

# Visual Evoked Potentials, Short Wave-Length Automated Perimetry, Standard Automated Perimetry, Contrast Sensitivity and Stereoacuity Testing in Visually Asymptomatic Eyes of Patients with Multiple Sclerosis

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## Abstract

**Purpose:** To evaluate the efficacy of pattern visual evoked potentials (PVEP), standard automated perimetry (SAP), short-wavelength automated perimetry (SWAP), contrast sensitivity (CS), stereoacuity testing in detecting subclinical visual impairment in visually asymptomatic patients with multiple sclerosis (MS) and no history of optic neuritis

**Methods:** Twenty-seven eyes of 27 patients (7 males, 20 females, average age 33.81±9.33 years) with confirmed diagnosis of MS, underwent PVEP with 60-minute arc and 15-minute arc check sizes, SAP (Humphrey 750-II, program central 30-2, SITA standard strategy), SWAP (Humphrey 750-II, program central 30-2 full-threshold strategy), CS with CSV1000E chart, Stereoacuity by the Randot stereoacuity (RSA) test. They were age and sex matched with twenty seven healthy volunteers as a control group.

**Results:** Stereoacuity score was significantly reduced in MS group compared with controls (p=0.007). P100 latency time for both 60-minute arc and 15-minute arc was significantly prolonged in MS group compared with controls (p=0.005, p=0.002 respectively). P100 amplitude for both check sizes significantly reduced in MS group compared with controls (p<0.001). When comparing MS patients with the control group significant differences were found for SAP mean deviation (MD), SWAP MD, SAP pattern standard deviation (PSD), SWAP PSD (p<0.001). By considering predefined criteria, asymptomatic MS patients have shown abnormal stereoacuity in 22.2%, abnormal VEP in 40.7%, abnormal CS in 37%, abnormal SAP in 44% and abnormal SWAP in 37% of patients.

**Conclusion:** Our results showed the probable presence of subclinical visual impairment among MS patients without optic neuritis history and no visual symptoms. This emphasizes the importance of the follow-up programs, even in asymptomatic patients with MS. Comparison of multiple tests could help in better understanding of silent visual impairment. However, performing VEP and perimetry test together are useful choices in the regular assessment of these patients.

**Keywords:** Short-Wavelength Automated Perimetry, Standard Automated Perimetry, Stereoacuity, Pattern Visual Evoked Potentials, Multiple Sclerosis

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## Introduction

Multiple sclerosis (MS) as an inflammatory demyelination disease in the central nervous system, is often associated with involvement of the visual pathway.<sup>1,2</sup> It would be costly<sup>3</sup> and leading cause of disability,<sup>4</sup> specially in young adult population. Visual pathway involvement including both afferent and efferent pathways in MS disease can lead to either clinically evident or subclinical manifestations. Various manifestations of ocular involvement include optic neuritis, ocular motor deficit, ocular inflammatory diseases. Even patients without clinical evidence of optic neuritis, and having normal visual acuities (VAs) may show visual dysfunction.<sup>4</sup> Subtle visual impairment in asymptomatic eyes of MS patients could be better detected by psychophysical tests such as low-contrast letter acuity charts.<sup>5,6</sup> Structural tests, also, like optical coherence tomography (OCT) as a newer technology, has shown axonal loss in MS patients without a history of optic neuritis.<sup>7</sup>

Evidence of postural instability and falling among MS patients, has been attributed to reduced binocular depth perception.<sup>8</sup> Randot stereoacuity (RSA) testing has been shown as an effective marker of subclinical disease activity in visually asymptomatic MS patients.<sup>9</sup> Visual field examination has an important role in monitoring progression and recurrence of the disease and standard automated perimetry (SAP), is utilized as a choice in neuro-ophthalmic practice.<sup>10</sup> However there are few reports about using short-wavelength automated perimetry (SWAP) in MS.<sup>11-13</sup> This technique is mostly utilized in glaucoma studies.<sup>14</sup> SWAP with its relatively selective function<sup>15</sup> may be more sensitive than conventional perimetry in detecting scotoma.<sup>16</sup>

Performing multiple tests has been reported to be useful for diagnosing visual pathway involvement in the visually asymptomatic MS patients, without history of optic neuritis.<sup>17</sup> However, there is little agreement about which examination is most sensitive. The aim of this study was to evaluate the efficacy of pattern visual evoked potentials (PVEP), SAP, SWAP, CS, stereoacuity tests in detecting subclinical visual impairment in a population of MS patients without history of optic neuritis and no visual symptoms.

## Methods

Twenty-seven eyes of 27 patients (20 females, seven males) with a confirmed diagnosis of MS according to the revised McDonald Criteria<sup>18</sup> were recruited at the Department of Neurology of Mashhad University of Medical Sciences. All patients had relapsing-remitting MS course and they had been in remission for at least six months before study. They were being treated with interferons (IFN  $\beta$ ). The patients were referred to Khatam-al-Anbia Eye Hospital, for complete ophthalmic examination. All patients were with  $20/20$  Snellen acuity in both eyes and without any ocular history of optic neuritis or visual symptoms (diplopia, color vision disturbances, blurred vision). Slit-lamp, tonometry, fundus examination and testing of color vision by Ishihara plates and relative afferent papillary defect (RAPD) test, were normal in all participants. They were age-matched and sex-matched with twenty-seven healthy subjects as a control group. There was no systemic disease in both groups and no neuro-ophthalmologic pathologies other than MS in patients group. Subjects with spherical ametropia >3 diopters or astigmatism >2 diopters were excluded. Our control samples have been chosen from medical students, and nurses of Khatam-al-Anbia Eye Hospital who have participated in our study voluntarily.

### **Randot stereoacuity testing**

RSA testing (RSA, Stereo Optical CO, Chicago, IL) was used at 40 cm, with polarized glasses over the best corrections of participants. The 10 circular disparate areas range from 20 to 400 seconds of arc was used. The confidence interval (CI) of 95% of control group was considered as abnormal RSA values.

### **Pattern visual evoked potentials recording**

PVEP recordings were performed by RETI-scan system (Roland Consult, Wiesbaden, Germany). According to International Society for Clinical Electrophysiology of Vision (ISCEV) standards, the PVEPs were recorded with a gold disc surface electrode placed at Oz and the reference electrode at the Fz with the ground electrode at the Cz. Participants had worn their appropriate corrections and monocular responses were recorded. Contrast of the checkerboard pattern stimulus was

97%. The checks were in two sizes, 15-minute arc and 60-minute arc. The reversal rate was 3/s and the observational distance from the monitor was 1 m. The responses to one hundred stimuli were averaged and banded-pass filtered was at 1-50 Hz. Limits of normal values were obtained by adding 2 SD to the mean latency values of 60-minute arc stimuli of control subjects.

### **CSV-1000E**

Evaluation of contrast sensitivity (CS) was performed by CSV-1000E Chart. This chart evaluates CS for each special frequency at 3, 6, 12, 18 cyc/deg. The participants were instructed to choose which patch of the pair contained the grating (top or bottom patch). Abnormal CS was the values of CS at least in one special frequency, which falling outside the gray area delimiting the normal range on the specific chart.<sup>17</sup>

### **Visual fields testing**

SAP and SWAP were performed with the same perimeter, Humphrey Field Analyzer (750 II HFA, Dublin, CA.) and the same program (central 30-2 threshold test). We utilized the Swedish interactive threshold algorithm (SITA) standard strategy for SAP and full threshold strategy for SWAP technique.

Both techniques were repeated twice with a 30 minute rest. The results of second examination were taken into consideration if reliability indices (fixation losses, false positives, and false negatives) were less than 25%. An abnormal visual field was considered according to an abnormal cluster defined as at least there were three abnormal points at the  $p < 0.05$  level or two adjacent points with one abnormal at the  $p < 0.01$  level for both SAP and SWAP techniques.<sup>12</sup>

### **Statistical analysis**

For statistical analyses, Student's *t* test or statistical non-parametric approaches was used. Correlations were utilized, where appropriate. Analyses were performed with the SPSS 11.5. Values of  $p < 0.05$  was considered statistically significant. To prevent potential intra individual clustering, created by the inclusion of both eyes of a subject in the analyses, the results of the right eye of each subject were considered in statistical analyses.

The study strictly adhered to the Tents of Declaration of Helsinki and the protocol was approved by the Ethical Committee of Mashhad University of Medical Sciences.

## **Results**

The mean age for both study groups was  $33.81 \pm 9.33$  years (range, 19-59 years). Disease duration was  $4.33 \pm 3.05$  years (range, 1-10 years). There was significant difference in RSA values between MS and control group ( $28.70 \pm 7.15$  arc seconds;  $23.70 \pm 3.56$  arc seconds, respectively,  $p = 0.007$  Mann-Whitney test). With respect to 95% CI level of the RSA values in control group (30 second of arc), 6 of 27 patients (22.2%), had reduced RSA score. There was no significant relation between disease duration and RSA values (Pearson test,  $r = 0.12$ ,  $p = 0.53$ ).

P100 latency time was significantly prolonged for both 60' and 15' checkerboard stimuli sizes in patients group comparing with controls ( $p = 0.005$ ,  $p = 0.002$  respectively, *t* test, Table 1). P100 amplitude was also significantly reduced for both check sizes in patients group in comparison with controls ( $p < 0.001$ , *t* test, Table 1). However, the results showed more reduction in amplitude and more delayed in latency time for the smaller check size in patients group ( $p < 0.01$ ,  $p < 0.001$ , respectively, paired *t* test). According to the predefined normal limits, 11 of 27 patients (40.7%) have shown delayed latency time.

Mean log CS was reduced significantly only at 6 cyc/deg in patients group compared with controls ( $p = 0.01$  Mann-Whitney test). Mean and SD log CS of each spatial frequency was summarized in Table 2. The abnormality rate at 3, 6, 12, 18 cycle/deg was 7.4%, 11.1%, 14.8%, 22.2%, respectively. CS was abnormal for at least one special frequency in 10 of 27 patients (37%).

When comparing MS patients and the control group significant differences were found for SAP mean deviation (MD), SWAP MD, SAP pattern standard deviation (PSD), SWAP PSD ( $p < 0.001$ ) (Table 3). Significant correlation was found between SAP MD and SWAP MD in patients group ( $p < 0.001$ , Pearson correlation, Figure 1). A significant correlation was also found between SAP PSD and SWAP PSD in patients group ( $p = 0.01$ , Spearman's rank test, Figure 1).

**Table 1.** P100 Latency time and amplitude results in two groups

| Parameters groups | 60° Latency (ms) | 15° Latency (ms) | 60° Amplitude (µv) | 15° Amplitude (µv) |
|-------------------|------------------|------------------|--------------------|--------------------|
| MS group          | 112.70±14.22     | 120.22±14.44     | 6.71±1.78          | 5.98±1.61          |
| Control group     | 103.62±7.49      | 110±8.00         | 9.18±1.98          | 9.04±1.71          |
| P*                | 0.005            | 0.002            | <0.001             | <0.001             |

Data are indicated in mean±SD  
\*: t test, MS: Multiple sclerosis

**Table 2.** Mean log CS of 3, 6, 12, 18 cyc/deg in multiple sclerosis and control groups

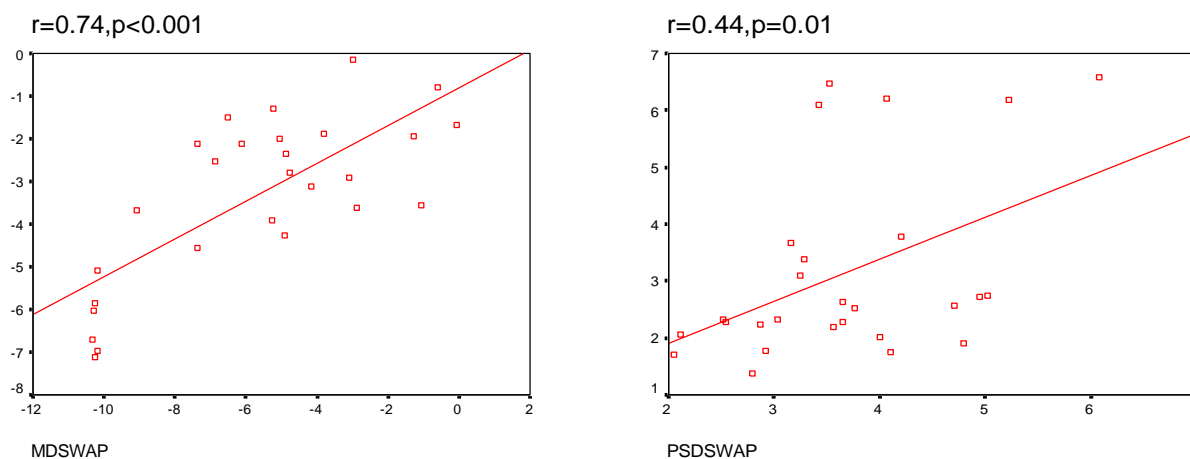
|               | MS group  | Control group | p     |
|---------------|-----------|---------------|-------|
| CS 3cyc/deg   | 1.82±0.18 | 1.85±0.10     | 0.42  |
| CS 6cyc/deg   | 1.94±0.17 | 2.05±0.15     | 0.01  |
| CS 12cyc/deg  | 1.63±0.26 | 1.67±0.17     | 0.76* |
| CS 18 cyc/deg | 1.19±0.22 | 1.23±0.25     | 0.45  |

MS: Multiple sclerosis, CS: Contrast sensitivity  
Data are indicated in mean±SD log CS.  
\*: t test

**Table 3.** Mean (SD) of mean deviation and pattern standard deviation values obtained with the two perimetric techniques in each of the two groups (t test)

| Parameters groups | MD (SAP)   | PSD (SAP) | MD (SWAP)  | PSD (SWAP) |
|-------------------|------------|-----------|------------|------------|
| MS group          | -3.35±1.92 | 3.14±1.63 | -5.73±3.24 | 3.67±0.99  |
| Control group     | -1.15±0.71 | 1.71±0.25 | -2.16±0.99 | 2.60±0.42  |
| P*                | <0.001     | <0.001*   | <0.001     | <0.001     |

MS: Multiple sclerosis, MD: Mean deviation, PSD: Pattern standard deviation, SAP: Standard automated perimetry, SWAP: Short-wavelength automated perimetry  
\*: Mann-Whitney U test, Data are dB



**Figure 1.** Correlations between mean deviation and pattern standard deviation of standard automated perimetry with the corresponding indices of short-wavelength automated perimetry in patients with multiple sclerosis

However there were no significant correlations for the MD and PSD of SAP with the corresponding indices of SWAP in control group ( $p=0.29$ ,  $p=0.35$ , respectively). With respect to the predefined criteria, abnormal SAP and SWAP has been found in 12 (44.4%) and 10 (37%) of 27 patients, respectively.

When the results of both SAP and PVEP tests were taken into consideration, 62.96% of patients were abnormal at least in one test. When we considered the abnormal results of all tests including PVEP, SAP, SWAP, CS and stereoacuity, 85.18% of patients had at least one abnormal test result.

## Discussion

This study evaluated PVEP, SAP, SWAP, CS and stereoacuity testing in the visually asymptomatic MS patients, without a history of optic neuritis in comparison with a control group. Most of the MS patients with acute optic neuritis report pain with eye movements, color disturbance, decreasing in vision and CS and visual field defects but even in unaffected eyes of MS patients and without ocular symptoms subclinical manifestation of optic neuropathy has been shown in several studies.<sup>9,13,17,23</sup> Results of our study showed that RSA score in patients group was significantly reduced in comparison with controls and the test detected abnormalities in 22.2% of patients. Sobaci et al,<sup>9</sup> reported the same results with more abnormality rate of RSA testing in patients in comparison with our study. One possibility is that, in contrast to their study, all of the patients in our study had relapsing-remitting (RR) course of MS. Sobaci et al attributed the higher rate of RSA abnormality due to the "alterations in interactions between higher-order neurons".<sup>9,19,20</sup> Although, whether retinal or optic nerve diseases would have considerable impact on depth of perception still needs more studies.<sup>21</sup> In the present study in just three cases we found abnormal results. This indicates that further studies on stereoacuity testing, on a larger sample of asymptomatic MS patients, are needed.

The findings of the PVEP in our study indicated that, the mean amplitude of P100 was reduced and the mean latency time in MS patients was prolonged in comparison with the control group. This confirms the results of the previous studies.<sup>9,23</sup> We have considered

increased latency time and decreased amplitude, representatives of demyelination process and axonal damage respectively.<sup>23</sup> In this regard, underlying pathology among MS patients even in the absence of optic neuritis is evident. It is more detectable by using smaller check size stimuli (15-minute arc). Reis et al examined 44 MS patients with or without history of optic neuritis. They found independent damage in all retinocortical pathways only in patients without history of optic neuritis. They suggested the important role of amplitude changes for axonal changes in these patients prior to optic neuritis.<sup>23</sup> This emphasizes the importance of repeated PVEP recordings in these patients during the follow-up.<sup>24</sup> According to our study, abnormal PVEPs were found in 40.7% of MS patients. There are many studies that report abnormal PVEPs in MS patients.<sup>24,25</sup> Halliday et al first reported 93% delayed responses in MS patients without a history of optic neuritis.<sup>26</sup> Mizota et al studied PVEP with 30' check size in 29 Japanese patients with MS. They found prolonged latency of the transient PVEP in 31% of MS patients and this lower rate finding of PVEPs abnormality in comparison with western countries was attributed, to the "racial differences, and use of different criteria for diagnosing optic neuritis".<sup>27</sup> That might be partly the cause of the low abnormal rate of PVEP which is detected in our study.

Our results show SAP was slightly more sensitive than SWAP. These different findings by the two techniques could be attributed to the various functions of them.<sup>12</sup> SWAP as a non-conventional perimetric technique, utilizes a 440 nm 1.8 band target at 200 msec duration on a bright 100 cd/m<sup>2</sup> yellow background stimulate blue-yellow ganglion cells.<sup>15</sup> It can therefore isolate a subgroup of retinal ganglion cells (RGC), the small, bistratified, blue-yellow cells which represents approximately 9% of the total number of the ganglion cells.<sup>16</sup> These RGCs in the koniocellular pathway have intermediate spatial and temporal resolution along the blue-yellow color axis. SWAP has been introduced as a clinical tool for early glaucoma diagnosis. It has been shown that the SWAP techniques could detect glaucoma visual defects 3-5 years earlier than SAP (white-on-white).<sup>16</sup> Therefore by considering the similarity between MS with optic neuritis and

glaucoma in their structural and functional aspects, it is logical to evaluate the MS patients with SWAP techniques.<sup>13,31</sup> On the other hand, SAP by using a small (0.47 degree) white flash (200 msec) on a dim white background (31.5 asb), acts as a nonselective test which can stimulate all retinal ganglion cell types.

According to our study SWAP MD and SWAP PSD had significantly lower scores in patients group than corresponding indices in control group. There are few studies about using SWAP in MS patients. These studies reported the efficacy of SWAP in evaluation of these patients.<sup>11-13</sup> In a more recent study by Kitsos et al, they examined 56 MS patients with and without optic neuritis by white on white perimetry, SWAP and OCT. The lower scores found in perimetry and OCT techniques in MS patients without optic neuritis, have been attributed to "subclinical episode of optic neuritis or to retrograde degeneration of nerve cells from subclinical postchiasmal lesions".<sup>13</sup> They found SWAP as an effective technique over conventional perimetry in evaluation of visual function of these patients.<sup>13</sup>

In the present study, SAP was slightly more sensitive than VEP which confirms the previous studies.<sup>28,29</sup> Therefore it confirms the importance of regular follow-up examination of visual field in the evaluation of visual pathway lesions in MS patients.<sup>10</sup>

Our findings show CS slightly less sensitive than PVEP in detecting hidden visual loss in asymptomatic MS patients which supports the previous reports.<sup>30,32</sup> They reported abnormalities in 90.9% of their patients by combination use of both VEP and CS tests. In the previous report by the author, Cambridge Low Contrast Grating test has been shown as an effective tool for detecting subclinical visual dysfunction in younger patients with MS.<sup>22</sup> The fact that CS is not significantly different in MS eyes (except in six cyc/deg), possibly due to the lack of history of optic neuritis or any visual complaints in our patients sample. In agreement to Sisto et al study,<sup>17</sup> in their smaller sample of patients, our study has shown abnormal involvement of CS at higher spatial frequencies.

In the present study, no single test could detect all of the visual involvement in our sample. This is possibly due to different

factors like, lack of a specific affected cellular type or visual function involved.<sup>17</sup> By considering the results of all tests, 85.18% of patients had at least one abnormal test result. Corallo et al evaluated 15 patients with MS by VEP, SWAP, conventional perimetry and frequency-doubling technology. They found 93.7% of abnormality by using all techniques and they emphasized the view that neurophysiologic and psychophysical tests complete each other and are not directly comparable.<sup>12</sup> This shows the importance of using multiple tests in the assessment of MS patients without optic neuritis.<sup>17</sup> Perimetry test as a psychophysical test could be affected by various factors like fatigue, lack of attention.<sup>12</sup> However VEP with its objective entity is rather preferred choice and by performing both tests in the asymptomatic patients we are able to detect and follow the functional silent damages to the visual pathways.

Unstudied left eye, and using different strategies between two perimetry techniques limit the strength of this study. Also, SWAP test could be affected by a number of factors including ocular media scattering, longer testing time followed by fatigue and loss of attention. On the other hand perimetric studies were performed by the same perimetrist who was masked about the study and the patients having no cataract or other abnormalities and the examinations not being performed in undesirable conditions which could possibly enhance the validity of the results were the positive points in our study. Further studies are required to assess the diagnostic performance of SITA-version of SWAP in MS patients. Also the study of stereoacuity testing with a larger sample of MS patients who are asymptomatic with normal acuity is recommended.

## Conclusion

Our results concluded the probable presence of subclinical visual impairment among MS patients without the history of optic neuritis and no visual symptoms. This emphasizes the importance of follow-up programs even in asymptomatic patients with MS. Comparison of multiple tests can help in a better understanding of silent visual impairment. However performing VEP and Perimetry test together are useful choices in the regular assessment of these patients.

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