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Glaucoma and Alzheimer's Disease – Common Pathomechanisms and Therapeutic Measures

Jaskra a choroba Alzheimera – wspólne patomechanizmy i metody terapii

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Summary

Throughout the life of an organism, its cells are being lost and regenerated at the same time. With age, the ability to regenerate diminishes, and the catabolic processes are in the ascendant. Normal aging is also associated with the constant loss of the neurons, continuing till death. This phenomenon is natural and inevitable; however, as soon as the physiological threshold is exceeded, the pathology known as a neurodegenerative disease begins. The group embraces not only a number of neurological disorders, like Alzheimer's disease or Parkinson's disease, but also glaucoma, an ophthalmic pathology. Contrary to the common knowledge, binding glaucoma to the increased intraocular pressure, the disease has numerous associations with the neurological diseases mentioned above. It has been shown, that glaucoma is significantly more common in the patients with Alzheimer's disease, and, that the mechanisms leading to the cell death in the optic nerve are very similar to the ones observed in neurodegeneration of the brain. The article analyzes current literature in attempt to review and systematize the knowledge regarding the coexistence of glaucoma and Alzheimer's disease. The results of the researches, the theories and hypotheses from the fields of the molecular biology, cytophysiology, pathophysiology, immunology and pharmacology were presented. Certainly, the knowledge on the pathomechanisms of neurodegeneration is crucial for finding the new therapeutic methods for glaucoma, as well as Alzheimer's disease.

Key words: glaucoma, Alzheimer's disease, neurodegenerative diseases

Streszczenie

Przez całe życie osobnicze dochodzi równolegle do utraty komórek organizmu i ich regeneracji. Wraz z wiekiem zmniejszają się zdolności regeneracyjne, a przewagę zyskują procesy katabolizmu. Starzenie się jest związane także z utratą komórek nerwowych, postępującą systematycznie i nieprzerwanie aż do śmierci. Jest to zjawisko normalne i nieuniknione, jednak gdy zostanie przekroczony fizjologiczny próg śmierci neuronów, możemy mówić o patologii – chorobie neurodegeneracyjnej. Do tej grupy zalicza się kilka jednostek chorobowych z zakresu neurologii, jak choroba Alzheimera i choroba Parkinsona, a także jaskrę, będącą domeną okulistyki. Na pozór jaskra, wciąż kojarzona powszechnie z podwyższonym ciśnieniem śródgałkowym, pozostaje w dość luźnym związku z pozostałymi wymienionymi jednostkami chorobowymi, jednak okazuje się, że wspólnych cech jest bardzo wiele. Wykazano, że jaskra istotnie częściej występuje u osób dotkniętych chorobą Alzheimera, zaś do zaniku komórek nerwowych w nerwie wzrokowym prowadzą mechanizmy podobne do tych, które obserwuje się w chorobach neurodegeneracyjnych mózgu. W niniejszym artykule podjęto próbę zbiorczego przedstawienia i usystematyzowania dostępnej wiedzy na temat podłoża współistnienia jaskry i choroby Alzheimera. Przedstawiono wyniki badań oraz teorie i hipotezy z zakresu biologii molekularnej, cytofizjologii, patofizjologii, immunologii i farmakologii. Niewątpliwie, zrozumienie patomechanizmów neurodegeneracji stanowi klucz do opracowania nowych sposobów leczenia zarówno jaskry, jak i choroby Alzheimera.

Słowa kluczowe: jaskra, choroba Alzheimera, choroby neurodegeneracyjne

INTRODUCTION

Alzheimer's disease (AD) is a chronic, multifactorial neurodegenerative disease which irreversibly damages the nerve cells of the cerebral cortex, especially in the region of association neocortex and the hippocampus. This process is a result of pathological mechanisms rather than accelerated physiological ageing. In a normally ageing brain, the metabolic activity is decreased

in the area of subiculum and in the dentate nucleus, while the AD is characterized by a lowered activity of the entorhinal cortex. Histopathologically, the AD, unlike physiological ageing, causes a loss of entorhinal and hippocampus field CA1 neurons as well as a decrease in the central temporal lobe volume (1). Other histopathological features of the AD are: extracellular senile plaques composed of β-amyloid and fibrillary degeneration (a fibre network formed by Tau protein neurofibrils) (2, 3). Although these lesions allow a certain diagnosis, they are accessible only through post-mortem examination. Clinical diagnosis of the AD is difficult and often lacks precision as the delay between first symptoms and the diagnosis is usually 2-4 years. Diagnosis and differentiation is carried out on the basis of symptoms, psychological tests results (e.g. Mini-Mental State Examination) and by means of exclusion of organic disorders (4, 5). While mental fitness among healthy population is on constant level with only gradual deterioration of the recent memory and slowing-down of information processing, persons with AD suffer from profound impairment of cognitive functions and different forms of dementia. Cognitive disorders are characterized by memory and speech issues as well as problems with other basic cognitive functions, which are noticeable by others and easily detected during tests but do not impair normal functioning. Whereas dementia is characterized by progressive, generalized decline in cognitive functions in many areas, including memory, and one additional – learning, orientation, speech, understanding and ability of evaluation, which is profound enough to hinder normal functioning. Over time, AD persons lose the ability to perform the most basic activities like verbal communication, moving, food intake or sphincter control (5, 6). In the USA, AD is the 7th most common cause of death and 5th most common among people of 65 and more years old. Only in the USA 5.3 million people suffer from AD (7). It is estimated that in the age group of 65-74 years old, 5-10% of the population is affected by dementia while in people over 85 years old it is 25-50%. Alzheimer's disease is the most commonly occurring neurodegenerative disease and, depending on the criteria applied, consists of 50-80% of dementia cases. The hereditary form of this disease, connected with mutations of the amyloid precursor protein, presenilin 1 and 2 as well as of apolipoprotein ε4, occurs in only 5% of patients. In other cases it is of late-onset sporadic form.

Glaucoma is described as a disease of the optic nerve with distinctive lesions in the optic disc and typical changes in the field of vision with or without heightened intraocular pressure (IOP) (8). Therefore, intraocular pressure is of no diagnostic value for glaucoma. This is because 20-30% of glaucoma patients have IOP within normal limits i.e. typically 10-20 mmHg (9). It has also been established that intraocular pressure-lowering treatment does not guarantee a stabilization of the disease, which progress remains on 9-10% level per year, while in patients treated pharmacologically or surgically the disease progresses 20-25% (10, 11).

Glaucoma is the second most common cause of blindness in the world (12). According to the estimations by WHO, there are 66 million people living with glaucoma and approx. 12.5 million lost their vision due to this disease. These numbers are likely to increase along with demographic changes (8). With such devastating statistics, the information that despite intensive research, lowering the IOP is the only available therapeutic tactic is quite pessimistic (8, 13). Although heightened IOP is an important glaucoma progression risk factor, it is not the only one, others being age, binocular disease, pseudoexfoliation syndrome (PEX) and lower arterial systolic pressure (14).

The main element in the pathophysiology of glaucoma is the loss of retinal ganglion cells (RGCs) and their axons over many years. It leads to changes in the morphology of the optic disc and consequently to visual field defects, detectable when 40% of RGCs are already irreversibly lost (12, 15). It may happen that before a patient notices visual field defects, 90% of RGCs are lost (8). These cells are extremely susceptible to damage due to their intensive metabolism. To visualise this, let's imagine a cell body of a RGC enlarged to the size of an apple – the neuron would be 800 meters long! Energy expenditures are increased by the lack of myelin sheath from the retina to the cribrum and meeting those expenditures is rendered difficult by the structure of the blood vessels which are thin and of relatively rare texture. This makes the neurons susceptible to damaging factors like metabolic stress (hypoxia), free radicals, mechanical pressure or photooxidative damage (16).

RGCs die through apoptosis (although in a more advanced disease necrosis can also take place) with main regulators being protease enzymes – caspases. They are activated endogenously (connected with mitochondrial mediators) and exogenously (activated by extracellular ligands like TNF-α). Changes in the retinal extracellular matrix as well as activation of metalloproteinases may occur as a reaction to the heightened IOP, which disturbs the cell-cell and cell-extracellular matrix reactions and triggers a cascade of reactions leading to apoptosis. Heightened IOP may also disturb the transportation of growth factors, i.a. BDNF (brain-derived neurotrophic factor), and stimulate the synthesis of others e.g. TGFβ2. Circulatory insufficiency may also play an important role through direct damaging, as well as stimulation of apoptosis. Glutamate released by retinal cells as a reaction to hypoxia can also have a significant impact. It acts through several ionotropic receptors (NMDA, KA, AMPA) and metabotropic receptors (mGluR) causing an influx of Ca^{2+} to the cell, activating second transmitters and, as a result, death. A toxic influence of nitric oxide (NO) which is a product of synthetase 2 (NOS-2) has also been demonstrated (12). Other factors causing apoptosis are: dysfunction of mitochondria and oxidative stress connected with it and protein synthesis disorders – accumulation of β-amyloid (17). Some of the research show the role of immune system in pathophysiology

of glaucoma (18). This long and still incomplete list of possible mechanisms in which the death of RGCs takes place proves how significant and important the problem of optic nerve degeneration is in glaucoma. It has also been proven that lowering IOP by 20% does not improve the functioning of RGCs (19).

COEXISTENCE OF GLAUCOMA AND ALZHEIMER'S DISEASE

Up to this point, many studies have been carried out to irrefutably ascertain the neurodegenerative nature of glaucoma, but the first one in this direction was conducted by Hinton, Sadun et al. in 1986. They compared post-mortem the optic nerves of AD persons with nerves of healthy people of similar age and discovered that 8/10 AD persons had an extensive axonal degeneration of optic nerves, much different from changes related to normal aging (20). Later, Sadun and Bassi published the results of their research in which they determined the degeneration of RGCs and their axons in post-mortem histopathological examination of AD persons' eyes. It mostly concerned largest M cells and was not observed in the control group.

Based on these results, Bayer, Ferrari and Erb conducted an examination on 112 AD patients from Upper Bavaria in Germany. Glaucoma was diagnosed in 25.9% persons while no ocular hypertension was observed. In the control group, glaucoma was identified in 5.2% of patients only and OHT in 7.8%. Thus, a conclusion was drawn that a risk of glaucoma is greater for AD persons and also that their optic nerves are more susceptible to heightened IOP (21). Similar observations were performed by Tamura et al. in Japan, where they studied the incidence of primary open-angle glaucoma in AD persons. Glaucoma was diagnosed in 23.8% of 172 persons examined, occurring much frequently than in the control group (9.9%) and in average Japan population (7.6%). They also analysed the frequency of occurrence of the APOEε4 allele, apolipoprotein ε4 gene, however all they could prove was that APOEε4 occurs more often in AD persons which was of no relevance to the incidence of glaucoma (22). These studies show that more frequent incidence of glaucoma in AD persons is not racially dependent. At the same time, the thesis of increased incidence of AD in primary open-angle glaucoma persons was not confirmed (23).

PSEUDOEXFOLIATION SYNDROME (PEX)

Linnér et al. tried to prove the connection between PEX-related glaucoma and dementia, based on premises that PEX is a systemic disease which also manifests in AD as protein deposits in brain. Although the incidence of PEX in dementia persons was significant – 28.8%, it was not linked to the incidence of AD. The incidence of PEX was even greater in patients with vascular dementia. This may be explained by difficult differentiation between vascular lesions and AD, but the study makes drawing definite conclusions difficult (24).

β-AMYLOID

These are not the only attempts to link glaucoma and AD as finding such connection may open new diagnostic and therapeutic possibilities. I will focus on β-amyloid (Aβ). Although its role in AD is still discussed, it is known that senile plaques play an important role in pathophysiology of AD. They are composed of Aβ which is formed by polymerizing peptides stemming from amyloid precursor protein (APP) The ones which most easily aggregate and are the most toxic are those containing 42 first amino acids – the isoform Aβ42. They damage the synaptic transport by blocking synaptic receptors, impairing ion transport and having a toxic effect on nerve cells, what damages mitochondria and activates apoptosis through caspases (25, 26). **In experiments performed on animal models of glaucoma, increased levels of Aβ and caspases were observed: 3. and 8. in RGCs layer and in the optic nerve of eyes with high IOP** (27, 28). **In other studies, an Aβ fragment** (25-35) **was neurotoxic both to nerve cells of cerebral cortex as well as to RGCs** (29, 30).

These findings became the basis for the development of new methods for treatment of glaucoma which aim at blocking the synthesis and aggregation of Aβ. Although the tests of these potential drugs are on experimental level, the results are promising. In an experiment on rats, 3 substances were used: 1) β-secretase inhibitors decreasing the formation of Aβ, 2) anti-Aβ antibody, 3) Congo red which inhibits aggregation and neurotoxicity of Aβ. All three methods proved very successful (anti-Aβ antibody in particular), slowing down the apoptosis of RGCs and decreasing its intensity. However, truly spectacular results were achieved by combining of these 3 preparations – apoptosis was reduced by 84% (31). Considering that Aβ is inseparably linked with AD, the results described may be of use in the treatment of this disease as well.

GLAUCOMA AND ALZHEIMER'S DISEASE AS TAUOPATHIES

A different protein-tau-plays a documented role in the pathology of AD. Physiologically, tau protein stabilizes the cytoskeleton of neurons, although in AD it undergoes hyperphosphorylation, creating paired helical filaments and causing neurofibrillary degeneration. Hyperphosphorylated tau disintegrates microtubules and aggregates normal tau, MAP proteins 1 and 2 and ubiquitin, creating neurofibrillary tangles. These insoluble structures damage the functions of cytoplasm and impair axonal transport which can lead to cell's death (32). Pathologic form of tau protein was found during an examination of intra-operative samples collected from glaucoma patients, whereas it was not found in the control group. Particularly high level was registered in retinal horizontal cell (33).

Studies of tau protein are currently being conducted. Therapies differ: some inhibit kinases connected with tau protein, other modify the formation of microtubules. Recently, methylene blue, which blocks the

aggregation of tau, has passed the 2nd phase of trials. Eighty-one per cent slow-down of AD symptoms progression in treated persons, in comparison with the control group, was observed (34). Maybe this type of neuroprotection of the optic nerve, although methylene blue dyes the sclera in blue, will find use as well?

HEAT SHOCK PROTEINS

One more matter connected with protein synthesis is worth raising. Heat shock proteins (HSP) prevent the aggregation of denatured proteins and serve as chaperones, facilitating protein folding, changing and restoring normal protein conformation and transmembrane transport. The role of HSP-70 and its ATPase was studied, with a conclusion that the induction of HSP-70 connected with inactivation of ATPase can be effective in AD treatment (35). An increased level of HSP-60 and HSP-27 in glaucoma eyes was observed along with an increased level of anti-HSP antibodies in blood. Whereas geranylgeranylacetone, through an increase of HSP-72 level in RGCs, protected cells against glaucomatous damage. The drug, although not clinically trialled yet, seems to be promising because of its low toxicity and possibility of receiving it per os (16).

GLUTAMATE EXCITOTOXICITY

Glutamate is an amino acid occurring in large quantities in the retina and acts as an excitatory neurotransmitter, both in the retina as well as in the whole central nervous system. It acts through ionotropic receptors (iGlu) – connected with ion channels: NMDA (N-methyl-d-aspartate), AMPA (α-animo-3--hydroxy-5-methyl-4-isoxazolepropionate), KA (kainate), and metabotropic (mGlu) – connected with G protein: eight subtypes divided into 3 groups (36). Ionotropic receptors, especially NMDA, act excitatory via an increases influx of CA^{2+} and NA^{+} ions to a cell. Some level of their activity is necessary for the functioning of neurons, but when glutamate occurs in excess, the ion channels do not close and a large concentration of calcium ions lead to apoptosis, what is also connected with activation of NO synthase. The positive feedback of NMDA activation with metalloproteinase 9 intensifies the destructive activity (16, 37). Whereas the metabotropic receptors act differently: those of group I act excitatory while those of groups II and II – inhibitory. This is why mGluR antagonists of group I and agonists mGluR of group II and III can act neuroprotectively (36).

The glutamate transporter system is the only mechanism of glutamate removal from the extracellular fluid. These transporters include GLT-1 (glutamate transporter 1 – on bipolar cells), EAAC1 (excitatory amino acid carrier 1 – on retinal neurons) and GLAST (glutamate aspartate transporter on Müller cells) (38). In genetically modified mice deprived of EAAC1 and GLAST, death of RGCs and damage to the optic nerve has been observed. Excitatory toxicity of NMDA receptor, successfully blocked by memantine (see below), was not the sole reason for this but also the oxidative stress mechanism resulting from glutamate synthesis impairment in Müller cells with GLAST deficiency (39). These disorders were also observed in AD patients – to a much greater degree than in healthy persons of similar age. At the same time healthy elderly people examined, showed an impairment of glutamate transport of greater degree than younger, healthy persons (40).

In 2003, the FDA approved an NMDA receptor antagonist memantine under the trademark “Namenda” for AD treatment. It is one of the low-affinity open-channel blockers and as such it maintains high efficacy without showing serious side effects. Second generation memantine derivatives, NitroMemantines, which are supposed to have an enhanced neuroprotective efficacy while maintaining safety, are currently being tested. MK-801 is another highly efficient NMDA receptor blocker, however, due to a longer binding time with the receptor, it blocks neuron’s normal functioning – a patient becomes not only more sleepy but downright comatose. Other drugs of slightly higher affinity than memantine cause hallucinations (phencyclidine, so-called angel dust) or are anaesthetics (ketamine) (41). Pre-clinical studies *in vitro* and in animal models proved the efficacy of memantine and similar drugs e.g. bis(7)-tacrine in neuron death prevention, however these results were not sufficiently confirmed during clinical trials – in 2009 its efficacy was not higher than that of placebo in phase 3 trial. This does not mean that studies of neuroprotection in glaucoma will be discontinued – perhaps combining preparations of different targets is necessary? (42, 43).

NITRIC OXIDE

Another element connecting glaucoma and AD is nitric oxide (NO), produced in large quantities by cerebral vessels of AD persons. Aβ also induces the synthesis of NO through microglia cells and astrocytes, while APOE stimulates the synthesis of NO in microglia laboratory models (44). Over activity of NO synthase modifies the proteins through nitration which leads to creation of neurotoxic aggregates, S-nitrosylation which damages and changes the functions of certain proteins, also disrupting the neurotransmission and transcription of genes, causing neurodegeneration as a result (45).

An increased level of NO in aqueous humour of glaucoma persons (compared to healthy persons) was noted, although exactly opposite results were also presented (46-49). These discrepancies show how complex and ambiguous is the role of NO in the pathogenesis of glaucoma. However, Neufeld et al. proved in their studies in animal model of glaucoma that blocking the NO synthase NOS2 by aminoguanidine decreases the loss of RGCs by 10% (50). It seems that this might be another method for protecting the optic nerve.

ROLE OF VASCULAR FACTORS

Vascular factors play an important role in the pathogenesis of glaucoma. The Early Manifest Glaucoma Trial has shown that the risk factors of primary

open-angle glaucoma (POAG) are: lower systolic perfusion pressure, lower systemic pressure and cardiovascular diseases in history. In the Rotterdam Eye Study, people with ocular perfusion pressure lower than 50 mmHg have a four time greater risk of developing POAG than people with perfusion pressure of ca. 80 mmHg. It is not entirely clear whether the ischemia is secondary to heightened IOP due to abnormal flow autoregulation or that circulatory disturbances are the primary cause of glaucomatous damage. The most significant are the perfusion variations as they carry a greater risk than its gradual decrease. These disorders are connected with the impairment of vascular regulation of the eye and caused by a number of pathologies like atherosclerosis, vasospasm, endothelium dysfunction (51).

The significance of vascular factors was also observed in the pathogenesis of AD. It is widely known that dementia may be caused by vasogenic ischemia (multi-infarct brain damage). Although it has been observed during autopsy studies that vasogenic lesions in brain occur more often in AD persons than in healthy people of similar age. This can be explained by the incidence of cerebral amyloid angiopathy. β-amyloid, AD-specific, may deposit not only in senile plaques but also in blood vessels, causing damage to the endothelium and blocking the vascular lumen, what causes a disorder of vessel reactivity and their mechanical occlusion (52). If we assume that similar changes occur in eye vessels, we will discover another connection between AD and glaucoma. Additional common denominator is the fact that a lower arterial blood pressure (i.e. diastolic pressure ≤ 70 mmHg) is a risk factor for dementia and AD incidence. The dependence is not entirely explained, although it has been proved that a decrease in cerebral flow precedes neuropathological changes in AD patients (52). It has been proved that carbonic anhydrase inhibitors used in glaucoma treatment, both local (Dorzolamide, Brinzolamide) as well as general (Acetazolamide), not only lower the IOP but also improve the flow in eye blood vessels. The latter also increases the cerebral flow (53). Protective action of Dorzolamide on RGCs, against the influence of apoptosis-inducing factors has also been proved (15). Currently, the use of anhydrase inhibitors in AD differentiation and vasogenic dementia is being investigated (in the case of the latter, flow increase is lower than in AD) (54). However, in the treatment of AD, anhydrase activators are more likely to be used as it is the anhydrase function impairment that is connected with AD and brain function disorders (55, 56).

OXIDATIVE STRESS AND FREE RADICALS

As mentioned in the introduction, oxidative stress and excessive synthesis of free radicals (FR) play an important role in pathology of neurodegenerative diseases. Mitochondria play a substantial role in the mechanism of oxidative stress as they are the source of free radicals because of intensive oxidation-reduction reactions taking place inside of them. The ATP produced in mitochondria also plays an important role – if it is not synthesised in a sufficient amount, it may disturb cell's energy balance and, in consequence, lead to its susceptibility to proapoptotic and necrotising factors. Numerous mitochondrial anomalies in glaucoma persons have been described, which concerned the trabeculation in filtration angle cells – DNA damage to these cells leads to their apoptosis and difficulties in aqueous humour outflow (57). Mitochondria absorb 85% of O_2 consumed by the cell but FR can derive from external sources, to which the eye is strongly exposed after all. FR do not spare the very mitochondria, impairing their function. Thus, a vicious circle is set in motion: errors in functioning of electron transport chain in mitochondria generate FR: peroxide anion (O2-•), hydrogen peroxide or hydroxide radical (•OH), and these react further, damaging lipids, proteins and nucleic acids of a cell, also those that form mitochondria. There are antioxidant mechanisms protecting from FR – peroxide dismutase, catalase, glutathione peroxidase and micromolecular substances like vitamin C and E. Unfortunately, these mechanisms are not always capable of meeting the needs – what results then is the so-called oxidative stress. Tezel and Yang have proven that less than 70% of RGCs submitted to glaucoma stimulation conditions for 48 hours survived, despite caspase activity inhibition. With additional use of tempol – a free radical scavenger, the survival rate increased additionally by 20%. Therefore, FR lead not only to apoptosis through caspase activation but also damage cells directly. Other mechanisms of their influence are: inhibition of growth factors (neurotrophins) secretion, oxidation and conformation change of functionally significant proteins, synthesis of toxic end products of glycation, modification of extracellular matrix (i.a. activation of metalloproteinases), impairment of glia cells functioning and activation of inflammatory response. Stopping the activation of these processes is often difficult or even impossible and RGCs continue to die, despite lowering the IOP (58).

The described above blood flow disorders occurring in glaucoma, also play an important role in the generation of FR. Secondary (i.e. related to other diseases), and especially primary vasomotor deregulation (i.e. congenital predisposition for vasospasm) play a significant role in FR generation through instability of ocular flow. Periodic decreases of the flow occur in primary open-angle glaucoma, leading to a decrease in tissue oxygenation. The flow then reverts to normal but this initiates oxidative damage and inflammatory reactions rather than recovers full functionality (reperfusion injury). Astrocytes play a key role in this phenomenon as they are activated in case of ischemia and pressure increase, producing numerous molecules including NO which, in turn, when reacting with O_2, produces a highly toxic peroxynitrite ($ONOO^-$) radical. Proapoptotic phenomena occur: DNA ruptures, slowdown of its repair, damage of proteins with not repair systems whatsoever (59).

Analogous phenomena occur in an AD person's brain. Probably a vicious circle is initiated: toxic Aβ induces protein and lipid oxidation as it possesses residue which, especially in presence of transition metals, has a catalytic properties. This leads to cell function impairment and, as a result, to their death, which manifests as memory deterioration. On the other hand, oxidative stress may cause an accumulation of Aβ – a pathological mechanism which fuels itself. It has been proven that in people with cognitive disorders (whose histopathology is similar to AD), the level of nonenzymatic antioxidants in blood and the enzyme antioxidant activity were lower than those of the control group, and levels of oxidation markers were increased (60).

Numerous substances, many of natural origin, have been studied for limiting the phenomenon of oxidative stress in eye Gingko biloba inhibits the oxidative stress on mitochondrial level, poliphenols (tea, red wine, dark chocolate and coffee) possess antioxidative properties: 3-methyl-1,2-cyclopentanedione is a peroxynitrite scavenger, wine poliphenols (e.g. Resveratrol) inhibit the synthesis of endothelin-1 and dark chocolate lowers arterial pressure and dilates blood vessels. Other antioxidants are: anthocyans, ubiquinone, melatonin, vitamin E, N-acetylcarnosine or L-carnitine (61-64). Maybe these compounds will be of use in AD and glaucoma treatment.

CEREBROSPINAL FLUID PRESSURE

There are interesting observations which link AD, glaucoma and lowered intracranial pressure. In a study performed by Silverberg et al., in which cerebrospinal fluid (CSF) pressure in AD persons was analysed, heightened pressure was observed in 3.9% of patients examined. These patients were usually younger and more mentally efficient. In the group without heightened CSF pressure 24.1% had pressure values below normal, which is a much higher percentage than in normal population. It can be assumed that lowering of CSF pressure is connected with cerebral atrophy in the course of this neurodegenerative disease. Whereas Berdahl et al. studied the CSF pressure in primary open-angle glaucoma persons. What turned out was that mean CSF pressure was 33% lower in glaucoma persons than in healthy persons, regardless of age. Higher C/D ratio in persons with lower CSF pressure was also observed. It seems that the key role is played by trans-lamina cribrosa pressure difference, so a heightened IOP and/or lowered CSF pressure. As AD persons have lower values of CSF pressure, they are much more predisposed to optic nerve damage even with relatively low IOP (65, 66).

NEUROTROPHINS – GROWTH FACTORS

Some of the works point to the role of deficiency of neurotrophins – brain-derived neurotrophic factors. Neurotrophic hypothesis says about an impairment of retrograde transport in the optic nerve head, which leads to an inhibition of growth factor supply to RGCs and induces their apoptosis. Impairment of receptor transport to neurotrophins has also been observed. Brain-derived neurotrophic factors (BDNF) are particularly important for the survival of RGCss. Experimental administration of BNDF to the lateral geniculate body reduced the death rate of developing RGCs and adding it to cultures of mature RGCs prolonged their survival. Some studies show that intravitreal administration of BDNF prolongs the survival of damaged mature RGCs. Marin et al. studied the possibility of using gene therapy: they administered a viral vector with BDNF gene into the vitreous chamber, acquiring a 20% lower RGCs death rate in the treated group. Other neurotrophins of antiglaucoma activity are: insulin-like growth factor (IGF), glial cell-derived neurotrophic factor (GDNF) and ciliary neurotrophic factor (CNF). The role of these substances is still not entirely clear and researchers differ in opinions as to their actual part in the pathology of the optic nerve (67).

Neurotrophins are an indispensable element for proper functioning of the nervous tissue. Not the synthesis alone but also the transport of these growth factors is essential. This element is impaired in AD by an AD-specific cholinergic degeneration and difficulty in axonal transport through Aβ and tau protein fibrils. BDNF plays a crucial role in the above-mentioned processes of cognition, learning and memorizing, hence its importance in the pathology of dementia. The level of the protein and its mRNA and receptor for BDNF are decreased in hippocampus and neocortex of AD persons. A specific loss of BDNF was observed in neurons affected by the fibrillary degeneration, while BDNF itself dephosphorylates Tau protein, performing a protective function. Cholinergic innervation and NMDA receptors are responsible for the regulation of BDNF. During studies in rats, memantine, an NMDA receptor agonist used in AD treatment, increased the level of BDNF and its receptor.

In the pathogenesis of AD, nerve growth factor (NGF) plays an important role. Its level in AD increases in the frontal cortex, occipital cortex and in the hippocampus and decreases in basal ganglia, what may indicate a disorder of its retrograde transport. NGF regulates the functioning of cholinergic neurons. In a case of its deficit, these neurons shrink and their enzymatic activity responsible for cholinergic transmission declines. Therefore, studies into gene therapy aimed at increasing the NGF synthesis are being carried out (68).

Dependencies governing the pathophysiology of neurotrophins in AD and glaucoma are far more complex than it has been presented in this study. However, the cases described above prove that growth factors are present in the whole nervous system as well as in the eye (which, after all, is also an outgrowth of the brain) and regulate the functioning of this complicated microenvironment. Manipulation of their amount and activity is yet another possibility of treating neurodegenerative diseases.

IMMUNOLOGY

One of the mechanisms leading to neurodegeneration are inflammatory factors. In the brain, microglia, astrocytes and endothelium cells act as antigen-presenting cells. In AD, changes in the morphology of microglia, which is a sign of its activation, astrogliosis (increase in number, size and motility of astrocytes), presence of activation markers and proinflammatory mediators (MHC class II, Cox-2, MCP-1, TNF-α, IL-1β, IL-6) and an increased level of chemokines, cytokines and their receptors have been demonstrated. Aβ plaques are the initiating factor and, although the way they function is not entirely clear, its aggregates induce the synthesis of proinflammatory chemokines, cytokines, prostaglandins and complement components by activation of microglia, probably through TLR 2 and 4 receptors (69). This leads to an activation of T cells and to changes in $CD4^+$ and $CD8^+$ population levels. The latter possess cytotoxic qualities and play an important role in neurodegeneration by direct damaging of nerve cells or by causing demyelination. At the same time, evidence for a protective role of some populations of lymphocytes (synthesis of neuron growth factors) exists.

Immunology may be of use in AD treatment – studies into anti-Aβ antibodies administration gave promising results, however, side effects were serious. Despite this, the use of this therapeutic path is still being researched (70).

Engagement of the immune system into the neurodegenerative processes has been also observed in the course of glaucoma. Similarly to AD, the immune system performs both protective and neurodegenerative functions. The disease begins when the balance between these opposite processes is broken. Assumptions exist that some forms of glaucoma may be autoimmune neuropathies. As a result of the eye tissue injury in the course of glaucoma (IOP increase, vascular flow disorders, generation of FR) the immune system activation threshold is crossed. Macro- and microglia are activated, initiating an inflammatory response through antigen presentation and acting toxically through a synthesis of some cytokines. Activation of T cells, which initially perform a neuroprotective function, proceeds but an activation of long-lasting autoimmune neurodegeneration can occur. T cells of cytotoxic potential damage the neurons directly and the disorder of microglia functioning prohibits their inactivation. The role of humoral response in the pathology of glaucoma has also been proven: increased frequency of monoclonal gammapathies, increased level of autoantibodies against retinal antigens and optic nerve in serum and a deposition of immunoglobulins in glaucoma patients have been observed. The above-mentioned observations show that changes in neuron-glia-T cell interactions in connection with an increase of antigenicity constitute the axis of immunopathological mechanism in the course of glaucoma (71).

HELICOBACTER PYLORI

Somewhat related to the immune system is the *Helicobacter pylori* bacteria, which may be a link between AD and glaucoma. Kountouras et al. have shown that the *H. pylori* infection occurs more often in AD patients. It is possible that an autoimmune response starts as a result of molecular mimicry between antigens of bacteria and the nerve tissue. Other mechanisms mentioned are: overproduction of proinflammatory substances (IL-6, 8, 10 and 12, TNF-α, IFγ, leukotriens, prostaglandins and acute phase protein) connected with *H. pylori* infection and also synthesis of free radicals. *H. pylori* can influence the process of apoptosis, stimulate the aggregation of thrombocytes and leucocytes, increase the level of homocysteine and damage the blood vascular endothelium. The increase in homocysteine level is a result of an atrophic gastritis and malabsorption of vitamin B_{12} and folic acid. Eradication of *H. pylori* infection in persons with cognitive disorders could delay the progression of the disease.

Helicobacter pylori infection is also connected with ophthalmological and neuro-ophthalmological issues like anterior ischemic neuropathy, PEX glaucoma and primary open-angle glaucoma. Antibodies against *H. pylori* cross-react with antigens of ciliary body epithelium and induce apoptosis in trabeculation cells. Production of proinflammatory vasomotor substances and of proapoptotic activity damaging the optic nerve may be among other pathophysiological mechanisms. High incidence of *H. pylori* infections in glaucoma patients has been proven by in many studies, and liquidating this infection led to an improvement of glaucoma parameters like mean IOP and field of vision parameters. In the study by Kountouras et al. a high level of IgG antibodies, specific for this bacterium, has been observed in the aqueous humour of primary open-angle glaucoma and PEX glaucoma patients. Other studies did not provide any proof for a statistically significant connection. Due to a lack of sufficient data proving a direct effect of *H. pylori* on the pathogenesis of diseases discussed, further research is necessary, including an analysis of long-term effects of bacteria eradication on the course of these diseases (72).

CONCLUSIONS

The key to understanding why glaucoma occurs more frequently in AD persons is that both of these diseases belong to one group – neurodegenerative diseases. Processes governing their pathology are, as it can be seen in the examples described above, extraordinarily varied and complex. Different factors act on many levels, many interactions take place between pathophysiological planes, creating a rich network of dependencies. Better understanding of these systems and their interactions is a *condicio sine qua non* in creating new methods of treatment. Although a vision of introducing new therapies for these deeply impairing diseases is very optimistic, it still requires many additional studies and efforts of scientists of different fields.

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