Multiple Sclerosis and Related Disorders 63 (2022) 103824

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

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

Original article

The prevalence of internuclear ophthalmoparesis in a population-based cohort of individuals with multiple sclerosis

S.N. Hof [a,*], F.C. Loonstra [a], L.R.J. de Ruiter [a], L.J. van Rijn [b,c], A. Petzold [a,b,d], B.M. J. Uitdehaag [a], J.A. Nij Bijvank [a,b]

[a] Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Neurology, MS Center and Neuro-ophthalmology Expertise Center Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands
[b] Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Ophthalmology, Neuro-ophthalmology Expertise Center Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands
[c] Onze Lieve Vrouwe Gasthuis, Department of Ophthalmology, Amsterdam, The Netherlands
[d] Moorfields Eye Hospital, The National Hospital for Neurology and Neurosurgery and the UCL Queen Square Institute of Neurology, London, United Kingdom

ARTICLE INFO

Keywords:
Internuclear ophthalmoparesis
Internuclear ophthalmoplegia
Ocular motility disorders
Multiple sclerosis
Oculography
Eye-Tracking technology
Prevalence

ABSTRACT

Background: Internuclear ophthalmoparesis (INO) occurs in 15–52% of individuals with multiple sclerosis (MS) and is reliably detected by infrared oculography. Methods for diagnosing INO with infrared oculography and the association between INO and MS characteristics need confirmation. We aimed to describe INO prevalence and the clinical characteristics of individuals with MS and INO in a population-based cohort of individuals with MS born in the year 1966 (Project Y).

Methods: Previously described thresholds for the versional dysconjugacy index (VDI), assessed with standardized infrared oculography, were used to detect INO in participants of project Y. Clinical characteristics, visual functioning and complaints were compared between individuals with MS with INO and individuals with MS without INO.

Results: Two-hundred-twenty individuals with MS and 110 healthy controls were included. VDI values exceeding the threshold for INO presented in 53 (24%) individuals with MS and 19 controls (13%). INO was associated with male sex, greater disability, worse cognition and worse arm function in individuals with MS. There was no association with disease duration, visual functioning or complaints.

Conclusions: INO is prevalent among individuals with MS aged fifty-three and related to clinical characteristics of MS. INO was more frequently detected in healthy controls than previous studies, implying that oculography based diagnosis of INO requires further refinement.

1. Introduction

Internuclear ophthalmoparesis (INO) is a common eye movement disorder in multiple sclerosis (MS), characterized by slowed movement of the adducting eye relative to the abducting eye in horizontal saccades. This may cause complaints of (transient) diplopia or "blurring of vision" during horizontal eye movements (Frohman et al., 2005). The cause of INO in MS is demyelination of the medial longitudinal fasciculus (MLF). The MLF connects the abducens nucleus with the contralateral oculomotor nucleus in the brainstem which facilitates conjugate horizontal eye movements. INO may be easily missed in physical examination, especially in milder cases (Frohman et al., 2003).

Infrared oculography is a noninvasive method of quantifying eye movements which may be used to detect INO more reliably than physical examination (Frohman et al., 2003). Earlier studies using oculography to detect INO reported a prevalence of INO ranging from 35% to 52%, but these studies often lacked standardized methods (Jozefowicz-Korczynska et al., 2008; Meienberg et al., 1986; Polet et al., 2020). An earlier study using infrared oculography established quantitative criteria for diagnosing an INO and showed that up to 34% of individuals with MS may have an INO (Nij Bijvank et al., 2019). Furthermore, this study demonstrated that individuals with MS and an INO had a longer

Abbreviations: INO, Internuclear Ophthalmoparesis.

* Corresponding author.
E-mail address: s.n.hof@amsterdamumc.nl (S.N. Hof).

https://doi.org/10.1016/j.msard.2022.103824
Received 7 February 2022; Received in revised form 14 April 2022; Accepted 21 April 2022
Available online 25 April 2022

disease duration, more often a progressive disease course and more disability than individuals with MS without an INO. Individuals with MS and INO were also older than individuals without INO (Nij Bijvank et al., 2019). As the criteria for INO diagnosis in this study were based on the healthy control group of this specific cohort, the thresholds for INO diagnosis and findings are yet to be confirmed in other large MS cohorts.

The aim of the current study was to investigate the prevalence of INO in a cross-sectional population-based cohort of individuals with MS. Additionally, we investigated the clinical characteristics of individuals with MS and INO in this unique cohort of individuals with the same birth year (1966). Eliminating the confounding effect of age allowed us to assess the effect of disease duration. Finally, visual complaints and subjective visual functioning were compared between individuals with MS with and without INO.

2. Materials and methods

2.1. Study design and participants

For this cross-sectional study individuals with MS and healthy controls (HCs) were included from project Y, an observational cohort study of individuals with MS and HCs of the same birth year conducted at the Amsterdam University Medical Center (Amsterdam UMC), which is previously described (Loonstra et al., 2021). Project Y received approval from the medical ethical committee of the Amsterdam UMC, location VUMC and written informed consent was obtained from all participants. Inclusion criteria for project Y for individuals with MS included being born in the Netherlands in 1966, currently living in the Netherlands and a diagnosis of MS according to the 2017 criteria (Polman et al., 2011; Thompson et al., 2018). Inclusion criteria for HCs included being born between 1965 and 1967 in the Netherlands, currently living in the Netherlands and no history of MS. Subjects in project Y participated in either a study visit at the Amsterdam UMC, a home visit or a telephone interview, depending on feasibility and willingness. Only participants with a study visit at the Amsterdam UMC, including infrared oculography, were selected for the current analysis.

2.2. History and clinical assessment

Disease characteristics and history were obtained from an interview with the participants and from medical documentation review, including disease course, disease duration calculated in years from the first MS symptom, current use of disease modifying therapy (DMT), history of optic neuritis and vascular risk factors. Neurological and disability status were assessed with the expanded disability status scale (EDSS), Timed 25-foot Walk (T25FW) and 9-Hole Peg Test (9HPT) (Cutter, 1999; Kurtzke, 1983). Cognitive functioning was assessed using the symbol digit modalities test (SDMT) (Parmenter et al., 2007). Ophthalmological assessment included (best) corrected high- and low contrast visual acuity (HCVA and LCVA, respectively) using Sloan letter charts (100% for HCVA, 2.5% for LCVA) (Balcer et al., 2003). Subjective visual functioning was assessed in individuals with MS with the National Eye Institute Visual Function Questionnaire-25 (VFQ-25) (Mangione et al., 2001). Additionally, an in-house questionnaire focusing on complaints specific to problems with eye movement was included for individuals with MS (Nij Bijvank et al., 2019).

2.3. Infrared oculography and INO detection

Eye movements were measured with the Eyelink 1000 Plus eye tracker using the open-source DEMoNS protocol (Nij Bijvank, 2018; Nij Bijvank et al., 2018). In brief, participants were seated in front of a display monitor, with the head stabilized by a chin and forehead rest. Participants performed several visual tasks on the display, their eye movements being recorded by the infrared camera located just below and in front of the display monitor. Proprietary built-in algorithms were used for calibration and validation procedures.

The prosaccadic task of the DEMoNS protocol was used to diagnose an INO. The prosaccadic task contains 5 trials of 12 randomized horizontal prosaccades. Participants were asked to focus on and follow a target on the center of the screen. After a random time interval (1 - 3.5 s) the target jumps to an eccentric location 8° or 15° to the left or right, inducing a horizontal saccade. An in-house written open-source program written in MATLAB (MathWorks, Inc., Natick, MA) was used for automatic analysis of the eye movement data (Nij Bijvank, 2018). To pass quality control, at least 50% of centrifugal saccades needed to be acceptable for a participant to be included. Fig. 1 shows three examples of horizontal prosaccades of individuals with MS captured by infrared oculography.

The versional dysconjugacy index (VDI) of 15° horizontal prosaccades was used to diagnose an INO, as previously described (Nij Bijvank et al., 2019). In short, mean VDI values were calculated for the area under the curve (AUC) and peak velocity divided by saccadic amplitude (PV/Am) of the horizontal saccadic trajectory. The VDI is the ratio between the abducting and the adducting eye of these parameters (AUC or PV/Am) and describes the dysconjugacy between both eyes during a leftward or rightward saccade. A diagnosis of INO was made when the mean VDI-AUC exceeded 1.174 or the mean VDI-PV/Am exceeded 1.180 in horizontal leftward or rightward saccades. These thresholds were defined in a previous study comparing VDI parameters of HCs and individuals with MS (Nij Bijvank et al., 2019).

2.4. Statistical analyses

Data was visually and statistically assessed for normality. Independent t-tests or non-parametric test were used to compare continuous variables between individuals with MS with and without INO. The chi-square (X^2) test was used to compare categorical variables. T25FW was reported as the average time of two attempts. NHPT was reported as the average time of four attempts, consisting of two attempts per hand. Statistical analyses were performed using *R* statistical software (version 4.0.3) and RStudio (version 1.3.1093) (R Core Team, 2020; RStudio Team, 2020).

3. Results

3.1. Study population

Of all project Y participants, infrared oculography was performed in 229 individuals with MS and 116 HCs between December 19th 2017 and November 13th 2020. Infrared oculography could not be analyzed in six individuals with MS and two HCs due to excessive blinking. Three individuals with MS and four HCs were excluded from analysis due to technical difficulties during infrared oculography. Therefore, a total of 220 individuals with MS and 110 HCs were included in the analysis. Demographic and clinical characteristics of the study population are summarized in table 1. Individuals with MS were mostly female (73%), had a mean disease duration of 16 (±9) years and most often had a relapsing-remitting (RR) disease course (63%).

3.2. INO prevalence and characteristics

Overall, 53 (24%) individuals with MS were diagnosed with INO. The INO was leftward in 18 (34%) individuals, rightward in 16 (30%) individuals and bilateral (36%) in 19 individuals. Forty-three (61%) of the 72 INOs were diagnosed by both the VDI-AUC and the VDI-PV/Am criteria. Seventeen (24%) were only diagnosed with the VDI-AUC criterium and 12 (17%) only with the VDI-PV/Am criterium. Fig. 2 shows the distribution of VDI's of individuals with MS and an INO. The median VDI-AUC of an INO was 1.258 (IQR 1.183 - 1.467) and 1.243 (IQR 1.182 - 1.640) for the VDI-PV/Am.

Nineteen (15%) healthy controls had VDI values above the threshold

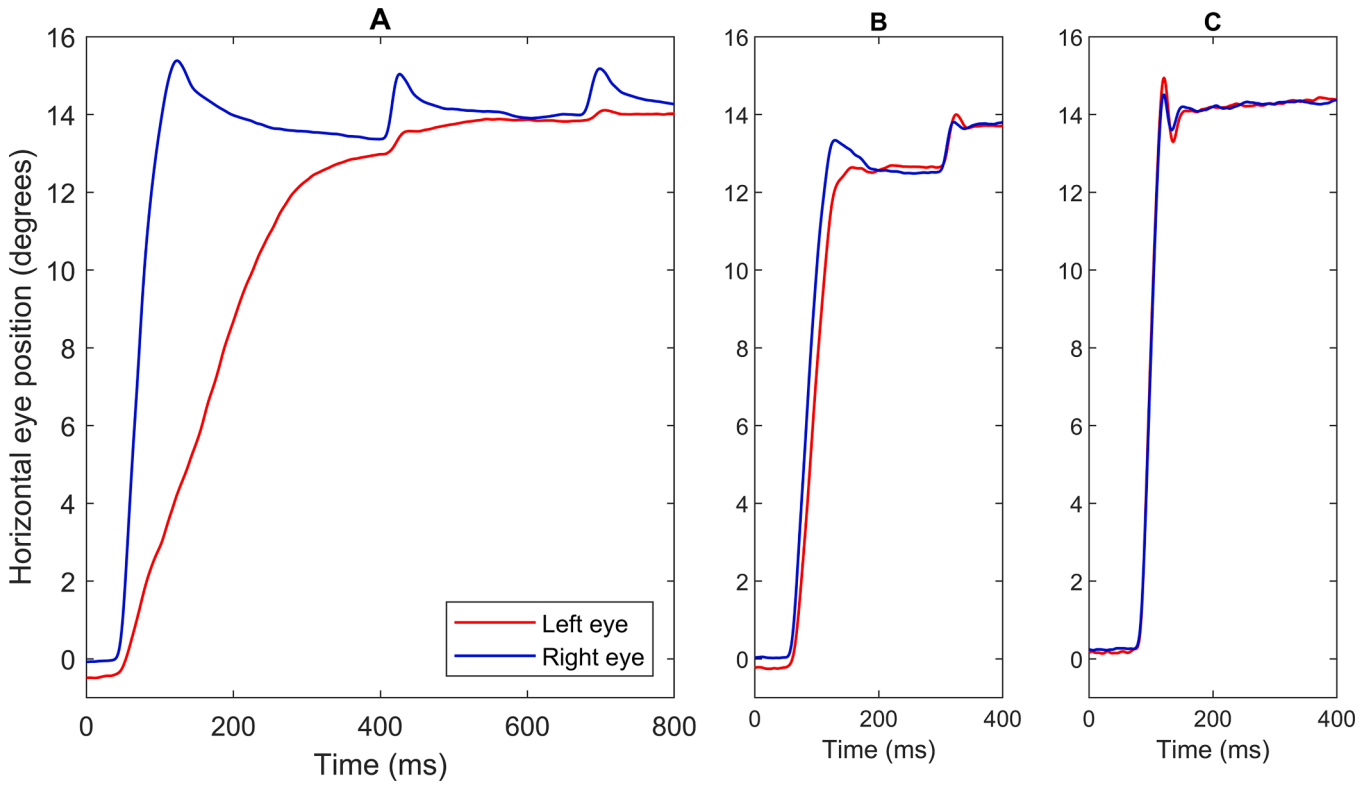

Fig. 1. Example saccades of individuals with MS (A-C) Horizontal eye position (y-axis) against time (x-axis) of a rightward saccade of 3 different individuals with multiple sclerosis, captured by infrared oculography. The blue line represents the right eye; the red line represents the left eye. (A) Rightward saccade with a clear adduction delay of the left eye and nystagmus of the right abducting eye; VDI-AUC 1.60 and VDI-PV/Am 3.88. (B) Rightward saccade with mild adduction delay; VDI-AUC 1.26 and VDI-PV/Am 1.12. (C) Rightward saccade without adduction delay; VDI-AUC 0.97 and VDI-PV/Am 0.93. Abbreviations: AUC = area under the curve; MS = multiple sclerosis; ms = milliseconds; PV/Am = peak velocity divided by amplitude; VDI = versional dysconjugacy index.

for INO. Twelve HCs surpassed the VDI-AUC threshold, 7 participants surpassed the VDI-PV/Am threshold and 3 HCs surpassed both thresholds. The median of VDIs above the INO threshold in the healthy control group was 1.194 (IQR 1.144 - 1.226) for the VDI-AUC and 1.176 (IQR 1.120 – 1.205) for the VDI-PV/Am (Fig. 2). These VDI values were significantly lower than the VDI values for INO's in individuals with MS for both the VDI-AUC ($p = 0.003$) and VDI-PV/Am ($p = <0.001$).

3.3. INO, demographics and disease characteristics

Table 1 shows the differences in demographics and disease characteristics between individuals with MS with and without INO. Compared to individuals without INO, individuals with MS and INO were more often male (43% compared to 22%, $p = 0.002$). There were no significant differences between male and female individuals with MS and an INO in disease course, disease duration, frequency of DMT use or disability (EDSS). Individuals with INO in general had higher disability (EDSS, $p = 0.044$). The median difference on the brainstem functional system of the EDSS was 1.0 ($p = 0.009$). Individuals with INO had more cognitive impairment on the SDMT with a mean difference of 4 points ($p = 0.046$) and worse upper extremity function on the 9-HPT with a median difference of 1 s ($p = 0.015$). Individuals with secondary progressive MS showed the highest prevalence of INO (33%), followed by primary progressive (28%) and relapsing-remitting MS (20%). However, there was no statistically significant association between disease course and INO prevalence ($p = 0.129$). Bilateral INO was significantly more prevalent among individuals with primary progressive (16%) or secondary progressive MS (15%) as compared to relapsing-remitting MS (4.3%) ($p = 0.016$). Individuals with MS with and without an INO had a similar disease duration, frequency of current DMT use, walking speed, low and high contrast vision and prevalence of a history of optic neuritis, vascular risk factors or vascular events.

The proportion of males was not significantly different in HCs with VDI values above the threshold as compared to healthy control with VDI values below the threshold for INO (44% vs. 24%, $p = 0.132$). Vascular risk factors were present in 20% of the HCs, similar to individuals with MS ($p = 0.572$). The prevalence of vascular risk factors in HCs with VDI values above the threshold for INO did not significantly differ from HCs with normal VDI values (25% vs. 19%, $p = 0.735$).

3.4. INO and visual complaints and functioning

The prevalence of visual complaints as assessed by the eye movement questionnaire within the INO and non-INO group is shown in Fig. 3. The majority of individuals with MS (59%) reported one or more visual complaints. Compared to the non-INO group, individuals with MS and INO more often reported complained of blurred vision (38% vs. 33%) and trouble focusing on stationary (27% vs. 22%) or moving objects (31% vs. 27%). However, these differences did not reach statistical significance. There was no difference in the prevalence of diplopia between the INO and non-INO group (13% vs. 15%, $p = 0.846$).

Table 2 shows the overall and subscale scores on the VFQ. Individuals with MS and INO reported a lower overall subjective visual functioning than individuals without INO (Median 92 compared to 94, $p = 0.137$), but this difference was not statistically significant. There were no significant differences on any of the VFQ subscales.

4. Discussion

This is the first study that applies predefined thresholds for diagnosing INO with standardized quantitative infrared oculography in a well-characterized population-based cohort of individuals with MS (Nij

Table 1
Demographic and clinical characteristics of individuals with MS and healthy controls.

	Individuals with MS Overall, $N = 220$[1]	INO, $N = 53$[1]	Non-INO, $N = 167$[1]	p-value[2]	Healthy controls $N = 110$[1]
Sex, female	160 (73%)	30 (57%)	130 (78%)	**0.002**	80 (73%)
Disease course[a]				0.129	NA
PPMS	32 (15%)	9 (17%)	23 (14%)		NA
SPMS	48 (22%)	16 (31%)	32 (19%)		NA
RRMS	138 (63%)	27 (52%)	111 (67%)		NA
Disease duration, y	16 (9)	16 (10)	16 (9)	0.915	NA
Current DMT use	95 (43%)	27 (51%)	68 (41%)	0.190	NA
EDSS	3.5 (2.5–4.0)	4.0 (3.0–4.5)	3.5 (2.5–4.0)	**0.044**	NA
SDMT[b]	52 (10)	49 (10)	53 (10)	**0.046**	NA
NHPT (*sec*)[c]	21.59 (19.41–24.37)	22.20 (20.50–26.27)	21.41 (19.00–24.02)	**0.015**	NA
T25-FW (*sec*)[d]	4.85 (4.15–6.20)	5.15 (4.40–7.11)	4.80 (4.05–6.12)	0.136	NA
HCVA, mean ODS[e]	54 (50–60)	54 (48–58)	54 (50–60)	0.270	NA
LCVA, mean ODS[f]	29 (22–35)	26 (20–34)	29 (22–35)	0.325	NA
History of optic neuritis	86 (39%)	25 (47%)	61 (37%)	0.167	NA
History of vascular risk factors[g]	50 (23%)	9 (17%)	41 (25%)	0.252	22 (20%)
History of vascular events[h]	5 (2.3%)	1 (1.9%)	4 (2.4%)	>0.999	0 (0%)

[1] n (%); Mean (SD); Median (IQR)
[2] Pearson's Chi-squared test; Welch Two Sample *t*-test; Wilcoxon rank sum test;
[a] Disease course unknown in 2 individuals;.
[b] SDMT data missing for 1 individual;.
[c] NHPT data missing for 8 individuals;.
[d] T25-FW data missing for 7 individuals;.
[e] HCVA data missing for 4 individuals;.
[f] LCVA data missing for 7 individuals;.
[g] Vascular risk factors include one or more of the following: hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation or vascular events.
[h] Vascular events include myocardial infarction and/or stroke. Abbreviations: DMT = disease modifying therapy; EDSS = Expanded Disability Status Scale; HCVA = high-contrast visual acuity; INO = internuclear ophthalmoparesis; IQR = interquartile range; LCVA = low-contrast visual acuity; MS = multiple sclerosis; NA = not applicable; NHPT = Nine Hole Peg Test; ODS = right (OD) and left (OS) eye combined; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SDMT = Symbol Digit Modalities test; SPMS = secondary progressive multiple sclerosis; T25-FW = Timed 25 foot Walk Test. INO = individuals with MS and INO based on combined detection: either cutoff of 1.174 of the versional dysconjugacy index area under the curve or 1.180 of the versional dysconjugacy index peak velocity/saccadic amplitude.

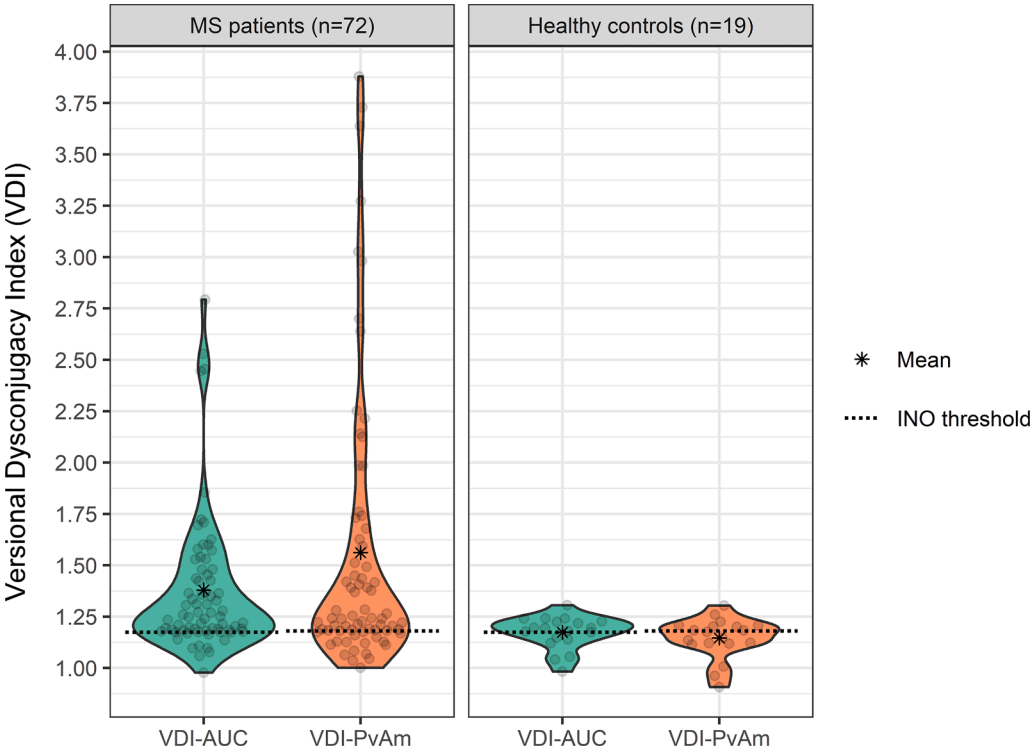

Fig. 2. Distribution of VDI values surpassing thresholds for INO Distribution of the VDI-AUC and VDI-PV/Am surpassing the threshold for INO. INO detection thresholds are indicated by the dashed lines (VDI-AUC = 1.174, VDI-PV/Am = 1.180). The median VDI-AUC of an INO in individuals with MS was 1.258 (IQR 1.183 - 1.467) and median VDI-PV/Am 1.243 (IQR 1.182 - 1.640) (mean VDI-AUC 1.380 ± 0.342; mean VDI-PV/Am 1.562 ± 0.677). The median of VDI-AUC above the INO threshold in the healthy control group was 1.194 (IQR 1.144 - 1.226) and median VDI-PV/Am 1.176 (IQR 1.120 – 1.205) (mean VDI-AUC 1.174 ± 0.079; mean VDI-PV/Am 1.147 ± 0.098). VDI values surpassing the thresholds were significantly higher in individuals with MS compared to healthy controls for both the VDI-AUC ($p = 0.003$) and VDI-PV/Am ($p = <0.001$). AUC = area under the curve; INO = internuclear ophthalmoparesis; MS = multiple sclerosis; PV/Am = peak velocity divided by amplitude; VDI = versional dysconjugacy index.

Bijvank et al., 2019). We found that 53 (24%) of the 220 included individuals with MS had an INO.

Present data are consistent with previous studies which reported the prevalence of INO to range from 15% to 34% in MS using clinical tests (Downey et al., 2002; Jenkins, 2007; Jozefowicz-Korczynska et al., 2008; Muri et al., 1985; Serra et al., 2003; Servillo et al., 2014) and

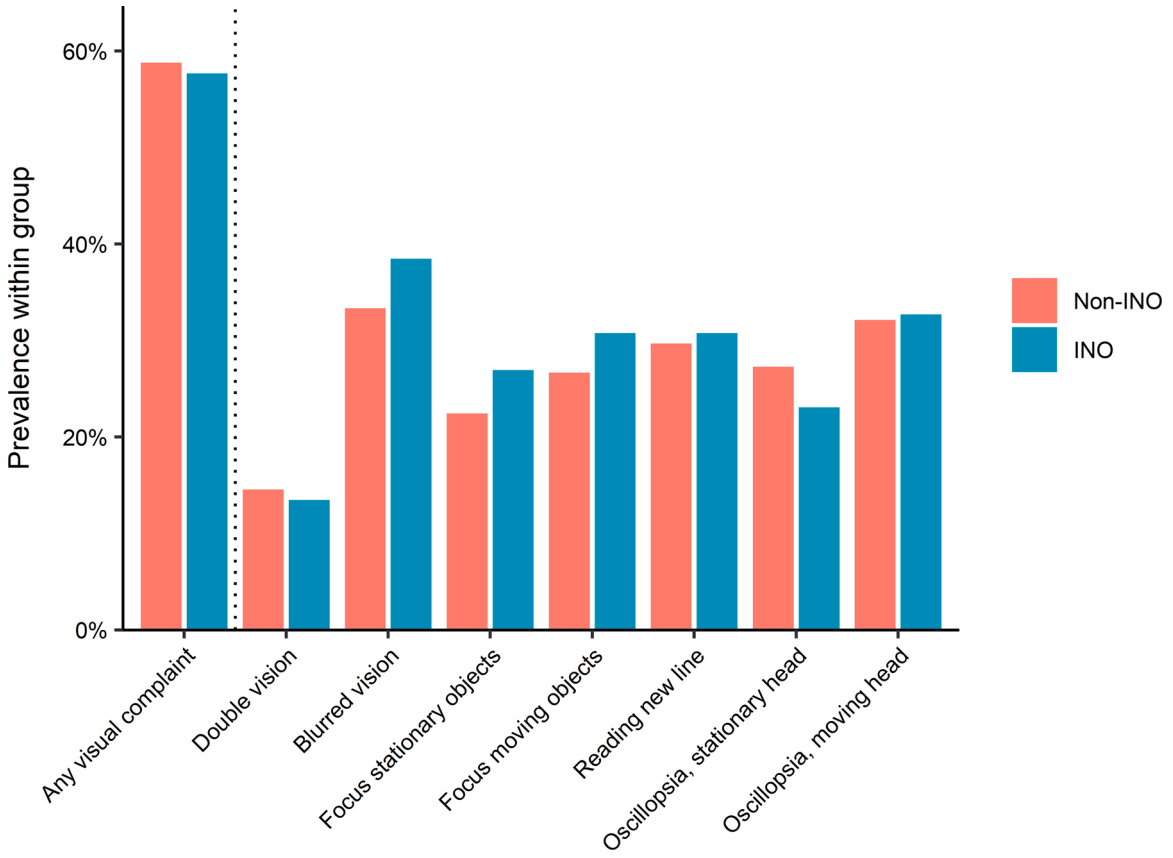

Fig. 3. Visual complaints among individuals with MS Prevalence of complaints (of any severity) on the eye movement questionnaire of individuals with MS with and without INO. There were no statistically significant differences in the prevalence of complaints between the INO and non-INO group overall or for any of the visual complaints. INO = internuclear ophthalmoparesis; MS = multiple sclerosis.

between 34% and 52% when using more sensitive methods, such as infrared oculography or electro-oculography (Jozefowicz-Korczynska et al., 2008; Meienberg et al., 1986; Nij Bijvank et al., 2019; Polet et al., 2020). However, most of these studies are based on small sample sizes and rely on clinical tests with low sensitivity or oculography measures that lack standardized methods to diagnose INO. The previous study using identical methods and thresholds for diagnosing INO found an INO prevalence of 34% (Nij Bijvank et al., 2019).

An association between male sex and a diagnosis of INO is one of the most robust findings in the current study. Our previous study also found that INO was more prevalent among male individuals with MS. However, other studies investigating the association between sex and INO are unfortunately unavailable (Nij Bijvank et al., 2019). The fact that we found no sex differences in HCs with VDI values above the threshold, makes an effect of sex on ocular dysconjugacy, independent from MS pathology, less probable. The greater prevalence of INO among male individuals with MS may reflect the greater susceptibility of men with MS to disease progression and neurodegeneration (Bove and Chitnis, 2014). This is supported by the higher general disability in the INO group.

INO was associated with more disability, worse cognition and worse arm function in the current study. These results confirm findings from earlier studies that showed an association between INO and EDSS scores (Nij Bijvank et al., 2019; Polet et al., 2020; Serra et al., 2003; Servillo et al., 2014). The EDSS brainstem functional system was strongly associated with INO, signifying the validity of quantitative oculography in evaluating brainstem function. Ocular motor dysfunction has been related to cognitive impairment in previous studies, although this concerned other abnormalities than INO (Fielding et al., 2015; Nij Bijvank et al., 2021). Of note, the SDMT requires the participants to make a series of saccades while they are searching for the correct digit for each symbol. Eye movement disorders may therefore decrease performance on the SDMT regardless of cognition (Chen et al., 2020). Additionally, both INO and cognitive dysfunction may be more prevalent with advancing disease, without a direct causal relation.

In our previous report there was an association between INO, longer disease duration and higher age (Nij Bijvank et al., 2019). The advantage of project Y is that it allows us to restrict the analysis of these associations to disease duration. In the current study we found no association between disease duration and diagnosis of INO, which may imply that age is a more important factor than disease duration in the prevalence of INO.

We found no statistically significant association between a diagnosis of INO and visual complaints or subjective visual functioning. Earlier research showed that individuals with MS and INO reported more complaints of double vision, blurred vision and trouble focusing on stationary and moving objects (Nij Bijvank et al., 2019). Additionally, two previous study found a relatively high prevalence of INO (56–58%) among individuals with MS and visual complaints (Jasse et al., 2013; Tilikete et al., 2011). It should be noted that visual complaints are quite prevalent in the current study population which consists of individuals with MS aged 53 years. The majority of individuals with MS reported at least some visual complaints in the current study, regardless of INO, which may obfuscate any additional effect of INO on visual complaints. These visual complaints may also be independent from MS. Considering the prevalence of INO and visual complaints in general may increase with age, investigating the relation between INO and visual complaints in younger individuals with MS earlier in their disease course may yield different results.

We found some HCs with VDI values surpassing the threshold for

Table 2
Visual functioning in individuals with MS with and without INO.

VFQ scale	Overall, *N* = 220[1]	INO, *N* = 53[1]	Non-INO, *N* = 167[1]	
Overall [a]	93 (87–96)	92 (87–95)	94 (87–97)	
General health	50 (25–50)	50 (25–50)	50 (25–50)	
General vision	80 (60–80)	80 (60–80)	80 (60–80)	
Ocular pain	100 (88–100)	100 (88–100)	100 (88–100)	
Near activities	92 (83–100)	92 (75–100)	92 (83–100)	
Distance activities	92 (83–100)	92 (75–100)	92 (83–100)	
Social functioning	100 (100–100)	100 (100–100)	100 (100–100)	
Mental health	94 (88–100)	91 (81–94)	94 (88–100)	
Role difficulties	100 (75–100)	100 (75–100)	100 (75–100)	
Dependency	100 (100–100)	100.0 (100–100)	100 (100–100)	
Driving [b]	83 (75–100)	83 (75–94)	83 (77–100)	
Color vision	100 (100–100)	100 (100–100)	100 (100–100)	
Peripheral vision [c]		100 (75–100)	100 (75–100)	100 (5–100)

[1] Median (IQR) [2]Wilcoxon rank sum test;.
[a] VFQ data missing for 3 individuals;.
[b] VFQ-driving data missing for 34 individuals;.
[c] VFQ-peripheral vision missing for 4 individuals. There were no statistically significant differences in VFQ scores between the INO and non-INO group overall or for any of the subscales. Abbreviations: INO = internuclear ophthalmoparesis; IQR = interquartile range; VFQ = visual functioning questionnaire.

INO. In the overall population, INO most often has a vascular etiology (Keane, 2005). We did find vascular risk factors in 25% of HCs with VDI values above the threshold for INO. However, the prevalence of vascular risk factors in these controls was not significantly different from individuals with MS or HCs with normal VDI values. Moreover, as depicted in Fig. 2, the distribution of VDI values above the threshold in HCs differs from the distribution individuals with MS and INO. The VDI values in HCs are close to the threshold, while in MS they often greatly surpass the threshold. This may imply a lack of specificity for the current VDI thresholds, rather than an actual diagnosis of INO in HCs. Additionally, there may be overlap between VDI values representing pathological INO in one individual and values representing benign physiological internuclear delay in another. The current study design with participants of a single birth year is unsuitable for validating or re-defining the VDI thresholds, especially since age may be an important factor in the prevalence of INO. Large scale studies with individuals with MS and HCs of varying ages are needed in order to validate the currently used VDI thresholds.

The potential limitations of this study include its cross-sectional design. It is still unknown how oculographic features and visual complaints of INO develop over time. We speculate that individuals with MS may adapt to INO over time resulting in less visual complaints. Additionally, not all participants of project Y (62%) received oculography. Only participants with a full study visit were eligible for oculography. Although a substantial amount of individuals with MS and high disability had oculography measurements, participants with advanced disease and disability were less likely to participate in a full study visit. This may have resulted in an underestimation of the prevalence of INO in MS, since INO is more prevalent in individuals with MS with greater disability. Furthermore, while all participants with MS were born in 1966, the birth year of HCs ranged from 1965 to 1967. Considering age may be an important factor in the prevalence of INO, this variation in age may have affected the prevalence of INO in the healthy control group and its comparison to the prevalence of INO in the MS group. However, since age variation in the healthy control group is limited to 3 years, this is unlikely to have affected the results significantly. Finally, the study visit of HCs did not include all the assessments done in individuals with MS, such as SDMT and assessment of visual complaints. While this data is not essential to the objectives of this study, it may have provided insightful context to the results found in individuals with MS.

The prevalence of INO and its associations with clinical characteristics found in the current study highlight the relevance of assessing INO in MS using quantitative oculography. Further validation studies are required to guarantee the robustness of the currently used VDI thresholds in individuals with MS with varying demographic characteristics.

Funding acknowledgements

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. Project Y was financially supported by the FriendsLottery in The Netherlands, the Dutch MS Research Foundation and VUmc Fonds – MS Center Amsterdam.

CRediT authorship contribution statement

S.N. Hof: Formal analysis, Writing – original draft, Visualization. **F. C. Loonstra:** Validation, Investigation, Data curation, Writing – review & editing, Project administration. **L.R.J. de Ruiter:** Validation, Investigation, Data curation, Project administration. **L.J. van Rijn:** Conceptualization, Methodology, Writing – review & editing, Supervision. **A. Petzold:** Conceptualization, Methodology, Writing – review & editing, Supervision. **B.M.J. Uitdehaag:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. **J.A. Nij Bijvank:** Methodology, Software, Investigation, Writing – review & editing, Supervision.

Declaration of Conflicting Interests

S.N. Hof, F.C. Loonstra, L.R.J. de Ruiter and L.J. van Rijn declare no conflict of interest. A. Petzold reports personal fees from Novartis, Heidelberg Engineering, Zeiss, grants from Novartis, outside the submitted work; and AP is part of the steering committee of the OCTiMS study which is sponsored by Novartis. AP is part of the steering committee of Angio-OCT which is sponsored by Zeiss. He does not receive honorary as part of these activities. The NIHR BRC at Moorfields Eye Hospital supported AP. B.M.J. Uitdehaag has received consultancy fees from Biogen Idec, Genzyme, Merck Serono, Novartis, Roche and Teva. J. A. Nij Bijvank is supported by the Dutch MS Research Foundation, grant nr. 18–1027.

Acknowledgements

The authors would like to express their gratitude to all participants, neurologists, MS-nurses and research assistants that participated in project Y.

References

Balcer, L.J., Baier, M.L., Cohen, J.A., Kooijmans, M.F., Sandrock, A.W., Nano-Schiavi, M. L., Pfohl, D.C., Mills, M., Bowen, J., Ford, C., Heidenreich, F.R., Jacobs, D.A., Markowitz, C.E., Stuart, W.H., Ying, G.-S.G.-S., Galetta, S.L., Maguire, M.G., Cutter, G.R., 2003. Contrast letter acuity as a visual component for the multiple sclerosis functional composite. Neurology 61, 1367–1373. https://doi.org/10.1212/01.wnl.0000094315.19931.90.

Bove, R., Chitnis, T., 2014. The role of gender and sex hormones in determining the onset and outcome of multiple sclerosis. Mult. Scler. J. 20, 520–526. https://doi.org/10.1177/1352458513519181.

Chen, M.H., Chiaravalloti, N.D., Genova, H.M., Costa, S.L., 2020. Visual and motor confounds on the symbol digit modalities test. Mult. Scler. Relat. Disord. 45, 102436 https://doi.org/10.1016/j.msard.2020.102436.

Cutter, G.R., 1999. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 122, 871–882. https://doi.org/10.1093/brain/122.5.871.

Downey, D.L., Stahl, J.S., Bhidayasiri, R., Derwenskus, J., Adams, N.L., Ruff, R.L., Leigh, R.J., 2002. Saccadic and vestibular abnormalities in multiple sclerosis: sensitive clinical signs of brainstem and cerebellar involvement. Ann. N. Y. Acad. Sci. 956, 438–440. https://doi.org/10.1111/j.1749-6632.2002.tb02849.x.

Fielding, J., Clough, M., Beh, S., Millist, L., Sears, D., Frohman, A.N., Lizak, N., Lim, J., Kolbe, S., Rennaker, R.L., Frohman, T.C., White, O.B., Frohman, E.M., 2015. Ocular motor signatures of cognitive dysfunction in multiple sclerosis. Nat. Rev. Neurol. 11, 637–645. https://doi.org/10.1038/nrneurol.2015.174.

Frohman, E.M., Frohman, T.C., Zee, D.S., McColl, R., Galetta, S., 2005. The neuro-ophthalmology of multiple sclerosis. Lancet Neurol 4, 111–121. https://doi.org/10.1016/S1474-4422(05)00992-0.

Frohman, T.C., Frohman, E.M., O'Suilleabhain, P., Salter, A., Dewey, R.B., Hogan, N., Galetta, S., Lee, A.G., Straumann, D., Noseworthy, J., Zee, D., Corbett, J., Corboy, J., Rivera, V.M., Kramer, P.D., 2003. Accuracy of clinical detection of INO in MS: corroboration with quantitative infrared oculography. Neurology 61, 848–850. https://doi.org/10.1212/01.WNL.0000085863.54218.72.

Jasse, L., Vukusic, S., Durand-Dubief, F., Vartin, C., Piras, C., Bernard, M., Pélisson, D., Confavreux, C., Vighetto, A., Tilikete, C., 2013. Persistent visual impairment in multiple sclerosis: prevalence, mechanisms and resulting disability. Mult. Scler. J. 19, 1618–1626. https://doi.org/10.1177/1352458513479840.

Jenkins, P.F., 2007. The multiple facets of multiple sclerosis. Am. Orthopt. J. 57, 69–78. https://doi.org/10.3368/aoj.57.1.69.

Jozefowicz-Korczynska, M., Łukomski, M., Pajor, A., 2008. Identification of internuclear ophthalmoplegia signs in multiple sclerosis patients. J. Neurol. 255, 1006–1011. https://doi.org/10.1007/s00415-008-0819-5.

Keane, J.R., 2005. Internuclear ophthalmoplegia: unusual causes in 114 of 410 patients. Arch. Neurol. 62, 714–717. https://doi.org/10.1001/ARCHNEUR.62.5.714.

Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33. https://doi.org/10.1212/WNL.33.11.1444, 1444–1444.

Loonstra, F.C., De Ruiter, L.R.J., Doesburg, D., Lam, K.-.H., Van Lierop, Z.Y.G.J., Moraal, B., Strijbis, E.M.M., Killestein, J., Uitdehaag, B.M.J., 2021. Project Y: the search for clues explaining phenotype variability in MS. Mult. Scler. Relat. Disord. 0, 103337 https://doi.org/10.1016/j.msard.2021.103337.

Mangione, C.M., Lee, P.P., Gutierrez, P.R., Spritzer, K., Berry, S., Hays, R.D., 2001. Development of the 25-item national eye institute visual function questionnaire. Arch. Ophthalmol. 119, 1050–1058. https://doi.org/10.1001/archopht.119.7.1050.

Meienberg, O., Muri, R., Rabineau, P.A., Müri, R., Rabineau, P.A., 1986. Clinical and oculographic examinations of saccadic eye movements in the diagnosis of multiple sclerosis. Arch. Neurol. 43, 438–443. https://doi.org/10.1001/archneur.1986.00520050018014.

Muri, R.M., Meienberg, O., Müri, R.M., Meienberg, O., 1985. The clinical spectrum of internuclear ophthalmoplegia in multiple sclerosis. Arch. Neurol. 42, 851–855. https://doi.org/10.1001/archneur.1985.04060080029011.

Nij Bijvank, J.A., 2018. DEMoNS protocol for measurement and analysis of eye movements. protocols.io. 10.17504/protocols.io.ruad6se.

Nij Bijvank, J.A., Petzold, A., Balk, L.J., Tan, H.S., Uitdehaag, B.M.J.J., Theodorou, M., Van Rijn, L.J., 2018. A standardized protocol for quantification of saccadic eye movements: dEMoNS. PLoS ONE 13, 1–19. https://doi.org/10.1371/journal.pone.0200695.

Nij Bijvank, J.A., Strijbis, E.M.M., Nauta, I.M., Kulik, S.D., Balk, L.J., Stam, C.J., Hillebrand, A., Geurts, J.J.G., Uitdehaag, B.M.J., van Rijn, L.J., Petzold, A., Schoonheim, M.M., 2021. Impaired saccadic eye movements in multiple sclerosis are related to altered functional connectivity of the oculomotor brain network. NeuroImage Clin. 32, 102848 https://doi.org/10.1016/J.NICL.2021.102848.

Nij Bijvank, J.A., van Rijn, L.J.J., Balk, L.J.J., Tan, H.S.S., Uitdehaag, B.M.J.M.J., Petzold, A., Bijvank, J.A., van Rijn, L.J.J., Balk, L.J.J., Tan, H.S.S., Uitdehaag, B.M.J.M.J., Petzold, A., 2019. Diagnosing and quantifying a common deficit in multiple sclerosis. Neurology 92. https://doi.org/10.1212/WNL.0000000000007499 e2299–e2308.

Parmenter, B.A., Weinstock-Guttman, B., Garg, N., Munschauer, F., Benedict, R.H.B., 2007. Screening for cognitive impairment in multiple sclerosis using the symbol digit modalities test. Mult. Scler. 13, 52–57. https://doi.org/10.1177/1352458506070750.

Polet, K., Hesse, S., Cohen, M., Morisot, A., Joly, H., Kullmann, B., Mondot, L., Pesce, A., Lebrun-Frenay, C., 2020. Video-oculography in multiple sclerosis: links between oculomotor disorders and brain magnetic resonance imaging (MRI). Mult. Scler. Relat. Disord. 40, 101969 https://doi.org/10.1016/j.msard.2020.101969.

Polman, C.H., Reingold, S.C., Banwell, B., Clanet, M., Cohen, J.A., Filippi, M., Fujihara, K., Havrdova, E., Hutchinson, M., Kappos, L., Lublin, F.D., Montalban, X., O'Connor, P., Sandberg-Wollheim, M., Thompson, A.J., Waubant, E., Weinshenker, B., Wolinsky, J.S., 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann. Neurol. 69, 292–302. https://doi.org/10.1002/ana.22366.

R Core Team, 2020. R: a language and environment for statistical computing.

RStudio Team, 2020. RStudio: integrated development environment for R.

Serra, A., Derwenskus, J., Downey, D.L., Leigh, R.J., 2003. Role of eye movement examination and subjective visual vertical in clinical evaluation of multiple sclerosis. J. Neurol. 250, 569–575. https://doi.org/10.1007/s00415-003-1038-8.

Servillo, G., Renard, D., Taieb, G., Labauge, P., Bastide, S., Zorzon, M., Castelnovo, G., 2014. Bedside tested ocular motor disorders in multiple sclerosis patients. Mult. Scler. Int. 1–4. https://doi.org/10.1155/2014/732329, 2014.

Thompson, A.J., Banwell, B.L., Barkhof, F., Carroll, W.M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M.S., Fujihara, K., Galetta, S.L., Hartung, H.P., Kappos, L., Lublin, F.D., Marrie, R.A., Miller, A.E., Miller, D.H., Montalban, X., Mowry, E.M., Sorensen, P.S., Tintoré, M., Traboulsee, A.L., Trojano, M., Uitdehaag, B.M.J., Vukusic, S., Waubant, E., Weinshenker, B.G., Reingold, S.C., Cohen, J.A., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17, 162–173. https://doi.org/10.1016/S1474-4422(17)30470-2.

Tilikete, C., Jasse, L., Vukusic, S., Durand-Dubief, F., Vardanian, C., Pélisson, D., Vighetto, A., 2011. Persistent ocular motor manifestations and related visual consequences in multiple sclerosis. Ann. N. Y. Acad. Sci. 1233, 327–334. https://doi.org/10.1111/j.1749-6632.2011.06116.x.