EYES AS THE WINDOW TO THE BRAIN - A KEY TO THE SCHIZOPHRENIA PUZZLE

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Dear editor,

We read the paper by Jurišić et al. published in Psychiatria Danubina entitled 'New Insights into Schizophrenia: a Look at the Eye and Related Structures' with great interest (Jurišić et al. 2020). In this comprehensive review, the authors presented, summarized and discussed several relevant elements regarding retinal dysfunction in schizophrenia. Additionally, they gave an insight into understanding the pathophysiology of schizophrenia that can be obtained during eye examinations. Motivated by this paper we wished to emphasis a particular aspect of this topic namely the potential benefit of eye examinations in solving the riddle of schizophrenia.

Schizophrenia as an illness is still not fully clarified and presents a puzzle with many missing pieces. From a neurobiological perspective, it can be considered as a major psychiatric disorder with structural changes and atrophy of gray and white brain matter visible by several neuroimaging techniques (Jerotić et al. 2020). There is evidence that early identification and treatment of psychotic symptoms markedly improves clinical outcome in patients with schizophrenia. Thus, detection of measurable and reproducible biological indicators of the clinical signs and course of the disease may be important in establishing early diagnosis, the elucidation of pathogenic mechanisms and facilitating in monitoring the disease (Silverstein et al. 2020). The retina, as the only component of the central nervous system (CNS) that can be seen directly in live humans provides the opportunity for an accessible and non-invasive analysis of brain pathology in various neuropsychiatric disorders (Almonte et al. 2020). Previous research has suggested that changes in retinal structure may parallel or reflect changes in brain tissue. As such, retinal change could be a readily accessible marker of structural and functional brain integrity (Phadikar et al. 2017).

In vivo imaging of the retina as the first part of the visual pathway may present a promising approach for the early evaluation of degenerative processes in the CNS. From an embryological perspective, retinal nerve fibres can be considered as an extension of the brain. The eye has the great advantage of enabling easily accessible in vivo imaging, rendering the retina as a "window to the brain". Several studies have reported structural retinal abnormalities in patients with schizophrenia. It is hypothesised that retinal atrophy in schizophrenia may be the result of retrograde trans-synaptic axonal degeneration (RTSD) of retinal ganglion cells (RGC) and their axons in the optic nerve and the optic tract. This occurs following damage to the visual pathway posterior to the lateral geniculate nucleus (LGN) (Pergola et al. 2015). Trans-synaptic degeneration is a phenomenon in which damaged neurons spread injury to those previously unaffected, connected by a synapse and may occur in post-synaptic (anterograde) or in presynaptic neurons (retrograde). RTSD refers to progressive damage of RGCs secondary to synaptic dysfunction in the LGN in the thalamus, where optic nerve fibres are connected. The existence of lesions in the higher brain centre including LGN and primary visual cortex in schizophrenia are well documented (Dinkin 2017, Jerotić et al. 2020). Referring to this fact it can be assumed that RTSD could be a pathophysiological mechanism of possible retinal layer damage in patients with schizophrenia, which reflects neurodegenerative processes originating in higher brain centres (Jerotić et al. 2020).

Optical coherence tomography (OCT) represents great technological advancement in ophthalmology and in recent years is becoming a leading method for diagnosing and controlling the diseases that affect the retina and optic nerve. It provides high resolution, detailed information on specific retinal structures such as the retinal nerve fibre layer (RNFL) which contains axons of RGCs, the ganglion cell layer and the inner plexiform layer (IPL) which includes synaptic connections between the axons of bipolar cells and dendrites of RGCs (Phadikar et al. 2017). The use of OCT in schizophrenia is relatively novel and to date, several studies have analysed structural retinal changes in these patients (Pan et al. 2018, Jerotić et al. 2020). In fact, the retinal alterations may be the expression of progressive neurodegeneration of schizophrenia. In previous research, the most common OCT finding was global thinning of the retina, specifically global thinning of RNFL predominantly in the superior and inferior quadrants as well as reduced macular thickness and macular volume (Pan et al. 2018, Lizano et al. 2019, Kazakos & Karageorgiou 2020). Reduced macular volume was related to an increased expression of positive symptoms whilst RNFL thinning was related to disease chronicity. Generally, although conducted studies reported the existence of retinal structural alterations; certain differences in their findings were observed. Possible explanations for these inconsistencies may be differences in the study populations, variations in methodology of diagnostic approach, inadequate reporting of duration and dosage of antipsychotic therapy, presence of somatic comorbidities and the type of OCT scanners used (Jerotić et al. 2020).

Three meta-analyses conducted provide us with a better understanding and give good insight into the results of previous research related to retinal changes and corresponding OCT findings in patients with schizophrenia. These investigations emphasize the importance of assessing structural changes of the retina with the aim of solving the schizophrenia puzzle (Pan et al. 2018, Lizano et al. 2019, Kazakos & Karageorgiou 2020).

The results of the meta-analysis conducted by Pan et al. (2018) showed overall RNFL thinning, as well as reductions

in the inferior, nasal and temporal quadrants in patients with schizophrenia, when compared with healthy controls. Due to the relatively small sample size and insufficient data of included studies, they were unable to analyse the potential association between RNFL and the duration of illness and medication status. The conclusion drawn was that the RNFL thinning in patients with schizophrenia could be the result of neurodegeneration or neurochemical dysregulation. As such, retinal changes could be considered as biomarkers of progressive brain tissue loss.

The meta-analysis conducted by Lizano et al. (2020) encompassed wider retinal parameters with findings for RNFL, ganglion cell layer (GCL), IPL, macular volume, macular and choroidal thickness. Their analysis showed significant peripapillary RNFL thinning particularly in the nasal, temporal and superior quadrants as well as significant thinning of the GCL-IPL layer in patients with schizophrenia. No statistically significant differences were identified in other retinal or choroidal regions. Macular volume reductions were reported, however without differences in macular thickness. In this meta-analysis, the authors found that age, sex or OCT device used were not influential factors on RNFL or GCL and IPL thickness. This suggests that retinal imaging may have clinical value as a non-invasive diagnostic biomarker and thus may enhance our understanding of the pathophysiology of schizophrenia.

The most recent meta-analysis conducted by Kazakos and Karageorgiou (2020) confirmed the presence of RNFL thickness in schizophrenia with significant differences in the superior, inferior, nasal and temporal as well as overall RNFL thickness. The changes in OCT measurements in the macular area particularly GCL and IPL, macular thickness and volume were also observed. A particular strength of this study was the fact that they included the influence of smoking, diabetes mellitus, hypertension and antipsychotic medications on retinal structures.

The results of the above mentioned meta-analyzes strongly support the idea that multiple structural and functional retinal anomalies are present in schizophrenia with potential relevant clinical implications. Thus, morphological and functional examination of the retina may be a valuable supplementary method, which may help enhance our understanding of the neurobiological mechanisms involved in schizophrenia and their possible associations with clinical symptoms. Further investigations are necessary to obtain a more comprehensive understanding of the pathophysiology and neurodevelopment of this disease. However, some important elements need to be emphasized and should be taken into consideration when planning future research. Retinal changes can occur under the influence of systemic somatic disorders including diabetes, hypertension or specific ocular conditions as well as psychiaric medications. In respect to the impact of antipsychotic therapy, less volume of both GCL and IPL was found in patients with treatment-resistant schizophrenia compared to those responding to treatment. It is known that the dose and duration of therapy have an effect on retinal as well as cortical parameters. In addition, patients with systemic diseases such as diabetes or hypertension showed thinner GCL and IPL areas. Further, the presence of somatic comorbidities as important influencing factors should be evaluated using objective clinical findings and not only as data obtained by medical history.

In light of findings that support the concept of the eye as a "window to the brain", retinal anomalies may represent an important direction in elucidating neurodevelopmental etiopathogenesis in schizophrenia. The retinal changes may prove to be a useful biomarker tool for the early detection and diagnosis of schizophrenia whilst OCT may help identify at-risk individuals. This approach would contribute to better diagnosis, improved individualized treatment, reduce the associated stigma and may be the key to resolving the schizophrenia puzzle.

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