic nerve DIR hypersignal representing 42% of non-ON CIS. Three patients had a bilateral asymptomatic DIR hypersignal. Of the 113 included eyes, 48 (42%) had an optic nerve DIR hypersignal.

Optic nerve involvement and OCBs

In total, 47 (82.5%) patients had intrathecal IgG synthesis (data not available for 1 patient). Presence of OCBs was not associated with presence of asymptomatic optic nerve DIR hypersignal ($p=0.96$) or presence of optic nerve DIR hypersignal ($p=0.296$).

Optic nerve involvement and 2010 revised McDonald criteria

According to the 2010 revised McDonald criteria, 53 (93%) patients had DIS and 26 (46%) had DIT. Consequently, 25 (44%) had both DIS and DIT. Presence of asymptomatic optic nerve DIR hypersignal was not significantly associated with presence of DIS ($p=0.65$) but was significantly associated with DIT (asymptomatic Gd enhancement; $p=0.03$) and MS defined according to 2010 criteria ($p=0.017$).

Presence of optic nerve DIR hypersignal (symptomatic or asymptomatic) was not associated with presence of DIS ($p=0.61$) but was significantly associated with DIT ($p=0.006$) and MS according to 2010 criteria ($p=0.01$).

Optic nerve involvement and 2017 revised McDonald criteria

Data on OCB were missing for one patient presenting asymptomatic spinal cord and periventricular lesions. According to the 2017 revised McDonald criteria, 55 (96%) patients had DIS and 51 (89%) had DIT. Consequently, 49 (86%) had both DIS and DIT. Presence of asymptomatic optic nerve DIR hypersignal was not significantly associated with presence of DIS ($p=0.51$) or DIT ($p=1$) or MS according to 2017

criteria ($p=0.46$). Presence of optic nerve DIR hypersignal (symptomatic or asymptomatic) was not associated with presence of DIS ($p=0.97$) or DIT ($p=0.655$) or MS according to 2017 criteria ($p=0.362$).

Additive value of optic nerve as a fifth anatomical area for MS demyelinating lesion

Due to one asymptomatic nerve hypersignal, one additional patient would present DIS according to McDonald 2010 criteria by considering optic nerve as fifth anatomical area for MS demyelinating lesion. This additional patient did not present DIT according to McDonald 2010 criteria.

Due to one symptomatic optic nerve hypersignal, one additional patient would present DIS according to McDonald 2017 criteria by considering optic nerve as a fifth anatomical area for MS demyelinating lesion. This additional patient presented DIT according to McDonald 2017 criteria.

Optic nerve involvement and development of clinically definite MS at 24 months after CIS

A total of 23 patients presented a CDMS in the 24 months FU. We did not find any association between CDMS occurrence and presence of asymptomatic optic nerve involvement ($p=0.73$) or presence of optic nerve involvement (symptomatic or asymptomatic; $p=0.72$). More than half of our patients ($n=32$; 57.1%) were "early treated."

OCT findings

Within eyes with symptomatic optic nerve DIR hypersignal ($n=23$), we observed a significant temporal pRNFL thinning (mean (in μm) ± standard deviation (SD); 56.9 ± 11.64; $p<0.001$) versus HC (74.16 ± 10.07). Within eyes with asymptomatic optic nerve DIR hypersignal ($n=25$), we observed a significant temporal pRNFL thinning (65.52 ± 8.04; $p<0.001$) versus HC (74.08 ± 10.05). Within eyes with optic nerve DIR hypersignal ($n=48$), we still observed a significant temporal pRNFL thinning (61.39 ± 10.74; $p<0.001$) versus HC (74.11 ± 10.05). Within eyes without optic nerve involvement ($n=65$), we did not highlight any significant temporal pRNFL thinning (70.96 ± 9.28; $p=0.14$) versus HC (72.8 ± 11.0).

Discussion

Our results emphasize that involvement of optic nerve, symptomatic or not, is very frequent at the earliest clinical stage of RRMS and is associated with presence of gadolinium-enhancing lesion. Including optic nerve lesion as the fifth anatomical location may slightly increase the number of patients presenting DIS. We did not find association between optic nerve involvement on MRI at CIS and occurrence of CDMS at 2 years, possibly due to therapeutic intervention before CDMS occurrence.

In our study, findings showed that DIR sequence detected a hypersignal of optic nerves in about two-thirds of CIS patients including asymptomatic DIR hypersignal in one-third of CIS patients. Asymptomatic optic nerve involvement is as much frequent as symptomatic optic nerve involvement. Optic nerve is one of the most common anatomic areas of injury in MS, but its imaging is challenging and remains limited by some inherent artifacts surrounding the optic nerve and that are produced by the perineural CSF and the orbital fat, obscuring significantly the optic nerves. In conventional MRI protocols, the best diagnostic performance to detect acute ON is currently reached by T2-weighted MR sequences that include both fat and water suppression.[17] The utility of fat saturation using either short tau inversion recovery (STIR) or frequency-specific spectral presaturation inversion recovery (SPIR) techniques for the imaging of optic nerves has been previously demonstrated.[18–20] In a study evaluating optic nerve by MRI, using STIR sequence, in a series of 37 patients with history of ON, the presence of asymptomatic optic nerve lesion was observed in 20% of asymptomatic nerves, but these data were not collected closed to the CIS.[21] Moreover, authors found that visual evoked potentials (VEPs) were more sensitive than STIR sequence for detecting optic nerve lesions.[21] The major drawback of STIR technique concerns the high signal intensity from the perineural CSF leading to volume averaging between the signal intensity of the optic nerve on T2-weighted images and the CSF.[17] Combining fluid and fat suppression (2D coronal STIR FLAIR) improves the accuracy for the detection of optic nerve signal abnormalities by reducing susceptibility artifacts. Some of us have since demonstrated that the diagnostic performance of 3D-DIR sequence, used in this study, outperforms 2D STIR FLAIR sequence for the detection of optic nerve signal abnormalities in patients with ON, with a reported sensitivity and specificity of 95% and 94%, respectively. However, this study only focused on patients with symptomatic ON and did not investigate optic nerve demyelination in visually asymptomatic CIS patients.[11] In accordance with our results on a CIS population, we previously showed in MS that asymptomatic optic nerve DIR hypersignal was observed in 20% of patients.

Moreover, this proportion may have been underestimated because every patients included in this study were previously affected by uni- or bilateral ON.[12] More recently, Sartoretti et al.[13] identified retrospectively an asymptomatic DIR hypersignal in 78% of 95 MS patients without visual symptoms within the past 3 years. However, the authors cannot affirm that symptomatic ON did not occur in some patients before the 3 years included in the study design.

Some previous neurophysiological studies have demonstrated the ability of VEP to reveal asymptomatic involvement of optic nerve in MS patients without ON, in a percentage ranging from 35% to 93%, by showing delayed VEP latency or decrease in amplitudes.[22,23] Indeed, OCT studies in CIS have showed that the retinal nerve fiber layer is reduced not only in eyes with a history of ON but also in eyes without any clinical event of ON.[15,24,25]

In this study, we found a significant association between asymptomatic optic nerve demyelinating lesion and diagnosis of RRMS according to McDonald 2010 criteria. In a recent analysis comparing the performance of the 2010 McDonald and 2016 MAGNIMS criteria for MS diagnosis, the MAGNIMS network showed only a minor improvement in sensitivity of predicting development of a second attack by adding optic nerve as a fifth location for DIS criteria, with a reduced specificity.[7] They found optic nerve involvement in 54% of 241 CIS patients. However, this evaluation of optic nerves was not homogeneous in the CIS cohort as it was based only on VEP in most patients (91%), while only 3 of them had optic nerve MRI and 19 had both MRI and VEP assessment. These data did not provide sufficient evidence for adding optic nerve in the 2017 revision of DIS criteria for the diagnosis of MS. Although we did not perform VEP at the same time, our results argue for the utility of 3D-DIR sequence, a very sensitive optic nerve MRI sequence for demyelinating lesions detection, coupled with OCT analysis in further studies to determine the effect of including optic nerve assessment as an additional DIS criterion. Including optic nerve as a fifth anatomical area for MS demyelinating lesions in our patients cohort would have slightly increased the number of patients presenting DIS. Furthermore, our results also highlight that optic nerve lesions as asymptomatic optic nerve lesions are associated with the presence of gadolinium-enhancing lesions and may therefore reflect a higher inflammatory disease activity. This observation might suggest that patients with a CIS in whom optic nerve lesion is identified are more likely to have active disease and have a higher risk for conversion to clinically definite MS, which is consistent with the higher risk of relapse(s) in patients presenting with ON in association with OCB and clinically silent brain lesions.[4] So, we could postulate that a more intensive monitoring may be warranted in the patients who have an optic nerve lesion but do not fulfill the 2010 and 2017 McDonald criteria. According to our results, it could also be discussed that presence of optic nerve lesion(s), as asymptomatic gadolinium enhancement and OCB, may help to demonstrate DIT in MS. This point cannot be analyzed specifically by our cross-sectional analysis but needs a longer longitudinal FU study in a larger cohort taking into account an important bias factor represented by early and different MS treatments applied to CIS that may delay the second clinical relapse and T2 lesion burden increase. Indeed, more than half of our patients have been treated before development of CDMS. CINOCIS study inclusions are currently ongoing and a longer longitudinal FU with a larger cohort is warranted.

We did not observe any significant link between the presence of an optic nerve hypersignal and DIS or OCB. However, a very high proportion of patients presented DIS or OCB and a very narrow proportion did not. It would be important to increase the size of our cohort to be able to compare those groups. In our study, the MRI protocol only included 3D sequences. The 3D imaging has probably increased our ability to detect small (but $\geq$3 mm) demyelinating lesions suggestive of MS and consequently the number of patients presenting DIS.

This study has some limitations. We acknowledge our exploratory study was limited by its quite small size. The absence of histopathological data regarding optic nerve injury and the absence of VEP analysis may raise doubts about the specificity of the signal abnormalities observed. However, the DIR sequence was highly pathologically specific for detecting MS cortical lesions in a previous post-mortem verification study,[8,26] and corroboration of optic nerve involvement was provided by OCT evaluation which showed a corresponding retinal thinning in all patients with DIR optic nerve hypersignal symptomatic or not, and the absence of significant retinal thinning in patients without optic nerve involvement in comparison with HC. Then, we did not evaluate the inter-scanner reliability of DIR sequence, which may be important to broaden its scope and to enable multicenter studies. Finally, we have assumed that the hypersignal found on 3D-DIR sequence was always related to silent demyelination, but another concomitant cause cannot be formally ruled out.

In conclusion, our study suggests that 3D-DIR sequence is a very sensitive tool to detect a hypersignal of the optic nerves in CIS patients, that this technique could be systematically included in the MRI protocol to get an optimal optic nerve analysis at the CIS occurrence, and may argue in favor of inclusion of optic nerve lesions detection in the next revision of MS criteria. Further studies including a larger cohort of patients are required to confirm these results and to assess the prognostic value of optic nerve lesions detected with DIR in patients suspected of MS.

Acknowledgements
The authors would like to thank Bayer for their constant support.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Bayer. Bayer had no role in study design, data collection/analysis/interpretation, or writing of the report.

References

1. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69(2): 292–302.
2. Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. *Lancet Neurol* 2016; 15(3): 292–303.
3. Miller D, Barkhof F, Montalban X, et al. Clinically isolated syndromes suggestive of multiple sclerosis, part I: Natural history, pathogenesis, diagnosis, and prognosis. *Lancet Neurol* 2005; 4(5): 281–288.
4. Tintore M, Rovira A, Rio J, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. *Brain* 2015; 138(Pt 7): 1863–1874.
5. Kuhle J, Disanto G, Dobson R, et al. Conversion from clinically isolated syndrome to multiple sclerosis: A large multicentre study. *Mult Scler* 2015; 21(8): 1013–1024.
6. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17(2): 162–173.
7. Filippi M, Preziosa P, Meani A, et al. Prediction of a multiple sclerosis diagnosis in patients with clinically isolated syndrome using the 2016 MAGNIMS and 2010 McDonald criteria: A retrospective study. *Lancet Neurol* 2018; 17(2): 133–142.
8. Geurts JJG, Pouwels PJW, Uitdehaag BMJ, et al. Intracortical lesions in multiple sclerosis: Improved detection with 3D double inversion-recovery MR imaging. *Radiology* 2005; 236(1): 254–260.
9. Calabrese M, Filippi M and Gallo P. Cortical lesions in multiple sclerosis. *Nat Rev Neurol* 2010; 6: 438–444.
10. Riederer I, Karampinos DC, Settles M, et al. Double inversion recovery sequence of the cervical spinal cord in multiple sclerosis and related inflammatory diseases. *AJNR Am J Neuroradiol* 2015; 36(1): 219–225.
11. Hodel J, Outteryck O, Bocher AL, et al. Comparison of 3D double inversion recovery and 2D STIR FLAIR MR sequences for the imaging of optic neuritis: A pilot study. *Eur Radiol* 2014; 24: 3069–3075.
12. Hadhoum N, Hodel J, Defoort-Dhellemmes S, et al. Length of optic nerve double inversion recovery hypersignal is associated with retinal axonal loss. *Mult Scler* 2016; 22(5): 649–658.
13. Sartoretti T, Sartoretti E, Rauch S, et al. How common is signal-intensity increase in optic nerve segments on 3D double inversion recovery sequences in visually asymptomatic patients with multiple sclerosis. *AJNR* 2017; 38(9): 1748–1753.
14. Schippling S, Balk LJ, Costello F, et al. Quality control for retinal OCT in multiple sclerosis: Validation of the OSCAR-IB criteria. *Mult Scler* 2015; 21(2): 163–170.
15. Gelfand JM, Goodin DS, Boscardin WJ, et al. Retinal axonal loss begins early in the course of multiple sclerosis and is similar between progressive phenotypes. *PLoS ONE* 2012; 7(5): e36847.
16. Outteryck O, Majed B, Defoort-Dhellemmes S, et al. A comparative optical coherence tomography study in neuromyelitis optica spectrum disorder and multiple sclerosis. *Mult Scler* 2015; 21(14): 1781–1793.
17. Aiken AH, Mukherjee P, Green AJ, et al. MR imaging of optic neuropathy with extended echo-train acquisition fluid-attenuated inversion recovery. *AJNR* 2011; 32(2): 301–305.
18. Guy J, Mao J, Bidgood WD Jr, et al. Enhancement and demyelination of the intraorbital optic nerve. *Ophthalmology* 1992; 99(5): 713–719.
19. Hendrix LE, Kneeland JB, Haughton VM, et al. MR imaging of optic nerve lesions: Value of

gadopentetate dimeglumine and fat-suppression technique. *AJR* 1990; 155(4): 849–854.

20. Johnson G, Miller DH, MacManus D, et al. STIR sequences in NMR imaging of the optic nerve. *Neuroradiology* 1987; 29(3): 238–245.
21. Miller DH, Newton MR, van der Poel JC, et al. Magnetic resonance imaging of the optic nerve in optic neuritis. *Neurology* 1988; 38(2): 175–179.
22. Diem R, Tschirne A and Bahr M. Decreased amplitudes in multiple sclerosis patients with normal visual acuity: A VEP study. *J Clin Neurosci* 2003; 10(1): 67–70.
23. Tartaglione A, Oneto A, Bandini F, et al. Electrophysiological detection of "silent" plaques in the optic pathways. *Acta Neurol Scand* 1987; 76(4): 246–250.
24. Oberwahrenbrock T, Ringelstein M, Jentschke S, et al. Retinal ganglion cell and inner plexiform layer thinning in clinically isolated syndrome. *Mult Scler* 2013; 19(14): 1887–1895.
25. Pérez-Rico C, Ayuso-Peralta L, Rubio-Perez L, et al. Evaluation of visual structural and functional factors that predict the development of multiple sclerosis in clinically isolated syndrome patients. *Invest Ophthalmol Vis Sci* 2014; 55(10): 6127–6131.
26. Seewann A, Kooi E-J, Roosendaal SD, et al. Postmortem verification of MS cortical lesion detection with 3D DIR. *Neurology* 2012; 78(5): 302–308.