Original Article

Influence of multiple sclerosis, age and degree of disability, in the position of the contrast sensitivity curve peak

A F Nunes[1], P M L Monteiro[1], M Vaz Pato[2]

Context: Contrast sensitivity (CS) function is one of the most important tests available for evaluating visual impairment. Multiple sclerosis (MS) can produce highly selective losses in visual function and psychophysical studies have demonstrated CS deficits for some spatial frequencies. **Aims:** This work studies the differences in CS between a group of controls and a group of MS patients, focusing on the location of the maximum sensitivity peak, shape of the curve, and determination of the most affected spatial frequencies. **Materials and Methods:** Using a sinusoidal stimulus the authors assessed CS function in 28 subjects with definitive relapsing remitting MS, and in 50 controls with acuities of 20/25 or better. The peaks of the CS curves were studied by fitting third degree polynomials to individual sets of data. **Results:** Compared with the control group, the CS function curve for MS subjects showed more deficits in extreme points (low- and high-spatial frequencies). Our results display significant CS losses, at the high-frequencies band level, in the beginning of the disease. When the disease progresses and the disabilities appear, there are greater losses at the low-frequencies band level. In average, the CS curve peaks for the MS group were shifted in relation to the control group. **Conclusions:** CS losses in the MS group suggest an association with ageing and disability level in the expanded disability status scale. The position of the CS function peak is influenced by MS, age, and degree of disability.

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Visual symptoms are common in patients with multiple sclerosis (MS), even when their visual acuity measured on the Snellen scale and other conventional clinical visual tests are within normal limits.[1]

Visual dysfunction occurs in 80% of patients with MS during the course of their disease, and is a presenting feature in 50%.[1] Despite the importance of visual dysfunction to disability and quality of life in MS, the quantitative assessment of vision in MS clinical trials has been traditionally limited to Snellen acuity.[2,3] Contrast sensitivity (CS) in MS has been investigated by several authors over the years and is, in general recognized as a useful tool in the evaluation of these patients.[4-8] However, given the multiplicity and lack of uniformity of tests and procedures performed, it is difficult to identify and analyze the total range of the changes of CS function in this group of patients.

The aim of this work is to study the differences in CS between a group of controls and a group of MS patients, focusing on the location of the maximum sensitivity peak, shape of the curve, and determination of the most affected spatial frequencies, using a psychophysical method and a sinusoidal grating stimulus. By comparing our methodology with previous ones, we hope to achieve a clearer view of CS function in MS patients, and establish the basis of a fast clinical protocol for routine evaluation of these patients.

[1]Department of Physics, University of Beira Interior, Remote Sensing Unit, [2]Department of Medical Sciences, University of Beira Interior, CICS - Health Sciences Research Centre, Neurologist in Hospital Sousa Martins, Guarda – Portugal

Correspondence to: Prof. Amélia F. Nunes, Department of Physics, University of Beira Interior, 6200 Covilhã, Portugal. E-mail: amnunes@ubi.pt

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Materials and Methods

Subjects

This study was approved by the Ethics Committee of Hospital Centre, and complied with the tenets of the Declaration of Helsinki. All participants gave their informed consent.

The study group consisted of 28 subjects, 5 men, and 23 women (mean age 37.8 years ± 8.58 years; mean disease duration 4.19 years ± 2.71 years), with relapsing-remitting clinically definitive MS.[9] with asymptomatic visual loss and a degree of disability in the expanded disability status scale (EDSS) ≤five. The Kurtzke EDSS, was used to characterize the state and progress of each MS patient. This method is based on the status of eight functional systems including visual. The scale varies from zero, corresponding to a normal neurological examination, to ten, corresponding to death by the disease. Patients with EDSS ≥5, present impairment to ambulation.[10] At the time of the visual evaluation all participants were in the remission period of the disease, at least 3 months after the last acute attack. Nine patients had a history of one or more unilateral acute optic neuritis (ON) and the affected eyes were excluded from the study. The control group consisted of 50 subjects, nine men and 41 women (mean age 37.6 years ± 8.0 years), tested just for the right eye. The study compared the performance of 46 responses from the MS group with that from 50 responses healthy subjects.

All volunteers, patients and controls, were subjected to a selected group of vision tests, which included pupil diameter measurement; visual acuity (with and without pinhole), Amsler gratings, and monocular direct ophthalmoscopy. Exclusion criteria for both groups were pupil diameters outside the range of three to five mm, best corrected visual acuity on the Snellen charts below 20/25, spherical refractive errors greater than ± 6.00 D or 2.50 D astigmatism, defective color vision and

changes in central vision with Amsler gratings, similar to those used by other researchers.[11-13] The control group was matched closely to the MS group in terms of age, best corrected visual acuity, and gender.

All MS subjects were selected from the Neurology Department in Hospital Center and the controls were randomly selected from the same region, with age and gender distributions similar to the MS group.

Psychophysical procedures

CS was measured at 5 m distance and with sinusoidal grating stimuli (vertical, oblique 14° to the right and 14° left of the vertical orientations) for 5 different spatial frequencies, expressed in cycles per degree (1.5 cpd; 3 cpd; 6 cpd; 12 cpd and 20 cpd). The stimuli were generated on a monochromatic video monitor and controlled by a microcomputer (the Mentor II B-VAT-SG video acuity tester with sinusoidal gratings). The screen was calibrated with the monitor calibration system optical RS232 by Cambridge Research Systems, using the calibration screen, and protocol suggested by the B-VAT manufacturers. The calibration screen consisted on a black square in a white background. The calibration procedure involved placing the optical sensor in the black square and adjusting the monitor brightness to obtain a specified luminance. The procedure was then repeated for the white screen area adjusting the monitor contrast. The psychophysical method used was based on a forced choice of three orientation alternatives, vertical, leaning to the right or left, and the contrast measured using a triple reversal staircase, as described by Corwin *et al*.[14]

The CS test was performed monocular beginning with the right eye. Spatial frequencies were evaluated from the lower to the upper range. The visual stimulus was presented at random orientation, starting at a high level of contrast (defined by the system) and decreased in steps of 0.1 log unit percentage of contrast (PC) (0.1 log PC), until the subject no longer recognized the orientation of the stimulus. At this point, the system recovered the contrast, equivalent to 0.2 log PC, and repeated the decrease until the stimulus was no longer detected. This last sequence was repeated to another non-detection point. The minimum contrast threshold (CT), for a given spatial frequency, is the average contrast percentage of the three stimuli presented previously to the non-detection points. The value of CS was then calculated by the reciprocal of the threshold contrast (equation 1). To avoid logarithmic units with negative value, that value was multiplied by 100, resulting in the following equation:

$$CS = \frac{100}{CT} \qquad 1$$

Data analysis

Data were treated statistically with the SPSS 19.0 software, applying the analysis of variance (One-Way ANOVA) (this is sufficiently robust to violations of normality for large samples [n >30]) and homogeneity of variance when the number of observations in each group was approximately equal. When these situations were not fulfilled, an alternative to this analysis was the non-parametric Kruskal-Wallis test. To study CS variability and possible interactions of several factors, a Multivariate ANOVA (General Linear Model) was applied. Linear correlation between variables was analyzed using Pearson correlation test for normal distribution variables and Spearman correlation test, when the normality criterion was not met.

Curve fitting to data points, applied a linear least squares method using software Curve Fitting Tool Box 2.2 in MATLAB (Matrix Laboratory) Version 7.10.0.499. A third degree polynomial function provided the best fit to data points in a logarithmical scale, in the Form:

$$CSF\ (\omega) = a\omega^3 + b\omega^2 + c\omega + d$$

Where the contrast sensitivity function (CSF) (ω) is the CS function, expressed in log units, ω is the spatial frequency expressed in (log cpd), and the parameters a, b, c and d are the polynomial coefficients.

Results

CS function

The average CS results for each of the five spatial frequencies assessed for the two groups of eyes (control and MS) are shown in Table 1. CS was decreased for the majority of spatial frequencies in patients with MS, with extreme frequencies being more compromised than middle frequencies.

ANOVA between the two groups (controls and MS), showed significant differences for all spatial frequencies, except for 3 cpd [Table 2]. For the analyzed spatial frequencies, the maximum mean CS for MS subjects was observed at 3 cpd, and in the control group was observed at 6 cpd. This observation suggests a difference in the function peak positions.

Third degree polynomial curves (equation 2) were fitted and their peaks determined for individual data in each group. R^2 values for individual data fitting presented a mean of 0.992 with an SD of ± 0.013. For each subject, the function peak was determined by the point where the 1st derivative changed sign. The means of all subjects CSF peaks, for control and MS groups,

Table 1: Contrast sensitivity mean values and standard deviations (expressed in log units) for control and multiple sclerosis groups, differences between group means, mean of all subjects contrast sensitivity function peak positions for each group, and peak displacement between groups

Variable	Group	Mean±Standard deviation	Differences
1.5 cpd	Control	2.003±0.131	0.074
	MS	1.929±0.130	
3.0 cpd	Control	2.283±0.138	–0.001
	MS	2.284±0.186	
6.0 cpd	Control	2.318±0.168	0.087
	MS	2.231±0.228	
12.0 cpd	Control	1.852±0.213	0.178
	MS	1.674±0.284	
20.0 cpd	Control	1.276±0.260	0.281
	MS	0.995±0.401	
Mean peak (y-axis)	Control	2.352±0.149	0.017
	MS	2.335±0.194	
Mean peak (x-axis)	Control	4.254±0.803 (cpd)	0.329 (cpd)
	MS	3.925±0.7331 (cpd)	

MS: Multiple sclerosis, cpd: Cycles per degree

are represented in Table 1. ANOVA showed a significant difference ($P < 0.05$) between the two group peaks along the x-axis [Table 2]. To visualize this tendency, third degree polynomial curves were fitted to CS means [Fig. 1] for control and MS groups. All spatial frequencies are expressed in (cpd), since this unit is more familiar to clinicians. However, data points in graphics and statistical treatment were performed in (log cpd) units.

Associations measures with CS in MS patients and control group

Associations between CS and several factors such as gender, time interval from the last acute attack, and duration of illness were not significant ($P > 0.05$). Association of CS with age and degree of disability in the EDSS scale was significant for one or more spatial frequencies ($P < 0.05$). Statistical results for Pearson correlations for these parameters (age and disability) are displayed in Table 2.

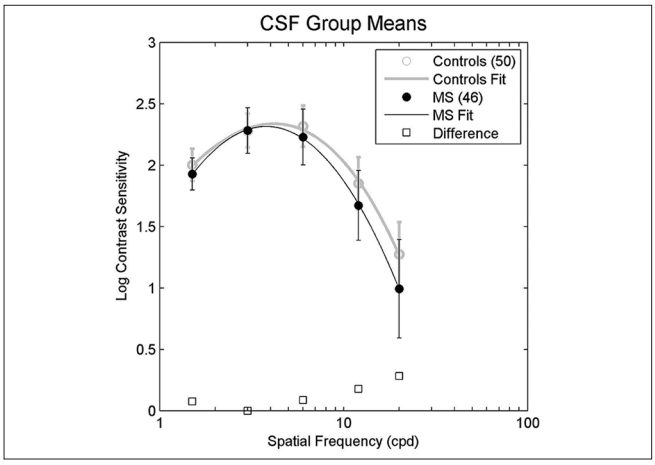

Figure 1: Contrast sensitivity function for control and multiple sclerosis groups. Mean values with standard deviation bars, differences between means, and best fit curves to mean values. Best fit curve for control means is CSF (ω) = −0.4995 ω^3 − 1.036 ω^2 + 1.856 ω + 1.706 with R^2 = 0.9974. Best fit curve for MS means is CSF (ω) = −0.09305 ω^3 − 2.303 ω^2 + 2.752 ω + 1.514 with R^2 = 0.9985

CS and age

Correlation between CS and age for the control group is significant ($P < 0.05$), at high spatial frequencies level (12 cpd and 20 cpd). For the MS group correlation with age is significant for all spatial frequencies. The correlation strength (Pearson coefficient R) is higher for the MS group when compared to the control group.

To perform ANOVA between CS and age effect, data from each group were divided into two subgroups: Young adults, from 25 years to 39 years of age ($n = 29$ eyes controls and $n = 26$ eyes MS), and middle age adults, from 40 years to 50 years of age (n = 21eyes controls and n = 20 eyes MS). ANOVA, between means of young, and middle age adults, shows no significant differences for the control group in all spatial frequencies ($P > 0.05$). However, in the MS group, differences between young, and middle age adults are statistically significant for all spatial frequencies [Table 2]. The mean curves for each subgroup illustrate these differences [Fig. 2].

Third degree polynomial curves (equation 2) were fitted and their peaks determined for individual data in each subgroup. ANOVA shows that the position of the function peak presents a significant difference between young and middle aged adults for the control group ($P < 0.05$), along the x-axis. For the MS group the position of the function peak presented a significant difference between young and middle aged adults ($P < 0.01$), along the y-axis. The means of all subjects CSF peaks, for control, and MS subgroups, grouped by age, are represented in Table 3.

CS and disability level (EDSS) In MS patients

MS group data were divided into two subgroups: Light disability, with EDSS ≤1.5 ($n = 26$ eyes) and moderate disability, with 2 ≤EDSS <5 ($n = 20$ eyes). Fig. 3 shows the mean CS curves grouped by level for disability. The correlation between CS and disability level (EDSS) was significant for low and intermediate spatial frequencies [Table 2]. However, this association was weak (correlation coefficient R below 0.5).

ANOVA for CS, according to disability level, showed significant differences between light and moderate disability

Table 2: Statistical analysis with *P* values and correlation coefficients

Statistical test	Groups and subgroups	Spatial frequencies (cpd)					Curve peak	
		1.5	3	6	12	20	X-axis	Y-axis
ANOVA one way	Control versus MS	0.007**	0.976	0.038*	0.005**[a]	0.000**	0.034*	0.625
	(Controls) Age	0.611	0.822	0.093	0.057	0.076	0.04*	0.309
General linear model	(MS) Age	0.003**	0.000**	0.000**	0.001**[a]	0.000**	0.605	0.000**
	(MS) Disability	0.000**	0.001**	0.000**	0.012*	0.055	0.275	0.000**
	Interaction age*disability	0.000**	0.007**	0.083	0.059	0.412	0.708	0.016*
Linear correlation	(Controls) Age R/P value	0.006/0.965	0.002/0.989	−0.120/0.405	−0.296/0.038*	−0.311/0.028**	−0.291/0.040*	−0.073/0.617
	(MS) Age R/P value	−0.403/0.005**	−0.527/0.000**	−0.580/0.000**	−0.404[b]/0.005**	−0.487/0.001**	−0.081/0.593	−0.556/0.000**
	(MS) Disability R/P value	−0.459/0.001**	−0.334/0.023*	−0.441/0.002**	−0.270/0.070	−0.192/0.211	−0.189/0.209	−0.398/0.006**

**Significant for 0.01,*Significant for 0.05, [a]Kruskal-Wallis test, [b]Spearman Correlation, R: Correlation coefficient, *P* value: Significant level, MS: Multiple sclerosis, cpd: Cycles per degree

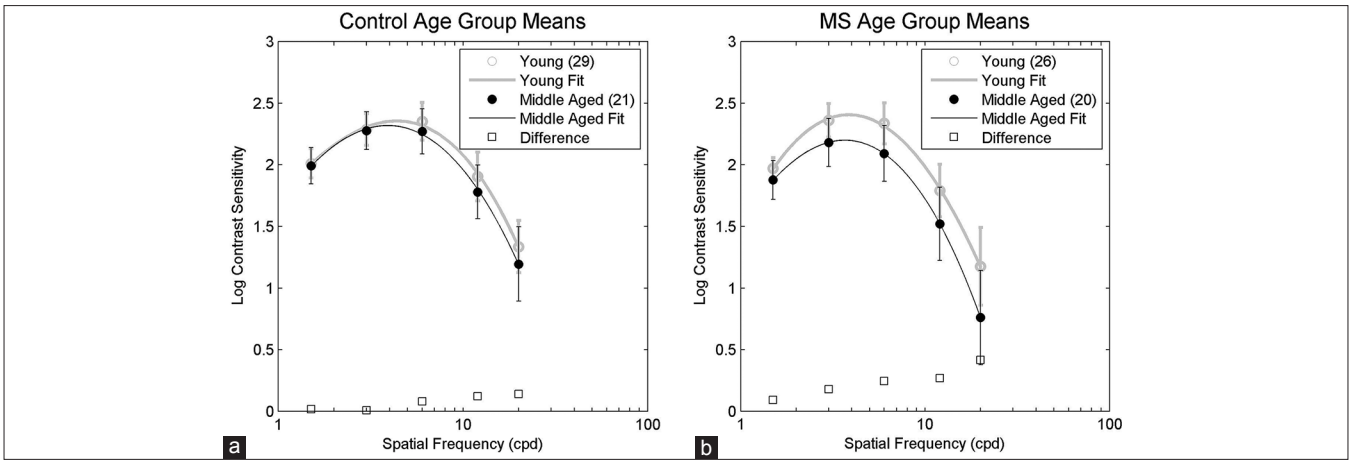

Figure 2: Contrast sensitivity function for control (a) and multiple sclerosis subjects (b) grouped by age. Mean values with standard deviation bars, differences between means, and best fit curves to mean values are presented

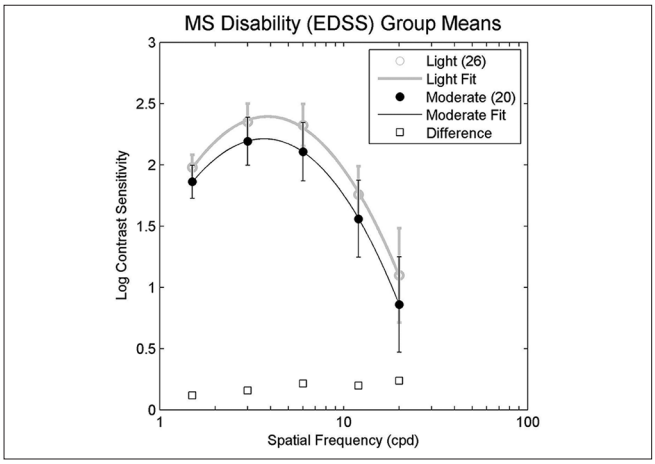

Figure 3: Contrast sensitivity function for multiple sclerosis patients, grouped by disability level in the expanded disability status scale. Mean values with standard deviation bars, differences between means, and best fit curves to mean values

subgroups, for all spatial frequencies [Table 2]. The mean curves for each subgroup illustrate these differences [Fig. 3].

Third degree polynomial curves (equation 2) were fitted and their peaks determined for individual data in each subgroup. ANOVA shows that the position of the function peak presents a significant difference between light and moderate level of disability ($P < 0.01$), along the y-axis. The mean of all subjects CSF peaks, for light, and moderate disability subgroups, are represented in Table 3.

Discussion

In our study, CS was decreased for the majority of spatial frequencies in patients with MS, with extreme frequencies being more compromised than middle frequencies except for 3 cpd, when compared with the control group, resulting in a shift along the x-axis towards the lower spatial frequencies. Associations between CS and several factors such as gender, time interval from the last acute attack, and duration of illness were not significant ($P > 0.05$) in the MS group of patients. However, in the MS group the association of CS with age

Table 3: Mean position co-ordinates and standard deviations (mean±SD) for all subjects contrast sensitivity function peaks in each subgroup

Subgroup	Mean peak (x-axis) (cpd)	Mean peak (y-axis) (log CS)
Age		
Control		
Young	4.459±0.894	2.370±0.139
Middle aged	3.972±0.563	2.327±0.160
MS		
Young	3.970±0.669	2.421±0.141
Middle aged	3.867±0.818	2.222±0.198
Disability level (MS)		
Light	4.022±0.661	2.411±0.154
Moderate	3.800±0.818	2.236±0.199

CS: Contrast sensitivity, MS: Multiple sclerosis, cpd: Cycles per degree

and degree of disability in the EDSS scale was significant for one or more spatial frequencies ($P < 0.05$). Age was by itself statistically correlated with CS in all frequencies in the MS group while only the higher frequencies were affected in the control group. The degree of disability, as a marker of the disease evolution showed significant differences in our study, for all the frequencies studied [Table 2].

MS is a demyelinating disease presenting, in the relapsing remitting form of our patients, with episodes of clinical signs and symptoms, However, also with a subclinical increase of demyelinating lesions that can produce dysfunction without visible signs, also in visual function.[1] In our study, there was a statistically significant difference in location for the CS curve peak towards lower frequencies in the MS group, when compared to the control group and this suggests that the evaluation of this function can be a useful tool for MS evaluation and following. This idea is also expressed by several authors, who refers to CS evaluation as the most sensitive technique for subclinical visual loss detection, when compared to other visual tests, such as color vision analysis and visual evoked potentials (VEP).[8,15,16] However, others suggest that this visual test is not useful for the evaluation of these subjects.[17] This

may occur because of a lack of uniformity between evaluation techniques and selection of the spatial frequencies band to be evaluated.

The majority of studies evaluates only a single spatial frequency, with 4 cpd being the most frequent one.[15,17,18] In clinical studies, where several spatial frequencies are evaluated, usually not enough frequencies are assessed for the trace of the complete CS curve. The most common case is the absence of a high-frequency or a low-frequency.[7,16] In studies where the complete function is assessed the protocols are not suitable for clinical evaluations, due to a long examination time,[4,5] or are applied in a darkened room.[7] In addition, the psychophysical method of adjustment, which was used in those studies, has been criticized due to low repeatability when compared to forced choice.[12] The present work complements available information either because the complete contrasts sensitivity function was assessed, but also because the protocol used is able to be used in a clinical setting, and it allows a better knowledge of subjects' visual behavior in terms of CS function.

In studies regarding change in CS in MS, where only the 4 cpd spatial frequency is evaluated, there is some controversy regarding its clinical value; while for some authors the reductions in CS are significant, others think the opposite.[7,17] These differences may be due to the use of 4 cpd, middle spatial frequency. Our results suggest that the band of middle frequencies is the one that presents less significant changes when compared to the control group [Fig. 1]. Furthermore, the study of the function peak through the adjusted function shows that although the difference between the maximal measured values to the control subjects and the MS group is statistically significant [Table 2], the difference between the average locations of the curve peak between groups is very small. This shows that in clinical terms the evaluation of CS with such low-frequency intervals may not be important due to the amount of time spent in the exercise.

To study the function peaks, we fitted to each eye data, the double exponential function suggested in previous CS studies parabolas, third and fourth degree polynomials, Gaussians, rational functions, and other functions.[19] The fourth degree polynomials always provided a perfect fit to each set of five data points. However, in many cases this function presented a waving behavior between two data points, which is not acceptable, hence, we tested other functions. The third degree polynomials presented the best R^2 values, when compared to other function types, and didn't display the waving behavior between data points.

There was a difference in location for the average CS curve peak position towards lower frequencies in the MS group, when compared to the control group [Fig. 1]. The curve peak study, showed a statistically significant ($P < 0.05$) difference between the two groups [Table 2], along the x-axis. However, this difference is small ($\Delta x = 0.329$ cpd). We believe that further studies should be done with a larger group of patients in order to confirm this data.

In the general population, it is accepted that above 40 years of age a slow decrease in CS function begins for intermediate and high-spatial frequencies, together with a shift of the curve peak towards low frequencies. These changes gradually increase and become significant above 60 years of age. Low-spatial frequencies are generally described as being less affected by age.[12,20,21] In our control group, there were slight, non-significant, losses in CS in subjects older than 40 years [Fig. 2a]. In the MS group, the decrease in CS was greater [Fig. 2b]. A possible explanation would be an early ageing of the MS subjects when compared to the general population. Other explanations cannot be ruled out, namely an increase of patient fatigue (frequent complaint of MS subjects when performing long tasks), which induces a poorer cooperation for the final part of the CS evaluation procedure (high- frequencies testing). This point deserves further and more detailed studies with a larger number of subjects in order to evaluate, which are the factors that contribute to the fact that the majority of MS patients presents a maximal sensitivity to contrasts at lower frequencies than it is observed in the control group. There was a difference in location for the average CS curve peak towards lower frequencies in the middle aged, when compared to the young subjects in the control group [Fig. 2a]. The curve peak study, showed a statistically significant ($P < 0.05$) difference between the two groups [Table 2], along the x-axis. However, this difference is small. There was a difference in location for the average CS curve peak in the middle aged, when compared to the young subjects in the MS group [Fig. 2b]. The curve peak study, showed a statistically significant ($P < 0.01$) difference ($\Delta y = 0.2$ log units) between the two groups, along the y-axis [Table 2].

Other factors also appeared to have an effect on CS change, such as the degree of disability, which have shown a significant linear association with CS test performance. However, these associations presented a weak linear correlation. We also observed that disease duration and time interval from the last acute attack does not seem to have a significant influence upon the decrease in CS.

The extent to which vision is affected by immune disorders/immunomodulatory therapies is not yet known and has been difficult to assess using traditional neurologic impairment scales such as the EDSS.[3,10] In spite of criticism related to the ability of the EDSS scale in visual function evaluation, our study shows that larger disability degrees (larger EDSS value) reflects more significant visual function losses than smaller or null disabilities [Fig. 3]. This confirms the importance of including a CS test when measuring disability induced by MS, as suggested by Balcer *et al*.[22,23] In agreement with other studies our data show larger losses, for low- and intermediate-spatial frequencies, associated with worsening of the disability degree [Fig. 3]. For MS subjects with light disability (EDSS ≤1.5) included in this study, CS function was affected at high-frequencies level.[5,7,23] This fact seems to suggest that the disease starts affecting CS for high-frequencies and, as it progresses, intermediate- and low-frequencies are also affected but at a larger scale**.** Losses at the high-frequencies band seem to indicate subclinical signs of neuronal deficits in the first years of MS. Losses for low-spatial frequencies and intermediate-low frequencies seem to be related to a greater degree of disability.

In respect to the curve profile, there was a difference in the average location for the CS peak in the moderate disability level, when compared to the light disability subjects in the MS group [Fig. 3]. The curve peak study, showed a statistically significant ($P < 0.01$) difference ($\Delta y = 0.17$ log units) between the two groups, along the y-axis [Table 2].

In conclusion, our study data shows that for early stage of the disease, CS evaluation for a single spatial frequency will be useful if a high-spatial frequency is used, since cases of a low-frequency evaluation only reveal losses when there is some disability degree measured in EDSS scale. However, visual acuity should be at least 20/25 for the resolution of a high-spatial frequency. If the visual acuity is lower but not <20/40, the 12 cpd spatial frequency is a better alternative, which also presents a significant difference in relation to the control group [Table 2].

CS evaluation in a low-spatial frequency (lesser than 2 cpd) seems to be more adequate for MS patients, except in the initial stage of the disease. When the patient shows no signs of disability or they are not significant, CS evaluation will be more appropriate for one high- spatial frequency (≥12 cpd). Our data show that MS subjects with low EDSS values (EDSS <1, 5), present CS losses only at the high frequencies band level. This applies to the relapsing remitting form of MS and further studies are needed for other forms of the disease rather than relapsing remitting.

Our data also showed a change in the CS curve profile, which seems to be associated to the disease evolution. In the beginning of the disease, the curve is affected at the high-frequencies band level. When the disease progresses the curve peak shifts vertically in the downward direction. CS function evaluation may be useful in the follow-up of MS patients, since it allows the evaluation of visual changes due to the ageing process (losses for high-and intermediate-spatial frequencies and curve peak shift) or an increase in disability (losses for all frequencies). However, it is important to perform other studies, applying the same methodology in other forms of MS, and evaluate the CS curve in more advanced stages of the disease.

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