Original article

Functional relationship between retinal sensitivity threshold values assessed by standard automated perimetry in glaucoma

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ABSTRACT

Objective: To study the correlation between the sensitivity threshold values of the different points assessed by the Humphrey Visual Field Analyzer (24-2 Swedish interactive threshold algorithm [SITA] standard strategy) in glaucoma patients.

Subjects, material and methods: Prospective cross-sectional study. One-hundred and four eyes of 104 glaucoma patients, defined by the appearance of the optic nerve head, were evaluated. Retinal threshold sensitivity points of standard automated perimetry (SA) with SITA Standard 24-2 program were obtained. The upper and the lower hemifields were studied separately. Pearson correlation coefficients were calculated between the mean threshold sensitivity value at each point of the visual hemifield and the rest of the threshold points in the same hemifield.

Results: Perimetric correlation maps between retinal threshold sensitivity values in the same hemifield were obtained. Most of the points showed moderate to high correlations (r ≥ 0.65, p < 0.001) with neighboring points and distant points in the same hemifield.

Conclusions: There is a functional relationship between neighboring and distant points in Humphrey Visual Field Analyzer (SITA Standard 24-2) in glaucoma patients. This correlation is related to the anatomical arrangement of ganglion cell axons. This fact enables perimetric patterns of glaucoma defects to be obtained.

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Relación funcional entre los puntos de sensibilidad retiniana de la perímetría automatizada en el glaucoma

RESUMEN

Objetivo: Estudiar la interrelación entre los 52 valores de sensibilidad retiniana obtenidos en la perímetría automatizada convencional (PA) tipo Humphrey con la estrategia Swedish interactive threshold algorithm (SITA) estándar 24-2 en pacientes con glaucoma.

Sujetos, material y métodos: Estudio prospectivo transversal en el que se incluyeron 104 ojos de 104 pacientes glaucomatosos diagnosticados por la apariencia de la cabeza del nervio óptico. Se recogió el valor de sensibilidad umbral de cada uno de los puntos de la PA SITA Standard 24-2, considerando cada hemicampo por separado. Se aplicó la prueba de Kolmogorov-Smirnov para demostrar la distribución normal de las variables, y se calcularon los coeficientes de correlación de Pearson entre los valores umbral de cada punto con todos los demás puntos del mismo hemicampo.

Resultados: Se obtuvieron mapas de correlación perimétrica entre valores umbral de un mismo hemicampo. La mayoría de los puntos evaluados mostraron correlaciones significativas \((r > 0.65; p < 0.001)\) entre puntos vecinos, así como entre puntos distantes dentro del mismo hemicampo.

Conclusiones: Existe una relación de dependencia funcional entre puntos vecinos y distantes en la PA de pacientes con glaucoma, en correspondencia con la distribución de los axones de las células ganglionares, que permite la obtención de patrones perimétricos del glaucoma.

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Introduction

Chronic simple glaucoma (CSG) is a progressive multiple factor optic neuropathy characterized by acquired loss of ganglion cells and their axons in the retina.\(^1\) The alteration of the retina nervous fiber layer (RNFL) is usually associated to changes in the morphology of the optic nerve head and to characteristic visual field defects.

Conventional automated perimetry (AP) has become the reference test for diagnosing and following up glaucoma neuropathy.\(^2\) In addition, structural evaluation of the optic nerve head and RNFL requires meticulous examination. For this reason, new objective imaging and diagnostic methods have been developed and standardized for glaucoma. For this reason, at present glaucoma is understood as a process in which the structure and function go through changes and current diagnostic methods exhibit different sensitivity levels in the detection of said changes.\(^3\)

At the functional level, the characteristic patterns of campimetric loss in glaucoma are related to the unique RNFL architecture (retinotopic distribution of ganglion cell fibers) and due to the well-known tendency to firstly affect the fibers of the superior and inferior poles of the optic nerve head. The macular area seems less vulnerable up to advanced stages of the neuropathy.\(^4,5\) This circumstance facilitates the identification of functional correlations between retinal areas that become involved at the same time throughout the glaucomatous disease.

The objective of this study was to assess and quantify the relationship between the 52 retinal sensitivity values of change in the Humphrey type AP with the Standard 24-2 Swedish interactive threshold algorithm (SITA) procedure for glaucoma patients.

Subjects, material and methods

All the patients accepted in the study signed an informed consent. The study protocol was approved by the Clinical Research Ethical Committee of Aragón (CEICA) and its design was adapted to the action lines described in the Helsinki declaration for biomedical research. One eye of each patient was included in the study and, if both eyes met the inclusion criteria, the eye to be included was chosen randomly.

Subjects

The study included patients with glaucoma selected in a prospective and consecutive manner from the glaucoma practices of our hospital. Said patients were defined on the basis of the characteristic appearance of the optic nerve head. The criteria comprised the appearance of a diffuse or focal staining of the neuroretinal ring with concentric increase of the cup, notch or both papillary signs\(^6\) independently of ocular pressure (IOP) and the AP result.

All the participants had to fulfill the following inclusion criteria: age comprised between 18 and 80 years, best corrected visual acuity (BCVA) \(\geq 5/10\), refraction and defect below 5 dpt of spherical equivalent and/or cylinder below 2 dioptries, transparent optic media (lens opacities <1 according to the Lens Opacities Classification System [LOCS] III)\(^6\) and anterior chamber open angle assessed by means of gonioscopy with Goldmann lens (grade \(\geq III\)). The patients excluded from the study were those having previous intraocular surgery history, diabetes or other systemic diseases, previous ophthalmological or neurological disease or use of medication that could interfere in the adequate execution of tests.
**Ophthalmological examination**

All participants underwent an ophthalmological examination that included refraction and keratometry, BCVA, slit lamp anterior biomicroscopy, gonioscopy with Goldmann lens, pachymetry (with OcuScan RxP Ophthalmic Ultrasound System, Alcon Laboratories Inc., Irvine, USA), posterior segment ophthalmoscopy with +78 D lens (Volk Optical Inc., Mentor, USA) with previous pharmacological miotics (0.5 tropicamide eyedrops) and papillary stereo photographs with Canon CF 60 DS1 retinograph (Canon Inc., Tokyo, Japan) and Canon EOS 1DS Mark III Digital camera (Canon Inc., Tokyo, Japan). At least 2 reliable AP were taken with the Humphrey Field Analyzer model 750i (Carl Zeiss-Meditec, Dublin, USA) perimeter with the standard SITA 24-2 program. If the fixation losses or rate of false positives or negatives exceeded 20% the test was repeated. The subjects in which a second perimeter was carried out and had reliability indices beyond normal limits were excluded from the study.

Threshold sensitivity value (in decibels) was obtained for each visual field point explored with the standard SITA 24-2 perimeter, numbering from 1 to 26 in the upper hemifield and 27–52 in the lower hemifields (Fig. 1), taking each hemifield separately. In addition the mean defect value (MD) and deviation over model (DOM) were taken for each AP.

![Functional correlation maps. Threshold points 1–9. Perimetric correlation maps obtained by calculating Pearson’s correlation coefficient (r ≥ 0.65, p < 0.001). Red: evaluated points. Dark green: point with the highest correlation with the evaluated point. Light green: rest of points within the same hemifield with a correlation of r ≥ 0.65.](image)

**Statistical analysis**

The statistical analysis was carried out utilizing SPSS version 15.0 for Windows (SPSS Inc., Chicago, USA). After demonstrating the normal distribution of the variables by means of the Kolmogorov–Smirnov tests, the Pearson correlation coefficients (r) were calculated between the threshold values of each AP point with all the other points in the same hemifield. The threshold sensitivities of the visual field points, registered in decibels (logarithmic units) were converted to a linear scale to facilitate calculus. As a high number of
Fig. 3 – Functional correlation maps. Threshold points 10–18. Dark green: point with the highest correlation with the evaluated point. Light green: rest of points of the same hemifield with the correlation of \( r \geq 0.65 \).

comparisons between variables were performed, the Bonferroni correction was applied and the statistical significance of the values was taken to be \( p < 0.001 \).

Results

One hundred and four eyes of 104 patients of Caucasian origin were included in the study: 81 open angle primary glaucomas, 20 pseudo-exfoliative glaucomas and 3 pigmentary glaucomas. The clinical characteristics of the population are summarized in Table 1. Prior to treatment, the patients exhibited good visual acuity (0.83 in the decimal scale) and IOP above 21 mmHg in all cases. In accordance with the AP results (average MD: \(-6.4 \pm 6.0 \) dB; DOM: \(5.0 \pm 3.6\)), the study included mainly patients with slight or moderate glaucoma. The Kolgomorov-Smirnov tests confirmed that all the analyzed variables followed normal distribution.

Figs. 2–7 illustrate the perimetric correlation maps with statistical significance (\( r \geq 0.65 \), \( p < 0.001 \)) obtained calculating Pearson’s correlation coefficient. These maps graphically depict the degree of relationship between each AP threshold sensitivity point and each of the remaining points in the same hemifield. To achieve greater clarity in the graphical representation of the results it was decided to establish a minimum correlation force between points of 0.65. Other points with significant but weaker correlations were not taken into account in the encoding of the maps. For their interpretation a color scale was applied, with the evaluated points marked in red, the point with the highest correlation degree with said evaluated points marked in green and the rest of points in the same hemifield having a relationship of \( r \geq 0.65 \) marked in light green. The correlation values of the opposite hemifields were calculated but not utilized for the study.

Discussion

AP is widely accepted as the functional test of reference for diagnosing and following up glaucoma. The retinotopic distribution of the RNFL as well as the anatomic relationships of the remaining elements comprising the visual system requires representing the space of vision in a characteristic and well-known manner. Accordingly, the visual field evaluations provide information about the visual field and the characteristics of the perimetric defects show a topographic correspondence with the location of anatomic alterations. This is also observed in glaucomatous neuropathy.
Fig. 4 – Functional correlation maps. Threshold points 19–26. Red: evaluated point. Dark green: point with the highest correlation with the evaluated point. Light green: rest of points in the same hemifield with a correlation of \( r \geq 0.65 \).

The perimetric correlation maps obtained in the instant study by means of statistical analysis show a distribution which is similar to the retinotopic architecture of the RNFL. This underlines the anatomical and functional relationship determined by the specific distribution of the retinal nervous fibers. This relationship between structure and function has also been demonstrated in recent studies through statistical correlations between perimetric values and objective RNFL measurements.\(^{11,12}\)

In what concerns the functional relationship between the points evaluated by perimetry, Strouthidis et al.\(^{13}\) endeavored to generate a functional interpoint correlation map within the same hemisphere in order to determine whether the degree of functional correlation between points is determined by the proximity thereof to the optic papilla and in the peripheral retina. The perimetry was performed with the Humphrey 24-2 perimeter (complete threshold strategy). The results exhibited good levels of association between the correlation power between points of the perimetry and the anatomic location of

<table>
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<th>Table 1 – Clinical data of the study population.</th>
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<td>Range</td>
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<td>Age (years)</td>
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<td>BCVA (decimal)</td>
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<td>IOP (mmHg)</td>
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SD: standard deviation; MD AP: mean deviation in automated perimetry; DOM AP: deviation over the model in automated perimetry; C/D: cup-disk quotient in stereo photographs; BCVA: best corrected visual acuity; IOP: intraocular pressure at baseline (without treatment).
said points in the peripheral retina, as well as their relationship with the retina nervous fiber layers. Similarly, González de la Rosa et al.\textsuperscript{14,15} carried out a statistical analysis of the correlation of the retinal sensitivity thresholds in each location and the rest of points evaluated by program 32 of the Octopus 1-2-3 perimeter in patients with glaucoma. The perimetry they performed was complete threshold. The results revealed a high-moderate functional correlation degree between adjacent and distant visual field points.

In the present study the perimetry was taken with the Standard 24-2 SITA program of the Humphrey Visual Field Analyzer. The SITA strategy is a threshold perimetry algorithm introduced by Bengtsson et al.\textsuperscript{16,17} in 1997. This strategy detects glaucomatous defects in short-term perimeter is and with lower variability than the complete threshold strategy, although said defects are more superficial and extense.\textsuperscript{16} The SITA strategy shortens the time taken by the tests by means of various techniques such as evaluation of surrounding points, information on the expected threshold values per age group and point location or the use of mathematical analyses to estimate the threshold value.\textsuperscript{16,19}

The fact that SITA is a strategy which takes into account the threshold values of surrounding points is a limitation in the design of the study and may have influenced some results in the functional relationship between evaluated points. However, the SITA algorithm has become the reference strategy for Humphrey perimeters for diagnosing and following up glaucoma. Accordingly, this study is valid from the clinical viewpoint. In addition, despite the differences between the designs of the studies, characteristic of the utilized samples and strategies, in general our results confirm those reported in previous studies carried out with complete threshold strategies.\textsuperscript{13,15} As shown in Fig. 8 which graphically illustrates the inter-relationship of specific points of the visual field with the rest of points of the same hemifield, as done by González de la Rosa et al.\textsuperscript{15} in their study but with the difference that they assessed the correlations of each point with the remainder of points of both hemifields with a complete threshold strategy.

In conclusion and on the basis of the results of the instant study there is a statistically significant relationship of functional dependence between adjacent and distant points in the Standard 24-2 SITA AP (Humphrey Visual Field Analyzer) of patients with glaucoma, matching the distribution of ganglion cell axons which enables the obtention of glaucoma perimetric patterns.

Fig. 5 – Functional correlation maps. Threshold points 27–35. Red: evaluated point. Dark green: point with the highest correlation with the evaluated point. Light green: rest of points in the same hemifield with the correlation of $r \geq 0.65$. 
Fig. 6 – Functional correlation maps. Threshold points 36–44. Red: evaluated point. Dark green: point with the highest correlation with the evaluated point. Light green: rest of points in the same hemifield with the correlation of \( r \geq 0.65 \).

Fig. 7 – Functional correlation maps. Threshold points 45–52. Red: evaluated point. Dark green: point with the highest correlation with the evaluated point. Light green: rest of points in the same hemifield with the correlation of \( r \geq 0.65 \).

Conflict of interests

No conflict of interests has been declared by the authors.

REFERENCES


Fig. 8 – Graphical representation of the determination coefficients ($r^2$) of 8 points of the visual field with the rest of points in the same hemifield, in analogy with the results of González de la Rosa et al. 15