

Validation and Test Characteristics of a 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25

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• **PURPOSE:** To determine whether a 10-Item Neuro-Ophthalmic Supplement increases the capacity of the 25-Item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) to capture self-reported visual dysfunction in patients with neuro-ophthalmologic disorders.

• **DESIGN:** A cross-sectional survey to examine the characteristics of a 10-Item Neuro-Ophthalmic Supplement to the 25-Item NEI-VFQ-25 in a cohort of patients with neuro-ophthalmologic disorders.

• **METHODS:** The 10-Item Neuro-Ophthalmic Supplement was designed previously by our research group by survey and focus-group methods. In the present study, the NEI-VFQ-25 and 10-Item Supplement were administered concurrently to patients and disease-free control subjects. High-contrast visual acuities with patient usual distance correction were measured with the use of Early Treatment Diabetic Retinopathy Study (ETDRS) charts.

• **RESULTS:** Diagnoses for patients ($n = 215$) included optic neuritis, multiple sclerosis, idiopathic intracranial hypertension, ischemic optic neuropathy, stroke, ocular myasthenia gravis, ocular motor palsies, and thyroid eye disease. Scores for the 10-Item Supplement had a signifi-

cant capacity to distinguish patients vs disease-free control subjects that was independent of the NEI-VFQ-25 composite score (odds ratio in favor of patient vs control status for 10-point worsening in Supplement scores: 2.7 [95% confidence interval [CI], 1.6, 4.6]; $P < .001$, logistic regression models that account for NEI-VFQ-25 composite score, age, and gender). Patients with visual dysfunction (binocular Snellen equivalents worse than 20/20) had significantly lower mean scores (9–21 points lower); these differences remained significant after accounting for age and gender ($P \geq .001$, linear regression). Supplement items and composite scores demonstrated appropriate degrees of internal consistency reliability.

• **CONCLUSION:** The 10-Item Neuro-Ophthalmic Supplement demonstrates a capacity to capture self-reported visual dysfunction beyond that of the NEI-VFQ-25 alone, which supports validity for this new scale. The use of the 10-Item Supplement in clinical trials and epidemiologic studies will examine its capacity to demonstrate treatment effects in longitudinal cohorts. (Am J Ophthalmol 2006;142:1026–1035. © 2006 by Elsevier Inc. All rights reserved.)

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DESPITE THE HIGH PREVALENCE AND IMPORTANCE of visual symptoms in patients with multiple sclerosis (MS) and other disorders that produce neuro-ophthalmologic findings, the impact of such symptoms on health-related quality of life (HRQOL) may not be captured entirely by current HRQOL scales (Tamhankar MA, abstract, presented at the North American Neuro-Ophthalmology Society Annual Meeting, March 2003).^{1–5} There are a variety of HRQOL questionnaires such as the 36-Item Short-Form Health Survey, the Visual Activities Questionnaire, and the Activities of Daily Vision Scale.^{6–16} However, the 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) has be-

come the most commonly used questionnaire that measures vision-specific HRQOL (Tamhankar MA, abstract, presented at the North American Neuro-Ophthalmology Society Annual Meeting, March 2003).^{2,3,5,11,13,16–28} The NEI-VFQ-25 was designed and validated with a multicondition focus group process and has been translated into several languages.^{18–21,23,24,29,30} However, patients with MS and other neuro-ophthalmologic disorders, particularly those disorders that cause double vision and eye movement abnormalities, were not included systematically in the focus groups or study cohorts that were used to derive content for the NEI-VFQ-25.

Although patients with MS and with ocular myasthenia gravis have scores on the NEI-VFQ-25 that are significantly lower (worse) than the scores of disease-free control subjects (Tamhankar MA, abstract, presented at the North American Neuro-Ophthalmology Society Annual Meeting, March 2003), we have shown that additional aspects of vision that are not captured by the NEI-VFQ-25 (or by the other scales that were mentioned previously), particularly double vision, difficulty focusing on or following moving objects, and difficulty with vision when the eyes are “tired,” are problematic for patients with neuro-ophthalmologic disorders.^{2,5}

The purpose of our study was to determine whether a 10-Item Neuro-Ophthalmic Supplement increases the capacity of the NEI-VFQ-25 to capture self-reported visual dysfunction in patients with neuro-ophthalmologic disorders. We also examined reliability, floor/ceiling effects, and other psychometric properties for the Neuro-Ophthalmic Supplement to determine the potential usefulness for future clinical trials and epidemiologic studies.

METHODS

• **PATIENTS AND DEMOGRAPHIC DATA:** This investigation was a cross-sectional survey to examine the characteristics of a 10-item Neuro-Ophthalmic Supplement to the NEI-VFQ-25 in a cohort of patients with neuro-ophthalmologic disorders. Patients who were evaluated by neuro-ophthalmologists in the Department of Neurology at the University of Pennsylvania were invited to participate. The Pennsylvania neuro-ophthalmology group follows a large cohort of patients with MS^{31,32} and patients with a variety of other conditions that are associated with afferent and efferent visual dysfunction. Disease-free control subjects included staff and family members of patients who participated in this study and who had binocular visual acuities of 20/20 or better. Study protocols were approved by the University of Pennsylvania Institutional Review Board. Written informed consent was obtained from each participant, and the study was conducted in accord with Health Insurance Portability and Accountability Act (HIPAA) regulations.

Demographic data that included age, gender, race, occupational status, and highest educational level attained were recorded for each participant; age and gender were covariates in statistical models. Although patients and control subjects were questioned to exclude other ocular comorbidities (besides refractive error), other comorbid medical conditions were not ascertained systematically as part of this study. For patients with neuro-ophthalmologic disorders, the following clinical characteristics were also ascertained: diagnosis, current symptoms, disease duration, disease-specific therapies (ie, immunomodulatory agents for MS), and comorbid ocular, neurologic, or medical conditions. For all patients, ambulation status was characterized in the following manner: no assistance, unilateral assistance (cane), bilateral assistance (walker), and wheelchair. Expanded Disability Status Scale scores were not available uniformly for patients with MS.³³

• **VISION QUESTIONNAIRES:** The NEI-VFQ-25^{17–20} was completed by all study participants. A 10-Item Neuro-Ophthalmic Supplement, which was designed by our research group who used survey and focus group methods (Tamhankar MA, abstract, presented at the North American Neuro-Ophthalmology Society Annual Meeting, March 2003),² was administered after the NEI-VFQ-25. Questionnaires were self-administered. Research assistants reviewed the instructions with each participant and answered any questions that arose. On completion of each questionnaire, the research assistant immediately reviewed the forms to ensure that all items were answered and that responses were legible; patients were asked to answer or clarify those items that were not legible or complete.

The NEI-VFQ-25 consists of 25 items that are presented in a Likert scale format in which patients are asked to rate the level of difficulty of particular visual symptoms or activities such as reading ordinary print in newspapers or driving. The NEI-VFQ-25 is a short-form version of the 51-Item National Eye Institute Visual Function Questionnaire, which is a vision-specific HRQOL instrument that was derived from a multicondition focus group process.^{17–20} The NEI-VFQ-25 was administered according to standard instructions. Patients were asked to answer all questions as though they were wearing their usual correction (glasses or contact lenses) for the visual activity that was specified.¹⁷ With the NEI-VFQ-25 scoring algorithm,¹⁷ the 12 NEI-VFQ-25 subscales were scored on a scale from 0 to 100, with 100 representing the highest level of function. NEI-VFQ-25 subscales are outlined in Table 1. As specified by Mangione and associates,^{17,20} the composite (overall) score for the NEI-VFQ-25 was calculated as the unweighted average of all items, except item 1 (24 items, excluding a single item for general health).

The 10-Item Neuro-Ophthalmic Supplement was administered with instructions that are similar to those provided for the NEI-VFQ-25. Items were presented in a Likert scale format that was identical to that used in the

TABLE 1. Demographic and Clinical Characteristics for Patient and Disease-free Control Groups in Studies to Examine Characteristics for a 10-Item Neuro-Ophthalmic Supplement to the 25-Item National Eye Institute Visual Functioning Questionnaire

Variable	All Patients (n = 215)	Multiple Sclerosis (n = 145)	Neuro-Ophthalmologic Disorders other than MS (n = 70)	Disease-Free Control Subjects (n = 65)
Age: Years (mean \pm SD)	45 \pm 13	44 \pm 10	46 \pm 17	38 \pm 12
Gender: Female (n)	148 (70%)	105 (74%)	43 (61%)	38 (58%)
Race: White (n)	182 (87%)	125 (89%)	57 (83%)	53 (83%)
Educational level: College graduate (n)	126 (59%)	87 (60%)	39 (56%)	39 (60%)
Currently driving (n)	197 (92%)	137 (94%)	60 (86%)	62 (95%)
Disease duration: Years [median (range)]	3 (0–40)	4 (1–40)	1.5 (0–25)	—
Ambulation status [median (range)]*	0 (0–3)	0 (0–3)	0 (0–3)	—
Binocular visual acuity (Early Treatment Diabetic Retinopathy Study, Snellen equivalent) [median (range)]	20/16 (20/12.5–20/200)	20/16 (20/12.5–20/80)	20/16 (20/12.5–20/200)	20/12.5 (20/12.5–20/20)
Worse eye (Early Treatment Diabetic Retinopathy Study, Snellen equivalent) [median (range)]	20/25 (20/12.5–20/250)	20/25 (20/12.5–20/250)	20/25 (20/12.5–20/250)	20/20 (20/12.5–20/40)
Better eye (Early Treatment Diabetic Retinopathy Study, Snellen equivalent) [median (range)]	20/16 (20/12.5–20/250)	20/16 (20/12.5–20/80)	20/16 (20/12.5–20/250)	20/16 (20/12.5–20/25)

MS = multiple sclerosis; SD = standard deviation.
 *Ambulation status: 0 = No assist device; 1 = unilateral (cane); 2 = bilateral (walker); 3 = wheelchair.

NEI-VFQ-25 and were scored on a 0 to 100 scale. Instructions and content for the 10-Item Supplement are presented in the Appendix (available at [AJOO.com](http://ajoo.com)). This questionnaire, which was described earlier, was designed on the basis of the survey and focus group methods in patients with MS, ocular myasthenia gravis, and other conditions that cause diplopia.² A composite (overall) score for the 10-Item Supplement was calculated as the unweighted average of the 10 items. To generate a combined score for the NEI-VFQ-25 with the 10-Item Supplement, the unweighted average of NEI-VFQ-25 (except item 1 [general health]) and Supplement items (average of 34 items) was determined.

• **VISUAL ACUITY TESTING:** High-contrast visual acuities were measured by retro illuminated Early Treatment Diabetic Retinopathy Study (ETDRS) charts at 3.2 m (Precision Vision, LaSalle, Illinois, USA).^{34–36} Standard protocols for the ETDRS charts were used, and patients wore their usual distance correction.³⁷ Visual acuity testing was performed for each eye separately and binocularly; binocular testing was included to provide a summary measure of overall visual functioning with both eyes open.^{38,39} Charts were scored letter-by-letter, and Snellen visual acuity equivalents (ie, 20/20) were recorded.⁴⁰

Eyes of each participant were designated as “better” or “worse” eyes on the basis of Snellen equivalents that were derived from ETDRS letter scores; *worse eyes* were defined

as those eyes with a Snellen equivalent of 1 line or more worse than the contralateral eye.²² If both eyes of a given patient had identical Snellen equivalents, then both eyes were designated as “better” eyes for purposes of analyses and correlations with vision questionnaire scores.

• **DATA ANALYSIS AND STATISTICAL METHODS:** Data analyses and calculations were performed with Stata statistical software (version 8.0; StataCorp, College Station, Texas, USA). Means and standard deviations were calculated for each NEI-VFQ-25 subscale, for the NEI-VFQ-25 composite (overall) score, for each item in the 10-Item Neuro-Ophthalmic Supplement, and for the Supplement composite score (unweighted average of 10 items). Scores for patient groups were compared with those for disease-free control subjects from our cohort (somewhat younger than patient groups) and with an eye disease-free reference group published by Mangione¹⁷ (older than our patient groups) with two-tailed *t*-tests with unequal variances. Comparisons of NEI-VFQ-25 subscale scores with control/reference groups were performed only after it was determined that the mean composite scores for the patient and control/reference groups were significantly different.^{17,20} Given the potential effects of age on vision-specific HRQOL, linear regression models that accounted for age were used to confirm differences in mean scores between patient and control/reference groups.⁴¹ Because three comparisons were performed, the Bonferroni-type adjustment

TABLE 2. Composite Scores for the 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25), 10-Item Neuro-Ophthalmic Supplement and NEI-VFQ-25 + 10-Item Neuro-Ophthalmic Supplement According to Binocular Visual Acuity and Patient Group

Variable	All Patients (n = 215)	Multiple Sclerosis (n = 145)	Neuro-Ophthalmologic Disorders Other Than MS (n = 70)	Disease-Free Control Subjects (n = 65)
NEI-VFQ-25 composite score (mean ± SD)*	86 ± 15*	88 ± 14	81 ± 18	96 ± 4
Binocular visual acuity [†] ≥20/20	89 ± 10	91 ± 9	87 ± 12	95 ± 4
Binocular visual acuity [†] <20/20	76 ± 21 [‡]	79 ± 18	68 ± 23	—
10-Item Neuro-Ophthalmic Supplement (mean ± SD)	77 ± 18	80 ± 15	70 ± 22	93 ± 7
Binocular visual acuity [†] ≥20/20	81 ± 15	83 ± 13	76 ± 18	94 ± 7
Binocular visual acuity [†] <20/20	68 ± 23	74 ± 18	55 ± 26	—
NEI-VFQ-25 composite + 10-Item Neuro-Ophthalmic Supplement (mean ± SD) [†]	83 ± 16	86 ± 13	78 ± 19	95 ± 5
Binocular visual acuity [†] ≥20/20	87 ± 11	89 ± 10	84 ± 13	95 ± 5
Binocular visual acuity [†] <20/20	73 ± 21	78 ± 18	64 ± 24	—

MS = multiple sclerosis; SD = standard deviation; NEI-VFQ-25 = 25-Item National Eye Institute Visual Functioning Questionnaire.

*Composite scores for the NEI-VFQ-25, 10-Item Neuro-Ophthalmic Supplement, and NEI-VFQ-25 + Supplement were significantly lower (worse) for patients vs disease-free control subjects, which accounts for age and gender ($P < .001$ for all comparisons of patient vs control groups, linear regression analyses). These differences from control subjects were consistent across patient groups.

[†]≥20/20 = 20/20 or better; <20/20 = worse than 20/20.

[‡]Composite scores for the NEI-VFQ-25, 10-Item Neuro-Ophthalmic Supplement, and NEI-VFQ-25 + Supplement were lower (worse) among patients with binocular visual acuities of 20/20 or better in all groups. Scores were slightly lower for the 10-Item Supplement and for the NEI-VFQ-25 + Supplement, which suggests an increased capacity for the Supplement to capture self-reported visual and ocular motility dysfunction in patients with neuro-ophthalmologic disorders.

would be a probability score of .017. However, because the three comparisons were derived from the same cohort of patient and therefore were intercorrelated, a more conservative significance level probability value of $<.01$ was used. Factor analysis was performed on the 10-Item Neuro-Ophthalmic Supplement to examine the interrelationship among the 10 items. Eigen values were used to determine the number of concepts or factors that were captured by the 10-Item Supplement (number of factors determined by the number of Eigen values ≥ 0.40).

Logistic regression analyses were used to assess the capacity of the 10-Item Neuro-Ophthalmic Supplement to distinguish patients from disease-free control groups independently of NEI-VFQ-25 composite scores, which accounted for age and gender. Spearman rank-correlations and linear regression techniques were used to examine the relation of NEI-VFQ-25 and 10-Item Supplement scores to ambulation status and to binocular, worse eye, and better eye visual acuities.

Percentages of patients who achieved the lowest possible score of zero (floor) and highest possible score of 100 (ceiling) were determined for each NEI-VFQ-25 composite and subscale score and for Supplement items and composite. Cronbach α score,²² which is a measure of the extent to which items within a single subscale correlate with the subscale score, was calculated for each NEI-VFQ-25 subscale and for the 10-Item Supplement as a measure of the reliability of the subscale's internal consistency. The acceptable minimum Cronbach α score is 0.70.

Item internal consistency, which is the degree to which each individual item measures the underlying construct, was measured with the use of Pearson correlations of each item to its respective subscale score (10-Item Supplement was considered as a single subscale). If an item measures the underlying construct represented by the subscale to which it was assigned (driving, for example), then the correlation between the item and subscale scores should be greater than 0.40.²³

RESULTS

DIAGNOSES FOR PATIENTS WITH NEURO-OPHTHALMOlogic disorders (n = 215) included MS, idiopathic intracranial hypertension, ischemic optic neuropathy, stroke, ocular myasthenia gravis, ocular motor palsies, and thyroid eye disease. Among 145 patients with MS, 47 patients had a history of acute optic neuritis. Patient groups were comparable with respect to age and educational levels (Table 2); patients with neuro-ophthalmologic disorders other than MS were somewhat less likely to be female, less likely to be currently driving, and to have shorter median disease duration. Because patient and disease-free control groups in this convenience sample differed with respect to age and gender, statistical models that were used for analyses that compared groups and examined the relation of NEI-VFQ-25 scores to visual acuity included age and gender as covariates. Median binocular visual acuities

(which were obtained with the use of ETDRS charts and were expressed as Snellen equivalents; Table 2) were 20/16 (range, 20/12.5 to 20/200) in the patient groups and reflected visual function among the better seeing eyes.

Accounting for age and gender, composite scores for the NEI-VFQ-25, 10-Item Neuro-Ophthalmic Supplement, and NEI-VFQ-25 + Supplement were significantly lower (worse) for patients vs disease-free control subjects ($P < .001$ for all comparisons of patient vs control groups, linear regression analysis; Table 1). NEI-VFQ-25 subscale scores were significantly lower (worse) for comparison of the patient vs disease-free control groups ($P \leq .01$), with the exception of color vision ($P = .28$, linear regression analyses that accounted for age and gender).

The effects of visual function on scores for the NEI-VFQ-25, 10-Item Neuro-Ophthalmic Supplement, and NEI-VFQ-25 + Supplement were examined in several ways. As demonstrated in Table 1, better visual function scores (binocular Snellen equivalents 20/20 or better) were associated with higher scores for all three questionnaires. Mean scores were 9 to 21 points lower for patients with binocular acuities worse than 20/20. These unadjusted differences in questionnaire scores between visual acuity categories were similar across patient groups (Table 1) and were statistically significant when accounting for age and gender ($P \leq .001$, linear regression). Rank-correlations of monocular visual acuities with questionnaire scores revealed slightly higher correlations with worse eyes ($r_s = 0.35$ for 10-Item Supplement; $r_s = 0.40$ for NEI-VFQ-25 + Supplement) compared with better eyes ($r_s = 0.27$ for 10-Item Supplement; $r_s = 0.31$ for NEI-VFQ-25 + Supplement).

Compared with the composite score for the NEI-VFQ-25 alone, the combined score for the NEI-VFQ-25 + Supplement demonstrated a greater capacity to distinguish patients with neuro-ophthalmologic disorders from disease-free control subjects. Accounting for age and gender, odds ratios in favor of participants with worse questionnaire scores being patients (vs disease-free control subjects) were greater for the NEI-VFQ-25 + Supplement (odds ratios in favor of participant being a patient if questionnaire score was worse by 10 points: 4.4; 95% confidence interval (CI), 2.5, 7.9) compared with the NEI-VFQ-25 alone (odds ratio, 3.9; 95% CI, 2.2, 7.2; $P < .001$ for all regression models). A 10-point difference was chosen as a reference for the odds ratios because this represents the magnitude of differences that were noted between disease and control groups in previous studies of the NEI-VFQ-25.¹⁷ Although odds ratios in these analyses were higher for the NEI-VFQ-25 + Supplement combined score as indicated earlier, there was substantial overlap of the 95% CI, which was consistent with the fact that, when considered separately, both the combined questionnaire and the NEI-VFQ-25 are good discriminators of patient vs control status. However, when models were constructed to examine the capacity for the 10-Item Supplement score to

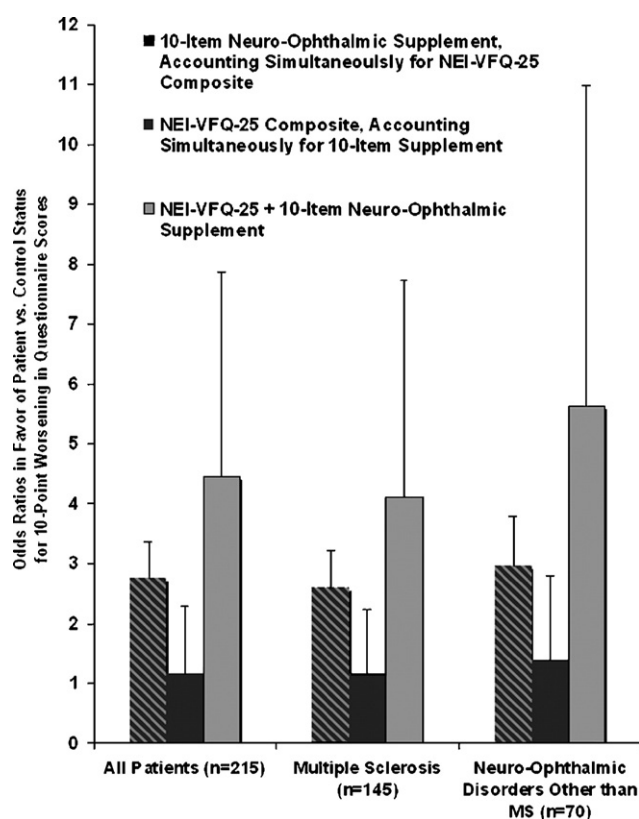


FIGURE. Logistic regression models demonstrate the capacity of the 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25; independent of the 10-Item Neuro-Ophthalmic Supplement), the 10-Item Neuro-Ophthalmic Supplement (independent of the NEI-VFQ-25) and the NEI-VFQ-25 + Supplement to distinguish patient vs control groups (odds ratio, 4.5). Although the odds ratio in favor of patient vs control status was 2.7 for a 10-point worsening in Supplement score ($P < .001$, which simultaneously accounts for NEI-VFQ-25 composite score), the NEI-VFQ-25 itself did not distinguish patient vs control groups to a significant degree when accounting for Supplement score (odds ratio, 1.2). Although odds ratios for the NEI-VFQ-25 composite score alone were significant (odds ratio, 4.0; 95% confidence interval [CI], 2.1, 7.2; $P < .001$), the NEI-VFQ-25 + Supplement was also a strong predictor of patient vs control status.

distinguish patient vs control status beyond that already afforded by the NEI-VFQ-25 composite score (models that accounted for NEI-VFQ-25 composite, age, and gender), the 10-Item Supplement was an independent predictor of patient vs control status (odds ratio in favor of participant being a patient if the Supplement score worse by 10 points: 2.7; 95% CI, 1.5, 5.7; Figure). When the 10-Item Supplement was examined separately with regard to capacity to distinguish patient vs control groups on its own, odds ratios in favor of patient vs control status for 10-point worsening in scores were 3.0 (95% CI, 2.1, 4.4) for all patients, 2.8 (95% CI, 1.9, 4.2) for patients with MS, and 3.5 (95% CI, 2.2, 5.6) for neuro-ophthalmologic disorders other than MS. These data remained robust when results for the

TABLE 3. Estimates of Floor and Ceiling Effects and Internal Consistency Reliability for 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) Subscale and Composite Scores Among All Patients (n = 215)

NEI-VFQ-25 Subscale (number of items)	Mean Score \pm SD	Median	Ceiling Effect (n)*	Floor Effect (n) [†]	Cronbach α [‡]
General health (1)	61 \pm 23	50	26 (12%)	4 (2%)	N/A [‡]
General vision (1)	78 \pm 17	80	46 (21%)	0	N/A
Ocular pain (2)	83 \pm 20	88	92 (43%)	1 (0.5%)	0.78
Near vision (3)	84 \pm 20	92	90 (42%)	0	0.85
Distance vision (3)	84 \pm 18	92	75 (35%)	0	0.76
Vision specific					
Social functioning (2)	94 \pm 12	100	161 (75%)	0	0.74
Mental health (4)	82 \pm 21	88	50 (23%)	0	0.84
Role difficulties (2)	83 \pm 23	88	105 (49%)	3 (1%)	0.86
Dependency (3)	93 \pm 17	100	162 (75%)	2 (1%)	0.82
Driving (2)	81 \pm 24	88	65 (30%)	9 (4%)	0.74
Color vision (1)	97 \pm 12	100	194 (90%)	0	N/A
Peripheral vision (1)	83 \pm 23	100	121 (57%)	0	N/A
NEI-VFQ-25 composite score	86 \pm 15	91	15 (7%)	0	0.96

NEI-VFQ-25 = 25-Item National Eye Institute Visual Functioning Questionnaire; SD = standard deviation.

N/A = Not applicable because there is only one item in the subscale.

*Percentage of patients with scores at the maximum (100) is $\geq 20\%$.

[†]Percentage of patients with scores at the minimum (0) is $\geq 20\%$.

[‡]A measure of the extent to which items within a single subscale correlate with the subscale score, calculated for each NEI-VFQ-25 subscale and for the composite as a measure of the reliability of the subscale's internal consistency; acceptable minimum, 0.70.

NEI-VFQ-25, 10-Item Supplement, and the combined score for the NEI-VFQ-25 + Supplement were dichotomized on the basis of whether scores were greater than or less than or equal to the mean composite score for a published NEI-VFQ-25 reference group (mean reference score, 92 points).¹⁷ Odds ratios for all questionnaires were statistically significant ($P < 0.05$ for all) and had magnitudes between 2.8 and 5.8.

Patients with MS and other neuro-ophthalmologic disorders in this study had NEI-VFQ-25 composite and subscale scores (Table 3) that were similar to cohorts with glaucoma⁹ and with early age-related macular degeneration (Complications of Age-related Macular Degeneration Prevention Trial participants with 20/40 or better visual acuity in each eye).²² Composite scores for our patient cohort were significantly lower than the scores for a published eye disease-free reference group (86 ± 15 vs 92 ± 7 ; $n = 118$ for reference group; $P < .0001$, two-sample t -test with unequal variances).¹⁷ NEI-VFQ-25 subscale scores were significantly lower (worse) for all patient vs and disease-free control group comparisons ($P \leq .025$), with exceptions of color vision ($P = .16$ to $.26$, all patient groups), dependency ($P = .06$ for the MS group), and general vision ($P = .06$ for the MS group, logistic regression analyses that account for age and gender). Although the Optic Neuritis Treatment Trial (ONTT) at 10-year follow-up evaluation used the 51-Item NEI-VFQ,

the subscale scores for the NEI-VFQ-25 were similar to those previously reported for participants in the ONTT (composite scores were not calculated for the ONTT cohort).^{3,25} With the exception of color vision, NEI-VFQ-25 subscale scores in our patient cohort were 1 to 5 points lower than those recorded for ONTT participants.^{3,25} As noted in the ONTT, subscale scores in our study were lowest for general health, which is a subscale that does not contribute to the NEI-VFQ-25 composite score.

Psychometric properties of the NEI-VFQ-25 (Table 3) were similar to those that recently were demonstrated in other diseased and nondiseased cohorts.^{22–26} Ceiling effects ($>20\%$ of patients at highest possible score of 100) were seen for 11 of 12 NEI-VFQ-25 subscales among all patients in the cohort. In contrast, floor effects ($>20\%$ at lowest possible score of 0) were not observed for any NEI-VFQ-25 subscale (Table 3). When the 10-Item Neuro-Ophthalmic Supplement was analyzed as a potential subscale (Table 4), the proportion of patient scores at the maximum was 7%, which is substantially lower than the 20% cut-off for ceiling effect. For composite scores, percentages at the ceiling were 7% for the NEI-VFQ-25 vs 2% for the NEI-VFQ-25 + Supplement for patients. Percentages at the ceiling for the control cohort were 14% for the NEI-VFQ-25 composite vs 6% for NEI-VFQ-25 + Sup-

TABLE 4. Estimates of Floor and Ceiling Effects, Item Internal Consistency, and Internal Consistency Reliability for 10-Item Neuro-Ophthalmic Supplement, All Patients (n = 215)

Neuro-Ophthalmic Supplement Item	Mean \pm SD	Median	Ceiling Effect (n)*	Floor Effect (n) [†]	Item-total Correlation, Cronbach's α ^{‡§}
Item 1: Difficulty when eyes tired	73 \pm 24	75	63 (29%)	4 (2%)	0.73 [‡]
Item 2: Difficulty in bright sunlight	78 \pm 25	75	92 (43%)	6 (3%)	0.63
Item 3: Difficulty parking car	86 \pm 26	100	140 (65%)	10 (5%)	0.60
Item 4: Difficulty using computer	84 \pm 21	100	116 (54%)	2 (1%)	0.70
Item 5: Two eyes see differently	50 \pm 43	50	74 (34%)	70 (33%)	0.69
Item 6: Eye/lid appearance unusual	80 \pm 34	100	139 (65%)	21 (10%)	0.64
Item 7: Vision blurry, not clear, "fuzzy"	68 \pm 29	75	59 (27%)	15 (7%)	0.68
Item 8: Trouble focusing on moving objects	79 \pm 26	100	110 (51%)	6 (3%)	0.74
Item 9: Binocular double vision	87 \pm 26	100	159 (74%)	9 (4%)	0.55
Item 10: Ptosis	86 \pm 28	100	164 (76%)	13 (6%)	0.53
Composite score for 10-Item Neuro-Ophthalmic Supplement	77 \pm 18	80	14 (7%)	0	0.85 [§]
25-Item National Eye Institute Visual Functioning					
Questionnaire composite score + 10-Item Neuro-Ophthalmic Supplement	83 \pm 16	88	5 (2%)	0	0.96 [§]

*Percentage of patients with scores at the maximum (100) is $\geq 20\%$.

[†]Percentage of patients with scores at the minimum (0) is $\geq 20\%$.

[‡]The degree to which each individual item measures the underlying construct, measured through Pearson correlation of each item score with the 10-Item Supplement composite score. If an item measures the underlying construct represented by the subscale to which it was assigned (eg, driving), then the correlation between the item and subscale scores should be greater than 0.40.

[§]A measure of the extent to which items within a single subscale correlate with the subscale score, calculated for each 25-Item National Eye Institute Visual Functioning Questionnaire subscale and for the composite as a measure of the reliability of the subscale's internal consistency; acceptable minimum, 0.70.

plement composite. No patients had scores of 0 (floor) for either composite.

All multi-item NEI-VFQ-25 subscales demonstrated moderately strong levels of internal consistency reliability, with Cronbach α values that ranged from 0.74 to 0.86 (above the acceptable minimum of 0.70; Table 3). Similarly, Cronbach α score for the 10-Item Neuro-Ophthalmic Supplement was 0.85. Item-subscale correlations for the 10-Item Supplement (Table 4) were all >0.40 (range, 0.53 to 0.74), which indicates that each item measures, to an acceptable degree, the underlying construct of self-reported visual/ocular motility dysfunction. The overall Cronbach α statistic for the NEI-VFQ-25 was 0.96; adding the 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25 resulted in persistently high levels of internal consistency reliability (Cronbach α score, 0.96) in this cohort of patients with neuro-ophthalmologic disorders.

Factor analysis revealed that the 10-Item Neuro-Ophthalmic Supplement captures two distinct concepts (two Eigen values were greater than 0.40: factor 1 = 3.8; factor 2 = 0.8). Factor 1 explained 80% of variation in item scores. All items received a positive loading above 0.4 for factor 1. However, the loading values for item 6 (believing that eye or eyelid appearance is unusual; see Supplementary Material at AJO.com) and item 10 (ptosis) increased in factor 2 and were the only items with an absolute

loading value greater than 0.4. Similar results were obtained after orthogonal rotation was analyzed, which suggests that items that are related to eye/lid appearance may be distinct from those items that assess self-reported visual function.

DISCUSSION

THE RESULTS OF THIS INVESTIGATION DEMONSTRATE that adding a 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25 has a capacity to capture self-reported visual dysfunction beyond that of the NEI-VFQ-25 alone. Our data support validity for this new scale in neuro-ophthalmologic cohorts and suggest that performance of the 10-Item Supplement should be examined in combination with the NEI-VFQ-25 in longitudinal clinical trials and epidemiologic studies.

Vision-specific HRQOL questionnaires are designed to identify self-reported symptoms of disease, to evaluate the effectiveness of treatments, and to assess the impact of a condition on individual functioning.²³ Although previous studies have shown that the NEI-VFQ-25 alone can capture symptoms that are associated with MS and ocular myasthenia gravis, two disorders that commonly produce neuro-ophthalmologic findings (Tamhankar MA, abstract, presented at the North American Neuro-Ophthalmology Society Annual

Meeting, March 2003),^{2,5} these investigations also identified additional common and important symptoms that were not captured entirely by the NEI-VFQ-25. These studies of MS and ocular myasthenia gravis cohorts generated content items for the 10-Item Neuro-Ophthalmic Supplement through survey and focus group methods.

Similar to patients in other studies that involved the NEI-VFQ-25, patients with neuro-ophthalmic disorders experienced a decrease in visual acuity and other deficits. However, unlike patients in the other studies, patients with neuro-ophthalmic disorders, which included those with MS, experience additional factors that contribute to vision-specific HRQOL such as double vision, eye movement abnormalities, and changes in eye/lid appearance. These symptoms, in particular, are not captured by the NEI-VFQ-25; correlations between NEI-VFQ-25 composite scores and Neuro-Ophthalmic Supplement item scores were lowest for unusual appearance (item 6; see Appendix), diplopia (item 9), and ptosis (item 10). These items are likely important contributors to increasing the capacity of the NEI-VFQ-25 to distinguish patients with neuro-ophthalmic disorders from disease-free control subjects.

The NEI-VFQ-25 and the larger questionnaire from which it was derived (51-Item NEI-VFQ) have been used successfully to demonstrate reductions in vision-specific HRQOL in cohorts with optic neuritis, glaucoma, uveitis, age-related macular degeneration, diabetic retinopathy, central retinal vein occlusion, cataract, and keratoconus (Tamhankar MA, abstract, presented at the North American Neuro-Ophthalmology Society Annual Meeting, March 2003).^{2,3,5,11,13,16–28} Mean NEI-VFQ-25 composite scores in our investigation were lower than those reported for Latino patients who had various ocular diseases²³ and were also worse for many subscales than those patients with early age-related macular degeneration.²² These differences were noted, despite the fact that the patients in our cohort were younger, which suggests impacts of neuro-ophthalmologic symptoms on HRQOL that are independent of aging and may be captured in young patients.

The most important first steps in the determination of the usefulness of a self-report HRQOL measure include an examination of reliability and validity and a capacity to discriminate patients with the disease(s) of interest vs those patients without the disease.²³ In our investigation, the NEI-VFQ-25 alone was a good discriminator of patient vs control groups; however, accounting for NEI-VFQ-25 composite score, the 10-Item Neuro-Ophthalmic Supplement was a strong independent predictor of patient vs control status (Figure). These differences were seen for the overall patient cohort and for MS and other disorders, which supports the usefulness of the 10-Item Supplement for identifying self-reported visual dysfunction in a variety of neuro-ophthalmologic conditions.

After an examination of the Cronbach α score, which reflects reliability of a subscale's internal consistency (or

extent to which items within a subscale correlate with the subscale score),²² the addition of the 10-Item Neuro-Ophthalmic Supplement maintained levels of reliability for the overall scores (Tables 3 and 4). Cronbach α score for the NEI-VFQ-25 + Supplement was >0.95 , which is consistent with good levels of internal consistency and indicates that the additional (Supplement) items capture the underlying concept of vision-specific HRQOL. When considered as a separate subscale, the 10-Item Supplement demonstrated levels of reliability that were well within the acceptable range (Cronbach α score, 0.85, above the published minimum of 0.70; Table 4). Compared with current NEI-VFQ-25 subscales (which have fewer items, thus an expectedly lower Cronbach α scores), the 10-Item Supplement had higher Cronbach α scores in most cases.

Proportions of patients with scores at the floor (minimum score, 0) and ceiling (maximum score, 100) were very low for both the NEI-VFQ-25 composite score and for the 10-Item Neuro-Ophthalmic Supplement (floor effects, 0%; ceiling effects, 7% for both questionnaires; Tables 3 and 4). Ceiling effects reduced slightly to 5% when the Supplement was added to the NEI-VFQ-25. This may be attributable to the addition of items (Supplement adds 10 items) but may reflect, in part, the neuro-ophthalmologic nature of the symptoms in our patient cohort and the increased capacity of the combined questionnaire to capture these symptoms. Although the percentage of patients who received a 100 score (ceiling) on the composite for both the NEI-VFQ-25 and the NEI-VFQ-25 + Supplement was low, the scores were slightly higher than recorded in previous studies that included the patient reference group.^{17,38} This outcome may be caused by a younger patient cohort in this study compared with other studies (younger patients may be expected to have more scores at the ceiling). A control subject in our study was twice as likely to receive a composite score of 100 on the NEI-VFQ-25, but three times more likely to score 100 on the NEI-VFQ-25 + Supplement, than a patient. The floor and ceiling effects for the NEI-VFQ-25 subscales in other cohorts are similar to findings of our study, despite the relatively younger age of our patients.

The 10-Item Neuro-Ophthalmic Supplement appears to capture two distinct concepts, with eye/lid appearance representing a minor component. Although the first factor, which represents visual function, explained 80% of variation in item scores, analyses of factor loadings also suggested that items 6 (believing that eye/eyelid appearance is unusual) and 10 (ptosis) are correlated as one construct. Because this cohort included only 15 patients with ocular myasthenia gravis and thyroid eye disease (common causes of abnormal eye/lid appearance), definitive conclusions regarding whether items 6 and 10 may be eliminated from the Supplement (item reduction) should await further use of the Supplement in trials and epidemiologic studies of ocular myasthenia gravis and thyroid eye disease. These investigations will begin within the next year.

In previous studies, scores for the NEI-VFQ-25 have correlated significantly with visual acuity, which reflects the high impact of high-contrast acuity loss on HRQOL.^{2,3,13,22,23,27} Our investigation likewise showed significant correlations between the 10-Item Neuro-Ophthalmic Supplement scores and visual acuities measured binocularly and with each eye separately. Scores for all questionnaires (NEI-VFQ-25, 10-Item Supplement, and NEI-VFQ-25 + Supplement) were significantly lower (9 to 21 points worse) among patients with binocular acuities worse than 20/20. Binocular visual acuities, which are increasingly recognized as providing a measure of overall visual function as is present for daily activities, were significant predictors of questionnaire scores in our patient cohorts and in previous studies of visual function and HRQOL in patients with MS.^{2,24,42} These correlations were modest, despite their significance, with magnitudes of $r_s = 0.33$ ($P = .003$) in a previous MS cohort that examined binocular high-contrast acuity vs NEI-VFQ-25 composite scores.² Correlations were similar in the present cohort, and the low yet significant magnitude may reflect the subjective nature of HRQOL assessment and the relative values that are placed on particular domains of vision-specific HRQOL (driving, for example) by patients.

In contrast to other cohorts in which NEI-VFQ-25 scores have correlated most strongly with visual acuities in better-seeing eyes,^{3,20,22–24} questionnaire scores in our study were somewhat more reflective of worse eye acuities ($r_s = 0.41$ for NEI-VFQ-25 alone and 0.40 for NEI-VFQ-25 + Supplement for worse eye acuities; $r_s = 0.31$ and 0.32 for better eyes; $P < .0001$ for all correlations). This pattern of higher correlation for worse eyes may reflect the fact that a substantial proportion of our patient cohort had MS, which is a disorder that frequently produces subtle loss of function and axonal loss even in eyes with 20/20 or better visual acuity and no history of acute optic neuritis.^{1,31,32} Among patients with disorders other than MS in this study, correlations with NEI-VFQ-25 and NEI-VFQ-25 + Supplement scores were greater for better eyes ($r_s = 0.38$ vs $r_s = 0.31$ for worse eyes for both questionnaires).

Collectively, the results of this investigation support validity and feasibility for further testing of the 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25 in neuro-ophthalmologic and MS research and clinical trials. Investigations are ongoing to examine the usefulness of the 10-Item Supplement in longitudinal studies and to examine its correlation with clinical changes, relation to objective measures of ocular misalignment, and capacity to demonstrate treatment effects.

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APPENDIX: 10-ITEM NEURO-OPHTHALMIC SUPPLEMENT TO THE NEI-VFQ-25

THE FOLLOWING ARE ADDITIONAL QUESTIONS AND STATEMENTS ABOUT PROBLEMS THAT INVOLVE YOUR VISION OR feelings you may have about your vision condition. After each question, there will be a list of possible answers. Please choose the response that best describes your situation.

Please answer all questions as if you were wearing your glasses or contact lenses (if any). Please take as much time as you need to answer each question.

1. How much difficulty do you have performing tasks when your eyes are <u>tired</u>?	
	<i>(Circle One)</i>
None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5
2. Because of your vision, how much difficulty do you have identifying objects or performing tasks in bright sunlight?	
	<i>(Circle One)</i>
None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5
3. Because of your vision, how much difficulty do you have parking a car?	
	<i>(Circle One)</i>
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6
4. Because of your vision, how much difficulty do you have using a computer?	
	<i>(Circle One)</i>
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

For each of the following statements, please indicate if it is definitely true, mostly true, mostly false, or definitely false for you or if you are not sure.

5. I have a feeling that my two eyes see differently, even with correction (glasses or contact lenses).	
	<i>(Circle One)</i>
Definitely true	1
Mostly true	2
Not sure	3
Mostly false	4
Definitely false	5
6. I have a feeling that my eye or eyelid appearance is unusual.	
	<i>(Circle One)</i>
Definitely true	1
Mostly true	2
Not sure	3
Mostly false	4
Definitely false	5

For each of the following, please indicate if it is true for you all, most, some, a little, or none of the time.

7. My vision is blurry, not clear, or “fuzzy.”	
	(Circle One)
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5
8. I have trouble focusing on or following moving objects.	
	(Circle One)
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5
9. I have double vision with both eyes open that is not present when either eye is covered.	
	(Circle One)
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5
10. My eyelid(s) droop.	
	(Circle One)
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5