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Asian Journal of Psychiatry 70 (2022) 103042

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

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ARTICLE INFO

Keywords:
Psychosis
Fundus
Cerebrovascular risk
MRI
Tortuosity
Fractal dimension

ABSTRACT

Objective: Recent studies have examined retinal vascular abnormalities in schizophrenia as retinal vascular imaging is a non-invasive proxy to cerebral microvasculature. However, relation between retinal vascular abnormalities and brain structure is not well examined in schizophrenia. Hence in this study, for the first time, we examined the relationship between retinal vascular measures and brain white matter lesions in schizophrenia. We examined brain white matter lesions as they are considered a predictive marker for future adverse cerebrovascular event.

Methods: We acquired retinal vascular images of both eyes using a non-mydriatic camera and calculated retinal vascular diameter, tortuosity, trajectory and fractal dimension using validated methods. All patients underwent Magnetic Resonance Imaging of bran and we computed white matter hypo-intensities using Freesurfer software. We performed a linear regression analysis to examine the relationship between white matter hypo-intensities and retinal vascular measures controlling for age, sex, fasting blood sugar, creatinine, whole-brain volume, and antipsychotic dose.

Results: The regression model was significant in Schizophrenia patients (R=0.983;R2 =0.966;-F=10.849;p = 0.008) but not in healthy volunteers (R=0.828;R2 =0.686;F=0.182; p = 0.963). Among the retinal vascular measures, arterial tortuosity (β = 0.963;p-0.002), tortuosity (β = −1.002;p = 0.001) and fractal dimension (β = −0.688;p = 0.014) were significant predictors of white matter lesions.

Discussion: The current study's findings support the conclusion that retinal vascular fractal dimension and tortuosity are associated with changes in cerebral white matter and may be considered proxy markers for cerebral microvasculature in schizophrenia. Considering the relationship between white matter lesions and stroke, these observations could have important clinical implications to screen schizophrenia patients for risk of adverse cerebrovascular event.

1. Introduction

Schizophrenia is a severe mental illness with considerable morbidity and increased mortality. Emerging evidence from several lines of research suggests brain vascular pathology in schizophrenia (Najjar et al., 2017). Aberrations in angiogenesis, oxidative stress, endotheliopathy, and the dysfunctional blood-brain barrier are reported in schizophrenia and may contribute to the pathogenesis (Lopes et al., 2015; Najjar et al., 2017). Despite their proposed role, empirical evidence for the vascular factors in the pathogenesis are minimal, partially due to technical reasons. Direct examination of the cerebral small vessels is limited, difficult, and expensive with the available vascular neuroimaging techniques (Vranic and Mossa-Basha, 2020).

To overcome these limitations several studies have examined proxy

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https://doi.org/10.1016/j.ajp.2022.103042
Received 31 October 2021; Received in revised form 28 January 2022; Accepted 17 February 2022
Available online 19 February 2022

markers of the cerebral vasculature. Among these, cerebral white matter lesions are widely examined and hypothesized to be due to ischemia of cerebral microvasculature (Wong et al., 2002a, 2002b). The white matter lesions appearing as white matter hyper-intensities (WMHI) on the FLAIR sequence of the MR imaging are associated with other microvascular risk factors such as hypertension and diabetes mellitus (Debette and Markus, 2010). Longitudinal studies report an association between cerebral white matter lesions and increased risk of cerebrovascular accidents and dementia (Hu et al., 2020; Wardlaw et al., 2019).

Another proxy marker widely used to study cerebral microvasculature in dementia and stroke cohorts is retinal microvasculature (McGrory et al., 2017). Given the common embryological origin and neurophysiological properties, retinal micro-vasculature is considered the closest correspondent to cerebral microvasculature (Patton et al., 2005). Retinal vascular imaging allows non-invasive access to the cerebral microvasculature in living individuals using a simple tool, a fundus camera (Meier et al., 2016). Several studies have suggested associations between retinal microvascular measures and small vessel disease markers such as white matter abnormalities (Mutlu et al., 2016b; Wong et al., 2002a, 2002b), enlarged perivascular space (Mutlu et al., 2016a), and incident clinical stroke (Wong et al., 2002a, 2002b) supporting the view that retina is a portal to the brain. The association between cerebral white matter lesions and retinal vascular diameter, retinopathy, and altered retinal vascular bifurcation are reported in healthy individuals, dementia and stroke (Baker et al., 2010; Cheung et al., 2010; Haan et al., 2012; Longstreth et al., 2007; Qiu et al., 2009; Tirsi et al., 2009; Wong et al., 2002a, 2002b).

Interestingly, retinal vascular abnormalities in schizophrenia have been increasingly studied in the last few years. Studies have reported abnormalities in retinal vascular diameter, trajectory, tortuosity and fractal dimension (Appaji et al., 2019a, 2019c, 2019b, 2019d). Also, the association between retinal microvasculature and impaired working memory (Appaji et al., 2020) and brain cortical thickness have been reported (Korann et al., 2021). A few authors have also proposed retinal vascular abnormalities as a potential biomarker in schizophrenia (Hosak et al., 2018).

While these studies have provided preliminary evidence for abnormal retinal vascular measures in schizophrenia, to date no study has examined the relationship between retinal microvasculature and cerebral vasculature. Given the important contribution of cerebral vascular abnormalities to the pathophysiology of schizophrenia, it is important to examine the relationship between retinal microvascular abnormalities with the cerebral vascular abnormalities. As an examination of cerebral microvasculature in schizophrenia is challenging, an investigation of the relationship between retinal vascular measures and white matter signal abnormalities is desirable. However, to the best of our knowledge, no study has examined the relationship between retinal microvascular measures and brain white matter signal abnormalities. Such a study would give further validate the use of retinal microvascular measures as a proxy to cerebral microvasculature in schizophrenia.

Hence, in this study, we aimed to investigate the relationship between retinal vascular measures (diameter, tortuosity, trajectory and fractal dimension) and brain white matter lesion (measured as white matter hypo-intensity) in patients with schizophrenia. Our objective was to examine the relationship between cerebral white matter hypo-intensities and retinal vascular variables in patients with schizophrenia as compared to healthy volunteers.

2. Methodology

2.1. Subjects

We included 37 participants, including seventeen healthy volunteers (HV) and twenty persons with schizophrenia (SCZ). These individuals represent a subset of a previous study sample examining the retinal vascular tortuosity in schizophrenia and bipolar affective disorder (Appaji et al., 2019c). This subgroup also had an MRI scan with an average inter-assessment interval of 22 days between the MRI and a retinal fundus photograph acquisition. The patients were recruited from the clinical services of the National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India. A board-certified psychiatrist examined and clinically diagnosed all patients with schizophrenia according to the International Classification of Diseases – 10 (WHO, 1992). We excluded patients with comorbid substance abuse or dependence in the previous year except for nicotine abuse or dependence. We also excluded those with other concomitant axis-I mental illnesses, a lifetime incidence of non-communicable diseases such as hypertension, diabetes mellitus, stroke, ocular injuries, persons with metallic implants in the body, persons who are left or mixed handed, or a history of having received electroconvulsive treatment in the previous six months. We also excluded women who were currently pregnant or breastfeeding.

We recruited healthy volunteers [HV] through flyers, posters and word of mouth. We ruled out lifetime diagnosis of any Axis I mental illness in all HV using structured interviews for DSM-IV disorders (SCID-I) (First et al., 2001). In addition to the exclusion criteria mentioned for patients, HV having a history of psychosis in a first-degree relative was also excluded. Participants between the ages of 18 and 50 were included in the study. Institutional Ethics Committee approval was obtained. Each participant signed informed consent. Our research adhered to the tenets of the Declaration of Helsinki. The equipercentile score of the Brief psychiatric rating scale (BPRS) scores was used to grade the clinical symptom severity (Leucht et al., 2013). Clinical global impression scale (Guy, 1976) scores were used to measure functioning, and the Olanzapine equivalent does for antipsychotics was computed using a pre-established technique (Leucht et al., 2016). Corresponding chlorpromazine dose was first estimated for common depot antipsychotic medications (Danivas and Venkatasubramanian, 2013), which were then converted to olanzapine equivalents.

2.2. Retinal image acquisition

Following an explanation of the retinal image acquisition method, participants were made to sit for five minutes in a dimly lit room to allow for natural dilatation of the pupil. A skilled professional acquired the retinal images with a 40-degree field of view non-mydriatic camera. Both eyes' optic disc-centred colour fundus images were obtained using a valid approach reported earlier (Appaji et al., 2019c).

2.3. Measurement of retinal vascular features

The steps used to measure retinal vascular parameters are described in detail in our earlier manuscripts (Appaji et al., 2019a, 2019c, 2019b, 2019d). It is described in brief here. First, we performed a quality assessment to determine the acceptability of images for analysis. Then, we measured the retinal vascular diameter, tortuosity, trajectory and fractal dimension. (a) We used VAMPIRE (Vessel Assessment and Measurement Platform for Images of the REtina), a semi-automated tool, to calculate venular and arteriolar diameter. We measured the arteriolar and venular diameter of vessels passing between the zone of 0.5- and 2-disc diameters from the optic disc. We computed the cross-sectional span of the vessel mask perpendicular to the vessel's estimated axis after identifying venules and arterioles. We computed the Central Retinal Artery Equivalent (CRAE) for arterioles and Central Retinal Vein Equivalent (CRVE) for venules using a predefined process (Appaji et al., 2019b) (b) We defined arc length as the actual traced length of the vessel, and chord length as the length of the straight line drawn from the vessel's starting to the ending point and using a customized semi-automated tortuosity software built with MATLAB 2018a. Subsequently, we computed Simple Tortuosity (ST) of vessels in the radial zone, i.e., 0.5- to 2- disc diameters from the optic disc as the mean ratio of the arc length to the chord length. We used the customized semi-automated tortuosity software built with MATLAB 2018a (The

Mathworks Inc.) to measure the arc length and chord length of these vessels. ST was computed independently for each eye (left and right). Subsequently, we determined the mean of the tortuosity indices for the left and right eyes. The mean retinal venular tortuosity index (RVTI) and the mean retinal arteriolar tortuosity index (RATI) were computed independently (Appaji et al., 2019c) (c). We used a customized MATLAB algorithm that employed the box-counting method to calculate the fractal dimension described elsewhere (Appaji et al., 2019a). First, a skeletonized image of retinal venules and arterioles was generated and subsequently divided into equally sized square boxes and counted the number of boxes accommodating the line tracings. We calculated the fractal dimension (Df) for both eyes separately as the logarithmic gradient of the number and the size of the boxes with larger values indicating more complex branching patterns. Then, the average of left and right eye Df was calculated. (d) We computed the trajectories of vessels using a validated mathematical model described previously (Appaji et al., 2019d). We marked 20 points or more on the vascular trajectories traversing the infratemporal and supratemporal retinal areas, with each arm to the right and left of the optic disc having a minimum of 10 points. A custom MATLAB program subsequently detected and converted (via shifting the origin to the optic disc's center) the x and y coordinates of the marked points to new coordinates. Later, using a second-degree polynomial curve-fitting equation of least squares method, we converted coordinates' data. A larger P1 represents a steeper, narrower curve of the retinal vascular trajectory with arms close to the fovea and vice versa. P1 values were analysed as a single measure of retinal vascular trajectory as an indicator of steepness and width of trajectory parabola.

2.4. MRI acquisition and White matter hypo-intensity estimation

We acquired whole-brain anatomical T1 MPRAGE images using a 3 Tesla MRI scanner (Skyra, Siemens Healthcare, Germany) using the following parameters: repetition time of 2200 ms; time to echo of 2.45 ms; flip angle = 8; 256 by 256 matrix size; 1 mm slice thickness; 1 cubic millimetre voxels and 176 slices. During acquisition, we used foam rollers to limit head movement. None of the anatomical scans had visible structural abnormalities. White matter hypointensities (WM-hypo) are white matter lesions that appear dark on T1weighted MRI scans. The T1 weighted intensity of WM-hypos is related to the degree of tissue injury such that areas with higher impairment appear as hypointense. WM-hypo lesions calculated from T1 weighted images and FreeSurfer are strongly correlated to the WM-hyperintensity lesions obtained via T2-FLAIR. Empirical studies also have suggested comparability between T1w-WM-hypo lesions and T2FLAIR weighted WM-hyperintensity lesions (Wei et al., 2019). We processed images using T1 weighted images and the standard surface processing pipeline of the Freesurfer software package, version 5.3. (http://surfer.nmr.mgh.harvard.edu). Spatial intensity gradients among tissue types were used to identify WM-hypo. We processed the images to account for motion correction, intensity normalization, skull stripping, MNI template translation, segmentation, cortical surface generation, and parcellation. We manually reviewed the images for accuracy and corrected them as necessary during the processing.

2.5. Statistical Analysis

We compared the sociodemographic data between HV and SCZ were compared using independent t-test and chi-square tests. After logarithmic transformation, WM-hypo and retinal vascular measures were compared for differences between SCZ and HV using ANCOVA with age and sex as covariates. To examine the relation between retinal vascular measures and WMHI, we conducted a linear regression analysis with WM-hypointensities as dependent variable and retinal vascular measures (diameter, trajectory, tortuosity and fractal dimension) as predictor variables controlling for the potential confounding effect of age, gender, fasting blood sugar, creatinine and whole-brain volume. In addition to these, olanzapine equivalent antipsychotic dose was used as an additional regressor in SCZ. The regression analysis has the advantage of the mathematical interpretation of the association between variables of interest after controlling for potential confounders. To explore the causal pathways, it is essential to regress cases and controls separately to understand the mediating effects of multiple variables contributing to the outcome of interest.

3. Results

3.1. Comparison between SCZ and HV

Comparison of the demographic variables revealed that the two groups were matched on age- and gender in addition to biochemical parameters. However, the groups were significantly different in years of education. The groups did not differ significantly in brain volumetric measures. The groups showed significant difference in average fractal dimension and retinal venular trajectory (Table 1).

3.1.1. Relation between retinal vascular measures and white-matter hypo-intensities

When the whole group, including SCZ and HV, were analysed, the regression model was insignificant (R=0.665; R^2 =0.442; F=1.322; p = 0.281). Details are given in Table 2. The regression model was significant when the analysis was restricted to the SCZ sub-group (R=0.983; R^2 =0.966; F=10.849; p = 0.008). Among the variables, the average arterial and venous tortuosity indices and average fractal dimension were significant predictors. However, there was no significant association between the diameter or trajectory of the vessels and the WM-hypo. None of the biochemical or demographic variables predicted the WM-hypo. The results are summarized in Table 3. The regression model was not significant when the analysis was restricted to the HV sub-group (R=0.828; R^2 =0.686; F=0.182; p = 0.963). No individual measure

Table 1
Comparison of demographic and volumetric measures between groups.

Variable	SCZ Mean (SD)	HV Mean (SD)	t/χ2	P
Age	31.65 (5.62)	29.13 (5.16)	1.40	0.17
Male: Female	15:5	11:5	0.17	0.72
Years of education	14.45 (2.81)	17.94 (2.74)	-3.73	0.001 *
Illness duration [in months]	88.40 (73.23)	–	–	–
Blood Urea	18.81 (7.59)	21.15 (6.63)	-0.92	0.35
Serum Creatinine	0.89 (0.12)	0.89 (0.13)	-0.01	0.99
Fasting blood sugar	98.11 (13.08)	96.86 (10.36)	0.30	0.76
Whole brain volume (mm^3)	1075.94 (61.77)	1084.50 (105.77)	-0.28	0.77
Grey Matter Volume (mm^3)	602.26 (34.75)	622.86 (61.30)	-1.19	0.24
White Matter Volume (mm^3)	423.77 (34.79)	416.41(49.61)	0.50	0.61
WM-hypo (mm^3)	0.95 (0.21)	0.85 (0.19)	1.42	0.16
Average arterial tortuosity	1.03 (0.02)	1.03 (0.01)	0.12	0.18
Average Venular tortuosity	1.04 (0. 01)	1.02 (0.01)	0.58	0.10
Average CRAE	103.71 (15.73)	107.96 (19.71)	0.29	0.41
Average CRVE	213.04 (27.88)	209.06 (26.82)	0.65	0.66
Average FD	1.34 (0.07)	1.27 (0.06)	0.87	0.008 *
Average artery trajectory	1.03 (0.02)	0.36 (0.16)	0.16	0.10
Average vein trajectory	1.04 (0.01)	0.18 (0.07)	0.00	0.04 *
BPRS equipercentile score	30.80 (7.70)	–		–
Olanzapine equivalents	13.89 (6.63)	–		–

SCZ – patients with schizophrenia (n = 20); HV – healthy volunteers (n = 16); WMHI – white matter hypointensities; BPRS – Brief psychiatric rating scale; CRAE – central retinal artery equivalent; CRVE – central retinal vein equivalent; FD – fractal dimension

Table 2
Details of linear regression analysis in the whole sample.

	B	Std error	t	β	p	r
(Constant)	-0.881	5.465		-0.161	0.874	
Log10_Age	0.053	0.245	0.039	0.215	0.832	-0.037
Sex	0.067	0.073	0.289	0.914	0.372	0.375
Log10_FBS	0.160	0.418	0.075	0.383	0.706	0.093
Log10_Creatinine	-0.109	0.476	-0.069	-0.229	0.822	0.043
Log10_Average_CRVE	0.000	0.357	0.000	0.001	0.999	0.015
Log10_Average_CRAE	-0.237	0.410	-0.161	-0.577	0.570	-0.041
Log10_Vein_Avg_tortuosity	-1.885	3.328	-0.123	-0.566	0.577	-0.086
Log10_Art_Avg_tortuosity	3.307	2.495	0.304	1.325	0.200	0.473
Log10_Avg_FD	0.877	0.929	0.207	0.945	0.356	0.254
Log10_Vein_Avg_RT	-0.054	0.120	-0.114	-0.452	0.656	-0.060
Log10_Artery_Avg_RT	0.094	0.114	0.167	0.822	0.421	0.173
Log10_WBV	0.620	0.959	0.185	0.647	0.525	0.444

Log 10 – log 10 transformed values; B – unstandardized regression coefficient; β – standardized regression coefficient; r – correlation coefficient; p – significant at < 0.05; * Statistically significant difference; WM-hypo volume was the dependent variable; CRAE – central retinal artery equivalent; CRVE – central retinal vein equivalent; FD – fractal dimension; RT – Retinal Tortuosity; WBV – Whole brain volume; FBS – Fasting Blood Sugar.

Table 3
Details of linear regression analysis within SCZ sub-group.

	B	Std error	t	β	p	r
(Constant)	5.067	4.895	1.035		0.348	
Log10_Age	0.227	0.110	2.075	0.191	0.093	-0.092
Gender	0.053	0.044	1.196	0.256	0.285	0.270
Log10_FBS	0.157	0.275	0.572	0.089	0.052	-0.071
Log10_Creatinine	-0.439	0.249	-1.762	-0.313	0.138	0.182
Log10_Average_CRVE	-0.079	0.205	-0.387	-0.050	0.715	-0.037
Log10_Average_CRAE	0.362	0.175	2.072	0.253	0.093	-0.070
Log10_Vein_Avg_tortuosity	-12.932	1.766	-7.324	-1.002	**0.001** *	-0.467
Log10_Art_Avg_tortuosity	7.827	1.342	5.833	0.963	**0.002** *	0.568
Log10_Avg_FD	-2.720	0.732	-3.715	-0.688	**0.014** *	0.110
Log10_Vein_Avg_trajectory	0.123	0.052	2.392	0.324	0.062	-0.150
Log10_Artery_Avg_trajectory	0.197	0.104	1.897	0.358	0.116	0.271
Log10_WBV	-0.436	0.788	-0.554	-0.121	0.603	0.403
Log10_Olz_Eq	-0.091	0.059	-1.556	-0.270	0.180	-0.204

Log 10 – log 10 transformed values; B – unstandardized regression coefficient; β – standardized regression coefficient; r – correlation coefficient; p – significant at < 0.05; * Statistically significant difference; WM-hypo volume was the dependent variable; CRAE – central retinal artery equivalent; CRVE – central retinal vein equivalent; FD – fractal dimension; WBV – whole brain volume; Olz_Eq – Olanzapine equivalent of antipsychotic dose; FBS – Fasting Blood Sugar

significantly predicted the WM-hypo. Details are given in Table 4.

4. Discussion

To our knowledge, this is the first study examining the relationship between retinal vascular measures and white matter lesions in schizophrenia. The study suggests a significant relationship between retinal vascular measures [retinal vascular tortuosity, and fractal dimension] and white matter lesions [WM-hypo] in schizophrenia. Moreover, this association was significant even after correcting for the potential confounding effect of age, sex, antipsychotic dose, serum creatinine levels, fasting blood glucose and whole-brain volume.

Our findings are in accord with previous studies that reported an association between white matter lesions and retinal vascular measures in healthy individuals or other disease conditions; association between white matter lesions and FD (Hilal et al., 2014; McGrory et al., 2019),

Table 4
Details of linear regression analysis within HV sub-group.

	B	Std error	t	β	p	r
(Constant)	-24.475	59.014		-0.415	0.750	
Log10_Age	0.482	1.561	0.321	0.309	0.809	-0.038
Gender	-0.119	0.770	-0.479	-0.154	0.902	0.500
Log10_FBS	2.548	7.157	0.976	0.356	0.782	0.293
Log10_Creatinine	0.807	7.223	0.471	0.112	0.929	-0.104
Log10_Average_CRVE	0.778	3.630	0.350	0.214	0.866	0.045
Log10_Average_CRAE	-3.287	10.710	-2.239	-0.307	0.810	0.046
Log10_Vein_Avg_tortuosity	10.803	44.170	0.568	0.245	0.847	0.275
Log10_Art_Avg_tortuosity	-17.274	40.747	-0.902	-0.424	0.745	0.311
Log10_Avg_FD	0.407	8.502	0.074	0.048	0.970	0.266
Log10_Vein_Avg_trajectory	-0.818	4.494	-1.201	-0.182	0.885	-0.096
Log10_Artery_Avg_trajectory	0.244	1.007	0.377	0.242	0.849	0.308
Log10_WBV	4.332	9.613	1.419	0.451	0.730	0.465

Log 10 – log 10 transformed values; B – unstandardized regression coefficient; β – standardized regression coefficient; r – correlation coefficient; p – significant at < 0.05; * Statistically significant difference; CRAE – central retinal artery equivalent; CRVE – central retinal vein equivalent; FD – fractal dimension; WBV – whole brain volume; WM-hypo volume was the dependent variable

retinopathy (Wong et al., 2002a, 2002b), retinal vascular tortuosity (Kim et al., 2017; Kwa et al., 2002) have been reported. However, unlike previous studies, we did not find a significant relationship between retinal vascular diameter and white matter hypo-intensity (Hilal et al., 2014; Kwa et al., 2002; Mutlu et al., 2016a). Differences in subject characteristics could be a potential reason for the absence of association as the current study included young individuals whereas previous studies included comparatively older individuals. Also, the small sample size of the current study is another possibility as previous studies that examined the relationship between vascular caliber and white matter lesions had a greater number of subjects.

Interestingly, we noticed this association only in the SCZ and not in HV. A possible reason is the differential developmental abnormality seen in SCZ compared to HV, which may manifest in younger individuals with SCZ but not with HV. The role of differently expressed microvascular genes, altered endothelial metalcore processes, an impaired balance between pro and anti-angiogenic signals, altered neuronal signalling, and vascular inflammation are possible factors for augmented vascular pathology seen in SCZ (Katsel et al., 2017). A floor effect due to the lower load of WM-hypo and retinal microvascular abnormalities observed in HV may act as another possible confound (Andrade, 2021). Together, these findings provide preliminary evidence of an association between retinal fractal dimension, tortuosity, and cerebral microvasculature in schizophrenia. Future studies with a larger sample size could give definitive answers and until replicated, the current findings need to be considered preliminary.

The fractal theory offers us an opportunity to understand non-Euclidean geometrical structures and functionality. Fractals are self-similar patterns at different magnifications and have a structure on all length scales and every part is the same as the whole. Fractal dimension of retinal vasculature characterizes the distribution of the branching vascular system in two-dimensional space (Masters, 2004). While the reasons for fractals in retinal vasculature are not completely known, the diffusion-limited aggregation model of vasculogenesis is a possibility (Witten and Sander, 1981a). As per this model, the growth of vessels in the retina follows the direction of high shear stress provoked by the blood flow on the endothelium wall. It is established that microstructural changes reflected by a change in fractal dimension lead to altered permeability and diffusion, possibly mediated by increased porosity and decreased flow resistance. On the other hand, increased tortuosity leads to increased flow resistance and decreased diffusibility (Liang et al., 2019; Xiao et al., 2019). It is also important to note that the vasculogenesis in the inner retina is tightly linked to the oxygen requirement and maturation of photoreceptors and contributes to the fractal nature of the retinal vasculature (Kretzer and Hittner, 1988). Put together, the fractal dimension and tortuosity of the vessels contribute to the developmental processes within the retina. Interestingly, fractals have been reported in cerebral vasculature development as well (Bruner et al., 2005; Kędzia et al., 2002; Kuikka and Hartikainen, 2000; Yoshikawa et al., 2003). Considering the shared embryogenic properties of the retina and the brain, FD and tortuosity may be related to cerebral vascular development. Few studies have reported an association between retinal FD and neurodegenerative disease and stroke (Lemmens et al., 2020).

The underlying mechanism for the association between fractal dimension, tortuosity, and white matter hypointensity is not completely known. Both developmental factors and medication-induced side effects are proposed for the increased incidence of vascular adverse events in schizophrenia (Hennekens et al., 2005; Lin et al., 2008). As both cerebral and retinal vasculature have a common developmental origin, this association may reflect downstream effects of common pathophysiologic processes affecting the development of both retinal and cerebral microvasculature as explained above (Kreeke et al., 2018; Veluchamy et al., 2019). Abnormalities in retinal vascular fractal dimension and tortuosity may reflect the underlying cerebral small vessel abnormality and in turn result in white matter hypointensity, a proxy marker of cerebral small vessel disease. It is possible that a common genetic abnormality can result in pleiotropic phenotypic manifestations involving both retinal vascular changes and cerebrovascular changes, as seen in congenital syndromes. Susac syndrome is typically characterised by the presence of white matter hyperintensities in the corpus callosum and the presence of branch retinal artery occlusion (Dörr et al., 2013). A velocardiofacial syndrome due to 22q11 microdeletion is characterized by retinal vascular tortuosity, white matter abnormalities, and a significantly increased risk for psychosis (de Niro et al., 2013; Fiksinski et al., 2021; Schmitt et al., 2014). Similarly, Moyamoya disease is characterised by retinal vascular tortuosity and cerebral microvasculature abnormalities. Interestingly, psychoses and mood disorders are common neuropsychiatric comorbidities in moyamoya disease (Behere et al., 2012; Katsman et al., 2016; Kuribara et al., 2017; Richards et al., 2019).

At the same time, the increased prevalence of adverse metabolic risk factors in schizophrenia such as hypercholesterolemia and diabetes mellitus secondary to sedentary lifestyle or antipsychotic use (Mitchell et al., 2013) could also contribute to the retinal and cerebral vascular abnormalities. Whether the relation between retinal vasculature and WM-hypo is due to common developmental aberration or secondary to increased metabolic risk factors is unclear at this stage. Due to the cross-sectional study design, it is not possible to definitively attribute causality. Whether these mechanisms play a role individually or in combination to change the retinal vasculature and brain white matter needs scientific evaluation in longitudinal studies. Examination of drug-naïve first-episode schizophrenia patients and relatives of patients may give definitive answers.

Our findings have important theoretical and clinical implications. While several studies have examined retinal vascular measures in SCZ, there is limited data on the direct correlation between retinal vascular measures and brain structure or function; only one study has reported a relation between brain cortical thickness and caliber of retinal vasculature (Korann et al., 2021). The findings of our study provide further rationale for the use of retinal vascular measures as a proxy marker of cerebral vascular pathology. As discussed above, several studies have suggested brain white matter lesions and retinal vascular measures as a marker for future risk of adverse systemic and cerebral vascular events (Kawasaki et al., 2012; Wong et al., 2002a, 2001, 2002b; Wu et al., 2017). Additionally, it may be possible to use the retinal vascular measure to screen schizophrenia patients at risk of developing adverse cerebrovascular events. Considering the portable nature of the equipment and the minimal cost involved, the retinal vascular measure can be used as a screening tool in the community. Whether a combined biomarker with both retinal vascular measures and white matter lesions is better than individual modalities need to be examined in prospective longitudinal studies.

The findings from the regression model could also have potential implications in parametric modeling. Two rule-based modeling approaches, diffusion-limited aggregation, and Lindenmayer system (L-system) were used to model retinal vascular structure (Lindenmayer, 1968; Witten and Sander, 1981b). Since the growth rule of parametric L-system requires effective estimation of several parameters, modifications to the original L-system such as genetically tuned L-system are proposed in the last decade (Aghamirmohammadali et al., 2018). Parametric model fitting-based approaches in the future could focus on fractal dimensions like the attempts on vessel caliber (Araújo et al., 2018). The findings from the regression analysis give a preliminary idea about the effect of individual parameters and interactions between them. The differential findings across HV and SCZ suggest the possibility that the diseased and healthy groups may not follow similar growth rules and future modeling attempts need to include a richer database with images from both diseased and healthy. Future parametric studies may also need to account for the differential interaction between the parameters in healthy and diseased individuals.

A few limitations need to be considered while interpreting the

findings of the study. First, the sample size was small. Considering the exploratory nature of the study, we examined a small homogeneous sample. Pending replication in a larger sample, the findings must be considered preliminary. Second, all patients were on antipsychotic medications. Considering the adverse metabolic effects, the confounding influence of antipsychotic need to be considered while interpreting the results. It is important to note that the results remained significant after adjusting for the dose of the antipsychotic used and the retinal fractal dimension is unlikely to be influenced by antipsychotic medication. However, one cannot completely rule out the influence. Future studies in drug naïve, first-episode schizophrenia patients will overcome this limitation. Third, the cross-sectional design has inherent limitations in assessing the temporal relationship between the two measures. Future longitudinal studies examining both retinal vasculature and brain white matter lesions could delineate the nature of the temporal relationship between the two measures. Finally, while the exclusion of patients with diabetes mellitus, hypertension, and substance dependence increased the methodological rigor, it could affect the generalizability considering the prevalent comorbidity in schizophrenia.

5. Conclusions

To conclude, the findings from this study suggest a relation between retinal vascular tortuosity, fractal dimension, and WM-hypo in the brain. This relation between retinal vascular measures and brain white matter lesions supports the view that retinal vasculature could be a proxy for examining the cerebral vasculature. Considering the association between white matter lesions and adverse vascular events, the findings could have important clinical implications. The low cost of the equipment, non-invasive nature of the examination, and easy administration makes the retinal vascular measures a potential screening tool for adverse systemic vascular events in schizophrenia. The findings from this preliminary study need replication in future studies with larger sample sizes.

Future work should examine the causal pathways resulting in microvascular changes, the pathophysiology of microvascular changes especially in schizophrenia, and examine the specificity of the proposed model to schizophrenia in comparison to other disorders while controlling for all known confounding influences. Additionally, a longitudinal study with multiple data points for the same subjects will help us in understanding the correlation between the cerebral WM-hypo and microvascular changes in schizophrenia.

Sources of funding

Funding source: Department of Science and Technology, Government of India - (PI- Dr. Naren P Rao; IFA/12/LSBM/36; SR/CSRI/138/2015; SR/SATYAM/304/2015). The funding agency had no role in the interpretation of data or manuscript preparation.

Declaration of Competing Interest

Dr Shyam Vasudeva Rao is co-founder and Director of Forus Health Pvt Ltd. Dr. Naren P Rao has received research grants from Forus Health Pvt Ltd. Other authors report no conflict of interest.

Acknowledgement

None.

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