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Review Article

Ophthalmologic Manifestations in Schizophrenic Patients: A Review of the Literature

Marina Maria Gonzaga Moreira[1]*, Letícia Brandão Barbosa de Oliveira[1], Carlos Eduardo Ximenes da Cunha[1], Marina Viegas Moura Rezende Ribeiro[2] and Allan Maia Andrade de Souza[3]

[1]Medical Intern, Tiradentes University Center, Maceió-Alagoas, Brazil

[2]Doctor in Health Sciences, Professor of the Tiradentes University Center, Maceió-Alagoas; Specialist in Ophthalmology, Brazil

[3]Psychotherapist, Professor of the Tiradentes University Center, Maceió-Alagoas; Specialist in Psychiatry, Brazil

***Corresponding Author:** Marina Maria Gonzaga Moreira, Medical Intern, Tiradentes University Center, Maceió-Alagoas, Brazil.

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Abstract

Introduction: Schizophrenia is a severe psychiatric disorder characterized by various psychotic manifestations. The relationship between this disorder and ophthalmologic dysfunctions is well described in the literature. Examples of this are the numerous retinal alterations in schizophrenics and the deficits in visual perception. In addition, chronic use of antipsychotics can lead to several ophthalmologic manifestations.

Objective: To identify and explain the main ophthalmologic manifestations caused by schizophrenia and antipsychotic treatment.

Methods: This is an integrative literature review, using papers published in the last 20 years in the LILACS, SCIELO, PUBMED, Psycoinfo, Scopus and Google Schoolar databases. The review was produced in January 2021 using 18 scientific articles.

Results and Discussion: Based on the analysis of the data, the main findings were the changes in the retina, eye movement and visual perception in schizophrenic patients. The effects of antipsychotics on vision were also noted. It was observed that excessive dopaminergic activity generates hypersensitivity to color and compromises synaptic transmission in the retina. Antipsychotics, in chronic use, are able to generate damage and atrophy of the retinal pigment epithelium and elevate intraocular pressure (IOP). Moreover, it was noted characteristic abnormalities in eye movements and visual perception in schizophrenics.

Conclusion: Ophthalmologic involvement is one of the most important features of schizophrenia. Despite the existence of studies that prove the relationship between vision problems and schizophrenia, there is still a need for further research for a better understanding of the ophthalmologic consequences in these patients

Keywords: Schizophrenia; Ophthalmology; Retina; Distortion of Perception; Antipsychotics

Introduction

Schizophrenia is a severe and disabling psychiatric disorder characterized by psychotic manifestations that involve hallucination, delirium, disorganized speech, abnormal behavior and negative symptoms [1]. Epidemiological data indicate that the prevalence of this disorder is 1% in the general population, being equal between men and women and appearing earlier in males [2,3]. The etiology of schizophrenia is known to be multifactorial, comprising genetic and environmental factors [3].

The relationship between ophthalmologic problems and schizophrenia is well documented in the literature, and there is clear evidence that visual processing deficits are one of the most important manifestations in the course of this disease.[4] Studies have shown that schizophrenic patients have different visual abnormalities in the early components of the optic tract [3,4].

Among the various ocular manifestations of schizophrenia, we can cite reduced contrast sensitivity, visual hallucinations, distortion of shapes and light intensity, abnormal electroretinogram (ERG), and alterations in smooth eye movements [4]. It is also worth noting that the retina, being an embryonic extension of the brain, may be involved in the pathophysiology of visual impairment in schizophrenic patients [4,5].

Furthermore, due to the chronic nature of the disease, schizophrenic patients need to take antipsychotic medications for their entire lives, and these medications are divided into two categories: typical and atypical antipsychotics [3]. Considering the systemic effects caused by these psychotropics, they are related to the precipitation or exacerbation of acute glaucoma, because they cause an increase in intraocular pressure (IOP) [6].

Therefore, this study aims, through an integrative literature review, to identify and explain the main ophthalmologic manifestations in patients with schizophrenia.

Methodology

This paper is an integrative literature review about the existence of ophthalmologic symptoms related to schizophrenia. To contemplate the research, the PubMed, Lilacs, Scielo, PsycInfo, Scopus and GoogleScholar databases were used. The descriptors selected from the Health Science Descriptors (DeCS) of the Virtual Health Library (VHL) and MsSH Database were: Schizophrenia AND Ophthalmology OR Eye movement OR Retina OR Eye Disorders ; Antipsychotic AND Eye Disorders OR Ophthalmology. The following relation was then established: "Szhizophrenia OR Antipsychotic AND Eye Disorders".

Articles that cited in their abstracts ocular alterations associated with schizophrenia or resulting from the treatment of this psychic condition were included. A total of 28 articles were found, and 10 were excluded for not mentioning these alterations in the abstracts. Thus, a total of 18 articles were left, and all languages were considered for inclusion in the research.

Results

After analyzing the studies selected for the research, the main findings denoted in each one of the articles were briefly described (Table 1). The most common findings in the literature were: changes in the retina, eye movement and visual perception in schizophrenics, and the effects of antipsychotics on vision.

Year and autor	Resume
Souza VB., *et al.* 2008 [6]	By increasing IOP, some antipsychotics can contribute to the development of glaucoma.
Wójciak P, Stopa M, Rybakowski F, 2020 [9]	Excessive dopaminergic activity causes the color hypersensitivity seen in schizophrenia.
Jurišić D, Ćavar I, Sesar A, Sesar I, Vukojević J, Ćurković M, 2020 [10]	In schizophrenia, there is hypoactivity of the N-methyl-D--aspartate receptor (NMDAr). The reduction of NMDAr is associated with neural cytotoxicity, which leads to a neurodegenerative process and, destruction of retinal ganglion cells.
TAN, T. Schwitzer, J.-B. Conart, K. angioi-duprez, 2020 [11]	Patients with schizophrenia demonstrate attenuated photoreceptor and bipolar cell activity, pointing to a dysfunction in retinal synaptic transmission.
Meier MH., *et al.* 2013 [12]	Adults with schizophrenia may have wider retinal venules than members of the cohort with schizophrenia, suggesting a background of insufficient oxygen supply to the brain.
Razeghinejad MR, 2010 [15]	Phenothiazine - a chemical compound present in several antipsychotics - has a toxic activity on photoreceptors, being able to generate damage and atrophy of the retinal pigment epithelium.
Lmorita K, Miura K, Kasai K, Hashimoto R, 2020 [17]	Individuals with schizophrenia have distinct abnormalities in eye movements, perceived during smooth pursuit, saccade control, and visual search.

Morita K., *et al*. 2019 [18]	It has been reported that patients avoid looking at protruding regions of the face and this restriction is associated with lower accuracy in emotion recognition.
King DJ, Hodgekins J, Chouinard PA, Chouinard VA, Sperandio I, 2017 [20]	Optical illusions occur in schizophrenia because of the typical population produces a reliable and dissociation between the retinal image of an object and its perception, while patients with schizophrenia have reduced susceptibility.
Butler PD, Silverstein SM, Dakin SC, 2008 [22]	Disabilities in visual perception occur due to structural and functional damage to the retina, magnocellular pathway, and parvocellular pathway.

Table 1: Analysis of studies that signal a relationship between schizophrenia and ophthalmologic alterations.

Discussion

Schizophrenia and retinal disorders

Retina is a tissue with neuroectodermal origin whose main function is to transform light rays that reach the eye into electrical impulses [7]. When there is an interaction between light beams and photoreceptors present in the retina, an electrical signal is originated and directed to the bipolar cells and then to the ganglion cells, until it propagates through the optic nerve and reaches the area of the cortex responsible for vision [7]. The photoreceptor involved in visual perception is related to the intensity of light in the environment, thus, rods act in ectopic vision (night, less than 1 lux) and cones for photopic vision (day, more than 10 lux) [7].

The retina can present abnormalities in its physiology, such as what occurs in schizophrenic patients, for example. According to the literature, the excess dopaminergic activity that occurs in this psychiatric disorder determines the color hypersensitivity characteristic of schizophrenic patients [3].

Parallel to the exposed, the most accepted theory about the pathophysiology of schizophrenia postulates that the disorder results from excessive dopaminergic activity [7]. Considering that the ratin is an ocular structure rich in dopaminergic receptors (D1 or D2), when dopamine is released by retinal amacrine cells, it exerts a great influence in this region [8]. The current hypotheses indicate that the D2 receptors are mainly involved in the generation of excitatory responses, while the D1 receptors are responsible for inhibitory responses [8]. As a consequence of the excessive dopaminergic activity through the D2 receptors, there may be a hypersensitivity to color observed in schizophrenia [9]. Furthermore, a study showed that untreated schizophrenics showed a higher sensitivity to contrast when compared to healthy control groups. However, after initiation of antipsychotic treatment, this abnormality disappeared [9].

Studies involving an Electroretinogram (ERG) have shown that disturbances in dopamine metabolism directly affect the retinal response to light stimuli [8,9]. ERG findings in schizophrenia patients, when compared to healthy control groups, have reported reduced amplitudes of A waves from cones and B waves from rods [5,8]. It has also been exposed that patients with schizophrenia demonstrate attenuated photoreceptor and bipolar cell activity, pointing to a dysfunction in retinal synaptic transmission [4,5]. Remarkably, these abnormalities were partially normalized after 8 weeks of treatment, contributing to the hypothesis of a dopaminergic effect in the genesis of these retinal changes [5]. In addition, initial ERG findings suggested that acute psychosis may be characterized by abnormal photoreceptor function, whereas aberrant bipolar Müller cell function may occur in chronic schizophrenia, regardless of the level of symptoms [4,5].

Another function of dopamine in the retina is to weaken the communicating junctions that couple horizontal cells (HCs) [4]. HCs have the function of secreting GABA to nearby rods and cones, indirectly regulating the response of ganglion cells [4]. This uncoupling, brought about by the high level of dopamine, leads to a significant reduction in the reception fields of the stimuli brought by the cones and rods, consequently altering the transmission of images to the visual system in the brain [4].

Other neurotransmitter present in the retina that is affected by schizophrenia is glutamate [9]. Under normal conditions,

glutamate is the main excitatory neurotransmitter of the retina [8]. Modern studies with brains of schizophrenic patients have demonstrated dysregulation and hypoactivity of the N-methyl-D-aspartate receptor (NMDAr), generating excessive glutamate activity [10]. Reduced NMDAr is associated with neural cytotoxicity, which can lead to a neurodegenerative process and, consequently, destruction of retinal ganglion cells [9,10]. However, the relationship between altered glutamate and visual disturbances in schizophrenic patients has not yet been fully elucidated [9,10].

Several authors have suggested the involvement of vascular factors, associated mainly with the cerebral microcirculation, as the pathogenic mechanism generated by schizophrenia [11]. Data from a longitudinal study indicated that adult individuals with schizophrenia had wider retinal venules than cohort members who did not have schizophrenia, suggesting a history of insufficient oxygen supply to the brain [12]. In addition, wider retinal venules were associated with the extent of psychotic symptoms in adulthood and childhood [12]. In addition, the width of the retinal venous system may be a marker of familial susceptibility to psychosis [12]. Another study compared the width of the venous microvasculature between three groups: the control group and a group of twins, one of whom suffered from psychosis, while the other was healthy [12]. Twins with psychosis had wider retinal venous vessels than the control group, and in healthy twins this dimension was intermediate [9,12]. The literature, noting the potential risk of chronic hypoxia in the brain tissue of schizophrenic patients, suggests that basic aspects of retinal function may indicate reduced cerebral vascular health.

The use of antipsychotics and their consequences on vision

Antipsychotics are the basis of treatment for schizophrenia and are divided into two categories: typical and atypical [3,13]. The typical ones block dopamine postsynaptic receptors, mainly D2, and have activity in three other receptors: histamine H1 blockade, alpha1 adrenergic receptor blockade, and M1 muscarinic cholinergic receptor blockade [13]. The atypical antipsychotics act blocking the dopamine D2 receptors and the serotonin receptors, highlighting the 5-HT2A subtype [13]. However, every antipsychotic has peculiarities about each one of these receptors [13].

Evidence from several studies has shown that the chronic use of antipsychotic medicines can generate ophthalmologic manifestations [6,14]. Firstly, phenothiazine - a chemical compound present in several antipsychotics - has a toxic activity on photoreceptors, being able to generate damage and atrophy of the retinal pigment epithelium. It is clinically manifested with blurred vision, scotomas, dyschromatopsia, and nictalopia [11]. Moreover, the use of thioridazine, a typical antipsychotic, can cause pigmentary retinopathy, characterized by reduced visual acuity [10]. Additionally, typical antipsychotics, especially those with powerful antidopaminergic action, combined with weak anticholinergic effects (for example, haloperidol butyrophenone), have a high potential to produce dystonias [15].

As part of this, the literature shows that atypical antipsychotics have the capacity to elevate intraocular pressure (IOP). It occurs because the IOP is determined by a balance between the production of aqueous humor and its drainage [10]. This regulation is done, in part, by neurotransmitters that have their quantity altered by the use of this group of drugs [16]. Ziprasidone, for example, has a higher affinity for serotonin type 2A (5-HT2A) and dopamine type 2 (D2) receptors, and is a 5HT1A receptor agonist, indicating that this drug is able to inhibit serotonin reuptake, thus increasing its amount [15,16]. Considering that serotoninergic stimulation has an independent effect on IOP elevation, we can state that by increasing IOP, some antipsychotics may contribute to the development of glaucoma [15].

Eye movement alterations

Characteristics of eye movements in schizophrenics have been studied for decades. It is known that individuals with schizophrenia have characteristic eye movements and can be observed during smooth pursuit, saccade control, and visual search [17]. Eye movements serve as an output of cognitive processing and improved performance has been associated with better social functioning in schizophrenia [17]. It is important to note that smooth pursuit eye movements occur when there is a moving object and viewing it keeps the image stabilized in the fovea [18]. In individuals with schizophrenia the speed of eye movements tends not to follow the speed of the moving visual target [18]. Some studies point out that there may be genetic factors associated with these characteristics, and that the cerebral cortex plays an

important role in controlling eye movements, especially the medial temporal area, the medial superior temporal area, and the frontal eye field [18]. Saccades are rapid eye movements that bring the image of an object of interest to the fovea. In a study, it was found that participants with schizophrenia show more problems in suppressing reflexive saccades compared to healthy participants [19]. Antisaccadic tasks demonstrate inhibitory self-control, which is deficient in schizophrenic patients [19]. The characteristics of exploratory eye movements are closely related to the cognitive processes of individuals , and it is known that in schizophrenia there are visuocognitive impairments [19]. It has been reported that patients avoid looking at prominent regions of the face, and this restriction is associated with lower accuracy in recognizing emotions [19]. Some educational and intelligence influences may be involved in these effects [17]. Therefore, it can be seen that there is a neural, oculomotor, and social connection that still needs to be further studied [18,19].

Perception disorders

Perception is a very important cognitive domain in schizophrenia, since visual processing impairments negatively affect life in society [20]. It is a highly complex process that requires several interconnecting processes, including low-level and high-level integration mechanisms [20]. Visual impairments are well described in schizophrenia and occur due to structural and functional damage to retinal ganglion cell axons, magnocellular (M) pathway neurons, and parvocellular (P) pathway neurons [21]. More than 60% of schizophrenic patients are affected by visual perception disturbances [10]. There is diverse evidence for visual processing impairments, including abnormalities in contrast sensitivity; excitatory and inhibitory functions; and shape and motion processing [20].

Behavioral studies have revealed that patients with schizophrenia have decreased contrast sensitivity, i.e., they require more contrast to detect a grating [19,20]. Furthermore, greater deficits in contrast sensitivity were found when stimuli were presented dynamically rather than statically, suggesting greater impairment of the M pathway than the P pathway [22]. Magnocellular pathway dysfunction may also contribute to cognitive deficits in attention, working memory, and executive functioning [23].

Hallucinations are one of the best known features of schizophrenia. It is worth clarifying that hallucination and illusion are distinct perceptive phenomena. The confusion is made by understanding that in both there is a rupture with reality, however they are differentiated as to the existence or not of an external stimulus. "Hallucination is defined as the perception of an object, without its presence, without the respective sensory stimulus" [24]. On the other hand, in illusion, there is an external stimulus, but the brain misinterprets it. Schizophrenic patients tend to have visual hallucinations in 73% of the cases [25]. The intensity of hallucinations is associated with volumetric alterations in brain structures, including the gray matter in the frontal, parietal, and temporal regions, and in the paralimbic system [25]. Visual illusions alter our perception of physical reality; they demonstrate how the brain uses specific, highly adaptive mechanisms that are part of the perceptual organization, which structures visual input into an understandable pattern [25].

In addition, optical illusions expose disorders with perceptual deficits, such as schizophrenia [26]. This is due to the fact that the typical population produces a reliable and predictable dissociation between the retinal image of an object and its perception, while patients with schizophrenia have reduced susceptibility [26]. According to studies, however, resistance occurs mostly with high-level integrative illusions, while specific resistance occurs to only a few low-level illusions [19].

Conclusion

Ophthalmologic involvement is one of the most important features of schizophrenia. Most common visual disturbances in these patients are abnormalities in retinal structure and function, alterations in eye movements, changes in visual perception, and the side effects of antipsychotics. Despite the existence of studies that prove the relationship between vision problems and schizophrenia, more research is still needed for a better understanding of the ophthalmologic consequences in these patients. Therefore, a great integration of knowledge is needed to allow the interface between ophthalmology and psychiatry, so that it is then possible to stage and offer the best treatment for these patients.

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