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Ophthalmological and electrophysiological features of Parkinson's disease

Zmiany okulistyczne i elektrofizjologiczne w chorobie Parkinsona

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Summary: Purpose: Based on available literature, the authors describe the most frequent ocular diseases and symptoms, as well as bioelectrical dysfunction of the visual pathway in patients with Parkinson's disease (PD).
Material and methods: Data published in literature available in PubMed library. The most often ocular diseases, symptoms and the bioelectrical dysfunction were diagnosed using routine ophthalmological examination including tear film tests, perimetry, optical coherence tomography (OCT), color and contrast sensitivity tests, and electrophysiological recordings like EOGs, flash, pattern and multifocal ERGs, VEPs.
Results: The most frequent ocular diseases in PD are dry eye syndrome and glaucoma. At least 25% of PD patients manifest visual hallucinations. The most prominent bioelectrical dysfunction of the visual pathway was observed in outer layers of the retina (retinal pigmented epithelium, photoreceptors) and it was registered mainly in EOG, PERG and mfERG tests.
Conclusions: During examination of PD patents, general ophthalmologists should especially pay attention to diagnosis and treatment of glaucoma and dry eye syndrome. In PD visual deficits may occur without any noticeable changes in the routine ophthalmological examination. Electrophysiological recordings can explain, at least partially, visual dysfunction in course of PD.

Słowa kluczowe: choroba Parkinsona, współistniejące choroby i objawy ze strony narządu wzroku, EOG, ERG, PERG, mfERG, VEP.
Key words: Parkinson's disease, associated ocular diseases and symptoms, EOG, ERG, PERG, mfERG, VEP.

Parkinson's disease (PD) is an age-related neurodegenerative disorder, caused by a selective degeneration of dopaminergic neurons in the substantia nigra, which leads to impairment of the nigrostriatal pathway. Pathological changes in PD also concern other parts of the central nervous system, as well as the peripheral nervous system, but they are less prominent. Progressive loss of 6-8% of dopamine concentration every 10 years is a physiological finding attributed to age. However, when it decreases to 20% of the normal level, symptoms as bradykinesia, cogwheel rigidity, resting tremor and postural reflex impairment appear. The severity of these symptoms can be measured according to the Hoehn and Yahr Scale. Probable reasons leading to the premature death of dopaminergic neurons are genetic predisposition, accelerated aging, toxic factors, specific and non-specific central nervous system inflammations, chronic inflammatory reaction of the neuroglia, oxidative stress and proteins' metabolism disturbances leading to so called proteolytic stress. Five genes and few *loci* are known to be responsible for familiar prevalence of PD, which can be autosomal dominant, autosomal recessive, linked to chromosome X and mitochondrial inherited (1).

PD affects as many as 0.15% of the general population, but for persons over 70 years old the prevalence of this disease is even 10 times higher (2). Basing on this statistics, it is valued that about 70 000 people suffer from PD in Poland. With the aging of population, we can expect that number of patients increase to 110 000 persons in the year 2020. Therefore, PD becomes more significant social problem, especially that treatment with the dopamine precursor – levodopa allows patients to live a normal life span (3,4). Currently, the average age of the onset of the disease is 58 years old. PD affects men 1.5 times more frequently than women (2).

Diagnosis of PD is based on clinical symptoms and improvement of motor functions after treatment with levodopa. Beyond Positron Emission Tomography (PET), which reveals reduction of dopamine metabolism in the nigrostriatum, there is no other examination, which can confirm diagnosis of PD ante-mortem. However, because of low availability and high cost, this method is not common procedure. The definite diagnosis of PD can be confirmed only on base of postmortem examinations of the brains, which reveal degeneration of dopaminergic neurons in substantia nigra and cytoplazmic inclusion bodies in the neurons called Lewy bodies (LB). Meantime, the histological studies of the brains revealed, that even in specialized medical centers 25% of idiopathic PD were misdiagnosed (5). Therefore, there is strong need for searching new diagnostic methods.

Beyond the central nervous system, dopamine is also contained in amacrine subtype called A18 cells of the inner plexiform layer of the retina (6) (Fig. 1).

Although the density of these neurons is low, their widespread dendritic organization and long fine axons ensure overlap with neighboring dopaminergic or other amacrine cells as well

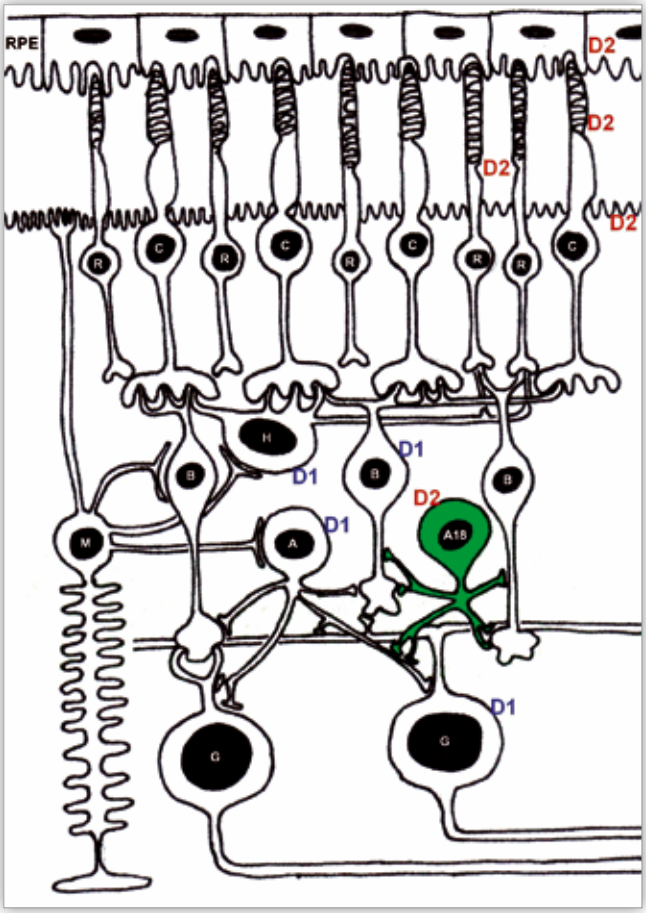

Fig. 1. Schematic diagram of the mammalian retina and localization of dopaminergic receptors.

Ryc. 1. Schemat budowy siatkówki u ssaków oraz lokalizacja receptorów dopaminergicznych.

RPE – Retinal pigmented epithelium, R – Rod, C – Cone, B – Bipolar cell, H – Horizontal cell, M – Müller cell, A – Amacrine cell, A18 – Dopaminergic Amacrine cell, G – Ganglion cell, D1, D2 – dopaminergic receptors of the retina (D1-receptor family – excitatory function, D2-receptor family – inhibitory function).

as bipolar cells and direct influence on them through synapses (7). Amacrine A18 cells are not known to make any synapses upon ganglion cells. Dopamine may also influence on other cells indirectly, because it can diffuse on distance of 3 mm, which equals the whole thickness of the retina (6). The levels of dopamine concentration in the retina are higher during the day and lower at night (7). The results of the studies indicate, that dopamine takes part in light adaptation (6,8), spatial contrast sensitivity and color discrimination (9-11), visuospatial problem solving, spatial working memory, oculomotor control (11), photoreceptors voltage-gated Ca^{2+} influx (12) and promotion of the photoreceptor renewal process (13). Dopaminergic receptors are spread across the whole retina. They are divided into two families: the D1-receptor family (subtypes D1 and D5) acts as excitatory, while the D2-receptor family (subtypes D2, D3 and D4) has the inhibitory function. D1-like receptors are found to be associated with horizontal, bipolar, ganglion and some amacrine cells, whereas D2-like receptors are present on rod and cone photoreceptors, outer limiting membrane, retinal pigment epithelium and – as autoreceptors – on amacrine A18 cells. In the ciliary retina dopaminergic receptors are likely to be involved in the cyclic regulation of intraocular pressure (14).

Ocular changes in patients with Parkinson's disease/ Zmiany okulistyczne w przebiegu choroby Parkinsona
Visual hallucinations/ Halucynacje wzrokowe
Dry eye symptoms/ Zespół suchego oka • ↓ tear film breakup time (TBUT)/ ↓ czas przerwania filmu łzowego • ↓ tear production (Schirmer's test)/ ↓ produkcja łez (test Schirmer'a) • corneal epithelial devitalization (rose bengal stain)/ nieprawidłowości w barwieniu różem bengalskim • presence of meibomian gland disease/ łojotok gruczołów Meiboma
Primary open angle glaucoma/ Jaskra pierwotna otwartego kąta
Decreased RNFL thickness (OCT)/ Zmniejszenie grubości warstwy włókien nerwowych siatkówki (OCT)
Abnormal eyelid and eye movements/ Nieprawidłowe ruchomość gałek ocznych i powiek • reduced blink rate/ redukcja częstości mrugania • decreased saccades performance/ upośledzenie ruchów sakkadycznych
Impaired visual functions/ Zaburzenia funkcji wzrokowych • decreased contrast sensitivity/ obniżenie czułości kontrastowej • decreased color discrimination (blue-yellow cone pathway)/ zaburzenia widzenia barwnego (zwłaszcza w osi niebiesko-żółtej)

Tab. I. Ocular changes in patients with Parkinson's disease.

Tab. I. Zmiany okulistyczne w przebiegu choroby Parkinsona.

Hence, ophthalmological changes can appear in course of Parkinson's disease as a result of generalized dopamine depletion. The most common ocular findings in PD are detailed in Table I.

Visual hallucinations affect about one-fourth of PD patients (15). They can be divided into 'simple' (without formed images) hallucinations, such as flashes of light and color or feelings of presence and passage, and 'complex' hallucinations – humans, animals, objects. The typical hallucinations in PD are most often complex with a sudden onset and duration of seconds, presenting one blurry moving image (person). Patients commonly try to interact with the hallucinations by walking towards it or by trying to touch it (16). In the past visual hallucinations in PD used to be attributed only to levodopa treatment. Nowadays it is known, that they can also appear in patients without any antyparkinsonian treatment (17). The risk factors of visual hallucinations are cognitive impairment, decreased dopamine level before next dose of levodopa (so-called "OFF" state), REM (Rapid Eye Movement) sleep dysfunction (18), longer disease duration and disease severity, higher levodopa dosage and longer duration of treatment (19), impaired color discrimination and contrast sensitivity (20), decreased visual acuity (19). Only one study investigated dependence of the electrophysiological changes on hallucinations and revealed increased latency of VEP P100-wave in PD patients with visual hallucinations, when compared with results obtained from PD patients without these symptoms (21).

PD patients should be considered at increased risk of having dry eye problems (22). Depending on the stage of PD, from 63.3% to 87.5% of patients complain of surface irritation, tearing, sandy sensation or other dry eye symptoms (17,22). In about 53.3% of new-diagnosed untreated patients the tear film breakup time (TBUT) were shortened, which suggests that

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deficit of the mucin layer seems to be the earliest noticeable abnormality of the tear film production (17). In more advanced stages of PD there is also a decrease in tears secretion, which can be measured using Schirmer's Test, tear meniscus height and rose bengal stain of the conjunctiva. The frequency of abnormal results of each tear film examination was about 50% (22). Presence of meibomian gland disease is also more frequent in PD subjects than in age-matched (AM) controls (22). The tear film's changes may be a consequence of autonomic dysfunction as a result of the existence of Lewy Bodies at sympathetic ganglia, substantia nigra and peripheral parasympathetic ganglia (23). There is a significant correlation between the rate of abnormalities observed in tear functions' tests and stage of disease measured by Hoehn-Yahr Scale (22). In PD dry eye symptoms are not only a result of disturbances in tear film production, but also significantly lower blink rate (17,22). It has been suggested, that this may be related to hypokinesia from decreased dopamine activity (17).

Visual field defects compatible with glaucoma are statistically more frequent compared to AM healthy subjects (24,25). Bayer et al. (24) have also observed glaucomatous appearance of the optic nerve head with significantly lower intraocular pressure (IOP) in PD patients. In this study all PD subjects with glaucoma were found to have primary open-angle glaucoma and its frequency was 23.7%, which was significantly higher when compared with the occurrence rate of 6.5% in the control group. The decrease in the retinal nerve fiber layer (RNFL) thickness, probably as a result of a loss of ganglion cells, have been recently reported in PD patients using optical coherence tomography (OCT) (26,27). These defects are probably a result of the underlying susceptibility of the retinal nerve fibers to apoptosis or even slightly increased intraocular pressure due to decreased dopamine levels (24,25).

Among other abnormalities, PD patients also demonstrate more errors in both pro-saccade and anti-saccade tasks (28-31), with a tend to recover after levodopa administration in so-called "ON" stage (31). The data from several studies have documented deficits in contrast sensitivity and color discrimination, mainly in the blue-yellow axis (32-36). The B-Y pathways stem from giant bistratified cone bipolar cells and project through bistratified ganglion cells to the interlaminar (koniocellular) neurons of the lateral geniculate nucleus (33). According to present knowledge, only this subpopulation of cone bipolar cells may project to amacrine subtype A18 cells (37), therefore the B-Y pathways are particularly susceptible in early stages of PD.

Dopamine plays role at initial stage in primary modulation of the retinal signal, because dopaminergic amacrine cells, together with horizontal cells, are responsible for the lateral interactions among visual channels (38). It is known from animal studies (39), that dopamine deficiency can cause disturbances of electrical conduction in the retina and the optic nerve. Thus, electrophysiological changes can be expected in course of PD. Until now only a small number of studies described electrophysiological abnormalities in Parkinson's disease and results were often inconclusive. To estimate a bioelectrical function of the retina and the optic nerve electro-oculogram (EOG), flash, pattern and multifocal electroretinograms (flash ERG, PERG and mfERG) and visual evoked potentials (VEPs) were performed (Tab. II).

Electrophysiological changes in patients with Parkinson's disease/ Zmiany elektrofizjologiczne w przebiegu choroby Parkinsona
EOG • ↑ light peak latency in untreated PD at stage 1 of H-Y/ ↑ latencji maksymalnej amplitudy EOG u nieleczonych pacjentów w 1. stadium zaawansowania choroby Parkinsona • ↑ light peak latency and ↓ light peak amplitude at stage 2 of H-Y/ ↑ latencji oraz ↓ maksymalnej amplitudy EOG w 2. stadium
Flash ERG • lower amplitude of b-wave to 1.0 Joule flash photopic stimulation/ obniżenie amplitudy fali b przy stymulacji błyskami światła o natężeniu 1 dżula
PERG • ↑ implicit time of P50-wave in new-diagnosed PD patients in early stages (H-Y 1-2)/ ↑ czasu utajenia fali P50 u nowo zdiagnozowanych pacjentów we wczesnych stadiach zaawansowania choroby Parkinsona (H-Y 1-2) • mean P50-wave implicit time is more increased at the lower contrast level (47% vs 96%)/ ↑ wydłużenie czasu utajenia fali P50 przy niższym kontraście (47% vs 96%) • shift of the peak of the tuning functions from 2.3 cycles per degree (cpd) in age-matched controls to 1.1 cpd in PD patients/ przesunięcie max amplitudy PERG z 2,3 cykli na stopień do 1,1 cykla na stopień
mfERG • reduced density of P1-wave/ obniżenie gęstości amplitudy fali P1 w pierścieniu 1 pochodzącym z obszaru plamki
VEP • ↑ P100-wave latency in untreated PD patients in early stages of disease/ ↑ latencji fali P100 u nieleczonych pacjentów we wczesnych stadiach zaawansowania choroby Parkinsona
• ↑ latency and decreased VEP amplitude in more advanced (H-Y 2-3) untreated PD patients/ ↑ latencji i ↓ amplitudy fali P100 u nieleczonych pacjentów z bardziej zaawansowaną chorobą (H-Y 2-3)

Tab. II. Electrophysiological changes in patients with Parkinson's disease.
Tab. II. Zmiany elektrofizjologiczne w przebiegu choroby Parkinsona.

Ikeda et al. (40) showed that increased light peak latency in EOG is found to be the earliest electrophysiological deficit in untreated Parkinson's patients at stage 1 of the Hoehn-Yahr Scale. The results obtained from patients who were examined after five years follow-up with progression to stage 2 of PD, revealed not only increased light peak latency, but also reduction of light peak amplitude in EOG. Electro-oculograms depend on the integrity of the retinal pigmented epithelium and the outer segment of photoreceptors (41), therefore authors (40) suggested that these cells of the retina might suffer the most from dopamine deficiency, because it is the extremity of its diffusion pathway from the inner plexiform layer. Moreover, impairment of photoreceptors renewal process may lead to reduction of light peak amplitude.

Full-field ERG is the result of the summed electrical activity of the retinal cells. It analyzes function of rod, cone, bipolar, Müller and amacrine cells. In the literature there are only few past studies describing changes in flash ERG recordings in PD patients. Nighthale et al. (42) observed a significant difference in amplitude of photopic flash ERG to 1.0 joule flash stimulation, but it was not found when 0.1 joule flash was used, nor in the implicit time at either stimulus intensity. In the earlier study,

Kupersmith et al. (43) found no difference in the oscillatory potentials between PD subjects and controls. Dopaminergic cells probably contribute to the flash ERG generation only partially, thus recordings of subtle changes in retinal function may be not revealed by this technique.

PERG test reflects bioelectrical function mainly of the macular ganglion cells (N95-wave), whereas P50-wave is not only under the influence the ganglion cells, but also cone photoreceptors of the macula. Holder (44) observed, that increased implicit time of P50-wave was not characteristic feature of the optic nerve's or the ganglion cells' dysfunction, but it was found in subjects with macular cone photoreceptors defect. Peppe et al. (45) observed a statistically significant difference between new-diagnosed PD patients in early stages (H-Y 1-1.5), of disease and control group in P50-wave implicit time at contrasts of 96% and 47%. The mean P50-wave implicit time were more increased at the lower contrast level. Ikeda et al (40), using contrast level of the checkerboard 90%, showed no significant difference in PERG responses between Parkinson's patients at stage 1 of Hoehn-Yahr Scale and controls. The electrophysiological changes in P50-wave implicit time appeared with disease progression to stage 2. Calzetti et al. (46) investigated patients with PD at stage 2-3 of the Hoehn-Yahr Scale, who had never been treated with levodopa or other antyparkinsonian drugs, using steady-state and transient PERG responses in three spatial frequencies (SF): 2.44, 1.74, 0.84 cycles per degree (cpd) and contrast level of the checkerboard – 97%. The only significant difference in PERG measurements was increased P50-wave implicit time of transient responses only for SF 2.44 cpd. Tagliati et al. (47) investigated Parkinson's patients at stage 1-3 of disease using steady-state PERG. Over a half of these patients were treated with levodopa. Authors observed a shift of the peak of the tuning function from 2.3 cpd in AM group to 1.1 cpd and a flattened shape of PERG amplitude in PD patients. Comparing the results of treated with levodopa patients with untreated patients, authors observed no significant PERG amplitude or phase difference. Peppe et al. (38) did not observe any shift of the peak of the tuning functions in PD patients. Because the center to surrounding antagonistic receptive field organization of ganglion cells produces larger responses at medium than low or high frequencies (38), we can calculate the PERG tuning ratio (TR) dividing medium by low SF PERG amplitude (47,48). The results of the electrophysiological studies (38,47,48) revealed an attenuated PERG tuning ratio (TR) in PD patients when compared to AM subjects, because aging affects all SFs, whereas in PD there is a selective loss in the middle-high SF region. Moreover, there is an inverse correlation between TR and severity of disease in untreated patients (47). During levodopa therapy spatial tuning functions in PD subjects tend to recover.

Only two studies investigated multifocal-ERG recordings in PD subjects. Moschos et al. (49) found that the mean P1 density amplitude of ring 1 (approximately foveal region) in PD patients was significantly lower when compared to controls. The dopamine action seems to be involved in glutaminergic (activating) transmission onto bipolar cells (50). The origin of P1-waves of ring 1 are mainly cone bipolar cells, which suggest dysfunction of foveal region of the retina. On the other hand, Palmowski-Wolfe et al. (51) did not observe any significant differences in waveform, amplitudes or latencies on the slow stimulation mfERG between three patients with mild to moderate stages of Parkinson's disease and four healthy volunteers. However, because of small number of patients in this study, further investigations are needed.

Pattern visual evoked potentials (PVEP) are generated in the occipital cortex, where dopaminergic innervation seems to be very low (40). From clinical practice it is known, that PVEP alterations are mainly seen during optic nerve diseases. Peppe et al. (45) recorded VEP responses to a vertical square-wave grating pattern and observed an increased P100-wave latency in new-diagnosed untreated PD patients in early stages of disease, which suggest the optic nerve disfunction. Ikeda et al. (40) did not report any significant difference from age-matched controls. Calzetti et al. (46) found in untreated patients in more advanced stages (H-Y 2-3) of PD not only an increased latency, but also a decreased VEP amplitude for both steady-state and transient responses for SF 2.44 cpd. Some authors claim, that substitution of levodopa decreases latency of VEP responses (45,52), while others do not support it (42). Results obtained from treated with levodopa patients are inconsistent (32,38,42,45).

In conclusion, nowadays PD patients live longer due to antyparkinsonian treatment, but levodopa does not provide constant high dopamine concentration and its deficit may affect visual pathway's function. This could be a cause of ophthalmological disturbances. During examination of PD patients, general ophthalmologists should especially pay attention to the signs of dry eye syndrome and glaucoma. The results of the very few electrophysiological studies indicate that electrophysiological changes may be detected even in untreated patients in early stages of PD and they can at least partially explain visual abnormalities observed in this group of patients. The most prominent bioelectrical dysfunction is observed in outer layers of the retina (retinal pigmented epithelium, photoreceptors). The electrophysiological examinations have a potential value in diagnosing of PD, but up today the results of these studies are often inconclusive. Therefore, to estimate their practical value in differential diagnosis, further research with higher amount of patients and longer follow-up are needed.

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