

Dysfunctions of the retina and other elements of the visual system in schizophrenia

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Summary

Schizophrenia is an illness with a large variety of symptoms, significant variability of the individual course, and still not fully explained etiology. It is suggested that genetic, infectious and immunological factors may be involved, and neurodevelopmental, neurodegenerative and neurotransmitter hypotheses have been proposed. Detection of the measurable and reproducible biological indicators of the clinical picture and the course, referred to as biomarkers, may be essential to elucidate the etiopathogenic mechanism of the illness. For schizophrenia, this function may be performed by the retina of the eye and other elements of the visual pathway. The observed abnormalities are of a structural and functional nature. They concern virtually the entire visual system, and, in accordance with the neurodevelopmental theory of schizophrenia, arise at the early stages of brain formation. What is essential – the specific structure of the human eye, its translucency, lack of myelin and low concentration of glial cells provide excellent opportunities for non-invasive assessment of the microstructure and function of the central nervous system. The following paper discusses the most important changes in the visual apparatus observed in patients with schizophrenia. Particular attention was paid to retinal vascular changes, anomalies in the electroretinogram and optical coherence tomography, structural and functional disorders of cortical centers and neurochemical disorders in the cells of the visual pathway.

Key words: schizophrenia, retina, pathogenesis

Introduction

Schizophrenia is a chronic disease affecting about 50 million people worldwide. It is characterized by disorders of the content of thinking (delusions), perception (auditory, visual and other types of hallucinations), negative symptoms (blunted affect, alogia, anhedonia, avolition, and asociality), and cognitive disorders (memory and executive

functions disorders) [1]. The nature and severity of complaints lead to a decrease in the quality of patient's life and disturbances in socio-occupational functioning [2], consequently exerting a significant influence on the economic dimension of the illness [3]. The variety of illness symptoms and the variability of the individual course do not facilitate the search for factors affecting the development of the illness. Numerous potential etiologic factors include, among others, genetic susceptibility, anatomical and functional changes in the brain, dysfunctions of neurotransmitter systems (dopamine, glutamatergic theory), neurodevelopmental theory, the influence of neuroinfections as well as psychological theories and premorbid personality traits [4].

Abnormalities in the visual processes in patients with schizophrenia have aroused the interest of researchers since the mid-20th century [5, 6]. Advances in diagnostic possibilities, as well as the specific structure of the human eye, its translucency, lack of myelin and low concentration of glial cells in the retina provide excellent opportunities for non-invasive assessment of the microstructure and function of the central nervous system [7]. At present, three characteristic features of the retina which can be assessed by non-invasive methods are postulated in schizophrenic patients: (1) microvascular dysfunction with venous widening; (2) impairment of photoreceptor and other retinal cells of the visual pathway; (3) abnormalities of retinal structure. It was suggested that these traits could be considered specific biomarkers of schizophrenia [8].

The purpose of the article is to present contemporary views on the relationship between the structure and the function of the organ of sight and the etiology, course and clinical picture of schizophrenia.

Structure and function of the retina

Retina develops from the same tissue (neuroectoderm) as the brain, and is the only part of the central nervous system that can be examined with the naked eye in its natural state in a living organism [9]. The process of seeing begins when electromagnetic waves interact with retinal photoreceptors – rods and cones, which become hyperpolarized. Hyperpolarization of cones leads to a depolarization of bipolar cells (ON bipolar cells) connected to retinal ganglion cells (RCG), focused in the ganglion cell layer (GCL). Their axons form a layer of nerve fibers that make up the optic nerve. The area of junction of bipolar cell axons with ganglion cell dendrites is called inner plexiform layer (IPL). Pulses from the rods undergo a more complicated route – from bipolar cells to rods via amacrine cells to retinal ganglion cells. Horizontal cells connect rods or cones neurons [10, 11]. The type of photoreceptor involved depends on the intensity of the ambient light – rods for scotopic vision (night, less than 1 lux), cones for photopic vision (day, more than 10 lux), both for mesopic vision (between 1 and 10 lux) [12]. The Retinal nerve fiber layer (RNFL) forms the optic nerve and runs into the lateral geniculate nucleus [9], from which retinal information is transmitted to the visual cortex [13]. The nutritional and support functions in the retina are performed by glial cells, which include Müller cells, microglial cells and astrocytes [14].

Changes in the vascular width of the retina in schizophrenia

Several authors suggested the involvement of vascular factors, associated mainly with the cerebral microcirculation, as a pathogenetic mechanism of schizophrenia. However, only the advances in retinal and fundal imaging techniques have made it possible to evaluate the vascularization of these regions as an exponent of cerebral vessels [14]. The first studies indicated a relationship between the wider retinal venules and an increased risk of stroke, dementia and hypertension [15]. At the same time, it is well known that cardiovascular disease is the most common cause of premature death in people with schizophrenia. This association is probably not only due to a higher prevalence of risk factors for cardiovascular disease in patients with schizophrenia, including side effects of antipsychotic drugs and lifestyle (smoking, low physical activity, high-calorie diet), but of a primary nature [16]. The observed more frequent occurrence of cerebrovascular diseases in schizophrenic patients as well as the larger diameter of venous vessels in this group in comparison with people suffering from hypertension, diabetes, chronic depressive disorders and chronic tobacco smokers may be the confirmation of this hypothesis [15]. In the group of 38-year-olds suffering from schizophrenia, monitored from the age of 11, in comparison with a properly selected group of healthy people, the same authors observed the expansion of venous retinal vessels, from which they made a conclusion about the potential chronic hypoxia of the patient's brain tissue. Furthermore, patients with wider vein vessels presented a greater severity of psychotic experiences in childhood [15].

Another large study [17] compared the venous microvasculature width among three groups: the control group and a group of twins, one of whom suffered from psychosis, while the other was healthy. Twins with psychosis had wider venous vessels of the retina than the control group, and in healthy twins this dimension was intermediate. There were no differences in the arterial blood vessels between the subjects. According to the authors, obtained results may indicate that the width of the retinal venous system could be a marker of familial susceptibility to psychosis.

The results of other studies indicate the correlation between the width of venous retinal vessels and the intelligence quotient evaluated in childhood and disorders of neuropsychological functioning in middle age [18].

Electroretinogram

Electroretinogram (ERG) is a non-invasive technique that registers light-induced electrical potential from the retina in response to standard flash stimuli. First, hyperpolarization of the receptors (a-wave) occurs, followed by the depolarization of bipolar cells (b-wave). Both types of waves are analyzed in terms of their amplitude and latency [13]. The first ERG study indicated a reduction in the b-wave amplitude in patients with schizophrenia [19], but it should be noted that this phenomenon occurred in patients after long, direct exposure to sunlight, so that it could result from retina's damage. Another study, of patients with schizophrenia without retinal disorders, showed a decrease in the amplitude of the a-wave in comparison to the control

group. This phenomenon was independent of the dose of the antipsychotic drug used [20]. According to the authors, it resulted from the impairment of the photoreceptor function associated with deficiency of omega-3 fatty acids.

In a similar study, Balogh et al. [21], when assessing patients with an exacerbation of the illness, observed a decrease in the amplitude of the a-wave with a negative correlation between the amplitude and the severity of positive symptoms. During the re-evaluation carried out after 8 weeks, along with the improvement of the clinical condition, an increase in the amplitude of the a-wave was noted. There were no differences between the latency of the a-wave and the amplitude of the b-wave between the patients (regardless of the severity of symptoms) and the control group.

Hébert et al. [22] evaluated healthy offspring of schizophrenic patients. The subjects from the risk group, in comparison with the control group, were characterized by a decrease in the amplitude of the b-wave from the rods, originating from Müller cells and reflecting the processes taking place in the bipolar cell layer of the retina. According to the authors, the observed abnormalities reflect the neurodevelopmental nature of schizophrenia.

Similar results were obtained by the largest so far ERG study in patients with schizophrenia, including 105 patients [23]. In addition, the authors assessed the latency of the b-wave, which was significantly increased in patients compared to the control group. In contrast to the results obtained by Balogh et al. [21], in the study of Hébert et al. changes in the ERG persisted despite the use of effective treatment.

The results obtained by the individual research teams indicate abnormalities of retinal function in patients with schizophrenia at the level of photoreceptors in the acute phase of the illness and at the level of bipolar and Müller cells in patients and the risk group regardless of their clinical status [9]. One of the potential mechanisms of these abnormalities is a deficiency in retinal cells of omega-3 fatty acids, similar to the deficit of these substances in the brain tissue of patients with schizophrenia [24]. A practical confirmation of these considerations is the improvement in clinical status observed in patients after supplementation with high doses of omega-3 acids [25] as well as the retinal function abnormalities observed in rhesus monkeys fed a diet low in polyunsaturated fatty acids [26]. It is also suggested that the abnormalities in the electroretinogram reflect retinal and cerebral disorders in the metabolism of dopamine and serotonin [27]. Hence, there are proposals to use functional methods, such as pattern electroretinogram (PERG), which allow assessing dopaminergic activity, among others, of ganglion cells [28].

Optical coherence tomography

Optical coherence tomography (OCT) is a non-invasive technique that allows assessing *in vivo* the individual layers of the retina with particular attention to the macula and the foveal center [29]. Images of cross-sections are created based on the phenomenon of interferometry. The image quality depends on the scanning speed and resolution. Modern OCT cameras can work at a speed of 20,000–52,000 scans/minute and a resolution of 1–4 μm . A faster scanning speed reduces the number of motion

artifacts, while a high resolution allows performing the test not only at the tissue, but also cellular level [7].

The first retinal examination in patients with schizophrenia using OCT brought mixed results. There was a reduction in retinal nerve fiber layer (RNFL) thickness and macular volume (MV) [30], one study found a relationship between the duration of the illness and the obtained RNFL and MV results [31]. The negative correlation with the duration of the illness was observed. The thickness of RNFL and MV decreased along with the subsequent years of the illness course, with the lowest parameters obtained in the chronically ill patients (> 10 years of illness). According to the authors, these results may suggest the use of the above parameters to monitor the course of the illness.

The subsequent studies confirmed the presence of isolated lesions consisting in reducing the thickness of the retinal nerve fiber layer and macular volume, more pronounced in patients who had undergone the last psychotic episode six or more months before OCT assessment compared with patients assessed within one month after the last exacerbation [32]. No differences compared to the control group were observed in the field of RNFL and MV, which, according to the authors of this study, may indicate a lack of damage to unmyelinated axons in patients with schizophrenia [33].

Celik et al. [34] evaluated the thickness of the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL) and inner plexiform layer (IPL) in patients with schizophrenia. All three of the above parameters were reduced compared to the control group, the GCL and IPL values were statistically lower for the drug-resistant patients compared to the group responding to the treatment [34].

Few studies have examined the relationship between changes in the thickness of individual retinal layers and the severity of schizophrenia. Chu et al. [33], using *the Scale for the Assessment of Positive and Negative Symptoms* (SAPS/SANS), found only a moderate relationship between macular volume (MV) and the severity of positive symptoms. Lee et al. [31] did not find any relationship between the thickness parameters of individual retinal layers and the results obtained by patients in *the Positive and Negative Syndrome Scale* (PANSS). Ascaso and et al. [32] did not directly compare the relationship between OCT results and the severity of symptoms, however, patients with a greater severity of retinal changes obtained an average PANSS score in the range of 70 to 92 points, and patients with less severe changes (psychotic episode to a month from the OCT examination) 90 to 118 points, respectively.

In one recent study, Samani et al. [29] evaluated 35 patients with schizophrenia and 50 people in the control group. There was a reduction in the thickness of the foveal center and nasal and temporal parafoveal retinal region in the patients compared to the control group. In terms of symptom severity, a negative correlation was found between the PANSS negative subscale and total retinal thickness in the nasal parafoveal retinal region and the outer nuclear layer (ONL). On the other hand, the general PANSS subscale showed a negative correlation with the nasal parafoveal ONL thickness. Duration of the illness showed a significant inverse correlation with the temporal parafoveal inner segment layer (ISL) thickness and the temporal parafoveal outer nuclear layer (ONL) thickness. There was no relationship between the thickness of the retina and the doses of drugs used. According to the authors, the obtained results

support the neurodegenerative theories of schizophrenia, the observed thickness loss of different retinal layers run parallel to the described brain neuron deficits. Reduction in the thickness of the retinal receptor layer (rich in NMDA receptors) may represent the dysfunction of these receptors, which may partially support the glutamatergic theory of schizophrenia [35].

Finally, the loss of thickness of the mitochondria-rich ISL layer can be associated with well-evidenced mitochondrial metabolism abnormalities in schizophrenia [36].

Visual pathway

Information from the retina is transmitted to the visual cortex through the lateral geniculate nucleus (LGN). This pathway represents almost 90% of the retinal afferents [13]. So far, no changes were observed in the total number of cells [37] and the volume of the lateral geniculate nucleus [38] in schizophrenic patients. The presence of abnormal connections between the pulvinar nuclei and the visual cortex was found, which may be responsible for deficits in visual attention characteristic of schizophrenia [39]. In other studies, a decrease in the number of neurons and the total volume of the pulvinar nuclei was observed [40], as well as disturbances of glucose metabolism in these structures in non-treated patients [41].

Many researchers reported irregularities within the areas of the cerebral cortex associated with the process of vision. Dorph-Petersen et al. [42] in post-mortem studies of people suffering from schizophrenia found a 25% reduction in the total number of striate cortex neurons and a 22% decrease in its volume compared to the control group. Reduction in the thickness of the primary visual cortex (Brodmann area 17) was observed using MRI in patients with the first episode of schizophrenia, which suggests it was not a consequence of an antipsychotic treatment [43]. Observed in another study [44], the reduction in the cortex thickness in the Brodmann area 16 was directly proportional to the severity of negative symptoms. Uranova and et al. [45] described abnormalities of the microcirculation in the visual cortex as compared to the control group, which, according to the authors, could indicate abnormalities in the blood-brain barrier.

One of the most commonly used tests in schizophrenia for the assessment of functional disorders is the examination of eye movements (eye tracking test). Impaired tracking movement is the phenomenon most frequently described in the literature in this group of patients, ranging from 51 to 85% of respondents [46, 47]. Similar abnormalities are observed in the saccadic movements test (saccade and antisaccade task). In 73% of the respondents with pronounced abnormalities in the antisaccade task, some atrophies within the frontal cortex were diagnosed in a tomographic examination [48]. When performing a functional assessment of the brain using fMRI (functional magnetic resonance imaging) during saccade task, the reduction of the medial temporal and the anterior cingulate activation was observed in patients. Conversely, controls show increased activation in the occipito-temporal cortex [49]. In a study using PET (positron emission tomography) with the use of fluoro-deoxy-glucose (FDG) in patients with schizophrenia, a decrease in metabolic activity in the primary visual cortex

was observed regardless of the duration of the illness and the type of treatment [50]. In another study comparing people with schizophrenia and with schizotypal personality with a control group, in the first two subgroups a decrease in metabolism was found in Brodmann areas 17, 18 and 19 [51].

Neurochemical disorders

One of the most critical neurotransmitters in the vertebrate retina is dopamine. It is mainly produced by amacrine and interplexiform cells. Its action takes place both by classic synaptic transmission and by diffusion through individual retinal layers. Consequently, it can affect all types of its cells (all types of retinal cells have dopaminergic D_1 and D_2 receptors) [52]. It seems that D_2 receptors are mainly involved in the generation of ON responses (stimulation), while D_1 receptors are responsible for the OFF responses (inhibition) [53]. As a consequence, excessive dopaminergic activity through D_2 receptors may lead to a hypersensitivity to color observed in schizophrenia, while low level of dopamine results in disturbances in color perception (e.g., in Parkinson's disease) [9]. Untreated schizophrenic patients demonstrated a higher contrast sensitivity compared to healthy controls [54]. In another study, the untreated first episode patients were also more sensitive to the contrast compared to the control group. After the initiation of an antipsychotic treatment these differences disappeared [55].

Dopamine metabolism disorders may directly affect oscillatory potentials, the evaluation of these disorders was the subject of one of the first reports on the relationship between dopamine and ERG abnormalities [56]. In this study, however, including a small group of participants, no differences were found between persons with schizophrenia ($N = 12$) and the control group ($N = 9$).

Another area of interest for researchers was the effect of dopaminergic drugs on ERG. In particular, a reduction of the b-wave with adaptation to the dark was observed after the high doses of neuroleptics (dopamine antagonists). However, this phenomenon does not necessarily have to be associated with the use of antipsychotic treatment because similar results have been obtained by the ERG assessment in healthy never medicated children of people diagnosed with schizophrenia [22].

In studies of animal models, in mice with the dopamine transporter gene knockout, which led to an increase in its level in the brain, but not in the retina, a decrease in rod sensitivity was observed [27]. In this study, mice deficient in D_1 receptors showed a decrease in the maximum amplitude of ERG, while those deficient in D_2 receptors showed an increase in oscillatory potentials.

Another neurotransmitter involved in the pathogenesis of schizophrenia is glutamate. It is released among others by ganglion and bipolar cells of the retina [57]. The glutamatergic theory of schizophrenia presupposes the hypofunctionality of the NMDA receptor with excessive glutamate activity exerting a neurodegenerative action, in the case of the retina that can potentially lead to the destruction of ganglion cells [58]. Under normal conditions, glutamate is the primary neurotransmitter that stimulates the human retina [14]. In an animal model, rats with reduced glutamate neurotransmission caused by glutamate-aspartate transporter (GLAST) blockade, a reduction

in b-wave amplitude in ERG was observed in Müller cells [59, 60]. So far, however, excess glutamate directly leading to retinal damage in patients with schizophrenia was not observed [31].

Theories underlying the role of serotonin in the pathogenesis of schizophrenia have historically been based on the psychomimetic effects of lysergic acid diethylamide (LSD), and then on the clinically proven exceptional efficacy of clozapine, which binds more strongly to serotonin 5-HT_{2A} receptors than dopamine D₂ receptors [61]. To date, there have been no studies to assess the relationship between serotonin and ERG in humans, and the results of the animal studies have had inconclusive results. In pigeons, in the conditions of serotonin deficiency, a decrease in the amplitude of the b-wave was observed, while in cats the increase of the amplitude of this wave was noticed [62, 63].

Another neurotransmitters occurring in the mammalian retina comprise glycine and gamma-aminobutyric acid (GABA). They are mainly related to the inhibitory processes in horizontal and bipolar cells. Numerous data indicate their potential role in the pathogenesis of schizophrenia, however, the impact of these compounds on the impairment of vision processes in patients has not been confirmed [64, 65].

One of the proposed mechanisms explaining ERG disorders in schizophrenia is a deficiency of omega-3 fatty acids. Docosahexaenoic acid (DHA) is found in large amounts in the central nervous system, especially in the outer segments of the retinal photoreceptors [66]. There are reports of low levels of omega-3 in red blood cells of schizophrenic patients, both untreated and those receiving neuroleptics [67]. In studies using magnetic resonance spectroscopy, disturbances in a membrane phospholipids have been observed in patients with untreated schizophrenia [68]. A reduction in the level of omega-3 acids in the brains of schizophrenic patients was also reported [24]. Based on the above observations, the relationship between omega-3 acids and the dopamine hypothesis of schizophrenia is suggested. Quantitative changes in polyunsaturated fatty acids are expected to affect the level of dopamine and the number of D₂ receptors in the brain [24].

Other disorders of visual processes in schizophrenia

Visual acuity disorders are a phenomenon commonly described in schizophrenic patients, occurring, according to different authors, with a frequency of 26% [69] to 70% [70]; similar observations have not been made for other psychotic disorders [71]. It seems that the described abnormal visual acuity can significantly affect the results of various tests performed in patients with schizophrenia, mainly probing the cognitive functions. Silverstein et al. [72] reported significant differences in spatial frequency processing depending on the severity of visual acuity disturbances in both patients and the control group. The presence of visual acuity disorders (but without other abnormalities, e.g., neurological) in 4-year-old children of mothers with psychotic history significantly increased the risk of developing schizophrenia (but not other psychoses) in later life [73].

In patients with schizophrenia, other abnormalities of the visual apparatus, such as lens opacities, cataracts or corneal pigmentation, are also more frequently observed

compared to the general population. It should be noted, however, that some of these abnormalities may be secondary, associated with the antipsychotic therapy [9].

Another frequent disorder in schizophrenic patients is strabismus [74]. This abnormality was diagnosed more often also in the group of children who later developed schizophrenia than in a healthy peer group [75].

It is interesting to note that there were no cases of schizophrenia in people with congenital blindness. The authors of two major discussions dealing with this phenomenon [76, 77] suggest the existence of several mechanisms explaining this phenomenon. Congenital blindness eliminates the visual and perceptual abnormalities characteristic of schizophrenia, the loss of the ability to assess the surroundings through sight is compensated by the higher efficiency of other senses, which leads to the reorganization of the cerebral cortex structure at the early stages of its maturation. People who are blind from birth have reduced flexibility of language functions and less dynamic control over the body, both of which can protect against schizophrenia-specific disorders of thinking and self-experiencing. The occurrence of blindness later (in the first few months of life) no longer has such a protective function, as is the innate loss of other sensory functions, e.g., inborn deafness. Congenital blindness does not reduce the risk of developing other mental disorders, which may additionally confirm significant relationship between the visual processes and the development of schizophrenia.

Recapitulation

Compared to other methods of the central nervous system research, retinal assessment is easy, non-invasive, painless, fast, and cheap. The retinal nerve fibers deprived of myelin constitute a specific anatomical model that allows treating the retina as a “window of the brain” [78]. Emerging new diagnostic methods allow for more and more accurate structural and functional imaging. The pattern electroretinogram (PERG), which assesses the function of ganglion cells with the possibility of dopaminergic transmission assessment [28], is particularly suitable for broader use in the context of the relationship between schizophrenia and the function of the visual system.

Structural and functional abnormalities in patients with schizophrenia affect practically the entire visual pathway, from the retina to the cerebral cortex. The changes are most likely to appear in the early stages of brain formation, according to the neurodevelopmental theory of schizophrenia [79]. Factors that may disturb the neuroectodermal formation of the visual system around the 4th week of pregnancy and consequently be responsible for the later anomalies observed in schizophrenia are very diverse. They may include the genetic factors, neurotrophic substances (retinoic acid), environmental impacts (viral infections, alcohol) and many others, impeding the development of the brain and the visual structures [13].

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