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Evaluation of Macular Vasculature in Patients with Schizophrenia Compared to Healthy Subjects

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Abstract

Background: The present study aims to evaluate the macular thickness and vasculature changes with a readily accessible method of Optical Coherence Tomography Angiography (OCT-A) in patients with schizophrenia compared to healthy individuals.

Methods: The present cross-sectional study was conducted in 2019 at Ibn-e-Sina Psychiatric Educational Hospital of Mashhad. Twenty-Two cases of schizophrenia treated with risperidone and 22 age-matched healthy individuals participated in the study. The severity of the disease was assessed using the Positive And Negative Syndrome Scale (PANSS) test. All participants underwent complete ophthalmic examination and OCTA imaging.

Results: There was a statistically significant difference for fovea full-thickness (P=0.021) and parafovea full retinal thickness (P=0.029) between schizophrenic and healthy subjects. Fovea full retinal thickness, parafovea full retinal thickness, Fovea vessel density, and parafovea vessel density were significantly lower in markedly ill schizophrenia patients than the moderately ill subgroup (P=0.027, P=0.017, P=0.034, P=0.015).

Conclusion: In the present study, retinal neural and vascular tissues could be used as a research model in schizophrenia. Foveal and parafoveal thickness was significantly lower in patients with schizophrenia than that of healthy subjects, but it does not necessarily mean that there is a degenerative process in the pathogenesis of schizophrenia.

Keywords: Disease severity, Macula, OCT-A, Schizophrenia

Introduction

Schizophrenia is one of the most common critical psychological disorders with a lifelong prevalence of approximately 0.6% to 1.9%; however, the exact pathophysiology is unclear(1). Although schizophrenia has been described as a single disease, it probably describes a spectrum of different abnormalities with heterogeneous etiologies and includes patients with different symptoms, therapeutic responses, and prognoses (2). To date, an important limitation for psychiatrists is that the diagnosis is based on the history and mental status examination. Unfortunately, there is no diagnostic laboratory test (3).

Scientists have identified various factors in the etiology of schizophrenia that helps to better understand the nature of the disease. Genetic, environmental, and biopsychosocial factors seem to have a significant role in the pathophysiology of the disease (4). For example, Hanson and Gottesman proposed that the genetic-vascular-inflammatory hypothesis of schizophrenia can explain the diversity of symptoms. Based on this hypothesis, environmental factors including infection, trauma, or hypoxia can trigger inflammatory responses in a genetically susceptible patient, causing damage to the micro-vascular system in the brain and leading to psychoses. The imbalance of neurotransmitters is one of the well-known mechanisms of the disease. Increasing in dopamine release, especially in mesocortical and mesolimbic pathways(5), a higher level of serotonin in the brain(6), selective dissolution of norepinephrine reward neurons in the central nervous system (7), and the dysfunction of GABAergic neurons in the hippocampus(8)are some examples of neurotransmitters imbalances suggested in recent studies.

Some studies, based on Magnetic Resonance Imaging (MRI), suggested a degenerative component in the pathogenesis of schizophrenia(9). The retina is an ideal candidate for research in neurodegenerative conditions for different reasons. From the embryologic perspective, the neurosensory retina, especially the nerve fiber layer, is an extension of the brain. From the anatomical aspect, the retina is a complex neural

network consisting of neurons and astrocytes that connect in the plexiform layers with a wide variety of neurotransmitters, including dopamine, serotonin, and Gamma-aminobutyric acid (GABA). Vascular supply of the inner two-thirds of the retina is by the central retinal artery, a branch of the ophthalmic artery; the latter directly originates from the internal carotid artery, which in turn, is the main vascular source of the brain(10). Furthermore, the eye has transparent media, enabling us to analyze the neural-microvascular structures with a readily available method named Optical Coherence Tomography Angiography (OCT-A).

OCTA is a non-invasive imaging technique for the evaluation of retinal and choroidal vasculature. It is safe, fast, and does not need any dye injection.

This study aims to evaluate the macular thickness and vasculature changes in patients with schizophrenia compared to healthy people with OCTA imaging.

Methods

The present cross-sectional study was conducted in 2019 at Ibn-e-Sina Psychiatric Educational Hospital of Mashhad. Twenty-two hospitalized known cases of schizophrenia, treated with risperidone as antipsychotics participated in the study. Two psychiatrists confirmed the diagnosis of schizophrenia in all cases based on DSM 5 criteria. The present study is consistent with the Declaration of Helsinki which is approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (IRB number: IR.MUMS.MEDICAL.REC.1398.035). The patient or his / her legal guardian signed the informed consent before participating in the study. Participants were evaluated for past medical history, pharmacological treatment, and psychological status. Patients with any other condition which could potentially affect the retinal neuro-vascular tissues such as using drugs (chloroquine, hydroxychloroquine, amiodarone, calcium channel blockers, and alcohol consumption) or having systemic or ocular conditions (glaucoma, diabetes, neurodegenerative diseases, uncontrolled hypertension, raised intracranial pressure, seizure, and collagen vascular disorders) were excluded from the study.

The demographic information, including age, gender, duration of smoking, predominant symptoms, and disease status were recorded. The patients with schizophrenia were divided into DITYL (duration of the illness ≤ two years) and DIMTY (duration of the illness > two years) subgroups.

A control group of 22 age-matched healthy individuals was recruited with no psychiatric, systemic, or ophthalmic disease and no history of consuming any medications or substances that affect the optic nerve, vessels, or retinal tissues.

Disease severity

The disease severity was assessed with the Positive And Negative Syndrome Scale (PANSS) test. PANSS questionnaire has already been described in detail; however, in brief, it is a medical scale developed in 1986 by Key, Fizsbein, and Opler to measure the severity of positive and negative symptoms in patients with schizophrenia [11]. It includes 30 items for evaluating three main symptom domains o24f schizophrenia; positive (7 items), negative (7 items), and general psychopathology (16 items). Each item is rated on a scale of 1 (absent) to 7 (extreme) (11). Patients are subdivided into four groups based on PANSS total score: mildly ill (up to 58), moderately ill (59-75), markedly ill (76-95), and severely ill (96-116) (12).

Ophthalmic examination

All participants underwent complete ophthalmic examinations including Best-Corrected Visual Acuity (BCVA) measurement with thumbing E chart, slit-lamp biomicroscopy, tonometry with Goldmann applanation tonometer, complete fundus examination with +90D condensing lens, and macular optical coherence tomography angiography (AngioVue RTVue XR Avanti, Optovue, Fremont, CA, USA, software version: 2018,0,0,18) with 3 * 3 mm scan size at the Khatam Al-Anbia Eye Hospital of Mashhad. The imaging was repeated if the quality index of the macular image was below 6/10. If any ocular abnormality was observed in the ophthalmic examinations (visually significant cataract, ERM, etc.), or if the image quality was below 0.6 for the second time, the eye was excluded from the data analysis. Only one eye of each participant was randomly regarded for data analysis.

Statistical analysis

Statistical analysis was performed using SPSS software (version 19). The Shapiro-Wilk test was used to confirm normal data distribution. Independent samples t-test and Chi-Squared test were used to ascertain proper matching of the two groups. The statistical significance of the difference in the fovea and parafovea full retinal thickness, inner retinal thickness, and vessel density between patients with schizophrenia and controls were determined using independent samples t-test or Mann-Whitney test. Pearson's or Spearman's correlation was employed to investigate the relationship between PANSS and OCTA parameters. A p-value less than 0.05 was considered statistically significant.

Results

Descriptive statistics

The participants included 22 patients with schizophrenia (11 males, 11 females) and 22 healthy individuals (12 males, 10 females)

(P=0.763). Two psychiatrists confirmed schizophrenia in all cases based on DSM 5 criteria. The schizophrenia group included the inpatients of Ibn-e-Sina hospital during a 6-month interval (2019) who had no history of medical conditions (such as glaucoma, diabetes, neurodegenerative diseases, uncontrolled hypertension, raised intracranial pressure, seizure, and collagen vascular disorder) or medications (chloroquine, hydroxychloroquine, amiodarone, calcium channel blockers, and alcohol consumption) which could affect the retinal neurovasculature. The mean ± SD age of schizophrenic and healthy participants was 35.86 ± 9.29 years and 34.36 ± 6.56 years, respectively (P=0.540). We collected PANSS score data from 21 participants; one patient with schizophrenia did not cooperate. In the schizophrenia group, the PANSS score was normally distributed, and the total PANSS score ranged from 53 to 116 with a mean ± SD score of 83.29 ± 13.77 (Table 1). According to this scoring, one patient had mild disease, and six cases had moderate disease, while twelve were markedly ill, and two individuals had severe schizophrenia. Based on the duration of the disease, six patients were identified as DYTIL, and thirteen patients had the disease with DIMTY chronology. The detailed charts and history were not available for three patients. All patients had risperidone as their antipsychotic regimen, with the mean ± SD dose of 4.40 ± 1.40 mg. Some patients occasionally used benzodiazepines, anticholinergics, and other antipsychotics to reduce agitation. Only three patients in the schizophrenia group and none in the control group were cigarette smokers (P = 0.73).

Ocular findings

In ophthalmic examinations, all cases in both groups had a BCVA of 20/20, and there were no significant ocular conditions that could affect the neurovascular tissues of the retina. The mean ± SD for intraocular pressure in the control and schizophrenia groups was 10.77 ± 1.41 and 11.18 ± 1.59 mm-Hg, respectively (P = 0.498). OCTA data from 3 patients in the schizophrenia group were unusable due to poor cooperation and low image quality indices. Only one eye of each subject was regarded for data analysis. Foveal full retinal thickness, fovea inner retinal thickness, parafovea full retinal thickness, parafovea vessel density, and fovea vessel density were evaluated and compared between the groups. Foveal full retinal thickness values were not normally distributed. Parafovea full retinal thickness (P=0.029) and fovea full-thickness (P=0.021) were significantly lower in patients with schizophrenia than those of healthy subjects (Table 2). We found no significant difference in OCTA parameters between the two genders in the control and schizophrenia groups.

We had OCTA data from 6 patients of DYTIL and 13 patients of DIMTY subgroups. Statistically significant differences were observed in fovea vessel density comparing those with DYTIL and DIMTY (P=0.016); however, no significant difference was demonstrated for other OCTA parameters.

OCTA parameters were analyzed based on disease severity. Mildly and severely ill patients were not included in statistical analyzes due to the small number of cases in each subgroup. Parafovea vessel density, fovea vessel density, fovea full-thickness, and parafovea full-thickness were significantly lower in the markedly ill than in the moderately ill group (P=0.015, P=0.034, P=0.027, P=0.017, respectively) (Table 3).

The probable relation between PANSS parameters and OCTA data was also evaluated. There was a significant negative correlation between parafovea full retinal thickness and PANSS-Anergia (r= -0.521, P=0.027), or total PANSS score (r=-0.500, P=0.035). No significant correlation was observed between other parameters (Table 4).

Discussion

This study was designed to investigate retinal neurovascular tissues in patients with schizophrenia compared to healthy individuals. Evaluation of various retinal parameters including, thickness and vascular density is easy, safe, readily available, and relatively inexpensive with OCT and OCTA.

In the present study, 22 patients with schizophrenia and 22 healthy cases participated. The data on mental status of the patients were obtained through PANSS besides a complete psychiatric interview. Only three patients in the schizophrenia group were smokers. Both groups were matched in terms of age and gender.

This study evaluated the macula with OCTA; this region roughly contains half of the retinal ganglion cells. It allows us to assess the vascular part of the macula, foveal and parafoveal vessel density, and the neural part including, the thickness of the foveal center, parafovea, and inner retina using the OCT technique. As mentioned earlier, new studies suggest a vascular inflammatory mechanism in the pathogenesis of schizophrenia. Therefore, concerning intimate correlation and integration between the retina and central nervous system, the possible changes in the neural part and the vascular part of the retina were examined in patients with schizophrenia using the OCTA. The results showed that the reduction in fovea and parafovea full retinal thickness in patients with schizophrenia was significant compared to the control group. Various causes have been suggested for retinal thinning, including drug toxicity, increased intraocular

pressure, ischemic vascular processes, and neurodegenerative processes. The question may be asked whether the difference in the fovea and parafovea full-thickness may be due to the neurodegeneration caused by any history of unmentioned/ unnoticed/ forgotten head trauma or similar cases (e.g., following convulsions / ECT) in the schizophrenia group.

In the present study, the total PANSS score ranges between 53 and 116, with a mean of 83.28. Parafovea vessel density, fovea vessel density, fovea full-thickness, and parafovea full-thickness were significantly lower in the markedly ill than in the moderately ill group. These observations reinforce the existence of a neurodegenerative part in the pathogenesis of schizophrenia. Based on the results of PANSS, a significant negative correlation was observed between parafovea full retinal thickness and anergia or total PANSS score, but there was no significant relationship between PANSS-positive and negative scores with OCTA parameters. Based on past psychiatric history, thirteen patients had DIMTY, and six patients had the DITYL disease. The reduction of fovea vessel density in DITYL patients with schizophrenia was significant compared to the that of DIMTY group.

The idea of using the retina as a part of the brain that can demonstrate similar changes has been already investigated, especially in neurodegenerative diseases. Hart et al. (2016) reported some retinal pathology in patients with Alzheimer's disease, including retinal nerve fiber layer thinning, ganglion cell layer degeneration, and vascular changes (13). In a brief report published (2020), Lee et al. found that the macular ganglion cell complex thinning could be used as a primary marker of neurodegeneration in Parkinson's disease (14). Recently, several studies investigated the role of OCT in patients with schizophrenia; however, the majority of them evaluated the peripapillary retinal nerve fiber layer and not the macula, and their results were highly controversial. In a study, Ascaso et al. evaluate

the retinal nerve fiber layer thickness in schizophrenic patients compared to the control group and demonstrated a significant reduction of overall and nasal retinal nerve fiber layer thickness in patients with schizophrenia (15). Contrarily, Chu et al. (2012) indicated no significant reduction in overall and peripapillary RNFL thickness or macular volume in patients with schizophrenia and schizo-affective disorder compared to the normal population [10]. Lee et al. (2013) assessed 30 patients with schizophrenia and 30 controls by spectral-domain-OCT technique. They found a significant reduction in macular volume, macular thickness, and peripapillary RNFL in patients with schizophrenia (16).

Mota et al., in a cross-sectional observational study published in 2017, showed a significant reduction in macular volume and macular thickness in patients with schizophrenia compared to the age/gender-matched group of healthy participants. This finding is consistent with the results of our study (17.) While Yilmaz et al. (2016) showed that the average macular thickness in the schizophrenia group was lower than that of the control group; however, the difference between the two groups was not significant (18).

The study of retinal microvascular changes in schizophrenia is a novel subject. The present study proposed that retinal neural and vascular tissues can be used as a research model in schizophrenia; however, the paucity of the published data and controversial results highlights the necessity for further studies. The limitations in this study included the possible effect of anti-psychotics on systemic and local ocular blood pressure and hemodynamic conditions of participants, level of emotional arousal and breathing conditions of these participants, and possible, undetected, simultaneous diseases like diabetes. Furthermore, the accurate drug history of the patients, especially the cumulative dose and duration of consumption, can be potentially confounding. The exact effects of antipsychotics such as risperidone, benzodiazepines, or mood stabilizers on retinal neuro-vasculature are unclear. A majority of included subjects were non-smokers which could be considered a strength of this study due to the possible effect of smoking on the retina, especially its vascular supply. Schizophrenia is a complex disease with different aspects. Functional and structural imaging of the brain and evaluation of retinal neurovascular tissues can help us better understand the pathophysiology of the disease. It is also suggested that further research will be performed with a larger sample size on a prospective cohort of patients with schizophrenia to better elucidate vascular changes over time and along disease course, with a particular focus on the pharmacological effect on these parameters.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of the present study.

Author Contributions

Conceptualization

Mehrdad Motamed Shariati, Maryam Naghib, Mohammad Reza Fayyazi Bordbar. Data curation: Maryam Naghib, Marziyeh Fotouhi. Formal analysis: Lida Jarahi, Mehrdad Motamed Shariati, Maryam Naghib. Funding acquisition: Mohammad Reza Fayyazi Bordbar. Investigation: Maryam Naghib, Mehrdad Motamed Shariati, Marziyeh Fotouhi. Methodology: Lida Jarahi. Project administration: Maryam Naghib, Mehrdad Motamed Shariati, Mohammad Reza Fayyazi Bordbar. Resources: Maryam Naghib. Supervision: Ramin Daneshvar, Mohammad Reza Fayyazi Bordbar. Validation: Mohammad Reza Fayyazi Bordbar, Ramin Daneshvar. Visualization: Mehrdad Motamed Shariati. Writing—original draft: Mehrdad Motamed Shariati. Writing—review & editing: Maryam Naghib, Ramin Daneshvar.

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