Special Focus, Ocular Surface and Cornea, Original Article

Evaluation of corneal sensitivity in multiple sclerosis patients

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Purpose: To measure the corneal sensitivity in patients with multiple sclerosis (MS), to compare it with normal values and to study its correlation with different disease characteristics. **Methods:** Corneal sensitivity of 28 MS patients was compared to corneal sensitivity of 28 age- and gender-matched normal controls. Corneal sensitivity was measured using the Cochet-Bonnet esthesiometer and was correlated to the duration, type and severity indexes of the disease. **Results:** Corneal sensitivity was comparable between both groups (P = 0.79). No statistically significant correlation was found between corneal sensitivity and the duration of MS (P = 0.55) nor the severity indexes of MS (expanded disability status scale [EDSS] P = 0.52, global multiple sclerosis severity score [MSSS] P = 0.64). Following subgroup analysis, only the primary progressive (PPMS) form of MS had a reduced corneal sensitivity with P = 0.023, while remittent-recurrent (RRMS), secondary progressive (SPMS), and clinically isolated (CIS) forms of MS did not have any reduction in the corneal sensitivity. "ROC curve analysis" showed an area under the curve of 0.48. **Conclusion:** In the exception of PPMS subtype, MS patients have similar corneal sensitivity in comparison to controls. Cochet-Bonnet esthesiometer does not seem to be a good diagnostic tool or a disease severity marker for patients with MS.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_3052_20

Quick Response Code:

Key words: Cornea, corneal sensitivity, multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease resulting in multiple demyelination plaques in the central nervous system (CNS).[1,2] This condition is characterized by a variety of symptoms that differ according to the anatomical location of the demyelinating lesions.[1,2] Ocular disorders secondary to MS include optic neuritis and internuclear ophthalmoplegia.[3] Fifth cranial nerve involvement has also been described including trigeminal neuralgia, and more recently, sensory deficit of the cornea.[3] Örnek *et al*.[4] reported a decrease in corneal sensitivity in patients with MS using the Cochet-Bonnet esthesiometer. Prognosis of MS is variable and difficult to predict. An onset of disease after the age of 40 and a primary progressive subtype seem to be of bad prognosis but these factors are not enough to predict the evolution of MS.[5,6] Mikolajczak *et al*.[7] showed that corneal nerve density obtained by confocal microscopy is decreased in patients with MS. The reduction of corneal nerve density was correlated to the severity indexes of MS (expanded disability status scale [EDSS] and global multiple sclerosis severity score [MSSS]), but not to the duration of the disease. Therefore, they concluded that corneal nerve density obtained by confocal microscopy is a promising marker of the severity of MS.

The Cochet-Bonnet esthesiometer is a valid instrument used to measure the corneal sensitivity and remains the most frequently used esthesiometer in clinical trials.[8,9] The purpose of our study was to compare corneal sensitivity in MS subjects to corneal sensitivity in normal subjects and to study its correlation with the duration, subtype and severity of the disease.

Methods

This is a comparative case-control study including subjects with MS and comparable controls (age- and gender-matched subjects free from MS). Subjects were enrolled from patients who visited the neurology outpatient clinic between November 2016 and November 2018. Ethical approval for this study was obtained by the ethics committee and the study adhered to the tenets of the Declaration of Helsinki.

Population

MS was diagnosed according to the McDonald 2010 diagnostic criteria for MS. All subtypes (clinically isolated syndrome [CIS], relapsing-remitting subtype [RRMS], secondary progressive subtype [SPMS] and primary progressive subtype [PPMS]) of MS were included in the study.[10,11] When tested, all RRMS patients were in remission. Patient and disease information were collected from the patient's medical records. The severity of the disease was measured using the EDSS assigned by a neurologist and the MSSS that was calculated from EDSS and disease duration.[12-14]

For each MS patient tested, a control subject of same gender and age was selected from patients visiting the ophthalmology

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Received: 27-Sep-2020 Revision: 26-Jan-2021
Accepted: 30-Mar-2021 Published: 25-Aug-2021

Cite this article as: Sukkarieh G, Ghorayeb R, Issa M, Koussa S, Waked N. Evaluation of corneal sensitivity in multiple sclerosis patients. Indian J Ophthalmol 2021;69:2421-4.

outpatient clinic in the same hospital. Exclusion criteria for MS and control subjects included the presence of any eyelid abnormality, keratoconus, corneal dystrophy, atopic or herpetic keratoconjunctivitis, scleritis, blepharitis, past or present uveitis, glaucoma, use of non-steroidal anti-inflammatory, analgesic or anti-glaucomatous eye drops, contact lens use in the previous year, history of eye trauma or surgery; as well as the presence of any of the following systemic diseases: diabetes mellitus, Sjögren's disease, Basedow's disease, sarcoidosis and amyloidosis; or the recent use of one of the following systemic drug therapies: estrogen-containing pills, antidepressants, beta-blockers and diuretics.[15-22]

Measurement

The corneal sensitivity of MS patients and control subjects was determined using the Cochet-Bonnet esthesiometer (Western Ophthalmics, Lynnwood, WA) with a 0.08 mm monofilament diameter. Corneal sensitivity was determined bilaterally because MS causes CNS lesions that are disseminated in time and space; hence the same patient could have different corneal sensitivities in their two eyes. The Cochet-Bonnet esthesiometer test was done by the same blinded ophthalmologist after manifest refraction was determined and prior to slit lamp examination and drop instillation. The cornea was first tested with the esthesiometer filament set at 6 cm; the length of the filament was then sequentially reduced by 0.5 cm until the stimulus was felt and the filament length was recorded.

Prior to inclusion, all patients signed an informed consent after receiving information explaining the test procedure and the purpose of the study.

Statistical methods

Corneal sensitivity had a significant departure from normality assumptions; therefore, nonparametric tests were used in the statistical analysis. The Wilcoxon Signed Rank test was used to compare corneal sensitivity between right and left eyes of all the subjects. The Independent-Samples Median test was used to compare the corneal sensitivity of the MS group to that of the control group. The role of corneal sensitivity as a diagnostic tool in MS was studied using the ROC curve analysis. The Spearman's Rank Correlation Coefficient test was used to study the correlation of corneal sensitivity with the duration and the severity indexes of the disease. The Independent-Samples Kruskal-Wallis test was used to compare corneal sensitivity between subtypes of MS. A *P* value less than 0.05 was considered to be significant. All the tests were two-tailed. Statistical analysis was done using the IBM SPSS statistics v24 software (IBM corp., Armonk, NY).

Results

Fifty-six patients (112 eyes), 28 in each group were in the study. Characteristics of included patients are presented in Table 1. Corneal sensitivity was comparable between the right and left eye in the MS group, in the control group and in both groups combined with respective *P* values of 1, 0.08 and 0.10. Following this observation, all the statistical analysis was done using the mean corneal sensitivity of the two eyes as a reference value for each subject.

No statistically significant difference in corneal sensitivity was found between the MS group and the control group ($P = 0.79$) [Table 2].

The role of corneal sensitivity as a diagnostic tool in MS was studied using the ROC curve analysis [Fig. 1]. The ROC curve analysis showed that the statistical performance of corneal sensitivity as a diagnostic tool for MS is poor with an area under the curve of 0.48.

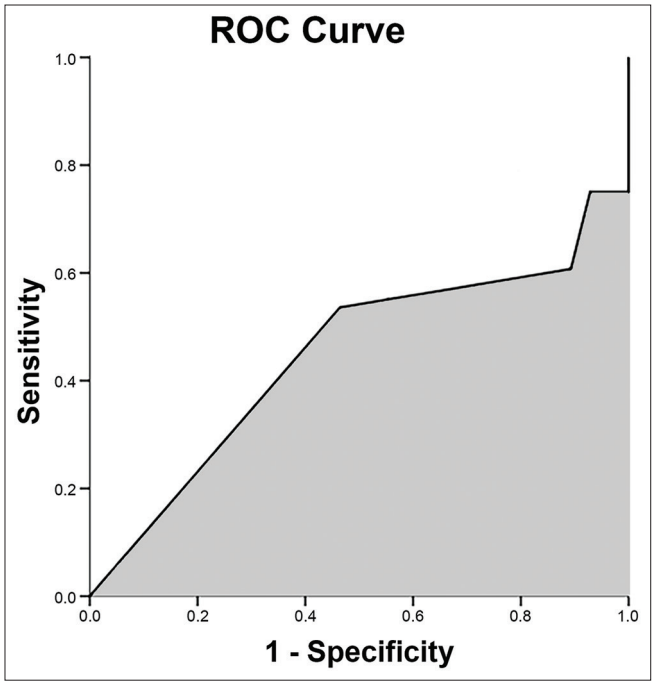

Figure 1: ROC curve showing the performance of corneal sensitivity as a diagnostic tool for multiple sclerosis

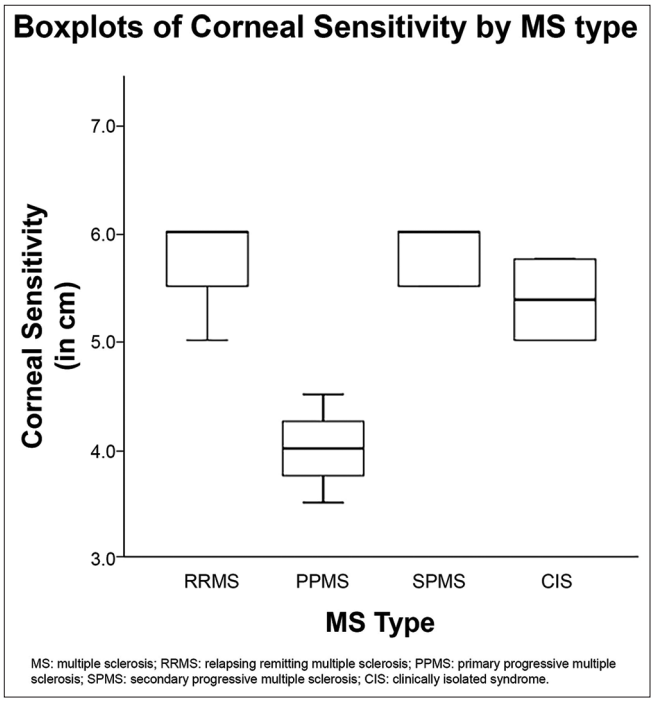

Figure 2: Graph showing comparison of corneal sensitivity between different subtypes of multiple sclerosis

Table 1: Characteristics and comparison of multiple sclerosis and control groups

Group	MS	Control
Number of subjects (number of eyes)	28 (56)	28 (56)
Age in years, mean (standard deviation)	40.61 (14.42)	40.61 (14.42)
Gender: Male (female)	26 (30)	26 (30)
Duration of MS in months: mean (standard deviation)	130.25 (98.60)	-
EDSS: median (interquartile range)	0 (5.3)	-
MSSS: median (interquartile range)	0.67 (4.87)	-
Disease subtype: Number of subjects (%)		
CIS	2 (7%)	-
RRMS	17 (61%)	
SPMS	6 (21%)	
PPMS	3 (11%)	

MS: Multiple sclerosis, EDSS: Expanded disability status scale, MSSS: Global multiple sclerosis severity score, CIS: Clinically isolated syndrome, RRMS: Relapsing-remitting subtype, SPMS: Secondary progressive subtype, PPMS: Primary progressive subtype

Table 2: Comparison of corneal sensitivity between multiple sclerosis (MS) and the control group

Group	MS	Control	*P*
Group size	28	28	-
Corneal sensitivity (cm): median (1st quartile - 3rd quartile)	6.0 (5.3-6.0)	5.8 (5.8-6.0)	0.79

MS: Multiple sclerosis

Table 3: Correlation of corneal sensitivity to the age of the patients, duration of the disease, EDSS score and MSSS score

MS patients	Age	Duration of the disease	EDSS	MSSS
Corneal sensitivity				
Spearman's rank correlation coefficient	–0.23	0.12	0.13	0.09
P	0.25	0.55	0.52	0.64

EDSS: Expanded disability status scale, MSSS: Global multiple sclerosis severity score

No correlation was found between the corneal sensitivity and the age ($P = 0.25$) of the patients, the duration of the disease ($P = 0.55$), the EDSS score ($P = 0.52$) and the MSSS score ($P = 0.64$) [Table 3]. Corneal sensitivity was reduced in the PPMS group with a median corneal sensitivity of 4 cm in comparison to the other subtypes of MS with medians of: 6 cm in RRMS and SPMS; and 5.5 cm in CIS ($P = 0.023$) [Fig. 2].

Discussion

The aim of the study was to evaluate corneal sensitivity of patients with MS, to correlate it to the duration, the severity and the subtype of the disease, and to evaluate its role as a marker of severity of the disease.

We found that corneal sensitivity is not significantly reduced in patients with MS. This is not in agreement with the study done by Örnek *et al*.[4] Since our study has a greater number of subjects and the statistical analysis we adopted is more valid (comparing the medians of the subgroups and not the means since the distribution of the corneal sensitivity in MS does not obey the normal law), we can say that our results are more representative of the reality.

We found no correlation between corneal sensitivity and age in the MS group. This is in disagreement with the result of the study of Mirzajan *et al*.[23] which has shown a decrease in corneal sensitivity with increasing age. In fact, there is probably a decrease in corneal sensitivity with age; however, our sample is too small to detect this difference.

We could not find a correlation between the decrease in corneal sensitivity and the severity of the disease (EDSS, MSSS) or the duration of the disease. These results are not in agreement with the study done by Mikolajczak *et al*.[7], which concluded that the importance of loss of nerve density of the cornea is proportional to the severity of MS. This disagreement can be explained by several facts. First, our results can be biased by a big number of subjects with an EDSS score of 0 (16 patients). To overcome this bias, our sample must be completed by recruiting more patients with a high EDSS score. Second, the Cochet-Bonnet esthesiometer allows a clinical and subjective measurement of corneal sensitivity while confocal microscopy gives an objective and anatomical measurement of the number of nerve endings. Hence, it is logical to consider that a reduction in the number of nerve endings of the cornea measured by confocal microscopy may exist without giving a decrease in corneal sensitivity that is important enough to be detected by the Cochet-Bonnet esthesiometer.

We found a decreased corneal sensitivity in the PPMS subtype of MS compared to the remaining subgroups. This finding is in agreement with the classification of MS in which the PPMS subtype has a worse prognosis and does not share the same physiopathology as the RRMS and SPMS subtypes. Hence, the reduced corneal sensitivity observed in the PPMS subtype could aid the neurologist to differentiate between PPMS and the rest of the subtypes of MS.

Limitations of this study include a small number of patients which affects the subgroup analysis and the fact that it is not prospective. Future works should focus on evaluating prospectively the evolution of corneal sensitivity in patients with PPMS because this will allow to assess the speed of deterioration of corneal sensitivity and the risk of neurotrophic keratopathy development. Another limitation in this study is that the nerve

endings' function was assessed using the Cochet-Bonnet esthesiometer but their anatomical integrity was not evaluated. This could have been done using a confocal microscope which was not available at the time the study was conducted.

Conclusion

In the study, it was found that patients with MS do not have a decreased corneal sensitivity compared to that of normal subjects with the exception of the subgroup with PPMS subtype of the disease. No correlation was found between corneal sensitivity and the duration or severity of the disease. Outside the PPMS subgroup of the disease, the use of the esthesiometer as a diagnostic tool and/or as a severity marker does not seem to be valid. Since corneal sensitivity is only decreased in the most severe subtype of MS, the PPMS subtype, further prospective studies including any PPMS subtype patient and only severe patients of other subtypes of MS should be done.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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