Evaluation of Retina and Choroid in Long Term HIV Infection Patients Receiving Antiretroviral Treatment

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ABSTRACT

Purpose: To evaluate changes in macular thickness, ganglion cell inner plexiform and choroid layer of long term Human Immunodeficiency Virus (HIV) infected patients by optical coherence tomography (OCT) who treated with antiretroviral therapy.

Matherials and Methods: The study included 50 HIV cases receiving antiretroviral therapy and 50 control groups. Best corrected visual acuity, anterior and posterior segment examinations were performed in both groups. Macula, optic disc and choroid layer measurements were performed with OCT device.

Results: The number of males / females in the HIV group is 37/13 and the average age is 42.7 ± 8.3 years, the number of males / females in the control group is 35/15 and the average age is 42.8 ± 8.1 years. No statistically significant difference was found in terms of age and gender in both groups(P = 0.96, P = 0.76 respectively). Avarage choroidal thickness is 267.5 ± 33.1µ in HIV group and 283.3 ± 24.8 µ in control group.(P=0.008) Average macular thickness is 299.8 ± 12.1 µ in HIV group and 316.1 ± 14.4 µ in control group.(P = 0.001) Retinal nerve fiber thickness is 102.9 ± 10.1 µ in the HIV group and 106.2 ±13.7 µ in the control group.(P = 0.173)

Conclusion:HIV patients who received treatment developed thinning in inner retinal layers and choroid layer over time compared to healthy individuals. It suggests that viral particles have degenerative effects on retinal cells by triggering autoimmune reactions. This situation has negative trophic effect on other layers and causes thinning in the macula and choroid.

Keywords: Ganglion cell-inner plexiform layer, HIV, Macular thickness, Retinal microangiopathy.

INTRODUCTION

The Human Immunodeficiency Virus (HIV), emerged in 1890, has led deaths by predisposing opportunistic infections causing Acquired immunodeficiency syndrome (AIDS). In the HIV infection, primary mechanism is predisposition to opportunistic infections (e.g. CMV retinitis, pneumocystis carinii pneumonia, Candida infections) by reducing CD4+ T lymphocyte count over time. In HIV infection, mortality and morbidity have significantly reduced and it has become a chronic disease by introduction of combination antiretroviral agents (cART) in the treatment in 1986.[1] Vision impairments are important comorbidity in these patients. Before cART era, opportunistic infections such as CMV were leading severe loss of vision and even blindness by causing retinitis.[2] By introduction of cART regimen, CMV-related ocular morbidity has been markedly decreased. In recent years, structural and functional alterations not resulting from infectious retinitis or not detected in retinal examination as well as unexpected reduction in visual function have been emerged following prolonged life expectancy after cART. These alterations were termed as HIV-related neuroretinal disorder (HIV-NRD).[3] The ophthalmological pathologies observed in relation with HIV-NRD includes abnormal electrophysiological tests,[4,5] decreased contrast sensitivity, loss of peripheral visual field and color vision disorders.[6] In relation with HIV, increased phagocytic activity in retinal pigment epithelium and injured cone genes in retina have been reported.[7]

Optical coherence tomography (OCT) is a revolutionary technology in the field of ophthalmology. The OCT can provide data about different retinal layers and choroid in a

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non-invasive manner. The aim of this study was to identify retinal and choroidal changes in HIV patients received long-term antiretroviral treatment by comparing healthy population. In addition, it was also aimed to observe effect of premature aging on choroidal and retinal layer shown in previous studies by selecting middle-aged patients without HIV retinopathy.[8]

MATERIAL AND METHOD

This is a prospective, cross-sectional, case-control study. The study included the patients collaboratively followed by infectious diseases and ophthalmology departments of Atatürk Training and Research Hospital, İzmir Katip Çelebi University. The study was approved by Ethics Committee and Institutional Board of Atatürk Training and Research Hospital, İzmir Katip Çelebi University. All HIV-infected patients and healthy controls gave written informed consent. The study was conducted in accordance to tenets of Helsinki Declaration. In all subjects, right eye was included to the study. The visual acuity was measured using Snellen charts and transformed to LogMAR. Biomicroscopic examination was performed to measure intraocular measurement and anterior segment assessment. The patients with refractive errors ranging from -3D to +3D spherical equivalent and those with ocular trauma or surgery were excluded. Posterior segment assessment was performed under pupil dilatation (using 1% tropicamide by 90 D lens. The patients with history of CMV retinitis or active opportunistic infections were excluded. Again, patients with intraretinal hemorrhage, venous dilatation, micro-aneurysms and retinal micro-angiopathy findings such as telangiectasia were excluded. In addition, patients with history of previous ocular disease such as diabetic retinopathy, glaucoma, macular degeneration, uveitis and optic atrophy; and those with systemic hypertension were also excluded.

The standard macular thickness, optic disc and choroidal thickness measurements were performed between 09:00 and 11:00 AM (due to diurnal effect) using OCT device. Choroidal thickness was measured at subfoveal region and 3 temporal and nasal points by 500-µm distance, which then averaged and included to analysis (Figure 1). In addition, ETDRS macular thickness map, ganglion cell complex and retinal nerve fiber layer (RNFL) measurements were also performed. Data were analyzed using SPPS version 21.0.

FINDINGS

The study included 50 HIV patients attending regular follow-up visits and 50 healthy controls. In the HIV group, there were 13 women and 37 men with mean age of 42.7±8.3 years (30-55 years). In the control group, there were 15 women and 35 men with mean age of 42.8±8.1 years (30-55 years). There was no significant difference in age, gender distribution, intraocular pressure, axial length and spherical equivalent between groups (Table 1). The visual acuity was 0.9 in both patient and control groups while all eyes included were phakic. Mean macular thickness was 299.8 ±12.1 µm in the HIV group and 316.1 ±14.4 µm in the control group ($p<0.05$; Table 2). Mean choroidal thickness was 267.5±33.1 µm in the HIV group and 283.4±24.8 µm in the control group ($p=0.08$; Table 3). Mean RNFL thickness was 102.9±10.1 µm in the HIV group and 106.2±13.7 µm in the control group ($p=0.17$; Table 4). As seen in Tables, subfoveal and mean choroidal thickness, central foveal and mean macular thickness as well as macular thickness at all quadrants and RNFL thickness at nasal, inferior and superior regions

Table 1: Demographic characteristics and ocular parameters of HIV and control groups

Parameters	HIV (n = 50)	Control (n = 50)	*p*
Age (year)	42.7 ± 8.3	42.8 ± 8.1	0.961*
Gender (Male/Female)	37/13	35/15	0.769*
Intraocular pressure (mmHg)	15.9 ± 1.8	15.9 ± 1.4	0.952†
Axial length (mm)	22.7 ± 0.6	22.9 ± 0.8	0.509†
Spherical equivalent (dpt)	-0.32 ± 0.7	-0.34 ± 0.6	0.813†
Disease duration (year)	8.8 ± 2.3	-	-
HIV-RNA(copy/mL)	173.6 ± 913.8	-	-
CD4+ T cell (cell/µL)	605.4 ± 279.5	-	-

**Mann-Whitney U test, †Independent sample t test Değişken t testi*
Values are presented as mean± standart deviation.

Table 2: Comparion of macular thickness and ganglion cell complex thickness between HIV and control groups

Macular Segment (µ)	HIV (n = 50)	Control (n = 50)	*p**
Foveal MT	254.2 ± 18.2	264.2 ± 16.4	0.005*
Mean MT	299.8 ± 12.1	316.1 ± 14.4	< 0.001*
Inner temporal MT	316.9 ± 24.2	328.8 ± 16.9	0.006†
Inner nasal MT	336.9 ± 17.9	346.4 ± 18.2	0.010*
Inner superior MT	335.9 ± 19.4	348.6 ± 16.5	0.001†
Inner inferior MT	330.5 ± 23.6	341.3 ± 20.4	0.016†
Outer temporal MT	278.4 ± 38.1	293.4 ± 16.5	0.013†
Outer nasal MT	310.4 ± 18.2	320.3 ± 16.1	0.005*
Outer superior MT	293.6 ± 23.8	304.1 ± 15.3	0.011†
Outer inferior MT	287.1 ± 30.3	298.4 ± 16.7	0.022†
Mean GCC	107.7±8.3	112.0±7.2	0.019†
Inner temporal superior GCC	107.5 ± 13.8	114.7 ± 8.1	0.054†
Inner temporal inferior GCC	106.8 ± 12.5	115.1 ± 8.9	0.146*
Inner nasal superior GCC	114.6 ± 12.6	123.6 ± 8.8	0.069*
Inner nasal inferior GCC	113.7 ± 13.2	122.6 ± 8.4	0.085†
Outer temporal superior GCC	90.1 ± 7.5	92.1 ± 10.1	0.150*
Outer temporal inferior GCC	91.7 ± 14.1	97.9 ± 11.8	0.059*
Outer nasal superior GCC	107.3 ± 11.2	115.5 ± 9.7	0.303*
Outer nasal inferior v	106.5 ± 11.6	117.8 ± 11.1	0.184*

MT. Macular thickness, GCC. Ganglion cell complex, µm=Micron
**Independent sample t test; †Mann-Whitney U test*
Values are presented as mean ± standard deviation

Table 3: *Comparison of choroidal thickness between HIV patients and controls.*

Choroidal thickness	HIV (n = 50)	Control (n = 50)	*p**
Subfoveal (µ)	275.5 ± 34.2	297.4 ± 28.3	< 0.001
Mean nasal (µ)	262.4 ± 34.1	269.3 ± 24.6	= 0.24
Mean temporal (µ)	271.6 ± 32.9	297.3 ± 28.1	< 0.001
Mean total (µ)	267.5 ± 33.1	283.3 ± 24.8	= 0.008

**Independent sample t test, µm= Micron*
Values are presented as mean± standard deviation

Table 4: *Comparison of RNFL thickness between HIV patients and controls.*

RNFL (µ)	HIV (n = 50)	Control (n = 50)	*p**
Whole RNFL	102.9 ± 10.1	106.2 ± 13.7	0.173†
Nasal RNFL	72.3 ± 15.8	86.7 ± 18.7	0.001†
Inferior RNFL	120.7 ± 24.1	136.7 ± 20.1	0.001*
Superior RNFL	120.9 ± 24.4	130.5 ± 19.7	0.033*
Temporal RNFL	73.4 ± 10.3	70.6 ± 18.2	0.340*

RNFL. Retina nerve fiber layer, µm=Micron
**Independent sample t test, †Mann-Whitney U test; µm= Micron*
Values are presented as mean± standard deviation

were significantly reduced in HIV-infected patients when compared to controls.

DISCUSSION

Classically, HIV infection can result in mortality and comorbidity predisposing opportunistic infections by leading AIDS. By cART protocol used since 1996, life expectancy has been prolonged as well as opportunistic ocular infections have been decreased. The disease has a chronic, slowly progressing course now.

Although a significant reduction was reported in infectious retinitis in some studies, it was shown that HIV patients had

significantly higher rates of visual impairment up to 40%.[9] These alterations which cannot be observed in fundus and not related to infectious retinitis are termed as HIV-related neuroretinal disorder (HIV-NRD).[3] HIV-NRD comprises a wide spectrum including neurological disorders.[3] In a comprehensive, prospective study, it was shown that HIV-NRD incidence was 1.9% at the start of study, which was reached up to 51% by cART after 20 years.10 In the same study, it was shown that mortality remained as high as 70% although CD4+ T cell counts and HIV-RNA viral load were improved. Although cART regimen slows disease progression, transforming to a chronic disease, HIV-NRD should be carefully considered. As HIV is transformed a chronic disease, chronic non-infectious loss of vision has become increasingly important. Our findings demonstrated thinning in peripapillary nerve fibers, choroid and macula as well neuroretinal degeneration.

In HIV-NRD, pathophysiology hasn't been elucidated yet. Hypotheses proposed include direct viral load, treatment-induced neuronal damage, chronic inflammation, micro-vasculopathy and biological aging.[11-12] There is an ongoing debate whether changes in HIV-NRD are related to CD4+ T cell count or persistent viremia (HIV-RNA). Demirkaya et al. suggested that viral load, cART regimen and genetic factors trigger mitochondrial toxicity, immunological response and micro-vasculopathy which, in turn, result in early aging of cell and that low CD4+ T cell count is associated to neuroretinal injury, thinner retinal nerve fiber layer, decreased color vision and contrast sensitivity while retinal vascular alteration are retinal blood flow changes are associated with viral load and chronic inflammation rather than CD4+ T cells.[3] In some studies, it was found that there was significant thinning in RNFL thickness in HIV-positive patients with low CD4+ T cell count when compared to those with high CD4+ T cell.[13, 14] However, no significant difference was observed in RNFL layer in other studies.[15] Similar to our study, Çetin et al. reported no significant thinning in RNFL thickness. This suggest that RNFL thickness is affected by other factors such as viral load, vascular pathologies, treatment and disease duration in addition to CD4+ T cell count. The study by Jabs et al. strongly suggested role of CD4+ T cells in the pathophysiology.[10] In that study, risk for HIV-NRD was increased by 2-folds in patients with CD4+ T cell count <100 while no significant difference was seen in patients with CD4+ T cell count of 100-200 or >200.

Many studies reported thinning at macular layers. Çetin et al. observed significant thinning in all layers, mainly in outer plexiform layer.[15] In our study, thinning was noted in both nasal and temporal regions. We attributed this to injury and thinning of choroidal layer due to chronic HIV-related inflammation. Demirkaya et al. proposed that mitochondrial dysfunction may also play role in the pathophysiology.[3] Given that choroid has highest vascularity in human body; thus, mitochondria is highly essential for choroid, we think that injured choroidal vascularity leads thinning particularly at outer retinal layers, resulting in electrophysiological changes, loss of color vision and decreased contrast sensitivity. Above-mentioned studies suggest that choroidal and vascular injury resulting from persistent viremia and chronicity may be predominant in pathophysiology rather than CD4+ T cell count. Although CD4+ T cell count can change during chronic disease course and even it can rise a certain level as reported by Jabs et al., failure to rule out HIV-NRD suggest that viremia and vascular injury may be more predominant.[10] The choroid has an apparent effect on blood supply and physiology of outer retinal layers. The changes in color vision and electrophysiological test previously shown in HIV-infected patients are suggestive for involvement of outer layers.[6,9, 16-17] This indicates that, although disease has a non-fatal, chronic course, it continues to damage visual function. To best of our knowledge, only study on choroidal structure in HIV patient on cART regimen was conducted by Çetin et al. who evaluated choroidal thickness and found no significant difference. In the subgroup analysis, authors showed that newly diagnosed patients had thinner choroid when compared to those on therapy. In our study, it was found that choroidal thickness was significantly decreased when compared to healthy controls. We think that vascular structures are affected by viral load and chronic inflammation and resultant vasculopathy affects choroid and retinal layers. These are normal findings of aging. In our study, long-term posterior segment changes in HIV-infected patients were compatible with premature aging. We think that this may result from negative effects of virus particles on cellular metabolism, mitochondrial dysfunction, micro-vasculopathy, direct injury of neuronal cells by virus and chronic inflammation.

Our study has some limitations including small sample size and shorter follow-up. Further studies with larger sample size are needed, particularly in choroid. Today, where HIV has become a chronic disease, it is obvious that vision is affected at subclinical level.

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