

Retinal Optical Coherence Tomography in Neurodegenerative Diseases (Review)

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S.N. Svetozarskiy, Clinical Resident, Department of Eye Diseases;

S.V. Kopishinskaya, PhD, Associate Professor, Department of Neurology, Psychiatry and Addiction Medicine, Postgraduate Faculty

Nizhny Novgorod State Medical Academy, 10/1 Minin and Pozharsky Square, Nizhny Novgorod, 603005, Russian Federation

Increased aging of the population makes problems of the diagnosis and treatment of neurodegenerative diseases socially more significant. The ability to use the retina as a “window” to the central nervous system has attracted great attention in recent years. Optical coherence tomography (OCT) is a non-invasive method for *in vivo* studies of various conditions to generate high-resolution images of the tissue cross sections under study. Retinal OCT parameters are considered to be potential surrogate biomarkers of early-stage neurodegenerative disorders, and have already been included in the guidelines for diagnosing neuromyelitis optica. This review summarizes and analyzes the current information on retinal changes according to OCT data in neurodegeneration *in vitro* and *in vivo* in Alzheimer's and Parkinson's diseases. The application of ultra-high resolution OCT for the diagnosis of the early stages of neurodegeneration is also considered. Morphological and functional links and possible mechanisms for the retinal lesions in Alzheimer's and Parkinson's diseases, and their similarities in glaucoma are discussed. The efficacy of using this method in the diagnosis of neurodegenerative processes at an early stage is likely to be increased by the development of instrumentation and improvements in the design study for carrying out investigations in different groups of patients, including those having hereditary diseases of the nervous system.

Key words: retina; biomarker; optical coherence tomography; Parkinson's disease; Alzheimer's disease; neurodegeneration.

Introduction. An increasingly ageing population in developed countries has made the problem of diagnosis and treatment of neurodegenerative diseases especially topical. Currently, numerous neuroprotective drugs are being developed, while reliable biomarkers and methods for monitoring the neurodegenerative process are scanty [1]. There are several markers which indirectly reflect the activity the process of apoptosis. In particular, there are methods for determining the concentration of pro-apoptotic proteins in the blood, but these are not widely used in medical practice. Magnetic resonance imaging is not a reliable method of neuronal degeneration evaluation, because it does not show a high level of correlation with the activity of the neurodegenerative process in short-term studies [2]. In neurodegenerative diseases the progressive loss of neurons increases with age, but no objective method for the measurement of this has been developed.

The retina and optic nerve form part of the central nervous system (CNS). The first three types of neurons of the visual analyzer — the photoreceptors, bipolar and ganglion cells, forming a vertical pathway of signal transmission, are located in the retina [3]. Between them there are amacrine and horizontal cells, which provide signal transmission and modulation in the horizontal direction [4]. The retinal nerve fiber layer consists of unmyelinated regions of the axons of the ganglion cells, which are covered with myelin where they leave the eyeball via the mesh-like plate of the sclera, and form the optic nerve. The retina as a “window” to the CNS

has attracted special attention in recent years [5–9]. There are several immutable anatomical prerequisites for this: the physiological transparency of the eyeball media, the unique structure of the retina with its low concentration of glial cells, and the absence of myelin. Furthermore, advances in science and technology have led to the development of new bioimaging techniques such as optical coherence tomography (OCT).

Optical coherence tomography. OCT is a non-invasive method for *in vivo* studies that yields high-resolution cross sectional images of tissues. The cross section image is made by combining multiple axial depth reflectivity profiles (A-scans). The image quality depends on the speed A-scans acquisition and their resolution [10–12]. The first commercially available OCT devices had a speed of about 400 A-scans per second, axial resolutions of 8–10 μm and a depth sufficient to explore all the layers of the retina. Modern high and ultra-high resolution OCT devices provide speeds of 20,000–52,000 scans per second and resolutions of better than 1–4 μm . Their high speed makes it possible to reduce the number of motion artifacts, while the high resolution enables research to be carried out, not only at a tissue level, but at cellular and subcellular levels as well. The depth of scanning has also increased, so choroid structure investigations have become feasible [13, 14].

In recent years retinal OCT has increasingly been used in the study of neurological diseases. Firstly for demyelinating diseases — multiple sclerosis and neuromyelitis optica,

Corresponding author: Svetozarskiy Sergey, e-mail: svetozarskiy@rambler.ru

and now the use of retinal OCT in these diseases has been recognised and is being actively developed [15–20]. Assessment of the retinal nerve fiber layer thickness is included in the guidelines for diagnosing neuromyelitis optica [21]. Research is being carried on in groups of patients with Alzheimer's and Parkinson's diseases, mild cognitive syndrome, various forms of optic nerve atrophy, stroke, spinocerebellar ataxia, hereditary diseases of the CNS, obstructive sleep apnea and prion diseases (Creutzfeldt–Jakob disease) [22–29].

This method is promising in relation to monitoring the activity of neurodegenerative processes in the course of studying the efficacy of pharmaceutical preparations [7, 30]. The high reproducibility of the results of examinations of the same patient by different specialists, and a high index of agreement by experts on the data obtained, makes OCT a well-suited technique for multi-center studies [31–35]. The prevalence of diffuse retinal changes over local abnormalities in neurodegenerative disorders determines the final conclusion made according to the findings of the OCT technique: focusing not on a qualitative description of optical phenomena, but mainly on the retinal thickness and its volume parameters. In this regard, most commonly used standard protocols include a quantitative assessment of the retinal ganglion cell layer and retinal nerve fiber layer thickness presented by the axons of the ganglion cells, and of the total macular volume (total volume of retinal tissue in the yellow spot area (macula) within a disc of a given diameter). This review summarizes the experience of applying OCT for the diagnosis of retinal neurodegenerative processes in experimental work and in the most common neurodegenerative diseases — Alzheimer's and Parkinson's diseases.

Experimental OCT diagnosis of retinal neurodegeneration. Damage to major subcellular organelles — the nucleus, mitochondria, Golgi apparatus — provides information regarding the onset of programmed cell death, apoptosis, much sooner than the appearance of the first changes at a cellular level. Under physiological conditions, the mitochondria in a cell are working as a structural and functional network. When a programme of apoptosis is triggered, a collapse of the mitochondrial network occurs, and the mitochondria become independent structures. Soon structural changes occur, including an increase in the permeability of the mitochondrial membrane, leading to the release of apoptotic molecules, such as cytochrome C, into the cytosol, and caspase cascade activation takes place [36, 37].

When studying apoptosis in cultured retinal ganglion cells, Tudor et al. [38] found a number of early morphological and optical changes. The mitochondrial network degradation when the mitochondria become independent structures occurs within 20 min of exposure to staurosporine, and after 60 min, the release of cytochrome C, which is an indicator of mitochondrial membrane disintegration, can be detected. Thus, data has been obtained in the time “window” between the beginning of the functional changes and the structural ones in the mitochondria. Using these morphological findings, the authors have developed a programme for analysis using an ultra-high resolution

OCT device, which allows them, automatically, to be able to distinguish between a control sample, a sample in the early stages of apoptosis 20 min after the staurosporine exposure, and a sample 30–60 min after such exposure, with an accuracy of 85%. The first stage involves the initial processing to remove noise, detect the cover-glass position and to correct imaging artifacts, caused by any tilting of the object under test. Then, the part of the image, containing the greatest number of cells (the region of interest, ROI), is selected automatically on the basis of the surrounding pixel intensities and adjustments for the cover-glass position. Each ROI is assessed, using 65 parameters such as entropy, range, standard deviation contrast, correlation coefficient, energy and homogeneity for each co-occurrence matrices along one of three X, Y, and Z coordinates, in order to reveal significant features in the OCT images of the retinal ganglion cells under physiological conditions and at different stages of apoptosis. Using a Gaussian mixture model a multidimensional distribution of the indicators, so-called feature space, is generated, in which clusters of healthy and apoptotic cell images are marked out, to provide the basis for the analysis programme. The distance from the point in the feature space, representing the cell clusters in the tested sample, to the healthy cell clusters point allows differentiation of the control sample from a sample at an early stage of apoptosis. The authors can state that the change in the optical parameters of the ganglion cell culture occurs, primarily, due to the reconfiguration of the mitochondrial network. Similar results were obtained in a study of retinal explants (*ex vivo*). Thus, this demonstrates the possibility of non-invasive quantitative assessment of the condition of retinal neurons using the OCT technique, and its application for the diagnosis of neurodegeneration at an early stage.

Retinal OCT has occupied an important place in experiments, for assessing the *in vivo* effects of neurotrophic drugs and the effects of cell therapy. In particular, OCT has been used for the study of retinal ganglion cell axon regeneration after optic nerve damage and subsequent stem cell therapy [39]. Experimental studies aimed at improving the quality of the images have played a significant role in the development of the OCT method and its application in the diagnosis of neurodegenerative processes. This may be achieved, not only by improving the technical performance of the device, but of the software as well; for example, by averaging a greater number of images [40]. Such techniques have helped to achieve a higher level of matching of the histological and optical picture from the internal limiting membrane of the retina to the outer layers of the choroid [41].

Retinal OCT in Alzheimer's disease. Alzheimer's disease (AD) is a steadily progressing neurodegenerative disease in which neuritic plaques (accumulation of beta-amyloid) and neurofibrillary tangles (containing tau protein) are formed in the CNS [42, 43]. Visual symptoms are often early complaints in AD and are accompanied by such pathological changes in the structures of the optic tract, as the deposition of beta-amyloid, the deterioration of blood flow in the retinal vessels, vacuolar degeneration of the ganglion cells and their axons within the optic nerve,

reduction of retinal nerve fiber layer thickness and neuron atrophy in the occipital lobe [44–52].

There are different opinions concerning the decrease in retinal nerve fiber layer thickness in AD [53]. One of the hypotheses is based on the fact that the pathogenic process in AD occurs not only in the cortex, but also in other parts of the CNS, particularly in the retina. A reduction in the number of retinal ganglion cells by 36.4% [54] is accompanied by the growth of glial cells, and by the deposition of beta-amyloid and tau protein in various layers of the retina and the optic nerve, which is similar to the processes going on in the cortex [46]. However, such a deposition of AD-associated proteins and their precursors in the retina is observed not only in AD but also in retinitis pigmentosa, age-related macular degeneration, other diseases, and during normal ageing [55, 56]. A second hypothesis concerns secondary lesions of the retinal neurons, focusing on the mechanisms of retrograde transsynaptic degeneration in the direction from the geniculocortical to the retinogeniculate pathway and anterograde degeneration in the corticogeniculate pathway [57–60]. A third hypothesis was inspired by epidemiological data: glaucoma develops more commonly, and has the most severe course, in patients with AD [61–63]. Indeed, pathological processes in AD and normal pressure glaucoma are quite similar at the level of the lamina cribrosa — the exit site of the optic nerve [64]. The pressure gradient at the level of the lamina cribrosa is determined by the difference between the intraocular pressure and the retrobulbar pressure of the cerebrospinal fluid (CSF). An increase in the gradient due to raised intraocular pressure, or reduced CSF pressure, leads to lamina cribrosa deformation in the direction of the retrobulbar space and to damage of the retinal nerve fiber layer. In severe AD, there is a decrease in CSF pressure, which may be caused by a reduction in its rate of production in the choroid plexus of the brain ventricles [65]. In AD, in addition to age-related physiological atrophy, there is a marked stromal fibrosis and deposition of amyloid-beta, immunoglobulins and complement system fragments on the basal membrane of the choroid plexus [66]. As a result, the rates of CSF production and regeneration in AD are reduced, while the CSF volume increases due to the atrophy of the brain [67]. Each of these mechanisms — primary, retrograde degeneration and glaucoma degeneration of the retinal ganglion cell and their axons (retinal nerve fiber layer) is likely to play a role at particular stages of the development of AD. New studies, considering the subtype, severity and duration of the disease, are needed.

According to the OCT data, the reduction of the retinal nerve fiber layer thickness is already determined by the early stages of AD, and in mild cognitive syndrome, in the absence of changes in the visual field and visual acuity, and is progressing with the development of the disease [68–72]. In the course of a meta-analysis, which included seven studies and involved the eyes of 324 patients with AD, it was confirmed that, in AD, a statistically significant decrease in the thickness of the retinal nerve fiber layer occurs in all quadrants [73]. In the study of the macular volume [74] and the retinal ganglion cell layer thickness [69, 75] a statistically significant reduction was also found,

both parameters correlating with dementia (mini-mental state examination score, MMSE). A correlation has also been found between the nerve fiber layer thickness and a number of pattern-electroretinogram characteristics, with the P50-N95 amplitude, in particular [76]. Defects in the lower part of the visual field correspond to a greater reduction in nerve fiber layer thickness in the upper half of the retina [47]. No correlation was found between the retinal nerve fiber layer thickness and the investigation data on visual evoked potentials [77]. The role of choroid thickness as an AD biomarker is currently being studied. Statistically significant reductions in the choroid thickness in AD patients have been identified according both to OCT data and to histological studies [78, 79].

Retinal OCT in Parkinson's disease. Parkinson's disease (PD) is a progressive multisystem neurodegenerative disease, which manifests itself through a number of motor and non-motor symptoms, developing due to the loss of dopaminergic neurons in the substantia nigra and other areas of the CNS [80]. In the retina, A18 amacrine cells are the main dopaminergic neurons [81]. They are involved in horizontal impulse transmission from the bipolar cells to other subtypes of amacrine cells, and further, to the retinal ganglion cells. The lack of dopamine results in disturbances to central vision, and to decreased colour vision and contrast sensitivity [82, 83]. Dopamine is also involved in retinal trophism, circadian rhythm formation, eye growth, and cell death [84–86]. Such symptoms as dry eyes, double vision, impairment of the visual searching functions, reading difficulties, fixation problems and complex visual hallucinations have been described in PD [80, 87–89].

The first study devoted to evaluating the nerve fiber layer thickness in PD, using the OCT technique, was performed in 2004 [90]. Most subsequent studies have shown a decrease in the retinal nerve fiber layer thickness and macular volume. In the meta-analysis, which included 13 studies, involving the eyes of 644 patients with PD, a statistically significant decrease in the retinal nerve fiber layer thickness in PD was found in all quadrants [91]. In analyzing the research results, the role of the device parameters must be taken into account. This is confirmed by the recent data obtained by Satue et al. [92] in a group of 153 patients with PD on two different OCT instruments — Cirrus and Spectralis. In both cases, the average retinal nerve fiber layer thickness was reduced in patients with PD compared to the control group. According to the information received through the Spectralis device, the retinal thickness in patients with PD was significantly reduced in all areas of the macula zone except for the fovea. However, with the Cirrus device, a difference in the thickness of the retina in the fovea and in two other areas was also revealed, but in the remaining six regions no statistically significant differences were found.

It is interesting to note that the majority of patients with PD have visual field defects similar to those in glaucoma, often in the absence of the nerve fiber layer thickness reduction at normal intraocular pressure [93]. In an OCT study, where all the retinal layers were measured [93], a statistically significant reduction was determined not only in nerve fiber layer thickness, but also in the ganglion cell layer, and the

inner and outer plexiform layers. Increased thickness was found in the inner nuclear layer (bipolar, amacrine, horizontal and Müller cells). Patients with secondary Parkinsonism syndrome were identified to have specific changes of retinal neuronal architecture [94]. Progressive supranuclear palsy is characterised by a thickening of the outer nuclear layer, and, in multisystem atrophy, in the outer plexiform layer; retinal thickness is decreased in both diseases.

Half of patients with PD were noted to have interocular asymmetry, with different retinal thickness in the fovea, according to the OCT data [95]. No differences were found in the papillomacular bundle thickness compared with the control group [92]. The authors found a statistically significant correlation between retinal thickness and the results of motor independence measurements according to the Schwab–England ADL scale, and the unified Parkinson's disease rating scale, UPDRS. In earlier works [96] a correlation between the foveal thickness and UPDRS measurements was also found. There was no correlation between the thickness of the inner retinal layers and contrast sensitivity [97].

Obviously, the axons are the first target in the neurodegenerative process, but our understanding of the relationships between the dopamine level, amacrine cells and the loss of ganglion cell axons in PD is still not complete.

OCT perspectives and limitations in the diagnosis of neurodegenerative processes. Diagnostic accuracy of OCT in retinal neurodegenerative diseases may be achieved only in the case of observing a particular judiciously selecting research algorithm [7]. The first step includes identification of a concomitant ophthalmic pathology: optically significant factors — cataracts, vitreous opacities, and diseases that damage the ganglion cell layer and nerve fiber layer — glaucoma, degenerative myopia, optic disk edema and a history of optic neuritis [98]. This requires thorough recording of the medical history and the availability of diagnostic tools in the clinic — a slit lamp, tonometer, refractometer, or their installation in the OCT device. Secondly, the physician must constantly control the quality of the images obtained [99–102]. Low signal intensity, incorrect selection of the study area, and patient tremor may significantly distort the results.

The first experience of the application of OCT in the diagnosis of neurodegenerative processes has revealed a number of unsolved problems, presenting a wide field for investigations. Databases of the normal values for each OCT device linked to the distribution by age, gender and ethnicity, are incomplete and need to be confirmed by more extensive research. Furthermore, mean values of the physiological reduction of retinal layer thickness with age should be collected in the course of a long-term follow-up.

Prospective application of this method in the diagnosis of neurodegenerative processes at an early stage is connected, on the one hand, with technological advances, i.e. the introduction of ultra-high resolution OCT devices, allowing specialists to study the retinal structure at cellular and subcellular levels, and with achieving high quality images of the deep structures to study the role of the choroid in neuronal death. On the other hand, it is important

to improve the design of the research. In this respect continuing investigations in those groups of patients with different degrees of severity of disease and clinical phenotypes, and in gene carriers of hereditary diseases of the CNS, will help in the study of the early preclinical stages of neurodegenerative diseases.

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