Peripapillary retinal nerve fiber layer and choroidal thickness in cirrhosis patients

Espessura da camada de fibras nervosas peripipilares da retina e coroide em pacientes com cirrose

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ABSTRACT

Purpose: To evaluate the effect of cirrhosis on peripapillary retinal nerve fiber layer and choroidal thickness with enhanced depth imaging optical coherence tomography. Methods: This cross sectional, single center study was undertaken at Bulent Ecevit University Ophthalmology department with the participation of internal medicine, Gastroenterology department. Patients who were treated with the diagnosis of cirrhosis (n=75) were examined in the ophthalmology clinic. Age and sex matched patients (n=50) who were healthy and met the inclusion, exclusion criteria were included in the study. Complete ophthalmological examination included visual acuity with Snellen chart, intraocular pressure measurement with applanation tonometry, biomicroscopy of anterior and posterior segments, gonioscopy, axial length measurement, visual field examination, peripapillary retinal nerve fiber layer, central macular and subfoveal choroidal thickness measurements. Results: The difference between intraocular pressure values was not statistically significant between cirrhosis and control group (p=0.843). However, mean peripapillary retinal nerve fiber layer thickness was significantly thinner in cirrhosis group in all regions (p<0.001) and subfoveal choroidal thickness was significantly thinner in cirrhosis group also (p<0.001). Moreover, central macular thickness of cirrhosis group was significantly thicker than the control group (p=0.001). Conclusion: Peripapillary retinal nerve fiber layer and subfoveal choroidal thickness was significantly thinner in cirrhosis patients.

Keywords: Cirrhosis; Peripapillary retinal nerve fiber layer; OCT; Subfoveal choroidal thickness

RESUMO

Objetivo: Avaliar o efeito da cirrose na camada de fibras nervosas da retina e na espessura da coroide através da tomografia de coerência óptica com imagem de profundidade aprimorada. Métodos: Este estudo transversal, de único centro, foi realizado no departamento de Oftalmologia da Universidade Bulent Ecevit com a participação do departamento de medicina interna e gastroenterologia. Os pacientes que foram tratados com o diagnóstico de cirrose (n = 75) foram examinados na clínica de oftalmologia. Foram incluídos pacientes correspondentes em idade e sexo (n = 50) que fossem saudáveis e possuíssem o critério de inclusão exigido pelo estudo. Realização de exame oftalmológico completo: acuidade visual com tabela de Snellen, a medida da pressão intraocular com tonometria de aplanação, biomicroscopia de segmento anterior e posterior, gonioscopia, medida do comprimento axial, exame de campo visual, camada de fibras nervosas da retina, macular central e medidas de espessura de coroide. Resultados: A diferença entre os valores de pressão intraocular não foram estatisticamente significativos entre os grupos cirrótico e controle (p=0.843). Entretanto, a espessura da camada de fibras nervosas da retina foi significativamente mais fina no grupo cirrótico em todas as regiões (p=0.001) e a espessura subfoveal da coroide também foi significativamente mais fina no grupo cirrótico (p=0.001). Além disso, a espessura macular central do grupo cirrótico foi significativamente mais grossa do que no grupo de controle (p=0.001). Conclusão: Por fim, as espessuras das camadas de fibras nervosas da retina e subfoveal da coroide foram significativamente mais finas nos pacientes com cirrose.

Descritores: Cirrose; Camada de fibras nervosas da retina; OCT; Espessura de coroide

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INTRODUCTION

Cirrhosis is a chronic liver disease that impairs the function of the liver by causing fibrosis of the tissue. Cirrhosis mainly occurs in patients with chronic liver diseases such as Hepatitis B-virus (HBV), Hepatitis C-virus (HCV) infection, alcoholic liver disease, non-alcoholic fatty liver disease, biliary diseases and autoimmune hepatitis. In addition, anything that damages the liver can cause cirrhosis. Model for End-Stage Liver Disease (MELD) and Child classification are most commonly used scales to classify the cirrhosis patients. Cirrhosis can be diagnosed by either histological evaluation of the liver biopsy samples and/or by using physical examination, blood tests and radiological findings. However, there is no cure for cirrhosis of the liver. The treatments are based on slowing down liver damage and reducing complications. The treatment options mainly vary with the stage of the illness and in part, depends on the cause of cirrhosis of the liver. Currently, there are several medications approved by the U.S. Food and Drug Administration (FDA) including interferon alpha, pegylated interferon, lamivudine, adefovir, entecavir, telbivudine, tenofovir, ribavirin, boceprevir, telaprevir, simeprevir, sofosbuvir are used for treatment of HBV and HCV infections. Furthermore, lifestyle modification, metformin, pioglitazone, ursodeoxycholic acid, statins and prebiotics are the therapeutic options in patients with non-alcoholic steatohepatitis (NASH) and cryptogenic hepatitis.

Although cirrhosis is the primary disease of liver, the systemic disorders due to cirrhosis such as hepatic encephalopathy, renal failure, immune suppression, coagulation disorders occur during disease progression and these systemic disorders may eventually lead to death. Eye is the one of the organs that may be affected by the disease. However, effects of cirrhosis on eye have not been evaluated sufficiently.

Ocular manifestations of HCV and HBV infections are dry eye, Mooren ulcer and retinopathy. In a recent study it was found that chronic HCV infection causes increased flare in anterior chamber and increased chorioidal thickness. Choroid is vitally important for the function of the retina. In the past, imaging techniques such as indocyanine green angiography, ultrasonography were used and gave limited information about the choroid. However, with the advancement of the spectral domain optical coherence tomography (OCT) and enhanced depth imaging (EDI) which was first described by Spaide, in vitro visualization of choroid resulted in understanding pathologic processes. OCT uses interferometry and low coherence light for high resolution cross section of the posterior segment tissues and it has the advantage of absolute measurement of nerve fiber layer thickness.

Aim of the present study is to evaluate the peripapillary retinal nerve fiber layer (RNFL) and choroid findings of cirrhosis patients with EDI-OCT.

METHODS

A cross sectional study was undertaken at Bulent Ecevit University Ophthalmology department with the participation of internal medicine, Gastroenterology department. Patients who were treated with the diagnosis of cirrhosis associated with HCV, HBV infection, non-alcoholic steatohepatitis (NASH) and also cryptogenic cirrhosis (n=75) were examined in the ophthalmology clinic. Age and sex matched patients (n=50) who were healthy and met the inclusion, exclusion criteria were included in the study. Informed consent was obtained from each participant and the study was conducted with the Declaration of Helsinki. The study was approved by Clinical Research Ethics Committee of the Bulent Ecevit University.

A detailed medical history was recorded and complete ophthalmological examinations including visual acuity with Snellen chart, intraocular pressure (IOP) measurement with applanation tonometry, biomicroscopy of anterior and posterior segments, gonioscopy, axial length measurement, visual field examination and peripapillary retinal nerve fiber analysis, central macular thickness and choroidal thickness measurements were done. Retinal analysis by EDI-OCT (Heidelberg Engineering, Heidelberg, Germany) were done after 30-40 minutes pupillary dilation by tropicamide 1%. All patients were evaluated at the same time period to eliminate the effects of diurnal variations of IOP and choroidal thickness. Visual acuity results were transformed to logMAR for statistical analysis.

Patients who had previous ophthalmic surgery, any ophthalmic disease preventing the view of the anterior chamber, posterior segment detail and retina analysis, glaucoma, pseudoexfoliation, senile macular degeneration, history of central serous chorioretinopathy, uveitis, axial length shorter than 22mm and longer than 24mm, systemic disease other than cirrhosis, autoimmune hepatitis, Wilson’s disease and alcoholic hepatitis were not included in the study.

Retinal nerve fiber analyze was done automatically in glaucoma mode of the EDI-OCT. A scan circle with a diameter of 3.45 mm was positioned manually at the center of the optic disc. The mean of hundred images was automatically analyzed by the OCT and measurements used for analysis included global as well as 6 regional subfields (nasal, nasoinferior, nosesuperior, temporal, temporoinferior and temporosuperior).

Macular thickness measurement was done automatically in retina mode, with horizontal scanning of 30x15 degree field. All scans were done in G-Dens mode which includes 37 B-scan images and with eye tracking mode on. Subfoveal choroidal thickness was measured manually. Images were taken in EDI mode, eye tracking on, which scans 30 degrees field and take 100 images. The best image was prepared by the EDI-OCT automatically. Subfoveal choroidal thickness was measured vertically from the outer border of the retinal pigment epithelium (RPE) to the choroidal-scleral interface after the image diameter was increased by 400%. All patients’ choroidal thickness measurements were done by 2 experienced ophthalmologist. If any disparity between the measurements occurs, mean of the 2 measurements was included in the statistical analysis (figure 1).

Cirrhosis was diagnosed either by histological evaluation of the liver biopsy samples and/or by using physical examination, blood tests and radiological findings. Besides, the cirrhosis patients were taking the available treatment in accordance with the occurrence of decompensation, characterized by ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, or variceal bleeding from portal hypertension. The patients with cirrhosis caused by HBV, HCV and NASH were using some of the drugs including pegylated interferon, lamivudine, entecavir, tenofovir, ribavirin, boceprevir, telaprevir and ursodeoxycholic acid.

SPSS 19.0 used for statistical analysis. Continuous variables are given with mean, standard deviation; qualitative variables
are given with frequency and percent. Shapiro-Wilk test set for test of normality. Kruskal-Wallis test for 3+ group comparisons and Mann Whitney U test and Bonferonni corrected Mann Whitney U tests used for 2 group comparisons for non-normal data. Pearson chi-square test used for crosstab comparisons. Spearman correlation analysis used to compare continuous variables. For all statistical comparisons with p value below 0.05 assumed as there is a statistically significant difference.

RESULTS

There is no statistically significant difference between the ages and genders of cirrhosis and control groups (p=0.753, p=0.470) (table 1).

Table 1
Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cirrhosis n=75</th>
<th>Control n=50</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Mean±SE</td>
<td>58.2 ± 11.0</td>
<td>59.3 ± 10.9</td>
<td>0.753</td>
</tr>
<tr>
<td>Female</td>
<td>38 (49.3)</td>
<td>23 (46)</td>
<td></td>
</tr>
<tr>
<td>Gender (n%)</td>
<td></td>
<td></td>
<td>0.470</td>
</tr>
<tr>
<td>Male</td>
<td>37 (50.7)</td>
<td>27 (54)</td>
<td></td>
</tr>
</tbody>
</table>

In the cirrhosis group 150 eyes and in the control group 100 eyes were included in the statistical analysis. In cirrhosis group 37 patients were diagnosed as HBV, 18 patients were diagnosed as HCV, 10 patients were diagnosed as non-alcoholic steatohepatitis (NASH), 10 patients were diagnosed as cryptogenic cirrhosis. The patients diagnosed as other than HBV and HCV were regrouped as non-infectious cirrhosis (NIC). Thus, cirrhosis group was sub-grouped as HBV, HCV and NIC.

Mean IOP was 13.9 ± 3.0 mmHg in cirrhosis group and 14.1 ± 2.7 mmHg in control group. The difference between IOP was not statistically significant between subgroups of cirrhosis patients (p=0.843). However, mean peripapillary RNFL thickness was significantly thinner in cirrhosis group in all sectors and subfoveal choroidal thickness was significantly thinner in cirrhosis group also. Moreover, central macular thickness of cirrhosis group was significantly thinner than the control group (table 2).

Table 2
Intraocular pressure and retina nerve fiber layer thickness values of groups

<table>
<thead>
<tr>
<th></th>
<th>IOP (mmHg)</th>
<th>RNFL-G (µm)</th>
<th>RNFL-N (µm)</th>
<th>RNFL-NI (µm)</th>
<th>RNFL-NS (µm)</th>
<th>RNFL-T (µm)</th>
<th>RNFL-TI (µm)</th>
<th>RNFL-TS (µm)</th>
<th>SFCT (µm)</th>
<th>CMT (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>14.1±2.7</td>
<td>102.9± 8.8</td>
<td>79.3±11.1</td>
<td>118.0±19.3</td>
<td>111.1±18.3</td>
<td>69.9±9.0</td>
<td>154.1±20.2</td>
<td>140.0±18.1</td>
<td>313.3±57.1</td>
<td>222.0±19.4</td>
</tr>
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<td>(n=100)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Cirrhosis Group</td>
<td>13.9±3.0</td>
<td>93.3±13.3</td>
<td>71.6±15.8</td>
<td>112.8±27.3</td>
<td>100.4±22.9</td>
<td>66.2±13.3</td>
<td>132.2±26.1</td>
<td>123.6±24.4</td>
<td>256.6±53.7</td>
<td>270.4±24.8</td>
</tr>
<tr>
<td>(n=150)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.843</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

IOP - Intraocular pressure; RNFL - Retina nerve fiber layer thickness; G - Global; N- Nasal; NI - Nasoinferior; NS - Nasosuperior; T- Temporal; TI - Temporoinferior; TS - Temporosuperior; S Subfoveal choroidal thickness

DISCUSSION

This is the first study that reports the effects of cirrhosis on peripapillary RNFL and subfoveal choroid thickness as far as we know. Cirrhosis patients had significantly thin RNFL in all segments of the optic nerve and subfoveal choroidal thickness (p<0.001). Moreover the mean difference between IOP values in both groups was not statistically significant (p=0.843). As a result, we could not explain the changes in the optic nerve RNFL with IOP. The RNFL changes may be result of vascular effects of the cirrhosis. There was no correlation between MELD and Child score with the IOP, RNFL or choroidal thickness (p=0.848, p=0.870 (RNFL- G), p=0.574).
Cirrhosis is a very important disease in the developing world. The response of the cells in liver to necrosis is collapse of hepatic lobules, formation of diffuse fibrous septa and nodular regrowth of liver cells. Histologic pattern of cirrhosis is nearly same in all diseases. There are many etiological factors causing cirrhosis. HBV, HCV and alcoholic cirrhosis are main causes of cirrhosis in developed world, HBV and HCV are main causes of cirrhosis in developing countries(21).

Cirrhosis can affect extra hepatic systems such as small vessels, kidneys, skin and eyes(22). There are several reports that support the relationship between dry eye and HCV-HBV infection(23,24). Moreover Mooren's ulcer, small vessel vasculitis causing necrotizing scleritis and peripheral keratopathy were reported with HCV infection(25). HCV also causes retinopathy characterized by posterior pole retinal hemorrhages, followed by cotton wool spots and peripheral retinal hemorrhages. Retinopathy of HCV is caused by complement mediated immune complexes resulting in vasoocclusion. HBV infection was found to be a risk factor of age related maculopathy(26). Roh et al. found association between HBV infection and age related maculopathy after adjusting the multivariate analysis for socioeconomic factors(27). There are some case reports that show maculopathy after adjusting the multivariate analysis to be a risk factor of age related maculopathy(28). Roh et al. found HBV infection was found with choroidal thickness resulting in vasoocclusion. HBV, HCV and alcoholic cirrhosis are main causes of cirrhosis in developed world, HBV and HCV are main causes of cirrhosis in developing countries(21).

In a pilot study Strobbe et al. investigated the subfoveal choroidal thickness and aqueous flare in patients with asymptomatic untreated chronic HCV infection. They found that asymptomatic HCV patients had thickened choroids and increased aqueous flare. Mean aqueous flare was significantly higher in HCV patients (8.37 ± 2.25 pc/ms vs 4.56 ± 1.45 pc/ms). Moreover, they stated that aqueous flare and choroidal thickness increase significantly with liver fibrosis(29). Results of the present study were not consistent with the study done by Strobbe et al. In the present study patients with cirrhosis had thinner choroidal thickness values than control subjects. This difference between the studies was probably because of the stages of the diseases. Our study group includes the cirrhotic patients with HBV, HCV and NIC. There was no correlation between CHILD score, MELD score, choroidal thickness and peripapillary RNFL. This makes us think that the metabolic changes in cirrhosis did not affect the RNFL and choroid changes.

In the present study the cirrhosis patients were using different kind of drugs for their treatment but ophthalmic adverse effect like thinning in peripapillary RNFL was not reported in either of the drugs except interferon. There are many studies that report interferon as a cause of retinopathy called interferon associated retinopathy(21). However, only 6 patients of HCV group was using interferon in the study and there was no interferon associated retinopathy in the study group. All groups were using different kind of drugs but there was no statistically significant difference between the groups in the mean of RNFL thickness. Thus, changes in the peripapillary RNFL and subfoveal choroidal thickness could not be because of the drugs.

There are some various reports investigating the choroidal thickness and glaucoma. Study done by Hirooka et al. found that choroidal thickness in nasal foveal region was thinner in normotension glaucoma. However, they found no difference because of the decrease in albumin values in cirrhotic patients, it is expected that reduced oncotic pressure in the vessels causes fluid influx to the vessels, and increase the choroidal thickness. We cannot explain the choroidal thickness values with metabolic results of cirrhosis also. As a result, thin RNFL seen in cirrhosis patients is probably because of the vascular effects of cirrhosis. In addition, Manjunath V. et al. reported that there was a weak correlation between central macular thickness and subfoveal choroidal thickness (r = -0.23, p=0.18)(29). Our results were consistent with the study.

In conclusion, peripapillary retina nerve fiber layer thickness thinning may be associated with the microvascular effects of cirrhosis in the absence of increased intraocular pressure. These cirrhotic patients are in active social life. They must be examined routinely to exclude retina nerve fiber layer thickness changes. Because of the systemic nature of the disease, other organs such as eye can be involved and easily overlooked. As far as we know present study is the first study that reports the retina nerve fiber layer thickness and choroid analysis in cirrhosis patients. There is no untreated patient group in the present study and the drugs could not be evaluated separately because of ethical reasons. These seem to be the limitation of the study. Future studies including larger populations are needed to understand the exact mechanism of optic neuropathy and decreased choroidal thickness.

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>IOP (mmHg)</th>
<th>RNFL-G (µm)</th>
<th>RNFL-N (µm)</th>
<th>RNFL-NI (µm)</th>
<th>RNFL-NS (µm)</th>
<th>RNFL-T (µm)</th>
<th>RNFL-TI (µm)</th>
<th>RNFL-TS (µm)</th>
<th>SFCT (µm)</th>
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<tbody>
<tr>
<td>HBV</td>
<td>14.8±2.6</td>
<td>93.8±12.7</td>
<td>72.1±15.5</td>
<td>113.9±29.0</td>
<td>100.7±24.9</td>
<td>67.9±12.7</td>
<td>131.0±25.0</td>
<td>123.5±24.2</td>
<td>251.3±50.8</td>
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<tr>
<td>HCV</td>
<td>13.3±3.5</td>
<td>93.5±12.3</td>
<td>70.3±15.1</td>
<td>111.7±25.1</td>
<td>101.3±20.1</td>
<td>65.8±12.4</td>
<td>133.9±25.3</td>
<td>126.8±27.2</td>
<td>246.9±56.1</td>
</tr>
<tr>
<td>NIC</td>
<td>12.8±2.6</td>
<td>92.1±15.3</td>
<td>71.9±17.3</td>
<td>111.9±26.7</td>
<td>99.0±22.0</td>
<td>63.6±14.9</td>
<td>132.8±29.1</td>
<td>121.0±22.2</td>
<td>275.1±53.4</td>
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<td>p-value</td>
<td>0.001</td>
<td>0.957</td>
<td>0.269</td>
<td>0.746</td>
<td>0.955</td>
<td>0.401</td>
<td>0.643</td>
<td>0.414</td>
<td>0.043</td>
</tr>
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</table>

IOP - Intraocular pressure; RNFL- Retina nerve fiber layer thickness; G - Global; N - Nasal; NI - Nasoinferior; NS - Nasosuperior; T - Temporal; TI - Temporoinferior; TS - Temporosuperior; SFCT - Subfoveal choroidal thickness
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