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Short Communication

Oxidative Stress and Altered DNA Repair Pathways in Pathogenesis of Primary Open Angle Glaucoma

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Epidemiological reports shown that glaucoma is second cause of vision loss. The newest reports postulated that approximately 60.5 million of people have glaucoma. Moreover, 8.5 million of glaucomatous patients irreversibly lost their sight. Reports presented by Quigely at al. underlined that the most frequent type of glaucoma is Primary Open Angle Glaucoma (POAG), which constitute about 90% diagnosed cases. Additionally, they postulated that the number of glaucoma cases may, increase to approximately 80 million, up to 2020 [1].

The molecular background of glaucoma has been widely studied, but its genetic basis has not been completely understood yet. It is suggested that elevated level of Intraocular Pressure (IOP) is the main risk factor for glaucoma development. However, age (over 40 years old) [2,3], race [4], sex [5] diabetes mellitus type 2 [6] and family history [2] are also assimilated to glaucoma risk factors. Moreover, following clinical parameters: myopic refractive error, optic disc shape, and corneal thickness are considering as an additional risk factors for glaucoma development [7-10]. Furthermore, oxidative stress, which is consequence of Reactive Oxygen Species (ROS) activity, is viewing as important risk factors in glaucoma pathogenesis. It is postulated, that appearance of oxidative stress may play crucial role in Retinal Ganglion Cells Death (RGC). Gilgun-Sherkiet al. suggested that glial cells and neurons, which are post-mitotic cells, are very sensitive for free radicals activity [11]. Additionally, it was found that brain possess the low level of antioxidant enzymes, therefore the neuronal cells may be especially susceptible to arise oxidative DNA lesions [12]. Thus, it is indicated that ROS may play crucial role in death of neuronal cells. Izzottiet al. found elevated level of oxidative DNA damage in trabecular meshwork cells of POAG patient in relation to healthy controls. Moreover, permanent exposure to ROS may lead to the optic nerve cell death and degeneration of RGC [13]. It is also suggested that increased IOP and loss of visual field correlated with elevated level of oxidative DNA damage. This observation was supported by Saccaat al. [2].

In human cells, we can found DNA repair mechanisms that protect cells against accumulation of DNA damage. It is wildly suggested that altered DNA mechanisms may play crucial role in development neurodegenerative diseases. Base Excision Repair (BER) is main repair pathway that takes part in removing oxidative DNA lesions. It is generally underlined that BER is active during all cell cycle; therefore it is essential for dividing and non-dividing cells [14]. It was proved that appearance of Single Nucleotide Polymorphisms (SNP) in genes encoding BER's proteins may affect the proper functioning of BER mechanism. Last data suggested that presence the 399Arg/Gln *XRCC1* gene polymorphism may lead to altered DNA repair. It is postulated that this polymorphic variant of *XRCC1* gene is localized at the junction of *ADPRT* - BRCT domain. Thus, it is suggested that it may be associated with disturbance in localization of the place of DNA damage and reduced ability to recruit proteins essential for BER pathway. Moreover, it was found that cells with 399Gln allele indicate decrease of DNA repair ability [15]. Our last data shown that presence of the 399Arg/Gln genotype of *XRCC1* gene may be associated with increased risk of POAG development [16]. Many studies focused on the role on SNP of *ADPRT* gene with the risk of development cancers as well as neurodegenerative diseases. It was indicated that the 762Val/Ala is the most frequent polymorphic variant of *ADPRT* gene. It was shown that presence of this SNP may reduce their activity by 40%. Decrease activity of *ADPRT* may lead to lower ability to recruit *XRCC1* and other BER proteins [17]. It is worth to underline that, presence changing in structure of *OGG1* gene may have relationship with changes in activity of this glycosylase. It was found that presence of 326Cys allele may decrease its activity by 40% [18]. Additionally, mouse with knock-out of OGG1 gene indicate elevated level of oxidative DNA damage. This finding may suggest that this gen plays important role in maintaining brain function [19]. Binding sites with RPA, APE1 and PCNA proteins, in the structure of MUTYH were found. Whereby, this glycosylase plays important role in BER pathway. Last data suggested that presence of 324Gln/His polymorphism may reduce activity of this glycosylase in by 33%. Moreover, the appearance of allele 324His may decrease repair ability of 2-OHA (1,2-dihydro-2-oksoadenine) paired with guanine [20]. AP sites, which are created by spontaneous loss of base or as a result of activity glycosylase, are mutagenic and cytotoxic. In normal conditions this kind of DNA lesions are removed by endonuclease AP. Last data shown the presence of SNP may lead to decrease of its activity [21].The appearance of changes in the structure of genes encoding main BER proteins may lead to disturbance in this mechanism. Our previous study indicated the elevated level of DNA strand breaks and endogenous oxidative DNA in lymphocytes patients with POAG in relation to healthy controls. Moreover, we pointed out increased lymphocyte sensitivity of patients with POAG on the impact of hydroxyl peroxide in relation to healthy controls. Also, we noticed that efficiency of oxidative DNA damage repair was decreased in group of POAG patients in relation to control group [16].

In conclusion we can gather that oxidative stress can be associated with altered base excision repair pathway. This fact may be an

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important prognostic factor for the development and progression of primary open angle glaucoma.

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