**Associations between multifocal electroretinogram (mfERG), standard automated perimetry (SAP) and optical coherence tomography (OCT) in non-acute Vogt-Koyanagi-Harada disease (VKHD)**

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**ABSTRACT**

**Purpose:** To evaluate associations between functional (SAP and mfERG) and structural (OCT)

measurements in patients with non-acute VKHD.

**Methods:** Cross-sectional study (Jul/Dec 17) with 18 patients with VKHD followed for minimum 12mo from disease onset with systematic evaluation and treatment protocols. SAP: central 24-2 Swedish Interactive Threshold Algorithm standard on Humphrey Visual Field Analyzer II®; mean sensitivity (MS): 52 test points excluding points immediately above and below blind spot; central sensitivity (CS): average value at 4 central points; values in decibel and linear 1/L units. OCT: Spectralis® linear 30 degrees horizontal and vertical scanning of fundus area centered on macular umbo. mfERG (61 hexagons): RETiscan System® following the International Society for Clinical Electrophysiology of Vision guidelines; P1 and N1 amplitudes and peak times calculated after excluding ring 5 values. Age and gender matched controls were included for SAP and mfERG. Generalized estimated equations were used for analyzing binary ocular data, Pearson correlation for correlations. This study was approved by Institutional Ethics Committee and followed Helsinki declaration

**Results:** SAP and mfERG parameters were significantly worse in VKHD patients than in normal controls. There were significant correlations between P1 and N1 amplitudes and MS (r=0.342 and r=0.381, p=0.041 and p=0.022, respectively); P1 and N1 peak times and MS (r=-0.364 and r=-0.345, p=0.029 and p=0.039, respectively); foveal thickness and N1 amplitude and P1 peak time (r=-0.354 and r=0.509, p=0.034 and p=0.002, respectively). Disrupted photoreceptors integrity on OCT was associated with decreased P1 and N1 amplitudes (p= 0.050 and p= 0.002, respectively) and reduced CS, fovea, PSD and MD values on SAP (p=0.007; p=0.045; p= 0.014 and p=0.011, respectively).

**Conclusions:** Measurements of SAP, mfERG and OCT correlated significantly with each other in patients with non-acute VKHD and were significantly worse than in controls.

**INTRODUCTION**

Vogt-Koyanagi-Harada disease (VKHD) is a systemic autoimmune disease that targets melanocyte-rich tissues such as the choroid.[1, 2] When prompt diagnosis is made and appropriate immunosuppressive therapy (IMT) is installed, visual prognosis is generally favorable, with 66% of patients having final visual acuity (VA) better than 20/40. [1, 2] Despite the good VA, some patients still complain of visual disturbances and other functional measurements are important to better understand the impact of the disease in retinal function.

Multifocal electroretinogram (mfERG) is an electrophysiological examination that objectively creates a functional map of the central retina by selecting electrical responses from both the photoreceptors and the inner retinal layers of the macular area, which are tested simultaneously. [3] In VKHD, mfERG has proven to be a useful and sensitive tool for the detection of early retinal damage, since its responses may be reduced in patients with normal VA and no obvious retinal atrophy. [4] It has also been shown that IMT in VKHD leads to an earlier, faster and better recovery of VA and a delayed and limited recovery of macular function measured with mfERG after 12 months of treatment. [5]

Standard automated perimetry (SAP) is a well-established tool for quantifying preserved central visual field (VF). It provides global indices related to VF and estimates visual sensitivities at individual locations. Loss of macular function can also be documented with SAP. [6] Yang et al. investigated the changes of color vision and central VF in a cohort of patients with VKHD. [7] They demonstrated that VF are much more severely affected by the disease than VA and its improvement lagged behind that of VA and color vision following IMT. [7]

Optical coherence tomography (OCT) is a rapid, non-invasive and objective method for obtaining structural measurements of all retinal layers. [6, 8] Studies report a significant association of the integrity of the junction of the inner and outer segments of photoreceptors (IS/OS junction or ellipsoid zone) and the cone outer segment tips (COST) line with VA, as a measure of visual function in various retinal diseases. [9, 10] In patients with non-acute VKHD, Zhou et al. showed a strong correlation between VA and disruption in COST line and/or ellipsoid zone evaluated by OCT in patients with non-acute VKHD. [11]

Recently, many studies have been published concerning the association between functional (mfERG and SAP) and structural (OCT) measures in many ocular diseases, such as retinitis pigmentosa [8, 12], retinal toxicity related to hydroxychloroquine [13, 14], glaucoma [6] and diabetic retinopathy [15]. All these studies highlight that the objective and reliable outcome measures for retinal structure and function are necessary to monitor disease progression and fundamental for establishing a therapeutic strategy and selecting treatable patients. Studies comparing functional and structural outcomes with these tools in patients with uveitis are scarce. [16, 17]

This study aimed to be the first in literature to evaluate the relationship between functional and structural measurements in patients with non-acute VKHD. The purposes of this study were (1) to assess retinal function using SAP and mfERG and establish the extent to which these two noninvasive measurements can detect functional loss, (2) to evaluate retinal structure using OCT and (3) to evaluate associations between functional (SAP and mfERG) and structural (OCT) measurements in patients with non-acute VKHD.

**MATERIALS AND METHODS**

*Study design and sample*

This cross-sectional study was conducted from July 1 to December 31, 2017 with 18 patients with non-acute VKHD who were followed at a tertiary center in São Paulo, Brazil. Inclusion criteria were: diagnosis of VKHD [18]; participants of an ongoing prospective study in which all patients had been followed from acute onset and were systematically followed up and treated as described below; a minimum 12-month follow-up from acute onset; and, non-acute disease, defined as disease duration ≥ 12 months from disease onset. All patients were initially treated with three-day intravenous methylprednisolone (1g) followed by oral prednisone (1mg/kg/d) with slow tapering. Four patients were maintained with oral prednisone, while 14 patients had associated systemic IMT.

Patients underwent a socio-demographic interview and ophthalmologic evaluation. Clinical data were obtained from the current ophthalmological evaluation, as well as from medical records. All patients had systematic evaluations with clinical, posterior segment imaging exams (fundus color photography, indocyanine green angiography, fluorescein angiography and enhanced depth imaging-OCT) performed at diagnosis, at one, three, and six months and thereafter every three months. Patients also had full-field electroretinogram (ffERG) and mfERG exams at diagnosis, at 30 days and at six-month intervals thereafter. A database was created for clinical record-keeping purposes.

Eighteen healthy age-matched subjects were enrolled as controls for SAP and mfERG measurements; control individuals were negative for any ocular disorders and for any systemic illness. Normal SAP was defined as a pattern standard deviation (PSD) within the 95% confidence limits, absence of any cluster of at least 3 test points with p<5% on the pattern deviation plot and a Glaucoma Hemifield Test (GHT) result within normal limits.

This study was approved by the Institutional Ethics Committee (CapPesq 2.289.034/17). Written informed consent was obtained from all participants and normal controls; all study methods adhered to the tenets of the Declaration of Helsinki.

*ERG measurements*

mfERG was recorded using the RETiscan System (Roland Consult®, Germany) following the International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines.[19] The tests were performed monocularly, after anesthetizing the cornea with one drop of proxymetacaine 0.5%, using ERG-Jet contact lens electrodes (Fabrinal SA, La Chaux de Fonds, Switzerland). Gold-cup reference and surface electrodes were placed on the subject’s forehead and temple, respectively. The pupils were previously dilated with 1% tropicamide, and the subject was light adapted for 10 minutes before the examination. The fixation target was clearly visible by all patients. The stimulus array consisted of 61 hexagons scaled with a 4.0 distortion and eccentricity factor randomly displayed on a cathodic ray tube monitor at a distance of 26 cm and directed at the central 30° of the retina. The luminance of the stimuli was modulated between black (0 cd/m2) and white (200 cd/m2), according to a modified pseudorandom m-sequence. The recordings were amplified and automatically bandpass filtered (filter range 10–100 Hz). The subjects were asked to fix their gaze on the red cross at the center of the stimulus screen. Recordings with artifacts from head movements, blinking or contact lens uncoupling were discarded and repeated. The responses were measured using scaled density regional averages in nV/deg2 to reflect the correct angular size for each hexagon stimulating the retina. The values of the ring 5 were excluded in order to have a more accurate spatial correlation between test points of SAP, mfERG and OCT measurements. The mfERG N1 and P1 amplitudes and P1 and N1 peak times were measured according to ISCEV guidelines. [19]

ffERG was performed using the RETI-port system (Roland Consult®, Germany). Exam recordings were done in accordance with the International Society for Clinical Electrophysiology of Vision guidelines using ERG-jet electrodes (Universe SA, La Chaux-de-Fonds, Switzerland). [20] Amplitude and implicit time of *a* and *b* waves of eight averaged stimulus responses for each phase were analyzed. The limits of normal values for each specific ffERG response were established at 95% confidence limits. The exam was considered normal when ffERG scotopic parameters in both eyes were within the limit of ±2 standard deviation in comparison with a normative database adjusted for age range.

*SAP measurements*

SAP was conducted using the Swedish Interactive Thresholding Algorithm (SITA) Central Standard 24-2 test (Humphrey Field Analyzer®, Carl Zeiss Meditec) with a Goldman III size stimulus on a 100 cd/m2 (31.5-apostilb) background for inclusion purposes and undilated pupils. The 24-2 pattern was chosen because its testing field closely matches the stimulus area of the mfERG responses. An optimal lens correction was used and the fellow eye was occluded with an eye patch. Reliability criteria were false positives, false negatives or fixation losses less than 20%. The mean deviation (MD), PSD, fovea and visual field index (VFI) values were analyzed. Mean sensitivity (MS) was analyzed for 52 test points, after excluding one immediately above and another below the blind spot. Central sensitivity (CS) was evaluated using the average visual sensitivity value at four central test points. For the purpose of calculation, values in decibel (dB) were converted to linear 1/L units, using the formula: 1/L = 10dB/10.

*OCT measurements*

OCT and EDI-OCT were performed using SD-OCT scanning (Spectralis® HRA+OCT, Heidelberg Engineering, Germany) of the macular area following pupil dilation with 1% tropicamide. The images were acquired using the automated eye alignment eye-tracking software (TruTrack; Heidelberg Engineering). The software scores the quality of the signal strength of the images on a scale from poor (0 dB) to excellent (40 dB). A quality index of at least 20 was required for all images. The built-in scan acquisition function termed “section” was utilized to acquire two high-resolution scans covering a linear 30º fundus area (6mm) in both the horizontal and vertical orientations and centered on the macular umbo. The horizontal scan was repeated with enhanced depth image (EDI) mode activated. Two experienced observers (FMSS and JHY) masked to visual acuities measured several variables. Foveal retinal thickness (FRT) was defined as the retinal thickness of the central 1.0mm; central retinal thickness (CRT) was defined as the mean retinal thickness of the central 6.0 mm and choroidal thickness (CT) as the subfoveal choroidal thickness on EDI-OCT horizontal scan. The OCT data were utilized to characterize the outer retinal structure of the macula, herein represented by the overall appearance of the hyper-reflective layer corresponding to the junction of the inner and outer segments of the photoreceptors (ellipsoid zone). The ellipsoid zone line that was a third band of high reflectance within the central 6.0 mm on tomograms was classified into three groups: Group 1, intact ellipsoid zone line; Group 2, focal disruption of the ellipsoid zone line of 500µm or less; Group 3, focal disruption of the ellipsoid zone line greater than 500µm.

*Data analysis*

Descriptive statistical analysis was performed to describe socio-demographic and clinical data, and distributions were summarized using mean and standard deviation (SD). Patients had both eyes included for analysis. Therefore, generalized estimated equations with Poisson distribution and log link function were used for analyzing binary ocular data and Bonferroni correction for multiple comparison. Additional Pearson correlation analysis was performed to determine the degree of associations between SAP, mfERG and OCT findings. A *p*-value <0.05 indicated a statistical significance. The Statistical Package for the Social Sciences version 22.0 software (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis.

**RESULTS**

*General characteristics*

Eighteenpatients (36 eyes, 16 female) with non-acute VKHD were evaluated. The mean age was 37.1±13 years and mean disease duration was 46.9±23.7 months. Patients’ clinical profile (**Table 1**) demonstrated that 81% of eyes had VA of 20/20 (14 patients had VA of 20/20 in both eyes; range of VA 20/20 to 20/60), 89% of eyes had a mild or moderate fundus classification in the worse eye and 33% of patients had abnormal ffERG. Anterior chamber cells and macular edema (clinical signs of activity) were present in 2 and 5 eyes, respectively.

*mfERG measurements*

All mfERG parameters were significantly worse in VKHD patients than in normal controls. Mean N1 amplitude (µV/deg2) was 9.3±3.0 for patients and 12.5±2.8 for controls (p<0.001); mean P1 amplitude (µV/deg2) was 35.2±11.0 for patients and 47.7±7.9 for controls (p<0.001); mean N1 peak time was 17.7±1.4 for patients and 16.6±0.9 for controls (p<0.001) and mean P1 peak time was 32.6±2.1 for patients and 31.01±1.3 for controls (p<0.001).

*SAP measurements*

All SAP parameters were significantly worse in VKHD patients than in normal controls. Main results were: mean MS (dB) value, 26.4±4.7 *versus* 29.6±1.4 (p=0.001); mean CS (dB) value, 30.1±3.9 *versus* 32.3±1.2 (p=0.006); mean fovea (dB) value, 32.8±5.1 *versus* 35.8±2.2 (p=0.002); mean VFI (dB) value, 90.9±12.9 *versus* 98.7±1.2 (p<0.001); mean MD (dB) value, -5.1±4.6 *versus* -1.5±1.3 (p<0.001) and mean PSD (dB) value, 3.7±2.9 *versus* 1.6±0.4 (p<0.001), for patients and controls, respectively.

*OCT measurements*

Twenty eyes (56%) of patients had an intact ellipsoid zone line (group 1), 5 eyes (14%) had focal disruption of the ellipsoid zone line of 500µm or less (group 2) and 11 eyes (30%) had focal disruption of the ellipsoid zone line greater than 500µm (group 3). Mean central retinal thickness was 297.0±21.4µm; mean foveal retinal thickness was 248.3±37.8µm; mean central macular volume was 8.5±0.5mm2 and subfoveal choroidal thickness was 329.5±99.5µm. The differences between these values among the three groups were not significant.

Intraretinal fluid was present in 2 eyes (7%) and subretinal fluid in one eye (3.5%) of patients. Retinal pigment epithelium (RPE) hyperplasia/hypertropia was present in 8 eyes (27%), while RPE atrophy was seen in 2 eyes (7%).

*Associations between mfERG and SAP measurements and ellipsoid zone line* *integrity on OCT* (**Figure 1**)

There were no significant differences between the three groups based on ellipsoid zone line integrity concerning age (p>0.999) and visual acuity (p=0.294).

Regarding mfERG results, the mean N1 amplitude (µV/deg2) value was 10.6±3.4 in Group 1, 7.8±1.5 in Group 2 and 7.8±1.6 in Group 3. There was a significant difference among the three groups (p=0.002). After multiple comparison post hoc test (Bonferroni correction for multiple comparison) significance was observed between groups 1 and 2 (p=0.001). The mean P1 amplitude (µV/deg2) value was 39.9±11.3 in Group 1, 32.5±8.5 in Group 2 and 27.7±6.1 in Group 3. There was a significant difference among the three groups (p=0.050). After multiple comparison post hoc test (Bonferroni correction for multiple comparison) significance was observed between groups 1 and 2 (p=0.043). Concerning mean peak time of N1 and P1, there were no significant differences among the groups.

Regarding SAP results there were significant differences among the groups concerning CS (p=0.007), fovea value (p=0.045), MD value (p=0.014) and PSD value (p=0.011). After multiple comparison post hoc test (Bonferroni correction for multiple comparison) significance was observed between groups 1 and 3 for CS (p=0.005), fovea value (p=0.042) and MD value (p=0.018); for PSD value significance was observed between groups 1 and 2 (p=0.015).

*Associations between mfERG, SAP and foveal thickness*

Concerning associations between mfERG and SAP results, reduced P1 and N1 amplitudes were significantly associated with reduced MS (*r*=0.342 and *r*=0.381, p=0.041 and p=0.022, respectively) and increased P1 and N1 peak times were significantly associated with reduced MS (*r*=-0.364 and *r*=-0.345, p=0.029 and p=0.039, respectively). Reduced N1 amplitude and increased P1 peak time were significantly associated with an increased foveal thickness (*r*=-0.354 and *r*=0.509, p=0.034 and p=0.002, respectively).

**Table 1:** Clinical features in 18 patients with non-acute Vogt-Koyanagi-Harada disease included in the study

|  |  |  |
| --- | --- | --- |
| **Features** |  |  |
| **Age,** mean ±SD | 37.1 | 13 |
| **Sex**, n (%) |  |  |
| Male | 2 | 11 |
| Female | 16 | 89 |
| **Duration** in months**,** mean ±SD | 46.9 | 23.7 |
| **Treatment groups** |  |  |
| Only corticosteroids | 4 | 22 |
| Corticosteroids and late immunosuppression (≥4 months) | 5 | 28 |
| Corticosteroids and early immunosuppression (<4 months) | 9 | 50 |
| **Severity according to analytic classification of eye fundus,** n (%)(worse eye)  Mild  Moderate  Severe | 11  5  2 | 61  28  11 |
| **Visual acuity, n (%) (eyes)**  20/20  <20/20 ≥20/60 | 29  7 | 81  19 |
| **Disease activity status, n eyes (%)**  *Clinical signs*  Anterior chamber cells  Macular edema  *Subclinical signs*  Optic disc hyperfluorescence (FA)  Perivascular leakage (FA)  Dark dots (ICGA)  Choroidal thickness fluctuation (OCT-EDI) | 2  5  9  4  36  13 | 5  14  25  11  100  36 |
| **ffERG,** n (%)  Normal\*  Abnormal | 12  6 | 67  33 |

FA: fluorescent angiography; ffERG: full-field electroretinogram; ICGA: indocyanine green angiography; OCT-EDI: enhanced-depth imaging optical coherence tomography; \*scotopic parameters in both eyes were within the limit of ±2SD in comparison with a normative database adjusted for age range

**Figure 1:** Comparisons of central sensitivity, fovea, MD and PSD values on standard automated perimetry and N1 and P1 amplitudes of multifocal electroretinogram among subgroups of patients with Vogt-Koyanagi-Harada disease and normal controls (p<0.05**†**)

MD: mean deviation; PSD: pattern standard deviation; Group 1, intact ellipsoid zone line; Group 2, focal disruption of the ellipsoid zone line of 500µm or less; Group 3, focal disruption of the ellipsoid zone line greater than 500µm; **†**Generalized estimated equations with normal distribution and logarithmic link function, supposing an interchangeable correlation matrix between the eyes; Concerning patients’ subgroups based on ellipsoid zone line integrity, after multiple comparison post hoc (Bonferroni correction for multiple comparison) significance was observed between the following: for N1 amplitude (µV/deg2), group 1 *versus* group 2 (p=0.001), for P1 amplitude (µV/deg2), group 1 *versus* group 2 (p=0.043); for CS (dB), group 1 *versus* group 3 (p=0.005); for fovea (dB), group 1 *versus* group 3 (p=0.042); for MD (dB), group 1 *versus* group 3 (p=0.018); for PSD (dB), group 1 *versus* group 2 (p=0.015)

**DISCUSSION**

In the present study, patients with non-acute VKHD had good VA (20/20 in 81% of eyes), mild to moderate fundus changes in 89% of eyes and normal ffERG results in 67% of the patients. Nevertheless, the retinal function measured by mfERG and SAP were significantly abnormal in patients with VKHD when compared to age and gender matched controls and 44% of eyes had some disruption of ellipsoid zone line on OCT.

VKHD is mainly a diffuse granulomatous choroiditis and the photoreceptors may be affected in an upstream phenomenon. By reflecting the electrophysiological responses from both the photoreceptors and the inner retinal layers, including the bipolar and Müller cells, mfERG is applicable in the evaluation of visual function in patients with non-acute stage of VKHD [3, 4]. Chee et al. showed that, in patients with non-acute VKHD, mfERG response was reduced, despite the absence of clinical apparent retinal atrophy and normal VA [4]. Similarly, we demonstrated that, in patients with good VA and mild/moderate fundus classification, there was a visual dysfunction noticed on mfERG results. These findings reinforce the previous hypothesis raised by those authors that these patients do in fact have some retinal damage, which may not be clinically detectable, and that conventional measures, such as VA, are not sensitive enough in the assessment of visual function in non-acute VKHD patients [4]. We also support the idea that mfERG seems to be a sensitive non-invasive tool and may be a useful adjunct in the management of patients with non-acute VKHD by detecting early retinal damage.

Furthermore, SAP is another functional exam that has shown to reflect the function of the retina, choroid and optic nerve. Yang et al. demonstrated that SAP is an independent test to measure visual function in patients with VKHD and that the impaired VF is generally in accordance with the inflammatory damage to the choroid and its adjacent tissues observed in this syndrome [7]. Our results of impaired VF results despite good VA reinforce that sub-clinical abnormal macular function is still present in certain patients although the intraocular inflammation is clinically controlled. In our sample, despite scarce clinical signs of activity, SAP values were significantly worse than in normal age-matched controls and this can explain, at least partially, the complain of unspecific visual disturbances.

Correlation of between these functional tests, i.e. mfERG and SAP, had been evaluated in non-inflammatory ocular diseases. Evaluating retinal toxicity with hydroxychloroquine, Lai et al. found that mfERG response amplitude correlated with 10:2 VF MD values and with the cumulative dose of hydroxychloroquine, providing supplementary quantitative information to VF findings [21]. In patients with open angle glaucoma, despite the small changes observed in mfERG and SAP, these two functional tests showed a reasonable correlation [22]. In diabetic patients, most responses of mfERG and short-wavelength automated perimetry (SWAP) were subnormal and showed a similar number of significant abnormalities regardless the presence of diabetic retinopathy [23]. Recently, functional tests were evaluated in patients with birdshot chorioretinopathy by Maihac et al. [16] They showed that a decreased P1 amplitude on mfERG were correlated to a worse MD on SAP. In our study, there were significant associations between SAP and mfERG results: MS on SAP correlated with P1 and N1 amplitudes and with P1 and N1 peak times on mfERG. It demonstrates that both mfERG and SAP are sensitive measurements of functional dysfunction in patients with non-acute VKHD.

Concerning structural changes observed in patients with non-acute VKHD, Zhou et al showed that OCT findings were localized in the outer retina and included thinning of the outer nuclear layer, thickening of the RPE, breakage or disappearance of the COST and/or ellipsoid zone lines.[11] Their results revealed a correlation between these findings and VA, since the group with intact COST and ellipsoid zone lines displayed the best VA. [11] In our study, we could not find a significant association between VA and patient’s subgroup based on ellipsoid zone line integrity. This discrepant result may be due to the very good VA of most of our patients. Nevertheless, patients in group 1 with an intact ellipsoid zone line showed better amplitude responses on mfERG and better CS, fovea, MD and PSD values on SAP than patients in groups 2 and 3, with disruption of ellipsoid zone line ≤ 500µm or >500µm, respectively. It is possible to infer that mfERG and SAP are useful and important tools to detect early retinal damage and evaluate visual disturbances presented by some patients with non-acute VKHD, despite good VA and mild anatomic alterations.

In our study we did find a correlation between foveal retinal thickness measured with OCT with functional parameters of mfERG and SAP. A reduced N1 amplitude and an increased P1 peak time were significantly associated with an increased foveal thickness. A study with cystoid macular edema in patients with recurrent uveitis of various etiologies showed a negative correlation between foveal thickness and mfERG values in area 1 [17]. Also, in patients with birdshot chorioretinopathy the longer implicit times of the N1 and P1 response were correlated with the presence of macular edema [16].

Our data highlighted that mfERG amplitudes and SAP parameters are reliable complementary tests to evaluate retinal function and they may be associated with disruption of ellipsoid zone line on OCT. Then, a possible question to be arise is whether functional test to choose. The clinical relevance of the mfERG is the possibility of an objective measure of retinal function that needs less effort and compliance of the patient in comparison to SAP. On the other hand, SAP can be found at any ophthalmological center even though it relies on patient cooperation.

The main shortcoming of our study is its modest sample size, which may limit the power to detect significant differences when subgroup analyses are performed. Even so, statistically significant differences were found.

The correlation of functional tests and structure changes are important to better understand the disease and play a role as a critical analysis of prognosis/severity. Functional (SAP and mfERG) and structural (OCT) exams are important in the follow-up of patients with non-acute VKHD to provide an extensive understanding and more refined evaluation of visual function. To our knowledge, the present study is the first to investigate the correlations between these measurements in patients with non-acute VKHD, differently from previous studies that compared only VA and structural measurements [4, 5, 7, 11]. In future studies, follow-up should be done with these patients to observe the dynamic changes that occur over time.

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