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Choroidal Features in Vogt-Koyanagi-Harada Disease: Imaging beyond the Retinal Pigment Epithelium with Spectral-Domain Optical Coherence Tomography

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Title Page

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The Abstract

Purpose: To assess enhanced depth imaging spectral-domain optical coherence tomography (EDI-SDOCT) findings in patients with Vogt-Koyanagi-Harada (VKH) disease, comparing to a normal population sample.

Methods: A retrospective review was performed using 18 eyes of 9 VKH patients and 18 eyes of 9 normal subjects who performed EDI-SDOCT. Choroidal thickness (CT) was manually measured on a 7-horizontal-raster scan centered on the fovea. Measurements on the fovea and 500, 1500 e 3000 μm from the fovea to the nasal and temporal side were registered. A total of 49 points were measured on each sample and grouped into quadrants: nasal-superior (NS), nasal-inferior (NI), temporal-superior (TS) and temporal-inferior (TI). Central retinal macular thickness (CRMT) and retinal macular volume (RMV) were determined. CT, CRMT, RMV were correlated with disease duration.

Results: The mean subfoveal choroidal thickness (F) in the convalescent stage was 312 μm (SD 130) and 394 μm (SD 97) in the control group (p=0.055). At 1500 and 3000 μm temporal to the fovea (T15 and T30) the choroid presented significantly thinner in the patients group (p=0.019 and p=0.047). Significant differences were also found in NS, TS and TI quadrants, (p=0.044, p=0.022, p=0.034), were the choroid showed to be thinner. Correlations between CT, CRMT, RMV and disease duration were not significant (p=0.469, p=0.706, p=0.915).

Conclusions: VKH patients presented thinner choroids in the convalescent stage, compared with normal subjects. This difference is more evident in the temporal quadrant. Choroidal evaluation in VKH patients with EDI-SDOCT seems to be helpful in monitoring the disease status.

Key Words: Vogt-Koyanagi-Harada, Choroidal Thickness, EDI, Spectral-domain Optic Coherence Tomography, Posterior Uveitis

Introduction

Vogt-Koyanagi-Harada (VKH) syndrome is a rare multisystem autoimmune granulomatous inflammatory disorder involving the eyes, inner ear, skin and meninges (Yanoff & Duker 2004; Pan & Hirose 2011). Clinically these patients may present with posterior uveitis with some extra-ocular findings as meningismus and cerebrospinal fluid pleocytosis, tinnitus, perception deafness, alopecia, vitiligo and poliosis.

The disease appears more frequently among Asians, Indians and Latin Americans. Females also have a higher probability of developing the disease, especially in their fourth to fifth decades (Yanoff & Duker 2004).

Ocular findings in VKH disease are bilateral panuveitis with multifocal serous retinal detachments (Read et al. 2001; Rao 2007; Pan & Hirose 2011). The foremost site of inflammation is the choroid. It begins with an autoimmune reaction against stromal choroidal melanocytes proteins secondarily affecting retinal pigment epithelium (RPE) and the retina (Moorthy et al. 1995; Damico et al. 2005; Sugita et al. 2006).

VKH syndrome is clinically divided into four stages (Read et al. 2001; Yanoff & Duker 2004; Pan & Hirose 2011). The prodromal stage is characterized by systemic, mostly neurological manifestations. The uveitic stage consists in an anterior and/or posterior bilateral uveitis, with hyperemia and swelling of the optic disc. It also includes focal areas of subretinal fluid or bullous serous retinal detachments. In the convalescent stage the eyes may display choroidal depigmentation (sunset glow fundus), alterations of the retinal pigment epithelium (RPE) with foci or lines of hyperpigmentation and nummular areas of chorioretinal atrophy, peripheral yellow-white lesions (Dalen-Fuchs nodules) and perilimbal vitiligo (Sugiura's sign). A chronic recurrent stage may present as acute iridociclitis accompanied by iris nodules and mutton-fat keratic precipitates. Other manifestations and complications, such as choroidal neovascularization, posterior subcapsular cataract, glaucoma and posterior synechiae, may occur at this phase.

In VKH syndrome, corticosteroids are the treatment keystone. Other therapy schemes contemplate immunosuppressive or biologic agents and anti-vascular endothelial growth factors (anti-VEGFs) (Bordaberry 2010).

Diagnosis is based on clinical presentation and ophthalmologic imaging modalities such as B-mode ultrasonographic imaging, fluorescein angiography (FFA), indocyanine

green angiography (ICGA) and optical coherence tomography (OCT) (Bouchenaki & Herbort 2001; Wylęgała et al. 2008; Bordaberry 2010).

Histopathologic studies (Perry & Font 1977; Inomata & Sakamoto 1990) have shown that lymphocytic infiltration is responsible to choroidal thickening in VKH disease. However, insufficient data concerning the choroid biomorphologic changes during the course of the disease is available. In vivo observation and monitoring of the ocular structure most affected by VKH could be crucial in a clearer understanding of its pathophysiology and monitoring of its treatment efficacy.

OCT is a non-invasive imaging method that enables cross sectional-images of the retina and the RPE (Wylęgała et al. 2008; Regatieri et al. 2012), allowing the acquisition of morphologic parameters and morphometric measurements, especially spectral-domain OCT (SDOCT).

Recently, Spaide et al (Spaide et al. 2008) described a technique called "enhanced depth imaging" (EDI), in order to solve this difficulty. This technique improves the view of the choroid, from Bruch membrane to the suprachoroidal space and sharper the tissue particularities. It also provides choroidal thickness (CT) measurements and the observation of choroidal abnormalities.

The aim of this study is to assess EDI-SDOCT findings in patients with VKH disease comparing to a normal population group. Differences between acute and chronic stage findings were also analysed.

Methods

Subjects

A retrospective review was performed based on clinical records of 9 patients (18 eyes) with the diagnosis of Vogt-Koyanagi-Harada (VKH) disease, followed in the Department of Ophthalmology of S. João Hospital Center, in Porto.

Inclusion criteria were patients with VKH disease respecting the revised diagnostic criteria of VKH disease, established by an international committee on nomenclature (Read et al. 2001), who were submitted to spectral-domain optical coherence tomography (SDOCT) examination.

None of the patients presented confounding simultaneous conditions such as history of ocular trauma or surgery, lymphoma, posterior scleritis, central serous chorioretinopathy, acute posterior multifocal placoid pigment epitheliopathy, idiopathic uveal effusion syndrome, ocular sarcoidosis, tuberculosis or lupus. Only 3 eyes of 2 patients had a refractive error superior to 5 diopters.

Demographic and clinical data including age, sex, ethnicity, best corrected visual acuity (BCVA), neurologic/auditory or integumentary findings, disease duration, treatment performed, slit-lamp biomicroscopy and indirect ophthalmoscopy description were collected. Information from retinal and choroidal morphological SDOCT findings was registered. Data on fluorescein and indocyanine green angiography findings was also registered.

Age and sex- matched healthy subjects with a refractive error of less than 4 diopters from a database of our Ophthalmology Department, who had been examined with a SDOCT, were used as controls.

Ethical approval was obtained from the S. João Hospital Center Ethics Committee for Health, and the Administrative Council and Local Office of Research from S. João Hospital Center, Porto. The tenets of Declaration of Helsinki were respected.

SD OCT imaging and analysis

The SDOCT images were acquired using the Heidelberg Spectralis OCT system (Heidelberg Engineering, Heidelberg, Germany), and an enhanced depth imaging (EDI) acquisition mode was also used to visualize the choroid.

The retinal analysis included a three-dimensional OCT volume generated by a 19-section raster scan with 512 voxels per depth-scan (A-scan), across a 20x15º field

centred on the fovea. A 6-mm high quality horizontal and vertical scan 30º through the fovea, with 768 voxels per A-scan was also used. Retinal thickness and volume measurements were performed using the system software automatic analysis. For choroidal imaging both the high definition lines as well as the 19-section raster scan were used in the EDI mode, using the follow-up tool for setting reference in order to obtain a perfect alignment between retina and choroid in every examination. Manual segmentation of the choroidal layer was performed dragging the reference line from the retinal boundary (internal limiting membrane) to the choroidal-scleral interface in each of the scans (Fig. 1). This manual segmentation of the choroidal boundary was reviewed by an ophthalmologist, experienced in operating an OCT device. Choroidal thickness (CT) was measured at the fovea (F) and at 500 μm, 1500 μm and 3000 μm intervals nasal (N5, N15, N30, respectively) and temporal (T5, T15, T30, respectively) to the fovea, through the entire field. In order to facilitate the graphic representation only the measurements in 7 of the 19 sections, one centred on the fovea and the others distanced by 740 μm from each other, were displayed. A total of 49 CT measurements were registered on both samples, and grouped into quadrants: nasal-superior (NS), nasal-inferior (NI), temporal-superior (TS) and temporal-inferior (TI).

Statistical Analysis

Statistical analysis was performed using the SPSS software version 20.0. Nonparametric tests were used: Mann-Whitney U test, Wilcoxon rank-test and Spearman's rank correlation test. A 95% confidence interval and a 5% level of significance were adopted; therefore, the results with a p-value <0.05 were considered significant.

Results

Eighteen eyes of 9 patients with VKH, with a M/F ratio of 2:7 and a mean age of 47.1 years (SD 9.5), ranging from 36 to 71 years. Eighteen eyes of 9 normal subjects with a M/F ratio of 1:8 and a mean age of 49.0 years (SD 6.2) were used as controls. There was no significant difference in the mean age between these two groups (p=0.152, Mann-Whitney U test). Both samples were predominantly female patients, with a total of 30 eyes of 15 women (83.3%) and 6 eyes of 3 men (16.7%).

Altogether, 4 out of 9 patients had neurological findings in the acute stage and 3 patients presented integumentary findings after onset of central nervous system or ocular disease.

Two patients were classified as presenting a complete diagnosis of VKH disease, according to the revised diagnostic criteria (Read et al. 2001). Five had an incomplete diagnosis and two a probable diagnosis.

The follow-up period since the diagnosis ranged from 7 to 600 months (0.58 to 50 years). The mean duration was 123 months (SD 181) and the median was 72 months.

All 9 patients were submitted to systemic corticotherapy in the acute phase. Five of these patients required another immunossupressive agent to control the inflammation.

Two patients presented bilateral recurrent disease. All the 18 eyes presented a sunset glow fundus in the convalescente phase. A total of 8 eyes of 4 patients presented ocular hypertension (OHT) during the follow-up period, requiring topical hypotensive medication. None of these patients required glaucoma surgery.

Characteristics of the study groups are depicted in table 1.

BCVA in the acute stage ranged from 20/200 to 20/25 (logarithmic of the minimum angle of resolution [logMAR] ranging from 1.00 to 0.1) and a median logMAR 0.4. BCVA in the convalescent stage was between < 20/200 and 20/16 (logMAR ranging from 3.00 to -1.0), with a median logMAR of 0.0. We found statistically significant difference (p=0.002, Wilcoxon rank-test) between acute and convalescent BCVA.

In the acute stage of disease, the mean central retinal macular thickness (CRMT), measured in the 1mm-diameter central ring was 673 µm (SD 186). The mean CRMT in controls was 279 µm (SD 16). The difference between median CRMT in acute stage patients and controls was statistically significant (p<0.0001, Mann-Whitney U test). The retinal macular volume (RMV) in the 6mm diameter ring in acute stage patients (mean

12.6 mm^3; SD 1.9) was also increased compared to controls (mean 8.7 mm^3; SD 0.4) ($p<0.0001$).

In the convalescent stage the mean CRMT decreased to 282 µm (SD 28) and VRM to 8.3 mm^3 (SD 1.5). When analyzing the same parameters in the convalescent phase, no differences were found in the CRMT (p=0.888, Mann-Whitney U test) and RMV (p=0.628) between the patient's group and controls.

However, the CRMT significantly decrease from the acute to the convalescent stage (p=0.012, Wilcoxon rank-test). Those differences were also found in the RMV (p=0.012).

The time of follow-up was not significantly correlated to CRMT (p=0.706, Spearman's correlation test) (Fig. 2) or RMV (p=0.915) in the convalescent stage.

None of the patients had an EDI-SDOCT evaluation of the choroid in the acute stage of disease, so there is no data concerning the CT in this phase. On the other hand, in the convalescent stage, the mean CT measured in the fovea (F) was 312 µm (SD 130), ranging from 49 to 551 µm. The mean CT in controls was 394 µm (SD 97), ranging from 221 to 580 µm. Differences weren't significant the patient's group and controls (p=0.055, Mann-Whitney U test).

Analyzing an horizontal scan crossing the fovea it is possible to verify that CT diminishes from the fovea to either nasal and temporal sides in both samples (Fig. 3).

Furthermore, measurements performed at 1500 and 3000 µm temporal to the fovea (T15 and T30, respectively) were significantly thinner in patients compared to controls, (p=0.019 and p=0.047, respectively, Mann-Whitney U test). The other measurements were closely statistically significant (N30 p=0.068; N5 p=0.059; F p=0.055; T5 p=0.051), except N15 (p=0.091). Overall, while analyzing the CT by quadrants, it was thinner in patients compared to controls in all the quadrants (Fig. 4). A statistically significant difference was found in NS, TS and TI quadrants (p=0.044, p=0.022, p=0.034, respectively). NI quadrant measurements weren't significantly different (p=0.118).

Correlation between subfoveal choroidal thickness (F) and follow-up period was not statistically significant (p=0.469, Spearman's correlation test), nevertheless there seems to be some negative correlation (Fig.5).

No significant correlation between either foveal retinal thickness or subfoveal choroidal thickness (F) and BCVA was found (p=0.467 and p=0,275, respectively) in the convalescent phase.

The treatment plan choice, either using corticosteroids or corticosteroids combined with other immunosuppressive agent, did not correlate to the subfoveal choroidal thickness (p=1.000, Mann-Whitney U test).

Considering ocular pressure, no significant differences were found in CT by quadrants between patients diagnosed with ocular hypertension (OHT) and those with no such history (NS p=0.122; TS p=0.173; NI p=0.274; TI p=0.360, Mann-Whitney U test). However, the choroid tends to be thicker among patients with OHT at all the macular quadrants compared to the other patients.

Discussion

Considering that VKH disease begins as an autoimmune reaction against stromal choroidal melanocytes proteins, secondarily affecting the RPE and the retina (Moorthy et al. 1995; Damico et al. 2005; Sugita et al. 2006), it is crucial to be recognized the importance of studying choroidal morphology throughout the disease. However, the RPE was a highly limiting factor in imaging the underlying choroids, due to its pigment density. Enhanced depth imaging modalities, using spectral-domain OCT, solved these difficulties, allowing imaging beyond the RPE. EDI-SDOCT is proving to be one of the most useful tools for choroidal morphologic evaluation (Spaide et al. 2008; Ishihara et al. 2009; Fong et al. 2011).

Previous studies showed the increase of CT in the active stage of the disease (Fong et al. 2011; Maruko et al. 2011). Unfortunately, due to the retrospective nature of this study, we didn't have any imaging of the choroid using EDI technique in the acute stage, precluding the comparison between choroidal measurements in acute versus convalescent stage. Only retinal measurements were obtained from the optical scans available in acute stages. A total of 4 VKH patients (8 eyes) performed SDOCT during the acute stage, repeating this examination while in the chronic stage, this time also using the EDI technique.

This study was also limited by the small size of the sample groups, especially in the acute stage.

Besides that, 3 eyes of VKH patients (16.7%) had a refractive error superior to 5 diopters which may have contributed to the heterogeneity of our findings. As has been studied, ocular axial length influences choroidal thickness (Fujiwara et al. 2009).

Otherwise, our control sample was very homogeneous, considering that, as already stated (Fong et al. 2011), healthy choroidal thickness may vary among study groups as a consequence of interracial variety. This sample was also sex and age-matched to the patients group.

We found a significant increase of both CRMT and RMV in the acute stage, compared to controls and to the convalescent stage. This finding is easily understandable, considering that retinal detachments and retina edema are usually found in the active phase of the disease. Similar findings were described by other authors (Yamamoto et al. 2011). However, neither CRMT nor RMV were significantly different between the

convalescent stage and the controls, meaning that no relevant macular changes were detected in our patients.

The mean duration of the disease was 123 months (10.3 years) since VKH disease diagnosis. Given the small size of our sample, the median appears to be a more reliable measure of illness' duration (median of 72 months). However, our study included patients with a wide range of follow-up period. Although previous studies showed a negative correlation between CT and duration of disease (Nakai et al. 2012; da Silva et al. 2013), with a mean period of disease of 52.5 months and 69 months, respectively, we didn't find a statistically significant correlation. This could be explained by the wide range of follow-up periods. We also found no significant correlation in the convalescent stage between CRMT and RMV and the duration of the disease.

In our study we found the urge to measure the choroid not only in the foveal region, or along a horizontal scan crossing the fovea, as has been previously done, but also to analyze the choroidal profile throughout the all macular area. This is the reason why a raster scan choroidal measurement was done. To our knowledge, this has not been done so far in VKH patients.

The median subfoveal choroidal thickness (F) was close to be significantly thinner in convalescent VKH patients, compared with controls ($p=0.055$), although all eyes had sunset glow fundus appearence. Another study (Nakai et al. 2012) concluded that choroidal thinning seems to be correlated to sunset glow fundus appearance in convalescent stage of VKH patients. Despite this, in our study we have demonstrated a significant choroidal thinning in NS, TS and TI quadrants in the convalescent stage of VKH disease, compared with the control group. The choroid was globally thicker in the temporal quadrants (TS and TI) compared to nasal quadrants, as has already been described (Ouyang et al. 2011). However, some temporal thinning was found in VKH patients, comparing to normal subjects. NI quadrant in the convalescent stage of the disease was not significantly thinner compared to controls. It has been demonstrated that the choroid is thinner in this inferonasal quadrant in normal subjects (Ouyang et al. 2011).

During convalescence, BCVA does not seem to be correlated neither with subfoveal choroidal thickness nor with subfoveal retinal thickness. The majority of the patients returned to 20/20 BCVA when they became into remission.

The present study also showed the same distribution of subfoveal choroidal thickness despite different treatment options. Early high doses of systemic corticosteroid

treatment (≥1mg/kg per day) proved to be correlated with better prognostic factors (Read et al. 2006; Chee et al. 2009), such as final BCVA. During the acute stage and to suppress the choroidal inflammatory levels as soon as possible, most authors recommend high dose systemic corticosteroids [e.g. i.v. (pulse) methylprenisolone 1000mg per day] followed by tapering oral schemes, lessening the probability of recurrence (Read et al. 2006; Lai et al. 2009; Bordaberry 2010). According to the prognostic factors of VKH disease (Chee et al. 2009) future visual acuity is inversely correlated to time of recovering.

In the current study, 4 patients (8 eyes) presented ocular hypertension during the follow-up period. We tried to analyse the relationship between the severity of choroidal thinning and the presence of this finding. No significant differences were found. Some authors (Maul et al. 2011; Mwanza et al. 2011) have already tried to find a correlation between glaucoma and choroidal thickness but found no significant results. Once a significant percentage of VKH patients develops glaucoma, SDOCT may be a good method to study not only the choroid, but also the peripapillary retinal nerve fiber layer.

Another critique to our study could be made to the method of choroidal measurement. Manual segmentation of the choroid is associated with errors and biases, because it is subjectively determined by the investigator. Furthermore it is hard to do accurate measurements of VKH choroidal outline due to frequent media opacities in VKH patients, from cataract or vitreous densifications, often overshadowing the image by decreasing the signal strength. An OCT incorporated software analysis system allowing choroidal thickness and volume measurements (similar to the one used to measure retinal thickness and volume) may surpass some unavoidable subjectivity.

Evaluation of the choroidal involvement in VKH patients, using EDI-SDOCT, at the moment of the diagnosis, could be helpful for the diagnosis, monitoring the status of the disease and assessment of treatment efficacy. EDI-SDOCT has been proved to detect low-grade VKH activity (Nakai et al. 2012), therefore quantitative measurement of choroidal thickness may be a valuable tool for longitudinal follow-up. We also believe that EDI-SDOCT may be a useful monitoring test in VKH treatment while tapering, helping to detect recurrence in the convalescent stage.

In summary objective morphologic evaluation of the choroid seems to be a useful non-invasive method in the assessment of VKH activity. While trying to map a choroidal profile, we found a significant choroidal decrease in the temporal quadrants. Further

studies could determine if there is a preferential pattern of choroidal map thinning in long-standing disease.

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Competing interests

Authors do not have conflict interests related to the development of this work.

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Figure Legends

Fig. 1. Manual segmentation of the choroidal layer. A reference line was manually positioned in the choroidal-scleral interface in each of the 19 horizontal scans. The choroidal thickness profile is represented by the black line in the bottom graphic, where we can also see the retinal profile through the same scan. The green vertical line crossing the fovea, measures the choroidal thickness in that point (276 µm). CSI-choroidal-scleral interface; BM – Bruch's Membrane

Fig. 2. Correlation between central retinal macular thickness and follow-up period in Vogt-Koyanagi-Harada disease group. Red circles represent individual patients' eyes (p=0.706, Spearman's correlation test).

Fig. 3. Graphic showing the mean choroidal thickness measurements in an horizontal scan through the fovea (F) and at 500, 1500 and 3000 µm nasal (N500, N1500, N3000) and temporal (T500, T1500, T3000) to the fovea.

Fig. 4. Choroidal thickness measurements by quadrants in Vogt-Koyanagi-Harada patients (first image) and controls (second image). TS, NS, TI, NI represent temporal-superior, nasal-superior, temporal-inferior and nasal-inferior quadrants, respectively. Mean values as well as standard deviation and statistic value are described. Mean measurements performed through the horizontal scan crossing the fovea at 500, 1500 e 3000 µm are also displayed.

Fig. 5. Correlation between central choroidal thickness and follow-up period in Vogt-Koyanagi-Harada disease group. Red circles represent individual patients' eyes (p=0.469, Spearman's correlation test)

Tables

Table 1. Demographic and clinical characteristics of controls and patients with Vogt-Koyanagi-Harada disease.

Description	Controls	Patients	p-value
No. individuals (eyes)	9 (18)	9 (18)	NA
Age mean±SD (years)	49.00±6.21	47.11±9.55	0.151
Male/Female, n	1:8	2:7	0.584
Disease duration, mean±SD (range in months)	NA	123.22±181.37 (7 to 600)	NA
Recurrence	NA	2	NA
Treatment			
-Systemic corticotherapy	NA	3	NA
-Systemic corticotherapy and other immunossupressive agent	NA	5	NA
-Missings	NA	1	NA
Clinical manifestations (acute stage)			
Meningismus	NA	3	NA
Tinnitus	NA	3	NA
Cerebrospinal fluid pleocytosis	NA	3	NA
Integumentary findings	NA	3	NA
Sunset Glow Fundus in convalescent stage (eyes)	NA	9 (18)	NA
Ocular Hypertension (eyes)	NA	4 (8)	NA

NA: non-applicable

Illustrations and Graphics

Fig. 1

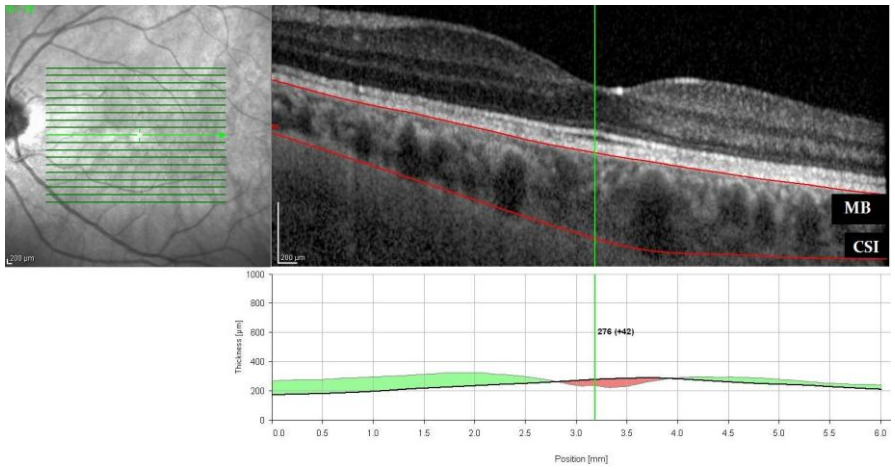


Fig.2

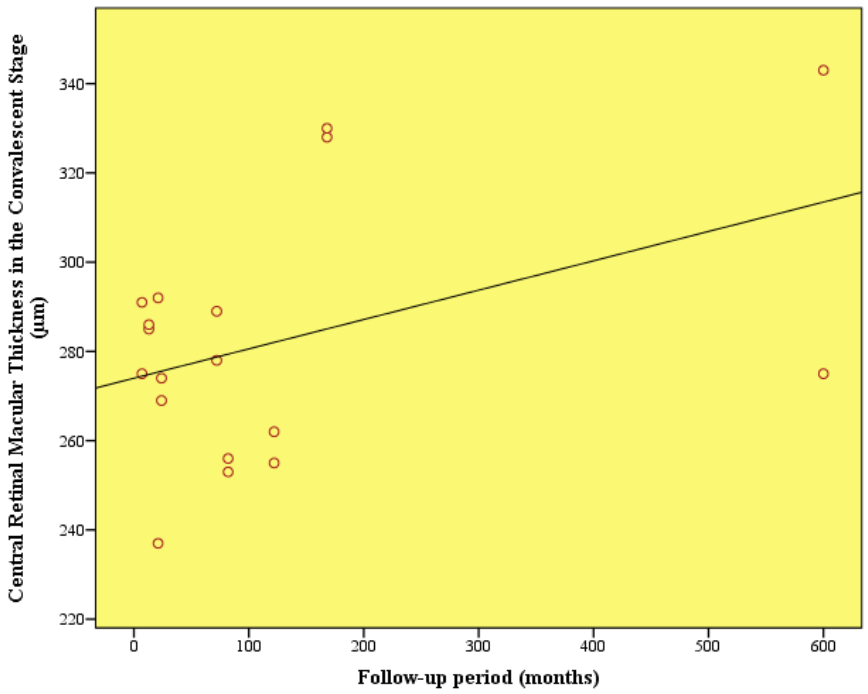

Central Retinal Macular Thickness in the Convalescent Stage (μm)
340
320
300
280
260
240
220
0
100
200
300
400
500
600
Follow-up period (months)

Fig. 3

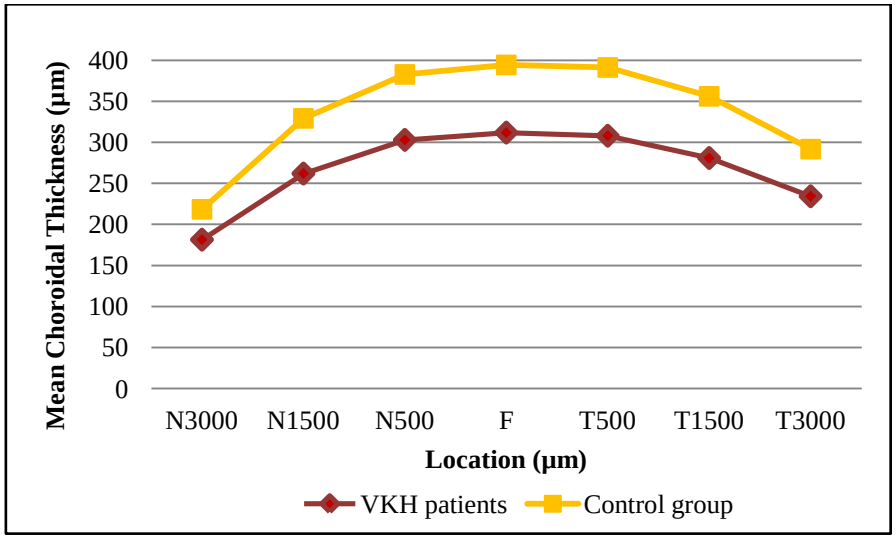

Mean Choroidal Thickness (µm)
400
350
300
250
200
150
100
50
0
N3000
N1500
N500
F
T500
T1500
T3000
Location (µm)
VKH patients
Control group

Fig. 4

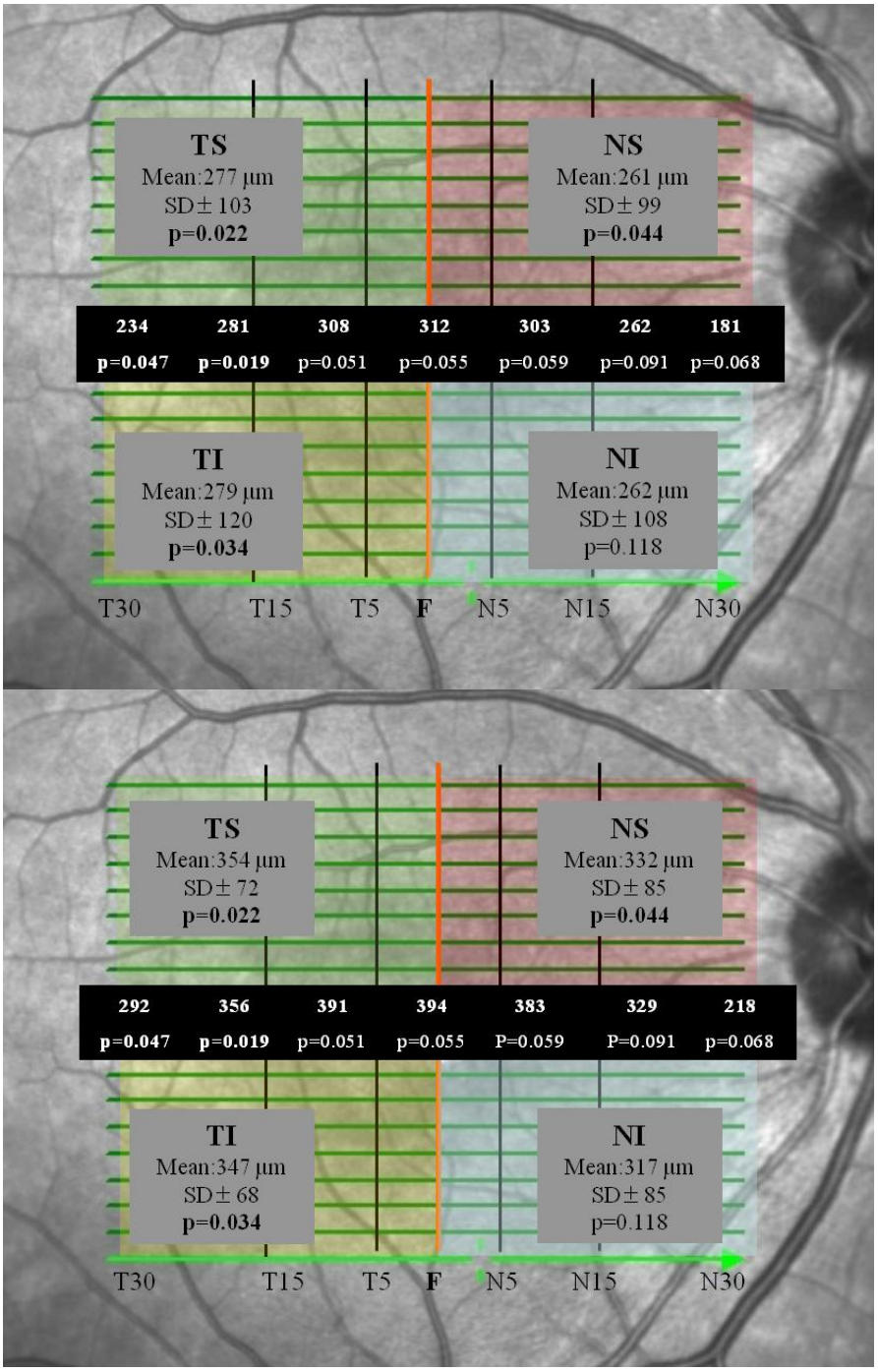
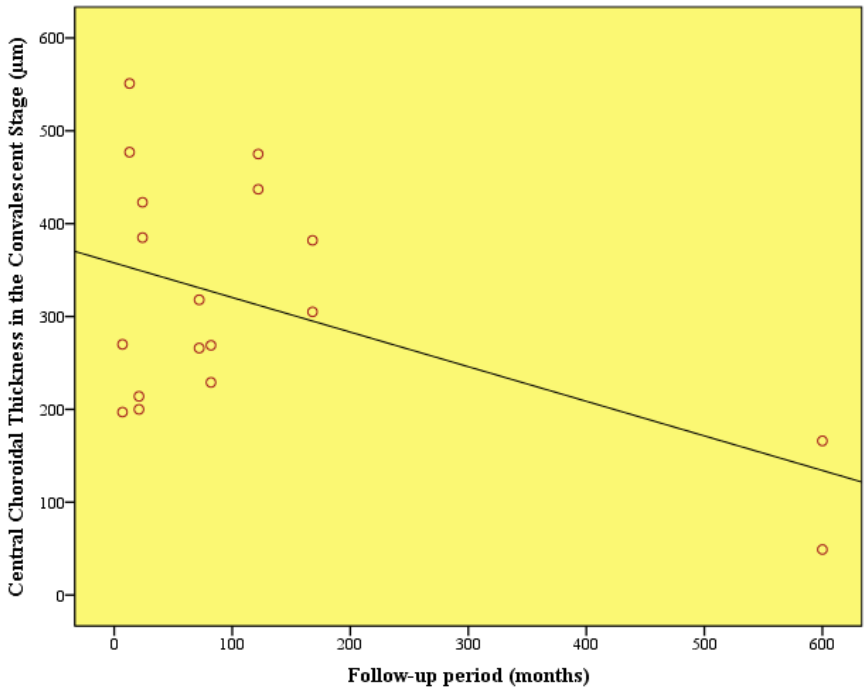

TS
Mean:277 µm
SD± 103
p=0.022
NS
Mean:261 µm
SD± 99
p=0.044
234 281 308 312 303 262 181
p=0.047 p=0.019 p=0.051 p=0.055 p=0.059 p=0.091 p=0.068
TI
Mean:279 µm
SD± 120
p=0.034
NI
Mean:262 µm
SD± 108
p=0.118
T30 T15 T5 F N5 N15 N30
TS
Mean:354 µm
SD± 72
p=0.022
NS
Mean:332 µm
SD± 85
p=0.044
292 356 391 394 383 329 218
p=0.047 p=0.019 p=0.051 p=0.055 P=0.059 P=0.091 p=0.068
TI
Mean:347 µm
SD± 68
p=0.034
NI
Mean:317 µm
SD± 85
p=0.118
T30 T15 T5 F N5 N15 N30

Fig. 5


Central Choroidal Thickness in the Convalescent Stage (μm)
600
500
400
300
200
100
0
0
100
200
300
400
500
600
Follow-up period (months)

Anexos

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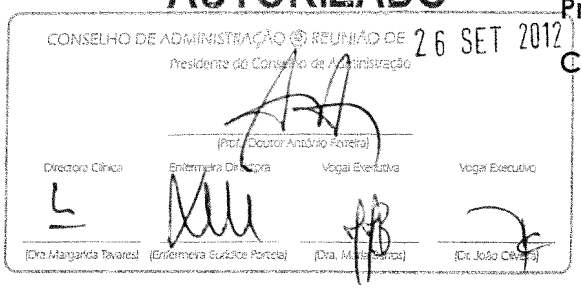

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Nome do Investigador Principal: Catarina de Fátima Ala Baraças

Título do projecto de investigação: Choroidal evaluation using enhanced depth imaging spectral-domain optical coherence tomography in Vogt-Koyanagi-Harada disease

Pretendendo realizar no(s) Serviço(s) de Oftalmologia do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

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O INVESTIGADOR/PROMOTOR

Catarina Baraças

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Adenda ao Protocolo do Projecto de Investigação:

"Choroidal evaluation using enhanced depth imaging spectral-domain optical coherence tomography in Vogt-Koyanagi-Harada disease"

→ O objetivo deste estudo passa pelas avaliações retro e prospectiva da coróide em doentes com Vogt-Koyanagi-Harada, através do método de imagem não invasivo, recentemente desenvolvido, e designado por enhanced depth imaging spectral-domain optical coherence tomography (EDI-SDOCT). Serão avaliadas as alterações morfológicas da coróide e investigadas as possíveis diferenças significativas entre os doentes em fase aguda e crónica/de convalescença.

Tratando-se de um estudo retrospectivo, mas também prospectivo, será pedido o consentimento informado a todos os doentes que realizarem o exame de imagem com EDI-SDOCT, no contexto do estudo em causa.

→ O título do projecto foi alterado por questões relacionadas com regras de publicação, sendo que o título final do projecto será: ***"Choroidal Features in Vogt-Koyanagi-Harada Disease: Imaging beyond the Retinal Pigment Epithelium with Spectral-Domain Optical Coherence Tomography".*** Os objectivos do estudo, bem como os dados necessários à realização do mesmo continuam a ser os mesmos.

14/01/2013 Catarina Baraças

SÃO JOÃO
HOSPITAL

COMISSÃO DE ÉTICA PARA A SAÚDE – H. S. JOÃO

PARECER

Título da Investigação: "Choroidal evaluation using enhanced depth imaging spectral-domain optical coherence tomography in Vogt-Koyanagi-Harada disease"

Investigador: Catarina de Fátima Ala Baraças

Orientador: Susana Costa Nunes Penas

Elo de ligação: Susana Costa Nunes Penas

Serviço onde se realizará a Investigação: Oftalmologia; dispõe de autorização do Exmo. Sr. Diretor do Serviço, Prof. Dr. Falcão Reis

Pretendendo a Dra. Catarina Baraças alargar o período de análise dos doentes com as caraterísticas descritas no projeto de investigação supra (projeto CES 198-12), assumindo assim um caráter prospetivo e não apenas retrospetivo, foi solicitada à CES a aprovação desta alteração.

Para o efeito foi redigida uma folha de Informação ao Participante e um Documento para obtenção de Consentimento Informado, em linguagem apropriada, que cumpre os requisitos éticos que estes documentos carecem.

As OCTs serão realizadas pela Dra Susana Penas, médica especialista do Serviço de Oftalmologia do HSJ e também orientadora desta Tese de Mestrado.

Por outro lado, a investigadora invoca que, por questões relacionadas com as regras de publicação, o **título final** do projeto deveria ser: **"Choroidal Features in Vogt-Koyanagi-Harada Disease: Imaging beyond the Retinal Epithelium with Spectral-Domain Optical Coherence Tomography"**.

Estas alterações não colocam reservas de natureza ética, pelo que proponho a esta CES a emissão de um parecer favorável à implementação do trabalho de investigação em apreço.

Porto, 25 de Janeiro de 2013

A relatora,

Raquel Ribeiro

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)
NÃO ☐
NÃO APLICÁVEL ☒

8. TERMO DE RESPONSABILIDADE

Eu, Catarina de Fátima Ala Baraças, abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 14 / Janeiro / 2013

Catarina Baraças

O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES de 21 / Janeiro / 2013

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética