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ORIGINAL COMMUNICATION

Detecting optic nerve lesions in clinically isolated syndrome and multiple sclerosis: double-inversion recovery magnetic resonance imaging in comparison with visually evoked potentials

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Abstract

Background and aim Optic neuritis (ON) is a frequent manifestation of multiple sclerosis (MS), traditionally diagnosed clinically and by visually evoked potentials (VEP). However, ON can also be assessed by MRI. Here we compare the diagnostic performance of 3D-double inversion recovery-MRI (3D-DIR) and VEPs in patients with definite MS or clinically isolated syndrome (CIS).

Methods 39 patients and 17 healthy controls were studied. Whole-brain-3D-DIR images (3T) were independently assessed for DIR-hyperintense optic nerve lesions (DHLs) by two neuroradiologists, and results related to quantitative VEP-parameters.

Results Interrater concordance for DHLs was high ($\kappa = 0.82$). No DHLs were observed in controls. In patients, abnormal VEPs, i.e. prolonged latencies, diminished amplitudes or abnormal latency or amplitude differences (re contralateral nerve) of the P100-component, were observed in 22, and DHLs in 32 of 78 optic nerves, the latter including 11 nerves with normal VEPs, 10 without clinical signs or history of ON, and 6 with both normal VEPs and no clinical evidence for ON. Using either abnormal VEPs and/or presence of DHLs and/or clinical evidence for ON as a compound reference criterion of optic nerve affection, sensitivity was significantly higher for 3D-DIR than for VEPs (91%, 95%-CI 77–98% vs. 63%, 95%-CI 45–79%, respectively, $p = 0.006$).

Conclusion DHLs are highly specific for optic nerve pathology. In the context of MS, 3D-DIR-MRI is a suitable tool to reveal acute or chronic optic nerve lesions and more sensitive than VEPs. The significance of optic nerve involvement in the diagnostic classification of CIS vs. definite MS requires further study.

Keywords Optic neuritis · Double inversion recovery MRI · Visually evoked potentials · Multiple sclerosis

Introduction

Optic neuritis (ON) is a frequent and characteristic manifestation of multiple sclerosis (MS). In the context of a clinically isolated syndrome (CIS), ON is associated with a high risk of conversion to definite MS [1]. Traditionally, ON is diagnosed clinically and by means of visually evoked potentials (VEP), commonly evoked by an alternating checkerboard pattern as visual stimulus. VEP were introduced into clinical neurophysiology by Halliday et al. in 1972 [2], who demonstrated that VEP latencies are increased in patients with ON. In acute ON, demyelination and axonal involvement lead to a reduction and dispersion of conduction speeds in optic nerve fibers, resulting in increased VEP latencies and decreased VEP amplitudes. VEPs are generally deemed suitable to also detect and diagnose chronic lesions after preceding ON. However, VEP latencies and amplitudes

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often recover considerably over a period of weeks to months after the acute phase of ON and are quite variable across healthy subjects. Moreover, VEPs depend significantly on the respective laboratory environment and equipment so that there are no generally valid reference values. Rather, it is recommended by the pertinent guidelines of authoritative societies that individual laboratories establish their respective own reference values [3, 4]. Consequently, published data on VEP sensitivity and specificity are sparse and quite heterogeneous [5, 6].

MR imaging of the optic nerves with standard spin-echo techniques is challenging due to the high intrinsic signal of intra-orbital fatty tissue. Spectral fat suppression techniques or short tau inversion recovery (STIR) sequences are thus often used for imaging ON [7]. The double inversion recovery (DIR) sequence, first described by Redpath and Smith,[8, 9], simultaneously suppresses signals from the fat-containing healthy white matter and the cerebrospinal fluid and has gained increasing popularity in recent years due to its superior performance in revealing inflammatory lesions of the cerebral white and grey matter [10, 11] and of the cervical spinal cord [12] in patients with MS. Recently, it was shown that DIR images may also be useful for the detection of ON [13] and that, moreover, the extent of ON-associated optic nerve lesions, hyperintense in DIR images, correlated with retinal axonal loss, determined by optical coherence tomography (OCT), and visual disability [14].

The recent MAGNIMS consensus guidelines [15] on MS-MRI criteria emphasized the importance of ON as a characteristic manifestation of MS and proposed to include optic nerve lesions as an additional anatomical site to fulfil the criterion of dissemination in space. This proposal, however, was not adopted in the latest (2017) update of the McDonald-criteria [16], because the authoritative panel felt that available data on MRI-, VEP, or OCT-derived ON diagnoses, without corresponding clear cut history or clinical evidence were yet insufficient to support such measure. Nevertheless, in recognition of the highlighted significance of ON in MS, the panel emphasized the preliminary nature of their own decision and strongly encouraged further research on this issue.

This paper seeks to contribute to the debate by studying optic nerve lesions in 3D-DIR-MRI-images from subjects with and without clinical evidence for ON and by relating the findings to VEP measurements.

Materials and methods

Patients and healthy volunteers

Data were analysed retrospectively. The patient group consisted of 39 consecutive patients: 27 women, mean age 38 ± 12 years; range 18–66 years; 15 patients with CIS, 22 with relapsing-remitting MS (RRMS), and 2 with secondary-progressive MS (SPMS); median Expanded Disability Status Score (EDSS) 1.75 (range 0–6.5, inter-quartile-range 0–3), who had undergone routine MRI between January and May 2014 and for whom VEPs were available within 1 year (80 ± 131 days). In 20 of these patients, VEPs had been acquired within +/− 3 days of the MRI-acquisition. Eleven of the 39 patients had symptoms of acute ON, and 11 patients had a history of prior ON, including 3 who had previous ON in both nerves and one who also had symptoms of acute ON in the same nerve so that, in total, 21 patients had symptoms of acute ON and / or a history of prior ON. Seven additional patients from the sample period who had no measurable VEP-response in their clinical routine examination were not included, to ensure that no patients entered the sample in which VEP measurements had failed for mere technical reasons.

DIR scans from 17 subjects (healthy or with unrelated disorders, 9 women, mean age 30 ± 8 years; range 21–49 years), served as controls; from this group VEPs were not available.

Patients were examined either because of a clinical attack or for a routine follow-up. They were recruited by the Department of Neurology of our institution, which runs a dedicated high-volume centre for MS and related disorders. Diagnoses were made by experienced neurologists and were based on the 2010 McDonald criteria where applicable.

VEP acquisition

Patients were exposed to a checkerboard pattern as stimulation. According to the 10–20 system, responses were collected from the occipital scalp near to the calcarine fissure, with one electrode placed 2.5 cm above the inion in the midline and a second electrode placed at *Fz* as a reference. VEPs were assessed because of a new clinical attack or to complete diagnostic examinations to establish the diagnosis of CIS or MS. The P100 component of the VEP was considered exclusively. VEPs that fulfilled one or more of the following absolute or relative threshold criteria were considered abnormal: latency > 120 ms, latency increase re contralateral nerve > 8 ms, amplitude < 1.44 µV, or amplitude < 50% re contralateral nerve. Cut-off values are based on own normative data obtained with own standardized stimulating and recording equipment.

MR image acquisition

Scans were performed on a 3T scanner (Achieva, Philips Healthcare, Best, the Netherlands) using a 16-channel array head coil. Our standard MR protocol for patients with suspected MS includes a 3D-DIR sequence covering the whole brain with the following acquisition parameters:

acquired voxel size: $1.2 \times 1.2 \times 1.3$ mm^3; acquisition matrix: 208×208; field of view: 250 mm × 250 mm; repetition time (TR): 5500 ms; echo time (TE): 328 ms; inversion time (TI): 2550 ms; TSE factor: 173; number of slices: 300; acquisition time: 6 min; and acquisition plane: sagittal. The same DIR sequence was used for the participants from the control group. Three-dimensional DIR source images were reformatted into 1.5 mm thick axial sections and into 1.0 mm thick sections in sagittal and coronal orientations.

MR imaging analysis

All data were analysed retrospectively. First, the data of control subjects and patients were pooled and assessed in pseudorandomised order by two experienced neuroradiologists (with 5 and 11 years of experience) blinded to diagnosis and clinical status on a standard PACS workstation (Sectra Workstation IDS7, Version 17.1.18.3596, Sectra Healthcare). Segments with circumscribed hyperintense signal in an optic nerve were categorized as lesions. Each optic nerve was assessed separately at different time points to minimise bias. A consensus read was done for cases with discrepant assignments with both readers still blinded, to obtain a uniform data set for subsequent analyses. Two patients had to be excluded due to severe motion artefacts and are not included in the numbers above.

In addition, one neuroradiologist assessed data from all patients with available VEP for quantitative analysis, recording length [mm] and semiquantitative estimates of the affected cross-sectional area (divided into quartiles) using the standard tools of the PACS system. In patients with ≥ 2 unilateral lesions, lesion lengths were summed up, and the maximum affected cross-sectional area used for this assessment. If the course of the affected segment of the optic nerve was off the standard axial plane, suitable oblique planes parallel to the relevant optic nerve segment were calculated from the 3D-DIR dataset for accurate measurement.

Statistical analysis

Descriptive statistics and contingency tables were created and statistical analyses performed using SPSS 25 (IBM). Inter-observer concordance between image readers was assessed with Cohen's kappa. Nonparametric tests and correlation analyses were used when appropriate. Standard sensitivity and specificity measures including confidence intervals were calculated using the online version of the "medcalc"-calculator (https://www.medcalc.org/calc/diagnostic_test.php). Differences in sensitivities were assessed with McNemar's test. Statistical differences with p values < 0.05 were considered significant.

Results

The overall interrater concordance regarding presence or absence of DIR-hyperintense lesions (DHLs) in 112 optic nerves of 39 patients and 17 controls was high ($\kappa = 0.82$). No DHLs were observed in the control group by either reader, indicating good to perfect specificity (100%, 95%-CI 80–100%).

Among patients, 23 of 39 exhibited DHLs according to consensus read data. Nine of these had bilateral DHLs so that 32 of overall 78 nerves exhibited ≥ 1 DHL (DHL+-nerves). The average (cumulative) lesion length was 15.4 ± 9.1 mm (mean ± SD), and the full cross-sectional area was affected in most cases (18/32, 56%). There were clinical signs or a history of present or past ON ("clinical evidence for ON", CE_{ON}) in 24 nerves from 21 patients (bilateral in 3 patients). 22 nerves from 20 patients showed abnormal VEPs (bilateral in 2 patients).

There was no statistically significant association between age, sex, EDSS-Score, or diagnosis (CIS vs. MS-RR vs. MS-SP) and the presence of DHLs or abnormal VEPs (Table 1). Nerves with DHLs exhibited significantly

Table 1 Baseline data, shown for all patients and separately for patients with or without DHLs, and patients with and without abnormal VEPs, respectively

	All ($n = 78$)	DHL+ ($n = 32$)	p (DHL + vs. DHL−)	VEP+ ($n = 22$)	p (VEP + vs. VEP−)
Age (years), mean ± SD	37.7 ± 11.7	37.0 ± 10.7	0.68*	40.3 ± 11.4	0.214*
Female sex (%)	69	59	0.14+	55	0.1+
EDSS, median (IQR)	1.75 (0–3)	1.5 (0–3)	0.84‡	2 (0.25–3)	0.24‡
Diagnosis (n) CIS/MS-RR/MS-SP	30/44/4	9/21/2	0.29†	8/13/1	0.95†

There were no significant associations

* t test

+Fisher's

‡Mann–Whitney

†χ^2

longer VEP-latencies and smaller amplitudes than nerves without (118.3 ± 11.7 ms vs. 102.8 ± 6.7 ms, $p < 0.001$; Fig. 1a, left; and 8.6 ± 4.7 µV vs. 10.6 ± 3.8 µV, $p = 0.02$, respectively; Fig. 1b, left). When only nerves with overall "normal" VEPs were considered ($n = 56$), the P100-latencies of DHL+-nerves were still significantly longer than those of DHL−-nerves (108.4 ± 4.6 ms vs. 102.4 ± 6.1 ms, $p = 0.003$, Fig. 1a, right). P100 amplitudes were also still lower in DHL + than in DHL−-nerves (10.9 ± 3.7 µV vs. 9.4 ± 4.5 µV; Fig. 1b, right), although the difference was no longer significant in the smaller subsample. For DHL +-nerves, there was no significant correlation between lesion length or affected cross-sectional area and VEP-parameters.

Eleven of the 32 DHL+ -nerves showed normal VEPs, 10 lacked CE_{ON}, and 6 had both normal VEPs and no CE_{ON} (Table 2). Conversely, 21 of the 22 nerves with abnormal VEPs also had DHLs (Table 2).

Using abnormal VEPs, and/or CE_{ON}, and/or presence of DHLs in 3D-DIR as a compound criterion of optic nerve pathology (which held for 35 of 78 nerves), the calculated sensitivity was significantly higher for 3D-DIR than for VEPs (91%, 95%-CI 77–98% vs. 63%, 95%-CI 45–79%; $p = 0.006$, McNemar, see Table 2), and also higher for 3D-DIR than for CE_{ON} (69%, 95%-CI 51–83%, $p = 0.039$, Table 2). Among the 40 optic nerves of the 20 patients, in whom VEPs had been acquired within ± 3 days of the MRI, 18 had optic nerve pathology according to the compound criterion specified above. Of these, 17 were DHL+, 13 showed abnormal VEPs, and 13 had CE_{ON}. Sensitivity was thus also highest for 3D-DIR (3D DIR 94%, 95% CI 73–100%; VEPs/CE_{ON} each 72%, 95% CI 47–90%), although the differences

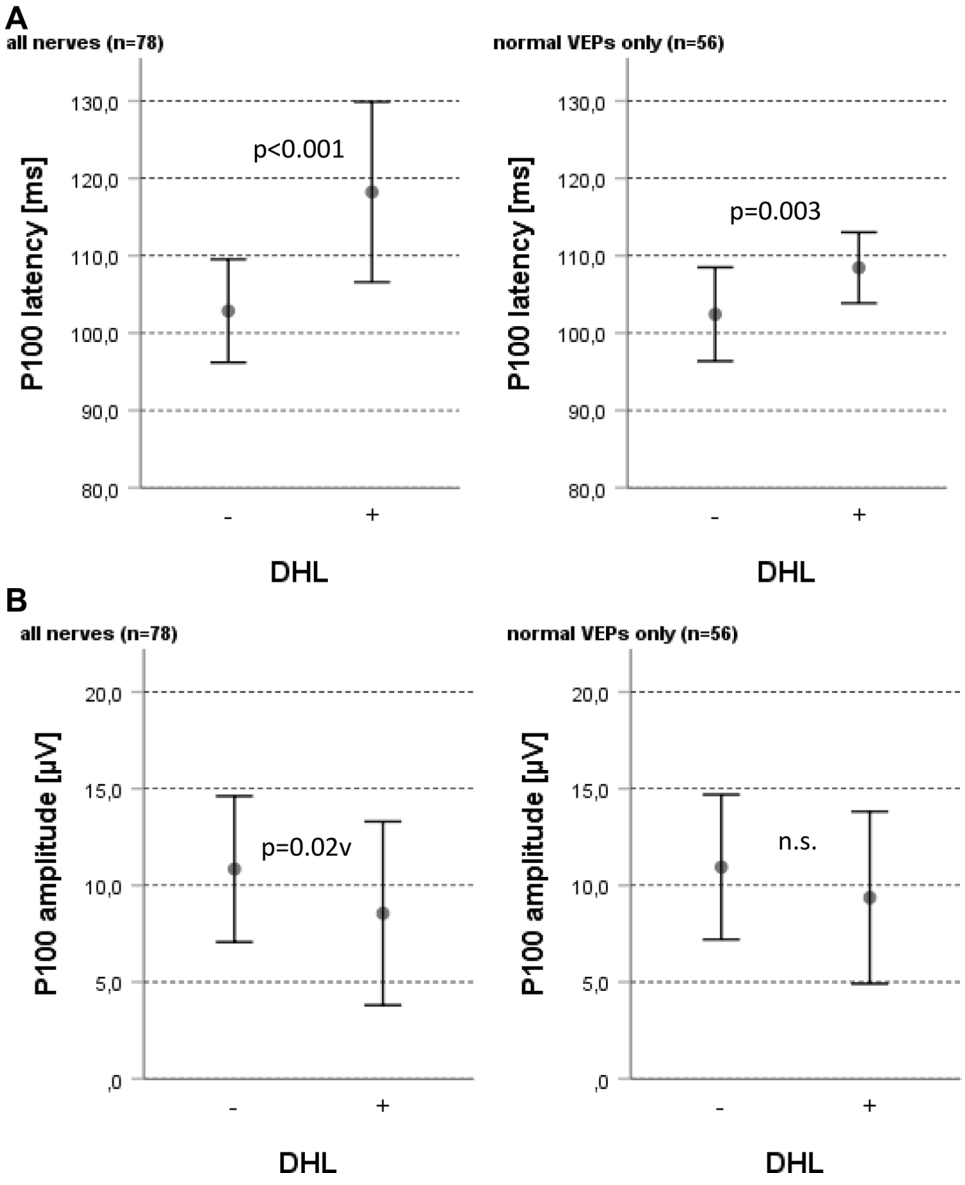

Fig. 1 Bar diagrams showing P100 latencies (**a**) and P100 amplitudes (**b**) for all optic nerves (left panels) and for those nerves that had normal VEPs, i.e. fulfilled none of the specified absolute or relative threshold criteria (see "Methods"). Overall, latencies were significantly longer and amplitudes smaller in nerves with DHLs than in nerves without. For latencies, this difference persisted and remained significant also for nerves in which VEPs were formally normal (right panels). For amplitudes, the difference persisted as well, although it was no longer significant in the smaller subsample. Error bars indicate standard deviations

Table 2 Contingency tables to compare sensitivities of DHLs, abnormal VEPs, and "clinical evidence for ON" (clinical signs of acute ON or history of previous ON)

Optic nerves with pathology according to compound criterion ($n=35$)					
		Abnormal VEP		Clinical evidence of ON	
		−	+	−	+
DHL	−	2	1	2	1
	+	11	21	10	22
	Abnormal VEP		−	6	7
			+	5	17

Data are displayed for all 35 nerves that showed evidence of pathology in any of the three diagnostic modalities (compound criterion, see text). The resulting sensitivities were significantly higher for DHLs than for VEPs ($p=0.006$, McNemar's test), and for DHLs than for "clinical evidence for ON" ($p=0.039$). There was no significant difference between the sensitivities of "clinical evidence for ON" and VEPs ($p=0.77$)

were statistically non-significant for this smaller subsample ($p=0.219$ and $p=0.125$, respectively, McNemar).

In the 11 patients who presented with clinically acute ON, 3D-DIR showed DHLs in all 11 affected nerves. In 10 of these 11 patients, VEPs had been acquired within +/- 3 days (re MRI), in the 11th patient 27 days prior to the MRI, but after ON symptom onset. 3D-DIR revealed DHLs in all 11 clinically affected nerves, whereas VEPs were abnormal in 9 of 11. By contrast, among the 54 nerves without CE_{ON} (from 36 patients), 11 showed (subclinical) optic nerve lesions according to the compound criterion, with DHLs observed in 10, and pathologic VEPs in 5 cases, yielding sensitivities of 91% (3D-DIR, 95% CI 59–100%) and 45% (VEPs, 95% CI 17–77%), respectively.

Finally, we performed subgroup analyses with patients stratified according to clinical diagnosis (CIS vs. RRMS vs. SPMS). VEP sensitivity (re compound criterion) was better in CIS (80%, 95%-CI 44–99%) than in definite MS (RRMS 39%, 95%-CI 23–58%, $n=22$; SPMS 50%, $n=2$), but 3D-DIR sensitivities were higher in all subgroups (CIS 90%, 95%-CI 55–100%; RRMS 91%, 95%-CI 72–99%, SPMS 100%).

Figure 2 illustrates the case of a 28-year-old female with right-sided retrobulbar pain, provoked by ocular movements, and blurred vision, i.e. typical ON-related symptoms. VEPs, acquired during the acute phase, showed formally normal latencies and amplitudes in both optic nerves, but an increased left-vs.- right latency difference of >8 ms (117.4 vs. 103.7 ms). Whole-brain 3D-DIR-MRI concordantly revealed a sharply delineated hyperintense lesion in the right optic nerve. Four months later, the patient converted to definite MS.

The second sample case (Fig. 3) is a 35-year-old female patient who presented with retrobulbar pain and an apical visual field defect of the right eye. VEPs were normal with P100-latencies of 108.2 ms (right) and 102.1 ms (left), and amplitudes of 10.1 µV and 12.9 µV, respectively. 3D-DIR-MRI, acquired on the following day, revealed a clear-cut, well delineated DHL in the right optic nerve.

Discussion

This study shows that (1) lesions in the optic nerves, as revealed by nerve segments with hyperintense signal in 3D-DIR MRI (DHLs), occur relatively frequently in patients with CIS or definite MS, sometimes even in cases without abnormal VEP-alteration or clinical signs or history of ON (CE_{ON}), that (2) the interrater agreement for presence or absence of DHLs is high, that (3) DHLs are specific for optic nerve pathology (though not necessarily for MS-related pathology), and that (4) the diagnostic performance of 3D-DIR regarding the detection of such optic nerve pathology is probably superior to that of VEPs.

The interrater concordance of $\kappa=0.82$ was somewhat lower than κ-values of 0.93 and 0.94 previously reported for 3D-DIR in the assessment of optic nerve lesions [13, 17], but still in the range of "excellent" concordance. Although this aspect was not directly addressed in our study, we would agree with Sartoretti et al. [17] who found a high interrater concordance even for inexperienced readers and emphasized the ease of optic nerve lesion detection in 3D-DIR, due to the generally high contrast and sharp demarcation of these lesions (cf. Figs. 2, 3).

No DHLs were observed in 17 control subjects. This finding confirms and extends previous data from 50 control subjects (patients with diseases unrelated to MS or the visual system), all of whom also had no optic nerve DHLs [17]. Taken together, the estimated 95%-confidence interval for the resulting 100% specificity, based on a total of 67 DHL-negative and no false-positive controls, would be 95–100%, indicating that any observable optic nerve DHL very probably reflects true optic nerve pathology. This does of course not mean that DHLs are specific for CIS/MS-related optic nerve pathology, as, e.g. inflammatory lesions due to neuromyelitis optica [13] may have a similar appearance in 3D-DIR.

For our patient sample, however, the near-perfect specificity of DHLs implies that, in cases with recognizable DHLs despite normal VEPs, these DHLs are likely to reflect true pathological changes and are not due to some artefactual signal alteration. The observation that among the 56 nerves with overall normal VEPs there was clinical evidence for ON in 5 of the 11 that were DHL+, in contrast to only 2 of 45 that were DHL negative ($p=0.002$, Fisher), further

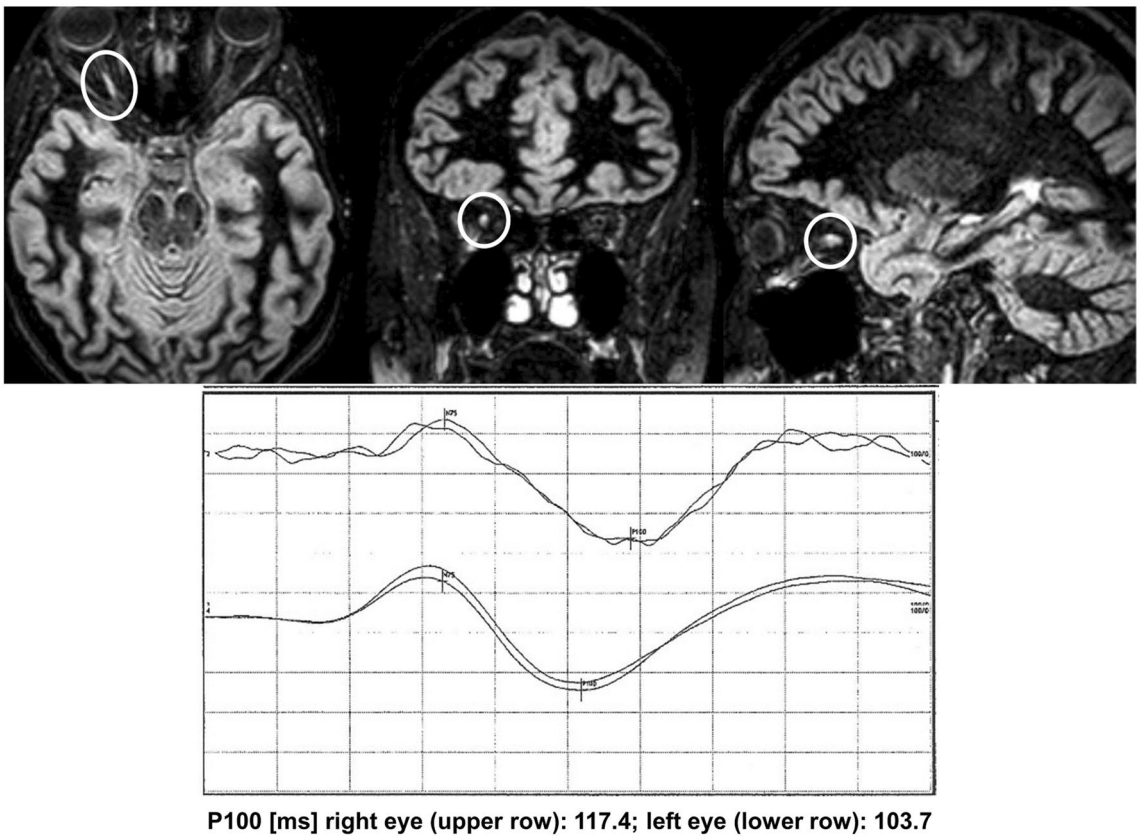

Fig. 2 28-Year-old female patient with symptoms of eye movement-related pain, colour desaturation and blurred vision of the right eye, finally diagnosed with ON and CIS. VEPs showed normal absolute latencies, but an increased latency difference between the affected and the unaffected eye of >8 ms (117.4 ms vs. 103.7 ms). In 3D-DIR, there is an obvious hyperintense lesion in the right optic nerve

corroborates that 3D-DIR generally provides added sensitivity compared to VEPs, rather than false positive findings.

Evaluating sensitivities of diagnostic instruments to detect optic nerve pathology is hampered by the fact that there is no "gold-standard" to non-invasively determine such pathology. In a previous study, Hodel et al. used clinical evidence of ON, confirmed by abnormal VEPs, as a reference for optic nerve disease, to compare the diagnostic performance of 3D-DIR and 2D-STIR-FLAIR MRI, and reported superior sensitivity and specificity for 3D-DIR of 95% and 94%, respectively. Their approach, however, though presumably suitable for such comparison, will inevitably miss that MR imaging may also reveal optic nerve lesions that are both subclinical and VEP negative, as shown here. We used a pragmatic approach, combining abnormal VEPs, clinical evidence or history of ON, and DHLs detected by 3D-DIR-MRI to a compound criterion of optic nerve affection. The advantage of this approach is that it combines the sensitivities of the individual components to cover any pathological changes as completely as possible. Conversely, its obvious drawback is that it also combines any potential deficits in specificity. This drawback, however, would attenuate rather than enhance any advantage in sensitivity of 3D-DIR over VEPs, given that its specificity for true optic nerve pathology is close to 100%. Our approach thus allows a valid comparison of 3D-DIR- and VEP-sensitivity, demonstrating that the former is very probably higher than the latter.

The matter is well illustrated in Fig. 1, which shows that VEPs are actually altered also in DHL+-nerves with formally "normal" VEPs"—albeit more subtly, so that these alterations do not exceed the specified thresholds. Of course, VEP thresholds could be modified to increase sensitivity. However, this would inevitably come at a cost in specificity, as shown by the substantial overlap in VEP parameter distributions in DHL+- and DHL−-nerves, respectively (see error bars in Fig. 1a, b).

In their recent study, Sartoretti et al. reported "subclinical" optic nerve lesions detected by 3D-DIR in 72% of a sample of 95 patients with definite MS [17]. In our study, we observed subclinical DHLs in only 10 optic nerves from 7 of 39 patients (18%). In that study, however, lesions were classified as "subclinical" if there was no clinically obvious visual loss, and no history of previous ON in the preceding 3 years [17], although the mean disease duration of their

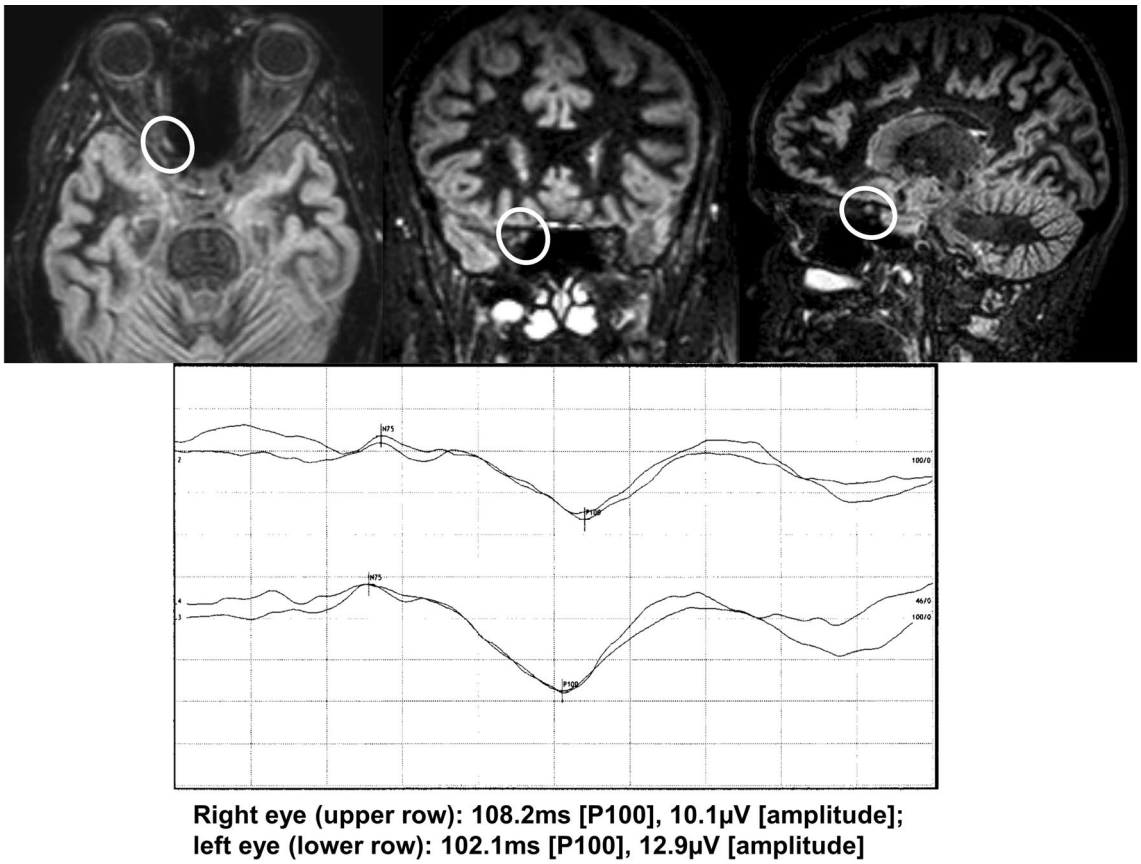

Fig. 3 35-Year-old female patient with right-sided retrobulbar pain. VEPs were normal with P100 latencies of 108.2 ms (right) versus 102.1 ms (left) a latency difference of 6.1 ms (still in the normal range) and normal amplitudes of 10.1 µV (right) vs. 12.9 µV (left). Whole brain 3D-DIR obtained the following day later revealed a clear-cut, well-delineated DIR-hyperintense lesion in the right optic nerve

MS-patients had been much longer (8.9 years). The reported high rate of "subclinical" DHLs may, therefore, at least in part, be due to clinical episodes of ON that had occurred prior to the 3-year time span. However, although the actual rate is thus probably closer to the 18% of our data or the similar 20% prevalence reported by Hadhoum et al. [14], there is congruent evidence that 3D-DIR can frequently reveal subclinical optic nerve lesions. Moreover, our study is the first to show that 3D-DIR can also detect lesions that are both subclinical and VEP-negative, which may be particularly useful in the early diagnostic workup in radiologically or clinically isolated syndromes. That the sensitivity difference favoring 3D-DIR over VEPs was particularly pronounced for the detection of lesions in the subgroup of patients/optic nerves without CE_{ON} (91%, DIR, vs. 45%, VEPs), i.e. for the detection of subclinical optic nerve pathology, is a corollary of this observation.

Obviously, the various diagnostic modalities to examine the anterior visual pathway are not mutually exclusive, and clinical examination, VEPs, MRI, OCT (if available) and other techniques can be combined to fully exploit their diagnostic potential. However, in the context of standardized diagnostic criteria it will be advantageous if the required workup is not only powerful, but also methodologically clear and succinct, easy to operationalize, easily applicable, and widely available. In addition, it is a specific charm of the 3D-DIR-MRI sequence used here that it is not a dedicated technique for orbital or optic nerve imaging, but rather a sequence originally designed to cover the whole brain, proven to be very useful also in the detection of parenchymal brain lesions, including cortical/ juxtacortical lesions in the context of CIS/MS. 3D-DIR-MRI may, therefore, be particularly cost effective for optic nerve imaging and can be readily integrated into routine MRI procedures that are part of the common diagnostic workup anyway.

In the decision not to follow the 2016 MAGNIMS proposal [15] to incorporate optic nerve lesions [16] into the 2017 McDonald criteria as a further criterion for dissemination in space, the panel referred to a recent study by Filippi et al. suggesting that such measure might actually diminish specificity, but not improve sensitivity regarding the prediction of CIS-to-MS-conversion [18]. This study, however, was

not specifically designed to examine this topic, had according limitations (e.g. pertinent data were available for about half of the patients only, and either VEPs or MRI could be used to reveal optic nerve pathology), and thus did not provide a conclusive evaluation of this issue. Our data indicate clearly that VEPs and MRI as diagnostic tools are not necessarily equivalent in this context, and strongly support the call for further studies [16], which should be done with suitable, well-defined diagnostic methodology. 3D-DIR-MRI, with its close-to-perfect specificity, superior sensitivity, and specific advantages as discussed above, is a key candidate for such reevaluation.

Our study has limitations. In addition to those already mentioned that are due to the lack of an ideal reference standard for optic nerve affection, there are limitations related to its retrospective design. Specifically, there was a considerable time gap between VEP and MRI acquisition in many patients. However, for the 20 patients, in whom VEPs and MRI were acquired almost simultaneously (within ±3 days), the sensitivity of 3D-DIR was still substantially higher than that of either VEPs or CE_{ON}, so that the better performance of 3D-DIR cannot be attributed solely to pathologic changes that occurred in the time gap between VEP- and 3D-DIR-MRI acquisitions. Still, and also because of the relatively modest sample size that precluded meaningful statistical evaluation of sensitivity differences in many subgroup analyses, confirmatory evidence from a larger-scale prospective study would be desirable. However, the consistent finding that the calculated sensitivity of 3D-DIR was always higher than that of VEPs in all subgroups provides confidence in the conclusions drawn from the present data set.

Conclusion

3D-DIR-MRI is a suitable instrument for the detection of acute or chronic optic nerve lesions in the clinical context of MS. 3D-DIR-MRI may detect subclinical lesions and appears to be more accurate than VEPs. For a reassessment of optic nerve pathology as a diagnostic criterion of definitive MS vs. CIS, it may be considered as a key candidate modality.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical standards The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. The study protocol was approved by the local ethics committee. Written informed consent of individual patients was waived for this retrospective analysis of anonymized data according to institutional guidelines.

References

1. Wikstrom J, Poser S, Ritter G (1980) Optic neuritis as an initial symptom in multiple sclerosis. Acta Neurol Scand 61(3):178–185
2. Halliday AM, McDonald WI, Mushin J (1972) Delayed visual evoked response in optic neuritis. Lancet 1(7758):982–985
3. American Clinical Neurophysiology S (2006) Guideline 9B: guidelines on visual evoked potentials. Am J Electroneurodiagn Technol 46(3):254–274
4. Odom JV, Bach M, Brigell M, Holder GE, McCulloch DL, Tormene AP et al (2010) ISCEV standard for clinical visual evoked potentials (2009 update). Doc Ophthalmol 120(1):111–119. https://doi.org/10.1007/s10633-009-9195-4
5. Tartaglione A, Oneto A, Bandini F, Spadavecchia L, Gandolfo E, Favale E (1987) Electrophysiological detection of "silent" plaques in the optic pathways. Acta Neurol Scand 76(4):246–250
6. Balnyte R, Uloziene I, Rastenyte D, Vaitkus A, Malciene L, Lauckaite K (2011) Diagnostic value of conventional visual evoked potentials applied to patients with multiple sclerosis. Medicina (Kaunas) 47(5):263–269
7. Onofrj M, Tartaro A, Thomas A, Gambi D, Fulgente T, Delli Pizzi C et al (1996) Long echo time STIR sequence MRI of optic nerves in optic neuritis. Neuroradiology 38(1):66–69
8. Redpath TW (1994) SFW. Imaging gray brain matter with a double-inversion pulse sequence to suppress CSF and white matter signals. MAGMA 2:451–455
9. Redpath TW, Smith FW (1994) Technical note: use of a double inversion recovery pulse sequence to image selectively grey or white brain matter. Br J Radiol 67(804):1258–1263
10. Wattjes MP, Lutterbey GG, Gieseke J, Traber F, Klotz L, Schmidt S et al (2007) Double inversion recovery brain imaging at 3T: diagnostic value in the detection of multiple sclerosis lesions. AJNR Am J Neuroradiol 28(1):54–59
11. Geurts JJ, Pouwels PJ, Uitdehaag BM, Polman CH, Barkhof F, Castelijns JA (2005) Intracortical lesions in multiple sclerosis: improved detection with 3D double inversion-recovery MR imaging. Radiology 236(1):254–260. https://doi.org/10.1148/radiol.2361040450
12. Riederer I, Karampinos DC, Settles M, Preibisch C, Bauer JS, Kleine JF et al (2014) Double inversion recovery sequence of the cervical spinal cord in multiple sclerosis and related inflammatory diseases. AJNR Am J Neuroradiol. https://doi.org/10.3174/ajnr.A4093
13. Hodel J, Outteryck O, Bocher AL, Zephir H, Lambert O, Benadjaoud MA et al (2014) Comparison of 3D double inversion recovery and 2D STIR FLAIR MR sequences for the imaging of optic neuritis: pilot study. Eur Radiol. https://doi.org/10.1007/s00330-014-3342-3
14. Hadhoum N, Hodel J, Defoort-Dhellemmes S, Duhamel A, Drumez E, Zephir H et al (2015) Length of optic nerve double inversion recovery hypersignal is associated with retinal axonal loss. Mult Scler. https://doi.org/10.1177/1352458515598021
15. Filippi M, Rocca MA, Ciccarelli O, De Stefano N, Evangelou N, Kappos L et al (2016) MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol 15(3):292–303. https://doi.org/10.1016/S1474-4422(15)00393-2
16. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G et al (2018) Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 17(2):162–173. https://doi.org/10.1016/S1474-4422(17)30470-2
17. Sartoretti T, Sartoretti E, Rauch S, Binkert C, Wyss M, Czell D et al (2017) How common is signal-intensity increase in optic

nerve segments on 3D double inversion recovery sequences in visually asymptomatic patients with multiple sclerosis? AJNR Am J Neuroradiol 38(9):1748–1753. https://doi.org/10.3174/ajnr.A5262

18. Filippi M, Preziosa P, Meani A, Ciccarelli O, Mesaros S, Rovira A et al (2018) 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 17(2):133–142. https://doi.org/10.1016/S1474-4422(17)30469-6