Validation of a symptom-based questionnaire for pediatric CNS demyelinating diseases

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PURPOSE Optic neuritis is a manifestation of numerous neuroinflammatory disorders. Recognition of current and prior symptoms may facilitate identification of an underlying multifocal neurologic disease. The purpose of this study was to determine whether a symptom-based questionnaire could inform clinical decision making by identifying children with visual complaints who may have a systemic demyelinating disorder.

METHODS Children with visual changes from non-demyelinating disease were compared with patients with confirmed pediatric-onset multiple sclerosis (MS) or neuromyelitis optica spectrum disorder (NMOSD). Participants completed a 21-item questionnaire to capture their recent (<30 days) and remote (>30 days) symptoms of neurologic dysfunction. The questionnaire scores were compared using *t* tests, and the 95% confidence interval for each group was used to determine a threshold score suggesting demyelinating disease.

RESULTS We enrolled 51 participants (30 females [59%]) with a mean age of 14.6 years (range, 4-21): 25 in the non-demyelinating disease group and 26 with MS/NMOSD. The mean questionnaire score for the non-demyelinating group was 5.0 points (95% CI, 3.3-6.9); for the MS/NMOSD group, 9.4 points (95% CI, 7.4-11.4) for the MS/NMOSD group ($P < 0.002$). Questionnaire results were dichotomized using a score of ≥7 as indicative of demyelinating disease, with 69% sensitivity and 72% specificity. An abbreviated questionnaire, using 8 questions that differed between groups, had a sensitivity of 65% and specificity of 92%.

CONCLUSIONS A symptom-based questionnaire is sensitive and specific for identifying children with CNS demyelinating disease and may be useful as a screening tool for children with vision complaints and possible demyelination. (J AAPOS 2019;23:157.e1-7)

Optic neuritis (ON) is an inflammatory disease of the optic nerve that can occur as an isolated event or as a symptom of a broader central nervous system (CNS) disorder. The neurologic differential diagnosis for a child with a first attack of ON includes a clinically isolated syndrome, acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS), or neuromyelitis optica spectrum disorder (NMOSD). ON may also occur at any time as a symptom of a relapsing disease, such as MS or NMOSD, as well as ADEM followed by recurrent or monophasic ON (ADEM-ON), or chronic relapsing idiopathic optic neuropathy (CRION). In a child presenting with ON, these disorders are differentiated by the clinical history, neurological examination, and the results of ancillary procedures, such as magnetic resonance imaging (MRI) and lumbar puncture.

Although the differential diagnosis for ON in children is broad, pediatric demyelinating disorders are rare, and subtle prior symptoms may go unrecognized by the family or practitioners. For example, paresthesias of the extremities are common symptoms in MS; however, disease flares are often transient and may resolve without treatment. As such, prior demyelinating attacks, which are essential to confirming an accurate diagnosis, may be underreported. In addition, the neurologic examination is influenced by the timing of symptoms relative to the examination and may not detect remote clinical signs, such as weakness or balance difficulties. With respect to imaging, hyperintense and/or gadolinium-enhanced signals in the white matter of the brain on MRI may result in new clinical findings but are frequently asymptomatic. In demyelinating disorders, the

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lack of concordance between the clinical features, examination abnormalities, and imaging findings highlights the need for additional tools to screen for disease flares and remote attacks.

Given the importance of a careful history, we designed a questionnaire to screen for current and prior symptoms suggestive of multifocal demyelination in the CNS in a child with presumed optic neuritis. This questionnaire was created for the Pediatric Optic Neuritis Prospective Outcomes Study,[1] which is a multicenter study supported by the Pediatric Eye Disease Investigator Group (PEDIG) that will examine longitudinal visual and neurologic outcomes after optic neuritis. The purpose of the questionnaire was to help the clinician assess the presence of symptoms suggestive of a systemic demyelinating disorder in a child with visual complaints.

Subjects and Methods

Children and teens with vision complaints presenting to the neuro-ophthalmology service in the Division of Ophthalmology at the Children's Hospital of Philadelphia (CHOP) were enrolled provided they had a normal intracranial brain MRI (non-demyelinating group). Because of the rarity of new onset pediatric optic neuritis in a single institution, we did not restrict this group to isolated optic neuritis but rather approached any child with visual complaints for enrollment. As the comparison group, participants with MS or NMOSD were recruited from the Pediatric Neuroinflammatory Program at CHOP. MS and NMOSD diagnoses were confirmed using consensus criteria.[2,3] NMOSD subjects had detectable antibodies to aquaporin-4 through a commercial laboratory. Other demyelinating and inflammatory diagnoses were excluded. The study was approved by the Institutional Review Board of CHOP, and written consent and assent was obtained for all participants. Privacy in accordance with the US Health Insurance Portability and Accountability Act of 1996 was maintained throughout the conduct of this study.

The Expanded Disability Status Scale (EDSS) is a standard tool used to quantify the neurologic examination findings in MS.[4] Verdier-Taillefer and colleagues[5] developed a 25-item questionnaire for adults about common MS problems (such as level of vision in the right eye, level of vision in the left eye, double vision, weakness of the right arm, weakness of the left arm, etc.) that capture the dimensions of the EDSS (visual function, pyramidal function, etc), and the adult patient rated their symptoms as mild, moderate, severe, or not present. The answers provided by the adults using the questionnaire predicted the EDSS score performed by the neurologist. For the present study, we used similar items to create a pediatric questionnaire that also captured the EDSS functional systems. The adult questionnaire lists symptoms (such as "bizarre feeling [pins and needles, constriction] in any party of the body"), whereas our questionnaire presents the symptom in the form of a question "Do you feel pins and needles (like your arm or leg fell asleep) in any part of your body?" to enhance understanding for the pediatric patient. Other modifications to the adult questionnaire include the removal of rare symptoms in pediatric MS and NMO, such as "tremor" and "difficulty speaking and swallowing" and the addition of common symptoms in children, namely, fatigue ("Do you have a hard time staying awake during the day or need to take a nap?" and "Do you have trouble in school or doing the things you like to do because you are tired?"). The adult questionnaire lists symptoms separately ("weakness of the right arm," "weakness of the left arm," "weakness of the right leg," and "weakness of the left leg" as four separate questions), which were combined in the pediatric version ("Do you have weakness in your arms or legs?"). We also altered the rating scale because our goal was to explore common pediatric MS symptoms at the time of the evaluation as well as prior symptoms rather than severity of current symptoms. Thus, our participants were asked whether they (1) currently had the symptom (within 30 days of the evaluation), (2) did not have the symptom within the past month but had a prior history (>30 days from the evaluation) of the same symptom, or (3) never had the symptom. For younger patients, parents assisted with questionnaire completion. On the same day, an EDSS was performed by a trained neurologist. An EDSS score of 0 confirms a normal neurologic examination will be found.

The demographics of each group were analyzed using descriptive statistics. The responses for the questionnaire (number of participants endorsing current or prior symptoms for each question) were compared using a χ^2 test. Each item of the questionnaire was scored as follows: 1 point was given for a current or prior symptom; 0 points, if the participant never had the symptom. The scores were calculated for each participant (maximum of 21), and mean, standard deviation, and 95% confidence intervals were calculated for each group. Using a cut-off score defined to be outside the 95% confidence intervals for each group, the sensitivity and specificity of the questionnaire to correctly identify participants with demyelinating diseases from those with ophthalmologic disease were calculated. The same exercise was repeated using only the questions for which answers differed significantly between groups. For this abbreviated questionnaire, the mean score and standard deviation were determined for each group. The cut-off was similarly applied, and the sensitivity and specificity were determined. To address whether a comprehensive neurologic examination could distinguish the groups, we explored the overall EDSS scores among the groups as well as the nonvisual (without the visual and brainstem sections) subscales. Using an EDSS >0 as a positive test result, the sensitivity and specificity for the EDSS to correctly identify demyelinating participants compared to the ophthalmologic cohort were calculated.

Results

A total of 51 participants were enrolled: 26 with MS and NMOSD (9 with a history of optic neuritis) and 25 with visual changes from non-demyelinating disease. The demographics and diagnoses of the participants are listed in Table 1. The results from the 21-item questionnaire, including the number of participants endorsing current or prior symptoms for each group, are presented in the Appendix A.

From this initial questionnaire, only the questions for which answers significantly differed between the groups

Table 1. Demographics

	MS/NMO cohort (n = 26)	Nondemyelinating disease cohort (n = 25)
Age, years, mean (range; median)	16.5 (4.7-21.5; 17.7)	12.3 (4.7-18.0; 13.2)
F:M	16:10	14:11
Diagnoses	MS (n = 24, 7 with history of ON) NMOSD with aquaporin-4 antibodies (n = 2, both with prior ON)	Pseudotumor cerebri (n = 5) Functional or transient vision loss (n = 5) Tumor (n = 4, incl. optic glioma [n = 2]; rhabdomyosarcoma causing orbital apex syndrome [n = 1]; Ewing sarcoma involving clivus [n = 1]) Migraines with visual disturbance, aura, or positive visual phenomena (n = 3) Diplopia (n = 2, incl. idiopathic CN VI palsy [n = 1], and decompensating esodeviation [n = 1]) Traumatic vision loss (n = 2) Ocular myasthenia gravis (n = 1) Neuroretinitis (n = 1) Idiopathic ON (n = 1) TED (n = 1)
Referral questionnaire score, mean ± SD (range)	9.4 ± 5.0 (7.4-11.4)	5.1 ± 4.3 (3.3-6.9)
EDSS, median (range)		
With vision	1.25 (0-4)	1.50 (0-4)
Without vision	0 (0-4)	0 (0-4)

CN, cranial nerve; *EDSS*, expanded disability status scale; *MS*, multiple sclerosis; *NMOSD*, neuromyelitis optica spectrum disorder; *ON*, idiopathic optic neuropathy; *SD*, standard deviation; *TED*, thyroid eye disease.

(Appendix A) were retained for the final questionnaire (Appendix B). Using only these 8 questions, the mean score for the non-demyelinating group was 1.64 ± 1.9 points (95% CI, 0.8-2.4) compared to 4.9 ± 2.6 (95% CI, 3.8-5.9) for the demyelinating participants (Table 2; $P < 0.001$). A score of 4 points or higher on these 8 questions occurred in only 2 of 25 (8%) of the non-demyelinating cohort compared with 17 of 26 (65%) of the demyelinating group. Using a score of 4 points with the 8-item questionnaire, the sensitivity was 65% and the specificity was 92% (Table 3).

A post hoc analysis was performed to compare the subset of demyelinating patients with remote vision loss from ON (n = 8) to the non-demyelinating participants with vision loss from other etiologies (n = 7). Vision loss was defined as visual acuity of <20/30 in one or both eyes. The scores on the questionnaire were significantly lower in the non-demyelinating group compared to the MS group ($P = 0.0055$; Table 2).

In the nondemyelinating group, a normal ophthalmologic and neurologic examination (EDSS of 0) occurred in 8 participants, whereas 9 additional non-demyelinating participants had a normal neurologic examination outside of the visual and brainstem systems. The remaining 8 non-demyelinating patients had mild neurologic signs on examination (non-zero EDSS total score). In the demyelinating group, 6 participants had an EDSS of 0, an additional 8 participants had a score of 0 for the functional systems other than visual and brainstem, and 12 had a nonzero total EDSS score. The EDSS had a sensitivity of 77% for identifying demyelinating disease, but the specificity was 32% as the non-demyelinating disease cohort presented with symptoms affecting the visual and brainstem function domains (such as diplopia). Without the visual and brainstem function scores, the sensitivity was 46% for an abnormal neurologic examination (defined as an EDSS of >0) correctly identifying those in the demyelinating group and the specificity was 68% (Table 3).

Discussion

We developed a questionnaire for ophthalmologists and neuro-ophthalmologists that could be used to distinguish patients with multifocal demyelinating disease, such as MS and NMOSD, from those patients with visual disturbances from other causes. The questionnaire had a sensitivity of 65% for demyelinating disease and a specificity of 92%. Thus, a positive response on the questionnaire does not confirm demyelinating disease, but few or no symptoms can be reassuring that disease extrinsic to the visual system is less likely. The questionnaire is brief (requiring only 5 minutes to complete) and can be easily administered during a clinical or research protocol examination without prolonging the visit. This tool can be used by clinicians to identify symptoms that are suggestive of relapsing inflammatory disease.

This study highlights the need for clinicians to question their patients with visual complaints about both current and prior symptoms of neurological diseases. Prior transient symptoms may not be recognized by the patient or parents as indicative of a demyelinating disorder and may not have a corresponding neurologic deficit on examination but are important in determining if a prior attack occurred. For example, a patient with a 2-week history of paresthesias that resolved prior to the onset of current visual symptoms could be identified using our questionnaire

Table 2. Comparison of scores for each test

Metric	MS/NMO group (n = 26)	Non-demyelinating group (n = 25)	*P* value[a]	Vision loss		
				MS/NMO group (n = 8)	Non-demyelinating group (n = 7)	*P* value[a]
8-item questionnaire: mean score (range)	4.9 (0-8)	1.6 (0-8)	<0.001	5 (2-8)	1.6 (0-3)	0.0055
EDSS: median score, (mean, range)	1.25 (1.4; 0-4)	1.5 (1.4; 0-4)	0.9155	2.25 (2.25; 0-4)	2 (2.7; 2-4)	0.5889
Without vision and brainstem systems	0 (0.7; 0-3.5)	0 (0.3; 0-2)	0.0882	1 (1.4; 0-4)	0 (0.1; 0-1)	0.0491

[a]Comparisons of means for the questionnaire was performed using the *t* test. The EDSS median scores were compared using the Mann-Whitney test. A *P* value of 0.05 was considered significant.

Table 3. Sensitivity and specificity

	MS/NMO (n = 26) vs non-demyelinating group (n = 25)		Vision loss in the MS/NMO group (n = 8) vs vision loss in non-demyelinating group (n = 7)	
	Sensitivity	Specificity	Sensitivity	Specificity
8-item questionnaire (cutoff ≥4)	65	92	63	100
EDSS (cutoff >0)	77	32	88	0
EDSS without the vision and brainstem systems (cutoff >0)	46	68	63	86

and thus alert the clinician to the possibility of a chronic disorder such as MS or NMOSD. For such a patient, an MRI of the C- and T-spine should be considered along with evaluation of the vision pathways.

A post hoc analysis was performed only in patients with vision loss in the demyelinating and non-demyelinating groups. Despite the small sample size, the questionnaire scores were significantly higher in the demyelinating group. The questionnaire differentiated demyelinating from non-demyelinating pathologies in patients with vision loss, thus supporting the use of the questionnaire in aiding the clinician in recognizing CNS demyelination extrinsic to the optic nerves.

The neurologic examination, as measured by the EDSS, was normal (excluding the visual and brainstem function scores) in 14 (54%) demyelinating and 17 (65%) non-demyelinating participants. Even a normal neurologic examination was insufficient to differentiate between the groups. The sensitivity of a non-zero EDSS (without vision and brainstem functions) to identify demyelinating patients was 46% compared with 65% for the questionnaire.

Our study is limited by the small sample size. Pediatric demyelinating disorders are rare, which limits study recruitment. In addition, for the non-demyelinating group, we selected children presenting to a neuro-ophthalmologist with vision complaints (not due to MS, NMOSD, or optic neuritis) and a normal intracranial MRI scan (beyond the optic pathway) to exclude other pathology that could cause neurologic symptoms or examination findings. Alternatively, the comparison group could have been children with isolated ON (without any prior clinical attacks, normal examination, and normal MRI), but the rarity of ON at a single institution made this not possible. Similarly, exploring the questionnaire in patients with a first presentation of a demyelinating attack was not feasible. The ophthalmologic disorders that were included may have actually had more symptoms than isolated optic neuritis, reducing the sensitivity of the questionnaire. Also, pain with eye movements is a key symptom in ON that was not included in our questionnaire but is important in distinguishing demyelinating from other causes of visual complaints. We acknowledge that the EDSS examiners were not masked to the participant group (demyelinating vs non-demyelinating) when performing the neurologic evaluation, potentially creating bias. A future study could be performed by administering the questionnaire to only new patients presenting with visual or neurologic complaints. The rarity of these diagnoses precluded this approach for the current study. Furthermore, we sought to create a questionnaire that would be useful to the clinician for identifying other symptoms of demyelinating disease in any child presenting with visual symptoms, not just those with confirmed optic neuritis.

In a patient with a suspected demyelinating disorder, the history and physical examination, along with ancillary testing such as MRI and lumbar puncture, are essential in making an accurate diagnosis. However, the wide spectrum of potential neurologic symptoms, lack of corresponding abnormalities on neurologic examination, and possible difficulty referring the patient to a pediatric neurologist expeditiously often challenge the ability to confirm a demyelinating disorder at the time of an attack. The use of a neurologic symptom questionnaire can aid the clinician in identifying features of demyelinating diseases.

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Appendix A. Questionnaire results

Domain	Question	Number of respondents with the symptom: MS/NMO group Now	MS/NMO group Prior	Non-demyelinating disease group Now	Non-demyelinating disease group Prior	*P* value
Vision	1. Do you have blurry vision?	4/26	9/26	9/25	6/25	0.235
	2. Do you have double vision?	2/26	5/26	7/25	6/25	0.109
	3. Do you bump into things because of your vision?	3/26	3/26	5/25	2/25	0.675
	4. Do you have trouble seeing colors?	0/26	4/26	3/25	1/25	0.090
	5. Has your prescription changed?	5/26	4/26	6/25	0/25	0.123
	6. Are you sitting closer to the TV or holding books or cell phones or other objects closer?	5/26	4/26	7/24	1/24	0.352
Weakness	7. Do you have weakness in your arms or legs?	8/26	8/26	5/25	0/25	0.002
	8. Do your arms or legs shake?	5/26	5/26	2/25	1/25	0.087
	9. Do you feel clumsy with your arms?	5/26	7/26	3/25	0/25	0.010
Walking	10. Do you lose your balance?	12/26	9/26	5/25	1/25	<0.001
	11. Do you have trouble walking?	8/26	8/26	3/25	0/25	0.001
Day-to-day	12. Do you have trouble going to the bathroom?	2/26	1/26	0/25	0/25	0.229
	13. Do you lose control over your bladder or bowel or feel like you might lose control?	3/26	3/26	1/25	1/25	0.364
Touch	14. Do you have trouble feeling things (like clothes touching your skin or feeling heat or pain) in any part of your body?	3/26	5/26	4/24	0/24	0.075
	15. Do you feel burning or numbness in any part of your body?	7/26	8/26	4/25	1/25	0.012
	16. Do you feel pins and needles (like your arm or leg fell asleep) in any part of your body?	5/26	10/26	5/24	1/24	0.011
Thinking	17. Do you have trouble remembering things?	14/26	3/26	7/25	3/25	0.148
	18. Do you have a hard time making decisions (reasoning or thinking)?	9/26	4/26	7/25	0/25	0.081
	19. Do you have trouble paying attention in class?	14/26	4/26	8/25	0/25	0.012
Fatigue	20. Do you have a hard time staying awake during the day or need to take a nap?	13/26	1/26	4/25	1/25	0.034
	21. Do you have trouble in school or doing the things you like to do because you are tired?	12/26	1/26	6/25	1/25	0.248

Only 1 participant in the entire cohort had a score of 0 for the questionnaire; this participant had multiple sclerosis. Six additional non-demyelinating participants (24%) had a score of 0 for all questions unrelated to visual function. One or more prior symptoms occurred in 11 participants (44%) in the non-demyelinating group, 6 (24%) of whom reported symptoms unrelated to vision. A total of 23 participants (88%) in the demyelinating group had prior symptoms, with 20 (77%) reporting prior symptoms unrelated to vision.

The mean total score on the questionnaire for the demyelinating group was 9.4 $\pm$ 5.0 points (95% CI, 7.4-11.4) compared with a total score of 5 $\pm$ 4.3 points (95% CI, 3.3-6.9) for the non-demyelinating group ($P = 0.0017$). A total score of 7 points or more occurred in 18 of 26 (69%) of the demyelinating patients compared with 7 of 25 (28%) of the ophthalmology cohort. Using a score of 7 as the cut-off to predict demyelinating disease in a patient presenting with visual complaints, the sensitivity was 69%, and the specificity was 72%.

Appendix B. Abbreviated 8-Item questionnaire and scoring algorithm

Question	Over the past month		Prior history
1. Do you have weakness in your arms or legs?	No (0 points)	Yes (1 point)	I do not have this now, but I did have this symptom in the past (1 point)
2. Do you feel clumsy with your arms?	No (0 points)	Yes (1 point)	I do not have this now, but I did have this symptom in the past (1 point)
3. Do you lose your balance?	No (0 points)	Yes (1 point)	I do not have this now, but I did have this symptom in the past (1 point)
4. Do you have trouble walking?	No (0 points)	Yes (1 point)	I do not have this now, but I did have this symptom in the past (1 point)
5. Do you feel burning or numbness in any part of your body?	No (0 points)	Yes (1 point)	I do not have this now, but I did have this symptom in the past (1 point)
6. Do you feel pins and needles (like your arm or leg fell asleep) in any part of your body?	No (0 points)	Yes (1 point)	I do not have this now, but I did have this symptom in the past (1 point)
7. Do you have trouble paying attention in class?	No (0 points)	Yes (1 point)	I do not have this now, but I did have this symptom in the past (1 point)
8. Do you have a hard time staying awake during the day or need to take a nap?	No (0 points)	Yes (1 point)	I do not have this now, but I did have this symptom in the past (1 point)
Sub-total score			
Total score			