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ORIGINAL ARTICLE

Widened retinal arteriolar and venular diameters are not an endophenotype of schizophrenia: A one-time cross-sectional study.

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Abstract

OBJECTIVES: Studies of schizophrenia endophenotypes may help clinicians better understand the etiopathogenesis and treatment of this mental disorder. The aim of the study was to determine if retinal arteriolar or venular abnormalities are an endophenotype of schizophrenia.
DESIGN: We performed a one-time cross-sectional study.
MATERIALS AND METHODS: We enlisted schizophrenic patients (n = 53) hospitalized in the Department of Psychiatry, University Hospital Hradec Kralove; their mentally healthy first-degree relatives (n = 53); and unrelated, age- and sex-matched mentally healthy controls (n = 49). We recorded all participants´ sociodemographic and, if relevant, clinical variables. Retinal imaging was carried out using a digital fundus camera (FF450 + IR). Outcomes included retinal vessel calibers measured using the software application VAMPIRE.
RESULTS: The study enrolled fifty-three schizophrenic patients (average age 32.1 years; males n = 38), an equal number of healthy relatives (average age 47.3 years; males n = 18), and forty-nine unrelated healthy controls (average age 32.2 years; males n = 35). Patients with schizophrenia had significantly increased retinal arteriolar diameters when compared to unrelated healthy controls (left eye p = 0.003; right eye p = 0.011) but not when compared to healthy relatives. The sizes of the retinal venules were not significantly different among the study groups.
CONCLUSIONS: Our cross-sectional findings do not support the notion that retinal microvascular anomalies are an endophenotype in schizophrenia. Longitudinal studies of this subject should be included in further research.

Abbreviations:

AL	- Arteriolar diameter, left
AR	- Arteriolar diameter, right
BMI	- Body mass index
CRVE	- Central retinal venular equivalent
DSM	- the Diagnostic and Statistical Manual of Mental Disorders
fMRI	- Functional magnetic resonance imaging
HR	- Healthy relatives
N/A	- Not applicable
RATI	- Retinal arteriolar tortuosity index
RVTI	- Retinal venular tortuosity index
SCH	- Schizophrenia
SD	- Standard deviation
UHC	- Unrelated healthy controls
VAMPIRE	- Vascular Assessment and Measurement Platform for Images of the Retina
VL	- Venular diameter, left
VR	- Venular diameter, right

INTRODUCTION

Schizophrenia affects 0.5-1% of the global population. According to a World Health Organization survey, it is one of the top ten illnesses that contribute to the global disease burden (Murray *et al.* 1996). The main clinical features of schizophrenia are delusions, hallucinations, disorganization of thought and behavior, negative symptoms, cognitive deficits, and motor/neurological signs (Arrango & Carpenter, 2011).

Despite the progress that has been made to date, the therapeutic results are far from satisfactory. According to estimates, one-fifth to one-half of schizophrenia cases are resistant to treatment. Treatment-resistant schizophrenia costs 3–11 times as much as schizophrenia in remission, costing the US healthcare system an estimated $34 billion (Nucifora *et al.* 2019). One of the reasons for treatment resistance is that the etiology of schizophrenia is still under study; accordingly, the current therapies are more symptomatic than causal. For this reason, research into the etiology of schizophrenia is important.

One of the ways to discover the causes of complex neuropsychiatric diseases, including schizophrenia, is research into their endophenotypes. Endophenotypes are measurable components along the pathway between genotype and clinical symptoms. They can be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature and are less complex indicators of genetic background than the disease itself. Endophenotypes for psychiatric disorders must meet a number of requirements, including association with a candidate gene, heritability (as determined by the relative risk of the disorder in family members), and disease association parameters (Gottesman & Gould, 2003).

The antisaccade task, prepulse inhibition of the startle response, inhibition of the P50 event-related potential and other measures of event-related potentials, along with neurocognitive deficits such as impairments in working memory, are some of the endophenotypes studied in schizophrenia (DiLalla *et al.* 2017). Despite the wealth of recent scientific evidence, further research into endophenotypes is necessary to elucidate the underlying genetic architecture of schizophrenia and to propose novel treatment targets (Greenwood *et al.* 2019).

Pioneering work in research on microvascular abnormalities in schizophrenia as visualized on retinal imaging was performed by Meier *et al.* (2013). Their study was based on the assumption that retinal and cerebral microvessels are structurally and functionally similar, but retinal microvessels can be measured noninvasively in vivo using retinal imaging. Meier *et al.* examined the subjects of the Dunedin study with schizophrenia (n = 27) versus individuals with hypertension (n = 110), individuals with unremitting depression (n = 188) and individuals with persistent tobacco dependence (n = 210) as comparison groups. All study members underwent retinal imaging of arteriolar and venular calibers at 38 years of age. The subjects suffering from schizophrenia had wider retinal venules than the comparison subjects, suggesting insufficient brain oxygen supply. Wider retinal venules were also associated with liability to psychotic symptoms. These findings support the opinion that retinal imaging could be used to better understand the pathogenesis of schizophrenia. In a review, Adams & Nasrallah (2018) concluded that the pathobiological abnormalities of the retina in schizophrenia may lead to elucidation of some of the underlying neurodevelopmental aberrations and may serve as biomarkers and perhaps an endophenotype of this serious mental disorder.

The aim of our study was to verify the hypothesis that retinal microvascular abnormalities are an endophenotype of schizophrenia.

MATERIAL AND METHODS

Participants

Patients (n = 53) and their healthy first-degree relatives (parents, siblings, children; n = 53) were recruited at the Department of Psychiatry, University Hospital Hradec Kralove, from 2016 to 2021. The patients ranged in age from 18 to 65 years, and both males and females were included. All patients were hospitalized and had a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 classification, with no other mental disorders present. In the same period, we also recruited a healthy control group of unrelated, age- and sex-matched individuals who did not have any known mental disorders (n = 49). These subjects were typically employees of the University Hospital Hradec Kralove, such as nurses or health care assistants. Other exclusion criteria included hypertension; heart disease; stroke; and disorders affecting retinal microvasculature, such as age-related macular degeneration or significant visual acuity deficits.

Tab. 1. Demographic and disease characteristics of the study subjects

Variable	Patients with SCH n = 53	HR n = 53	UHC n = 49	*p* values SCH vs. HR SCH vs. UHC HR vs. UHC
Age (years)	32.1 ± 9.6	47.3 ± 12.7	32.2 ± 8.4	< 0.0001 1.000 < 0.0001
Sex Males Females	 38 15	 18 35	 35 14	0.0003 1.000 0.0005
BMI (kg/m^2)	27.2 ± 5.9	26.2 ± 4.8	24.4 ± 4.1	0.457 0.002 0.210
Education (years)	12.6 ± 2.7	13.3 ± 2.3	14.0 ± 2.3	0.301 0.003 0.102
Long-term unemployment (over one year)	31	14	13	0.003 0.003 1.000
Marital status Single Married or living with a partner Divorced Widowed	 47 3 3 0	 11 28 10 4	 28 19 2 0	 < 0.0001 0.001 0.001
Smoking (yes)	33	14	15	0.0004 0.004 1.000
Smoking (cigarettes per day) 0 1-5 6-10 11-20 >20	 20 2 9 17 5	 39 3 5 5 1	 34 5 5 5 0	 0.0004 0.004 1.000
Diabetes mellitus (yes)	0	2	0	0.206 1.000 0.206
Age at the time of the first schizophrenic episode (years)	22.1 ± 6.4	N/A	N/A	N/A
Duration of schizophrenia (years)	10.4 ± 8.8	N/A	N/A	N/A

BMI: Body mass index; HR: Healthy relatives; N/A: Not applicable; SCH: Schizophrenia; UHC: Unrelated healthy controls.

Procedures

All participants´ demographic and clinical data were collected, including age; sex; education; employment; marital status; body mass index; tobacco use; and the presence of cerebrovascular diseases, stroke, heart disease, arterial hypertension, varicose veins, and diabetes mellitus. In the schizophrenia group, the patients´ age at the time of the first psychotic episode, the duration of the illness, and details on their medication use were all recorded. We also captured data on refractive errors and intraocular pressure in the patients with schizophrenia.

Retinal imaging was performed at the Department of Ophthalmology, University Hospital Hradec Kralove. Full-color photographs of both eyes were taken using a digital fundus camera FF450 + IR (Zeiss, Oberkochen, Germany). Each of the images measured 2588x1958 pixels. The photographs were captured at a visual angle of 30 degrees, nineteen times higher. The software application VAMPIRE (Vascular Assessment and Measurement Platform for Images of the Retina) was used to analyze the digital retinal images (Trucco *et al.* 2013). The sizes of the retinal arterioles and venules in the region 0.5-2.0 disc diameters from the optic disc margin were measured. The vessel calibers of the region´s six largest retinal arterioles and venules were summarized as the central retinal artery equivalent and the central retinal vein equivalent (Knudtson *et al.* 2003). We preferentially measured the trunks of the vessels. If their number in the assessed region was insufficient, we completed the measurement by evaluating the widest arteriolar and venular branches.

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Statistical analysis

To analyze the data, we used the statistical software IBM SPSS Statistics, version 23 (IBM Corp., Armonk, NY). For the quantitative parameters, we compared the study groups using ANOVA with Bonferroni post hoc tests if the values followed a normal distribution. The Kruskal-Wallis test and Mann-Whitney U test with a Bonferroni correction were utilized to compare the quantitative parameters of the study groups if the values were not normally distributed. The normality of the data distribution was assessed using the Shapiro-Wilk test. The chi-square test and Fisher´s exact test with a Bonferroni correction were applied to compare the qualitative parameters of the study groups. To assess possible associations of retinal vascular diameters with systolic blood pressure, diastolic blood pressure, intraocular pressure, spherical refraction and cylindrical refraction, we used Spearman´s correlation coefficients. Two-way ANOVA was applied to assess a possible association of the retinal vascular diameters in schizophrenia with the type of antipsychotic medication combined with the stage of schizophrenia. ANCOVA was used to evaluate possible associations of retinal vascular diameters with smoking and body mass index. The threshold for statistical significance was set at 0.05 in all cases.

Ethical issues

This study was approved by the Ethics Committee of the University Hospital Hradec Kralove (the approval reference number 201503 S12P). This study was carried out in accordance with the ethical principles outlined in the Declaration of Helsinki. Before participating in the study, after complete description of the study to the subjects, all participants provided written informed consent.

RESULTS

Demographic and clinical data

Demographic variables and relevant clinical variables were collected for all participants (Table 1). Patients with schizophrenia were significantly younger than their healthy relatives, who, in many cases were the patients´ mothers, but the unrelated healthy controls were not significantly different in age from the patients. The proportion of women was higher in the group of healthy relatives than in the other two study groups. The subjects suffering from schizophrenia had a higher body mass index than unrelated healthy controls. The unrelated healthy control individuals had a higher level of education than the patients with schizophrenia. The subjects with schizophrenia had a higher prevalence of long-term unemployment (over one year) than the other two groups and were typically single. Smoking was also most prevalent in the patients with schizophrenia. The following antipsychotic medications were prescribed to the patients with schizophrenia: Incisive first-generation antipsychotics, n = 8; multi-acting receptor-targeted second-generation antipsychotics, n = 23; second-generation serotonin-dopamine antagonists, n = 9; second-generation D2/D3 receptor antagonists, n = 1; and aripiprazole/brexpiprazole, n = 12.

Retinal arteriolar and venular diameters

We observed that patients with schizophrenia had significantly increased retinal arteriolar diameters when compared to unrelated healthy controls but not when compared to their healthy relatives. The diameters of the retinal venules were not significantly different among the study groups. Interestingly, both arteriolar and venular retinal diameters were always widest in schizophrenic patients and narrowest in unrelated healthy controls, with healthy relatives in between (Table 2). In the patients suffering from schizophrenia, the retinal vascular diameters were associated neither with refractive errors (p = 0.322-0.947) nor with intraocular pressure (p = 0.152-0.847). The retinal arteriolar and venular diameters in schizophrenia were also not associated with systolic or diastolic blood pressure (p = 0.05-0.923) or with the patients´ age, gender, body mass index or duration of schizophrenia (p = 0.105-0.975). The type of antipsychotic medication was not associated with the retinal vascular diameters in schizophrenia (p = 0.308-0.478), even if combined with the stage of schizophrenia (p = 0.457-0.894). The differences in the retinal vascular diameters among the three study groups were not influenced by smoking or body mass index (p = 0.488-0.956).

DISCUSSION

Key findings of the study

According to our results, patients with schizophrenia were significantly younger than their healthy relatives, which decreases the probability that the retinal vascular changes in schizophrenia were due to hypothetical long-term somatic factors. The schizophrenia subjects were characterized by a high body mass index, a low level of education, long-term unemployment, singleness and smoking. We discovered that patients with schizophrenia had significantly increased retinal arteriolar diameters when compared to unrelated healthy controls, but not when compared to healthy relatives. The diameters of the retinal venules were not significantly different among the study groups. Both arteriolar and venular retinal diameters were always widest in patients with schizophrenia and narrowest in unrelated healthy controls, with healthy relatives in between, in accordance with our preliminary results (Hosak *et al.* 2020).

We hypothesized that retinal microvascular abnormalities are an endophenotype of schizophrenia, but the results of our study failed to support this assumption.

Prior research related to the subject

The participants in the study by Meier *et al.* (2015) were 531 adolescent and young adult twins from the Brisbane

Tab. 2. Retinal microvascular diameters in the study subjects (in micrometers)

Variable	Patients with SCH n = 53	HR n = 53	UHC n = 49	*p* values SCH vs. HR SCH vs. UHC HR vs. UHC
AL				
Mean	128.5	121.7	117.6	0.104
SD	18.5	15.8	14.4	0.003
Minimum	95.9	91.7	90.0	0.639
Maximum	176.4	157.9	151.2	
AR				
Mean	129.2	122.2	119.7	0.083
SD	18.3	15.1	15.0	0.011
Minimum	86.8	87.5	93.5	1.000
Maximum	172.9	159.3	153.3	
VL				
Mean	208.8	203.6	203.3	0.714
SD	24.9	19.3	22.1	0.652
Minimum	162.1	155.1	163.1	1.000
Maximum	282.8	239.8	266.0	
VR				
Mean	209.7	204.5	200.9	0.687
SD	25.5	22.4	18.4	0.148
Minimum	158.6	151.9	168.0	1.000
Maximum	265.3	261.1	238.7	

AL: Arteriolar diameter, left; AR: Arteriolar diameter, right; HR: Healthy relatives; SCH: Schizophrenia; SD: Standard deviation; UHC: Unrelated healthy controls; VL: Venular diameter, left; VR: Venular diameter, right.

Longitudinal Twin Study and the Twins Eye Study in Tasmania. The authors compared the retinal venular diameters of people who had one or more symptoms of psychosis (n = 45), their unaffected cotwins (n = 24), and controls (n = 462). Individuals with one or more psychotic symptoms had wider venules (standardized mean = 0.29) than controls (standardized mean = -0.04; p = 0.03), while unaffected cotwins had venular diameters that were intermediate (standardized mean = 0.13) between the two groups, implying that wide retinal venules may be an endophenotype of psychosis. No differences were found in retinal arteriolar diameter between participants with and without psychotic symptoms. To our knowledge, this study by Meier *et al.* (2015) was the first to scrutinize retinal microvascular changes as a possible endophenotype of schizophrenia, and our present study is the second one.

Multiple retinal anomalies in schizophrenia were described in a review by Adams & Nasrallah (2018). According to the authors, widened venule caliber is one of the most consistent findings. Their opinion was based on two studies by Meier *et al.* (2013; 2015).

We do not think that our results contradict the findings of Meier *et al.* (2013; 2015), because the pathophysiology of inflammation includes vasodilation not only of venules but also of arterioles (Kvietys & Granger, 2012). All these results generally point to the presence of retinal vascular microinflammation in schizophrenia.

There have also been other works related to the topic of retinal microvascular changes in schizophrenia and other psychoses.

Retinal images of one hundred schizophrenia patients, bipolar disorder patients, and healthy volunteers were acquired using a nonmydriatic camera in a study by Appaji *et al.* (2019a). The average diameters of the venules and arterioles passing through the extended zone between 0.5 and 2 disc diameters from the optic disc were calculated for the left and right eyes. After controlling for sex and age, the groups differed significantly in terms of the average diameters of both retinal venules ($p < 0.001$) and retinal arterioles ($p < 0.001$). Patients with schizophrenia as well as those with bipolar disorder had significantly narrower arterioles and wider venules than their healthy counterparts. Patients with bipolar disorder had narrower arterioles and wider venules than schizophrenia patients.

According to Appaji *et al.* (2019c), retinal vascular tortuosity may be a more useful structural measure than caliber owing to its decreased susceptibility to pulse variations. The authors examined retinal vascular tortuosity in patients with schizophrenia (n = 79) and bipolar disorder (n = 86) compared with healthy volunteers (n = 78) aged 18-50 years using a nonmydriatic fundus camera. They measured the average retinal arteriolar tortuosity index (RATI) and retinal venular tortuosity index (RVTI). Significant differences were observed among the three groups for the RATI but not for the RVTI; both subjects with bipolar disorder and subjects with schizophrenia had significantly elevated RATI values compared to healthy volunteers. Bipolar disorder patients had significantly higher RATI values than schizophrenia patients.

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Appaji *et al.* (2019b) examined the retinal vascular trajectory in individuals with schizophrenia (n = 100) and bipolar disorder (n = 100) in comparison with healthy volunteers (n = 100) with a nonmydriatic fundus camera. The schizophrenia and bipolar disorder groups differed from the healthy volunteer group in retinal arterial and venous trajectories, but there was no difference between schizophrenia and bipolar disorder patients. The smaller trajectories of retinal arteries indicated flatter and wider curves in patients with schizophrenia and bipolar disorder than in healthy controls.

Using swept-source optical coherence tomography angiography in 30 patients with schizophrenia or schizoaffective disorder and 22 healthy controls, Bannai *et al.* (2022) detected an association between retinal microvascular dysfunction (in terms of vessel density and vessel diameter) and early-stage schizophrenia.

Korann *et al.* (2021) were the first to investigate the link between retinal vasculature as measured by fundus photography and brain structure as measured by magnetic resonance imaging. The authors enlisted 17 healthy volunteers and 20 schizophrenic patients. There was a significant negative correlation between the average central retinal venular equivalent (CRVE) and global cortical mean thickness in the patients with schizophrenia, especially in the frontal regions and posterior brain regions, but not in healthy volunteers. These observations suggest that retinal venular diameter may be useful as a proxy marker for abnormal neurodevelopment in schizophrenia.

In a study of 34 schizophrenia patients, 39 bipolar disorder subjects and 45 healthy volunteers, Appaji *et al.* (2020) found an association between retinal vascular caliber and working memory in patients with each of these mental disorders.

Even if the results of research into retinal microvascular abnormalities in schizophrenia are not fully cohesive, they generally support the genetic-inflammatory-vascular theory of schizophrenia, as published by Hanson & Gottesman (2005). The authors suggested that at least part of the etiopathogenesis of schizophrenia might be explained by genetically mediated brain microvascular inflammation. According to this hypothesis, repeated exposure to triggering events such as infections, hypoxia or physical trauma results in inflammatory reactions that damage the microvascular system of the brain and eventually impair brain metabolism. Genetic polymorphisms in inflammatory regulators may lead to hyperbolic inflammatory responses and thus cause schizophrenia symptoms. Our results pointing to possible retinal microvascular arteriolar inflammation in schizophrenia partially support this theory of Hanson and Gottesman, although we did not evaluate laboratory or genetic inflammatory markers.

Limitations of our study

Our study was limited in that it did not assess laboratory or genetic markers of inflammation. Additionally, because all study subjects were Caucasian, the results may not be relevant for other ethnicities. Furthermore, as we studied only hospitalized patients, the findings could be different in an outpatient population. Another limitation of our study is the fact that it is not clear whether microvascular abnormalities exist prior to the onset of schizophrenia or develop during the course of the disease. The small number of our study subjects, no assessment of the severity of psychotic features in schizophrenia and no application of diagnostic interviews in our study groups represent other limitations of our reserach.

Advantages of our study

On the other hand, the microvasculature of the retina and the brain share common morphological, physiological, and pathological characteristics. Thus, the examination of retinal microvessels through fundus photography is the best noninvasive technique available at present for an indirect evaluation of cerebrovascular status. Our group of schizophrenia subjects was homogenous in terms of their geographical origin and current clinical state. The findings of our study support the notion that vascular microinflammation plays a role in the etiopathogenesis of schizophrenia and suggest the necessity of further research in this field.

Avenues for further research

To further examine whether retinal microvascular abnormality is an endophenotype of schizophrenia, longitudinal studies of groups of schizophrenic patients are needed to capture symptoms as they change with disease progression, given that one of the criteria for an endophenotype is state independence (Gottesman & Gould, 2003). Additional avenues for schizophrenia research include verifying whether vascular abnormalities in the retina are related to vascular pathology in the brain, as detected by concurrent functional magnetic resonance imaging (fMRI); to cognitive performance; or to specific symptoms or syndromes (for example, positive and negative symptoms of schizophrenia). Polymorphisms and epigenetic changes in the genes related to immunoreactivity and blood laboratory markers of inflammation should also be investigated.

CONCLUSION

The current study´s findings justify further systematic investigation of retinal vascular abnormalities as a possible endophenotype in schizophrenia. If this endophenotype is reliably associated with schizophrenia, we may be able to intervene with anti-inflammatory or inflammation-modulating medication before clinical symptoms of the disease occur, not only in patients but also in high-risk individuals, while concurrently avoiding inducers of inflammation (Hanson & Gottesman, 2005).

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