Original article

Color blindness among multiple sclerosis patients in Isfahan

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Background: Multiple sclerosis (MS) is a disease of young and middle aged individuals with a demyelinative axonal damage nature in central nervous system that causes various signs and symptoms. As color vision needs normal function of optic nerve and macula, it is proposed that MS can alter it via influencing optic nerve. In this survey, we evaluated color vision abnormalities and its relationship with history of optic neuritis and abnormal visual evoked potentials (VEPs) among MS patients.

Materials and Methods: The case group was included of clinically definitive MS patients and the same number of normal population was enrolled as the control group. Color vision of all the participants was evaluated by Ishihara test and then visual evoked potential (VEPs) and history of optic neuritis (ON) was assessed among them. Then, frequency of color blindness was compared between the case and the control group. Finally, color blinded patients were compared to those with the history of ON and abnormal VEPs.

Results: 63 MS patients and the same number of normal populations were enrolled in this study. 12 patients had color blindness based on the Ishihara test; only 3 of them were among the control group, which showed a significant different between the two groups ($P = 0.013$). There was a significant relationship between the color blindness and abnormal VEP ($R = 0.53$, $P = 0.023$) but not for the color blindness and ON ($P = 0.67$). **Conclusions:** This study demonstrates a significant correlation between color blindness and multiple sclerosis including ones with abnormal prolonged VEP latencies. Therefore, in individuals with acquired color vision impairment, an evaluation for potentially serious underlying diseases like MS is essential.

Key words: Multiple sclerosis, color blindness, VEP, Ishihara test, optic neuritis

BACKGROUND

Multiple sclerosis (MS) is more common among the young and middle aged individuals.[1,2] The prevalence of MS in Isfahan is 73.3 per 100,000 people, nowadays, and it had an increase in the recent 5 years.[3,4] MS patients have various presentations such as loss of sensation, ataxia, loss of bowel and sexual function and neuro-ophthalmologic disturbances on basis of the site of plaque formation in central nervous system (CNS).[1] Majority of ophthalmologic signs and symptoms are initial presentations of MS, such as loss of visual acuity and diminished color vision.[1] Red-green color vision damage is the most reported color vision defects among the MS patients.[5] In Isfahan province, the most common initial manifestations of MS were sensory and visual impairments that highlight their importance, but unfortunately, the type of visual deficits was not clear.[3]

In most patients, an early distinguish of visual abnormalities can cause MS diagnosis in early stages of the disease.[1,6,7] It is well established that MS is associated with reduced high-contrast visual acuity (VA), color vision, contrast sensitivity (CS), and visual fields. It is commonly reported that MS preferentially damages red-green color vision, but more recent reports suggest that this is not the case.[5] There are various instruments for visual examination such as Ishihara for testing color vision abnormalities, especially red-green color one, that "is based on an ability to see patterns in a series of pseudoisochromatic multi-colored charts".[8,9]

Since MS prevalence has been increased in Isfahan in recent years,[4] we assessed the frequency of color vision blindness in MS patients and compared it with normal control population, in order to find an additional supplementary way to diagnose this disease more quickly in subjects with visual complaints. In addition, we evaluated the relationship between abnormal prolonged VEPs and those with

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the history of optic neuritis with color blindness in MS patients.

MATERIALS AND METHODS

Selection of participants

Our cross-sectional, case-control study was performed on 63 clinically definite MS patients and 63 normal control populations from March 2010 to February 2011 in the Kashani neurology clinic, Isfahan, Iran. Based on the last version of the Declaration of Helsinki, the research was approved ethically, and all participants were informed of our study and the testimonial was gained. MS patients were chosen on the basis of McDonald diagnostic criteria[10] by a neurologist randomly, and then the EDSS (Expanded Disability Severity Scale) was calculated for them. They were in remission. No participant was affected by any general disease other than MS. The control group were selected from the Kashani hospital staffs that matched on age in proportion of 1:1 to the case group. Anyone with the history of congenital color vision blindness, old retinopathy, non-MS related optic neuritis, history of drug consumption that might cause optic nerve damage or any history of eye trauma were not included into the study. All participants had a visual acuity of at least 20/200 in both eyes at the beginning of the study or best acuity score (measured as 20/X) one can achieve with glasses. All participants underwent full ophthalmic examination, including best-corrected visual acuity (BCVA) measurement and fundus examination after pupil dilation by an ophthalmologist. General information such as age, sex and general medical and ophthalmic history was gathered by a questionnaire.

Evaluation of participants

Ishihara plates were used for this study, because it is a simple, accessible, and feasible method for evaluating color vision. [11] According to the response to Ishihara test, participants were divided into normal and impaired color vision and then the frequency of the color blindness was compared between the case and the control group. Visual evoked potentials (VEPs), as see below, were carried out only on MS patients and the relationship between abnormal VEPs and color blindness were calculated. Also, the frequency of having the history of an acute or sub-acute vision loss, lasting more than 1 day, associated with pain on eye globe movements that defined as optic neuritis (ON), was calculated. Then optic neuritis patients were compared with color blind patients and those with abnormal VEPs in the case group. In all the included patients with history of ON, at least 1 month interval between the visual evaluation and the last episode of ON was considered.

Ishihara plate test

The test was made of a number of colored plates, called Ishihara plates; each of them contained a circle of dots, appearing randomized in color and size. The plates were made-up of a combination of primary and secondary color dots, that primary colors were arranged in simple patterns, usually as a number, and secondary one were as background. The healthy person must be able to read primary patterns correctly.[8]

All individuals were invited to seat at a distance of 1 meter from the plates, at daylight light intensity. Plates were read by the participants in order to be instructed, and anybody who read 2 or more of plates wrong were classified as impaired color vision.[12]

Visual evoked potentials

Patients were asked to look at the center of a black and white checkerboard with a distance of 1 meter, that its patterns were reversed frequently. The response to these changes was recorded by electrodes on the occipital scalp as a P100 peak in each eye, then the latency and amplitude of the P100 was measured separately.[1,13,14] The resulting waveforms included the C1 and P1 followed by the visual N1.[15] Visual evoked potentials (VEP) instrument that we used was from Negar Andishegan Co. Axon 4000s. VEP latency is more important than its amplitude in diagnosis of demyelinative disorders; therefore, we considered a P100 latency lasting more than 118 ms as abnormal.

Statistical analysis

Comparisons between proportions were undertaken using Chi-square test. We used the SPSS software version 16.0 for the statistical analysis, and the results with a level of $P < 0.05$ were considered statistically significant.

RESULTS

On the basis of McDonald's criteria, 13 males (21%) and 50 females (79%) with the mean age of 31.73 ± 8.54 years were included into the study. Out of the 63 participants of the control group, 27 (43%) and 36 (57%) were males and females, respectively with an average age of 32.75 ± 11.53 years. The EDSS was calculated between 0 and 7 with the mean of 1.5 ± 1.3 in the patients. There was no significant correlation between the EDSS of patients and the color blindness ($P > 0.05$). None of the cases were dropped out during the study. 12 patients (19%) had color blindness diagnosed by Ishihara test, but there was only 3 patients (5%) in the control group with unclear reason; this showed that there was a significant correlation between the color blindness and the MS disease ($P = 0.013$). 6 males and 28 females had abnormal response to VEPs but 7 males and 22 females had normal VEPs latencies. 10 color blindness persons had abnormal prolonged VEP latencies but only 2 of them had normal response that showed a significant relationship between the abnormal VEPs and the color

blindness (R =0.53, P = 0.023). 44 patients (6 males and 38 females) had history of ON and 19 patients (7 males and 12 females) did not. From whom with ON, 9 patients had the color blindness and 32 patients had abnormal response to the VEPs [Tables 1 and 2]. There was a significant correlation between the abnormal VEPs and ON (P < 0.001), whereas, it is not true for the color blindness and ON (P = 0.67).

Table 1: Comparison between optic neuritis and response to VEPs in MS patients

	History of optic neuritis			
	Positive	Negative	Total	*P* value
Response to VEPs				
Normal	12	17	29	***P*** < 0.001
Abnormal	32	2	34	
Total	44	19	63	

VEP: Visual evoked potentials; MS: Multiple sclerosis

Table 2: Comparison between optic neuritis and color blindness in MS patients

	History of optic neuritis			
	Positive	Negative	Total	*P* value
Color Blindness				
Yes	9	3	12	***P*** = 0.67
No	35	16	51	
Total	44	19	63	

MS: Multiple sclerosis

DISCUSSION

The present study was designed to evaluate the frequency of color blindness in MS patients in contrast to normal population, moreover, the correlation between the history of ON, impaired VEPs and the color blindness was assessed in MS patients too. According to the results, the frequency of color blindness was more in multiple sclerosis patients than in normal control group. In addition, the history of ON was more common in patients with abnormal prolonged VEPs than those with the color blindness.

The Ishihara Color Test is a test for red-green color deficiencies. While the full test consists of 38 plates, testing the first 24 plates gives a more accurate diagnosis of the severity of the color vision defect.[16] In our study, we found a relationship between the color vision deficit and an increased VEP latency.

Visual evoked potentials (VEPs) are caused by sensory stimulation of a subject's visual field. VEPs is a suitable tool for diagnosis of ON cases with equivocal clinical presentations.[17] Visual evoked potentials are very useful in detecting the blindness in patients that cannot communicate, such as babies or animals. Other applications include the diagnosis of optic neuritis, which causes the signal to be delayed. Such a delay is also a classic finding in multiple sclerosis. Visual evoked potentials is furthermore used in the investigation of basic functions of visual perception. Sometimes, VEPs is used to determine if someone is fraudulently alleging blindness.[18,19]

According to our study, a patient with history of deficits in color vision in addition to abnormal delayed VEPs, may be potentially a manifestation of multiple sclerosis disease, and complementary clinical and para-clinical work up is warranted.

Visual dysfunction is frequent and often irreversible. Afferent peregeniculate visual pathways (retina, optic nerves, chiasm, and tracts) are targets of inflammation, demyelination, and axonal degeneration. About 65% of the MS patients had a history of ON during their illness and it is known as the most common cause of vision loss among them.[20,21] As described before, ON usually presents with monocular, acute painful vision loss.[16] It is the heralding event in 15%-20% of patients. However, patients without a clinical history of ON also exhibit poor visual function, including worse scores on low-contrast acuity and color-sensitivity testing, when compared with age-matched controls.[7,22] It is well recognized that ON can lead to color-vision deficits, although the exact nature of this loss is unclear. It is consistent with an observation of Köllner that optic nerve disease leads to a preferential loss of red-green color vision.[23] Some reports have found this type of defect to be predominant in ON.[24,25] Others suggested that, blue-yellow defects is a more common color blindness type, or both type of color deficits are equally affected.[26] Travis and Thompson used the red-green (Rayleigh equation) and green-blue (Engelkin-Trendelenburg equation) Pickford-Nicolson anomaloscope in 18 patients with presumed ON and found mixed patterns of loss.[27] A review of findings from the optic neuritis treatment trial also found variable loss of color vision, although selective blue-yellow loss was more common in an acute phase; red-green loss was more common after 6 months.[28]

But, in our study, we found no relationship between ON and color blindness, and it is maybe due to our limited sample size or because only red-green color deficit was measured with Ishihara test in this study. In this study, no unusual or unexpected safety risks were found with VEP and Ishihara plate tests, and patients' compliance within the intervention was good.

CONCLUSIONS

In conclusion, the data further supports the correlation between the color-vision deficit and multiple sclerosis (with or without history of optic neuritis). This study suggests that physicians should carefully weigh the clinical and

para-clinical findings in people with color blindness, and if there is any doubt in diagnosis, we suggest complementary tests for the diagnosis of multiple sclerosis.

LIMITATIONS

The study had some limitations including small sample size for separating analysis of multiple sclerosis patients into 2 groups, with or without history of optic neuritis. Moreover, electrodiagnostic tests (except VEP in case group), neuroimaging, and formal perimetry were not taken in this study. Therefore, we recommend that future studies consider these limitations and consider larger MS population with different clinical courses, with or without history of optic neuritis.

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Authors Contributions

Vahid Shaygannejad designed and supervised the research. Khodayar Golabchi wrote the main part of the article. The ophthalmologic procedure was done by Alireza Dehghani. Fereshteh Ashtari and Majid Ghasemi surveyed and reviewed the manuscript. Sepehr Haghighi helped in editing, and Mahsa Mirzendehdel gathered the data. All authors have read and approved the content of the manuscript.

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