Original Article

Color vision versus pattern visual evoked potentials in the assessment of subclinical optic pathway involvement in multiple sclerosis

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Background: Optic pathway involvement in multiple sclerosis is frequently the initial sign in the disease process. In most clinical applications, pattern visual evoked potential (PVEP) is used in the assessment of optic pathway involvement. **Objective:** To question the value of PVEP against color vision assessment in the diagnosis of subclinical optic pathway involvement. **Materials and Methods:** This prospective, cross-sectional study included 20 multiple sclerosis patients without a history of optic neuritis, and 20 healthy control subjects. Farnsworth-Munsell (FM) 100-Hue testing and PVEPs to 60-min arc and 15-min arc checks by using Roland-Consult RetiScan® system were performed. P_{100} amplitude, P_{100} latency in PVEP and total error scores (TES) in FM 100-Hue test were assessed. **Results:** Expanded Disability Status Scale score and the time from diagnosis were 2.21 ± 2.53 (ranging from 0 to 7) and 4.1 ± 4.4 years. MS group showed significantly delayed P_{100} latency for both checks ($P < 0.001$). Similarly, MS patients had significantly increased total error scores (TES) in FM-100 Hue ($P < 0.001$). The correlations between TESs and PVEP amplitudes / latencies were insignificant for both checks ($P > 0.05$ for all). 14 MS patients (70%) had an increased TESs in FM-100 Hue, 11 (55%) MS patients had delayed P_{100} latency and 9 (45%) had reduced P_{100} amplitude. The areas under the ROC curves were 0.944 for FM-100 Hue test, 0.753 for P_{100} latency, and 0.173 for P_{100} amplitude. **Conclusions:** Color vision testing seems to be more sensitive than PVEP in detecting subclinical visual pathway involvement in MS.

Key words: Color vision, farnsworth-munsell 100 hue test, multiple sclerosis, pattern visual evoked potentials

Multiple sclerosis (MS) is an autoimmune-mediated neurodegenerative disease with characteristic inflammatory demyelination in the central nervous system.[1,2] Most patients present with a relapsing-remitting pattern of acute neurological dysfunction, with variable periods of remission punctuated by new exacerbations.

MS is often associated with involvement of the visual pathway that can lead to clinically evident manifestations, such as optic neuritis (ON), nystagmus, and diplopia, and to more frequent subclinical manifestations.[3] Psychophysical contrast evaluations and visual evoked potential (VEP) studies are preferred methods in evaluation of visual dysfunctions in patients with MS without history of ON.[4,5] The pattern visual evoked potential testing (PVEP) has also been shown to be more sensitive than contrast sensitivity at detecting hidden visual loss in patients with MS with 20/20 vision and without history of optic neuritis.[5]

Besides PVEP and contrast sensitivity abnormalities, a marked independent reduction (uncorrelated damage of retinocortical pathways) in color discrimination is frequently found along with other manifestations of optic nerve dysfunctions in MS patients.[6] In the majority of cases, visual function including color vision gradually improves as the patient recovers. Colors look 'washed out', and this symptom can be enhanced by fatigue or a rise in body temperature.

In this study, we aimed to determine the value of color vision testing in detecting subclinical optic pathway involvement in MS patients besides PVEP testing, which is a routinely used test in most clinical settings for this purpose.

Materials and Methods

Participants

20 patients with diagnosis of definite MS who had best corrected Snellen acuity of at least 20/20 in both eyes, no ocular history of optic nerve involvement, and minimum follow-up of 3 years were enrolled in this study. The research followed the tenets of the declaration of Helsinki. An informed consent was obtained from the subjects after explanation and possible consequences of the study. The research was approved by the institutional review board. The patients were under the care of the neurologist (SD) and had been in remission for at least 6 months before enrollment. The Expanded Disability Status Scale (EDSS) has been recorded during each visit to determine an extent of neurological disability. Patients with reversible disability of < 6 months duration and/or having any kind of visual complaint in the past and during the follow-up period were excluded. The patients were specifically asked for visual complaints including vision blur, visual loss, diplopia, periorbital pain, and color vision/contrast sensitivity disturbances (change in seeing traffic lights or in the brightness of colors in one or both eyes) throughout their life period at initial examination, and during the follow-up exams. Only the right eyes of participants were included in evaluations in order

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not to violate statistical independence. All the patients had undergone a thorough ophthalmologic examination, including tests for ocular misalignment by one of the investigators (FCG) before color vision and PVEP examinations.

20 age- and sex-matched healthy subjects without any known ophthalmic and systemic disease (including diabetes and systemic hypertension) comprised the control group.

Pattern visual evoked potential recordings

The PVEP recordings were performed using Roland-Consult RetiScan® system (Wiesbaden, Germany) on the basis of ISCEV (International Society for Clinical Electrophysiology of Vision) standards. In accordance with ISCEV clinical protocol,[7] monocular PVEPs (right eyes were selected in both groups) were recorded with gold disc surface electrodes. Active electrodes were placed on the scalp over the visual cortex at Oz with the reference electrode at Fz. The ground electrode was placed on the forehead. Refractions of the subjects were corrected with trial lenses before the recordings. Each subject sat in a moderately-lighted room, 1 meter in front of a 20 cm × 30 cm black-and-white video display monitor. The checkerboard stimulus subtended a visual angle of 5.7° vertically and 8.5° horizontally on either side of the fixation. Luminance was < 1 cd/m² for the black hexagons and 115 cd/m² for the white hexagons (contrast: 99%). The responses to a large (60-min arc) and a small check (15-min arc) were recorded. Background light was dimmed (approximately 20 cd/m²). The reversal rate was 1 per second. The responses to 100 stimuli were averaged. Subjects were instructed to fixate on a red marker at the center of the screen. If the cooperation of the subject was poor, the PVEP recording was repeated. Fixation stability, eye movements, and prolonged closing of the eye were monitored closely by an experienced electrophysiology technician throughout the entire testing period.

Color vision testing

Farnsworth Munsell 100 (FM-100) Hue test was used to score color vision abnormality. This test is performed using 85 color plates of equal saturation; each plate is subdivided into 4 boxes containing, respectively, plates with shadings of red, green, blue, and yellow. The examiner shows each box of plates separately. The plates are distributed randomly on the desk. The subject has to reorganize them according to progressive chromatic tonality (i.e. from red to green to blue and to yellow). An error score is calculated for each plate as the absolute value of the difference between the individual plate number and the number of the exact place for that plate. The total error score is calculated as the sum of the single scores for each of the 85 plates.

A computer software was used to determine the total error scores. Fig. 1 shows FM-100 Hue test result of a patient with an optic neuropathy.

Statistical analysis

The data are reported as mean value ± 1 SD (standard deviation). The differences between control and MS patients were statistically evaluated with Mann-Whitney U test. Spearman correlation coefficient was adopted to assess whether a correlation exists between the variables. The statistical analyzes were performed with the SPSS 15.0 software (Statistical Package for the Social Sciences; SPSS, Chicago, Ill). A P value of < 0.05 was considered statistically significant.

Results

Mean age was 34.2 ± 9.4 years (median: 32.5, ranging 21 to 52 years) and 33.2 ± 6.4 years (median: 34, ranging 23 to 44 years) in the study and the control groups. Female to male ratio was 11:9 in both groups. 19 patients (95%) had relapsing remitting (RR) and 1 patient (5%) had secondary progressive disease. Mean disease duration was 4.1 ± 4.4 years (ranging 1 to 21 years). Mean EDSS score was 2.21 ± 2.53 (range 0 to 7).

MS patients had significantly delayed P_{100} latencies for both checks [Table 1]. With respect to 95% confidence interval limit in control subjects, 11 MS patients (55%) had delayed P_{100} latency [Fig. 2a].

MS patients had reduced P_{100} amplitudes [Table 2] for only 2-min check. With respect to 5% confidence interval limit in control subjects, 9 MS patients (45%) had reduced P_{100} amplitudes [Fig. 2b].
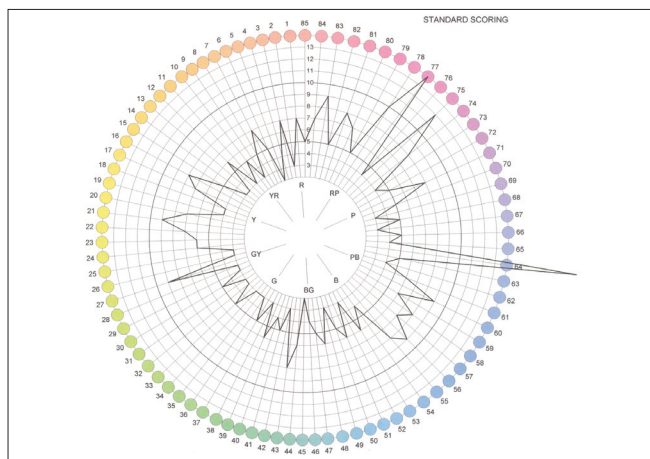
Compared to control subjects, MS patients had significantly

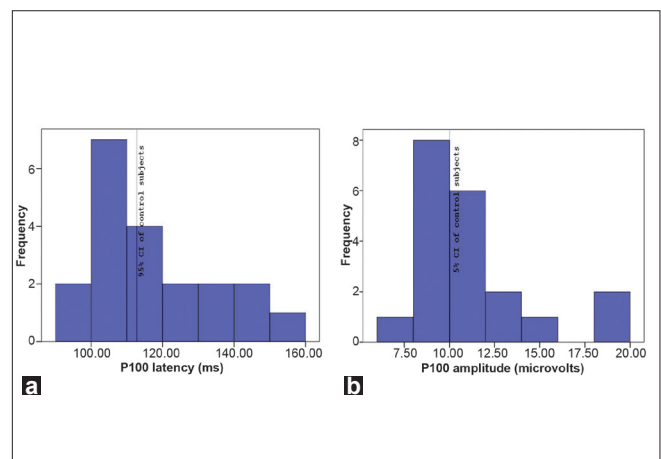**Figure 1:** Farnsworth-Munsell 100 Hue test result of a patient with optic neuritis

Figure 2: P_{100} latency (a) and amplitude (b) histograms of patients. Vertical lines represent the 95% (a) and 5% (b) confidence interval limits of the control group

Table 1: P_{100} latencies in multiple sclerosis patients and control subjects

Check size	P_{100} latency (ms)		
	Multiple sclerosis	Control	P
2°	117.0 ± 19.1	102.3 ± 4.8	0.006
15′	135.0 ± 25.7	108.8 ± 7.3	0.001

Table 2: P_{100} amplitudes in multiple sclerosis patients and control subjects

Check size	P_{100} amplitude (μV)		
	Multiple sclerosis	Control	P
2°	13.2 ± 3.4	16.1 ± 5.3	0.001
15′	12.5 ± 7.0	13.9 ± 7.1	0.512

Figure 3: Farnsworth-Munsell 100-Hue results of the groups a. (b) shows the histogram of FM-100 Hue test result of patients

higher total error scores in Farnsworth-Munsell 100-Hue test [Fig. 3a]. With respect to 95% confidence interval limit in control subjects, 14 MS patients (70%) had increased total error scores [Fig. 3b].

In diagnosing multiple sclerosis, areas under the ROC curve were 0.944 for FM-100 Hue test, 0.753 for P_{100} latency, and 0.173 for P_{100} amplitude [Fig. 4].

The correlations between P_{100} amplitude/latency and TES in FM-100 Hue test were both insignificant [Fig. 5a, b].

Discussion

Identifying subclinical disease activity in MS patients is far from straightforward. Visual dysfunction may occur up to 80% of patients with MS during the course of their disease and is a presenting feature in 50%.[8-10] An acute idiopathic demyelinating ON is frequently an initial clinical manifestation of the disease.[10] Most MS patients presenting with ON have a relapsing-remitting disease, whereby visual acuity recovers following resolution of acute inflammation. The patient population in this study mostly composed of relapsing-remitting disease and had no history of optic neuritis.

Halliday was first to describe delayed PVEPs in carefully examined MS patients who have never suffered ON.[11] Supporting the findings in the literature, 11 of 20 (55%) MS patients in this study had a P_{100} latency delay with respect to 95% confidence interval value of the control subjects. Frohman *et al.*[10] also found reduced P_{100} amplitudes and delayed P_{100} latencies for both 60-min arc checks and 15-min arc checks in MSwON (MS with optic neuritis) eye when compared to contralateral and control eyes. We, in this study, found delayed P_{100} latency for both checks in MSwoON (MS without optic neuritis eye). Similar findings have been reported previously.[12-14]

The FM-100 Hue test is one of the most-widely used clinical tests of acquired defects of color vision. It is reported to be one of the most useful clinical tests of acquired color vision defect in optic nerve disease, and more particularly optic neuritis.[15,16] An easy assessment and cost-effectiveness of FM-100 Hue test makes it a favorable test in diagnosing
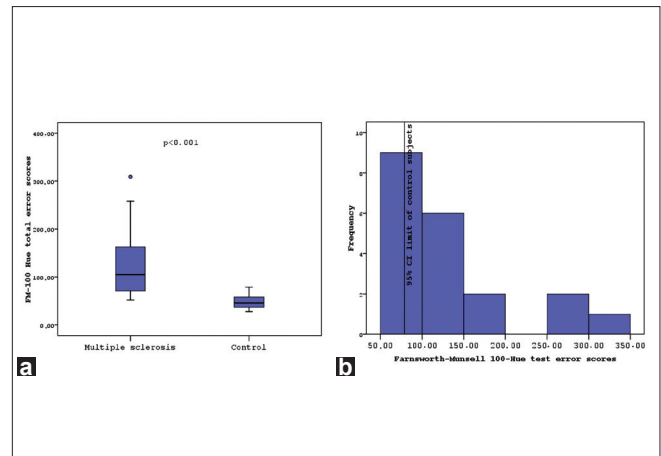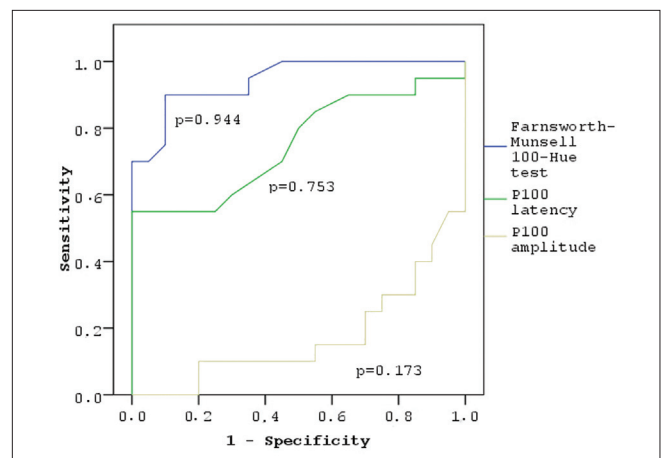
Figure 4: ROC curves of P_{100} latency, P_{100} amplitude and Farnsworth-Munsell 100-Hue tests in detecting subclinical optic pathway involvement in multiple sclerosis
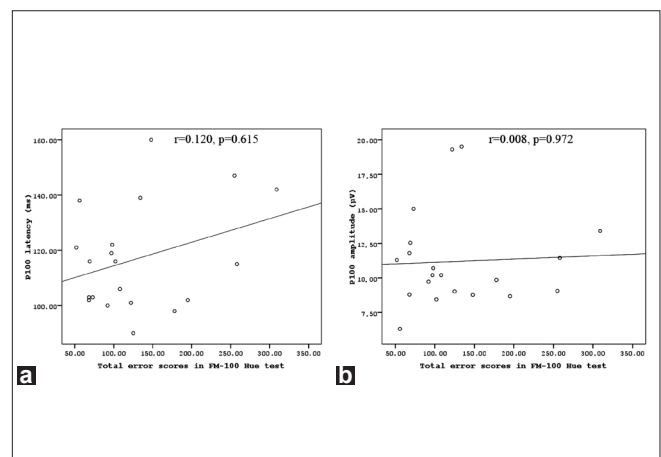
Figure 5: The correlations of P_{100} latency/amplitude a, b to the total error score in Farnsworth-Munsell 100-Hue test

optic pathway diseases. In this study, we showed that 14 of 20 patients (70%) had abnormal color discrimination while 11 (55%) had delayed P_{100} latency and only 9 (45%) had reduced P_{100} amplitude. These findings show that FM-100 Hue color vision testing should preferably be used instead of PVEP for detecting optic pathway involvement in MS patients. In a recent study, we also showed that PVEP testing is superior to OCT-assessed temporal retinal nerve fiber layer thickness for the same purpose.[17] In that study,[17] we found that 53.8% (21 over 39) had delayed P_{100} latency, however, only 30.8% (12 over 39) patients had abnormally thin temporal retinal nerve fiber layer thickness. Abnormally thin retinal nerve fiber layer is the result of anterior optic pathway involvement by means of retrograde axonal degeneration. In addition, possibly, long-duration and intensive anterior optic pathway involvement are required to result in structural changes in the retina. However, functional deficits such as, P_{100} latency delays and amplitude reductions may be a result of even mild involvements in any part of the optic pathway as it explores the function of visual cortex. For this reason, PVEP, a functional test, is more severely and frequently affected than OCT-assessed retinal nerve fiber layer thickness in MS patients. As a result of previous and present studies, we can order the values of the tests for detecting subclinical optic pathway involvement as FM-100 Hue assessed color vision discrimination, PVEP, and OCT-assessed retinal nerve fiber layer thickness analysis.

In this study, we included only the patients who did not report any visual complaint and had visual acuity of 20/20 during the follow-ups. Insignificant correlations between P_{100} latency/amplitude and total error are possibly related to the residual damage that the inflammation causes. There may be a subclinical optic pathway involvement, and this may cause P_{100} delay and amplitude reduction, and color vision impairment. After a period when the inflammation resolves, abnormalities in PVEP normalize frequently. However, this does not mean the resolution of the damage. The damage during each inflammation possibly leaves residual color vision abnormalities. This is probably the reason for the insignificant correlations between PVEP and FM-100 Hue test results. However, the small number of the patients included in this study requires further studies with larger series to explore this correlation better.

In conclusion, this study showed that FM-100 Hue color vision testing is superior to PVEP in detecting subclinical optic pathway involvement in MS patients. Easy assessment and cheapness of this test besides PVEP makes this conclusion valuable in neuro-ophthalmology practice.

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