



World Scientific News

WSN 57 (2016) 338-346

EISSN 2392-2192

The influence of environmental and genetic factors on development of glaucoma

Sylwia Florczak, Katarzyna Kempka*

Faculty of Biological Sciences, University of Zielona Gora, Poland

Faculty of Medicine, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Poland

*E-mail address: kakem@o2.pl

ABSTRACT

Glaucoma belongs to the heterogeneous group of diseases that lead to disorders in the field of vision, which are caused by elevated intraocular pressure. The common feature of these diseases is optic neuropathy, i.e. impairment of the eyesight, which results in the decreased vision. Untreated glaucoma is the second most common cause of blindness, after cataract. Unfortunately, usually in the initial phase, it does not exhibit any clear symptoms that would indicate this disease. The most common type is Primary Open-Angle Glaucoma (POAG), incidence of this type of glaucoma amounts to more than 50% of glaucoma cases in developed countries. The etiology is not fully understood yet. Probably both, the genetics and environmental factors, (among other heavy metals) impact the occurrence of glaucoma. Determination of the cause would help to improve the diagnostics of glaucoma and it would also provide basis, among others to biotechnologists and biologists, for searching for new medications. These studies are difficult and they require a lot of dedication and commitment, but interest in the etiology of these changes is still growing. This publication attempts to provide insight into the most important issues and possible causes of incidence, e.g. what is the impact of environmental pollution (concentration of selected heavy metals) and mutations of selected genes. We want to see if these polymorphisms occur in our country. If we will observe these changes, we want to check how often they occur and how they correlate with the concentrations of metal ions in the blood. Our research focus is on the detection of new glaucoma markers and better understanding of the etiology of this disease.

Keywords: Glaucoma, heavy metals, WDR, MYOC, genes

1. INTRODUCTION

Glaucoma belongs to the heterogeneous group of diseases that lead to disorders in the field of vision, which are caused by elevated intraocular pressure [1]. The common feature of these diseases is optic neuropathy, i.e. impairment of the eyesight. This results in the decreased vision. If it's untreated – then it is the second most common cause of blindness, after cataract. Unfortunately, quite often in the initial phase, it doesn't exhibit any clear symptoms that would indicate this disease [2]. It's estimated that even 79,6 million people worldwide may suffer from glaucoma in 2020 [3]. Elevated intraocular pressure is the most dangerous, because it leads to the development of glaucomatous optic neuropathy. The main causes include: amount of aqueous humour secreted by the ciliary body, resistance of outflow created by Schlemm's canal and trabecular system, amount of pressure in the episcleral veins [1]. There are several classification methods of glaucoma, but usually it is divided into: open-angle and close-angle glaucoma, primary and secondary glaucoma, infantile glaucoma and glaucoma with complex mechanism [1]. The most common type is Primary Open-Angle Glaucoma – POAG, incidence of this type of glaucoma amounts to more than 50% of glaucoma cases in developed countries.

2. AIM OF THE STUDY

The etiology is not fully understood yet. It is believed that both the genetics and environmental factors, among other heavy metals [4], impact the occurrence of glaucoma. Due to this reason, all the studies concerning search for the causes of development of the eye diseases are very important. Determination of the cause would help to improve the diagnostics of glaucoma and it would also provide basis, among others to biotechnologists and biologists, for searching for new medications. Such studies are difficult and they require a lot of dedication and commitment, but interest in the etiology of these changes is still growing. This publication attempts to provide insight into the most important issues and possible causes of incidence, i.e. what is the impact of environmental pollution (concentration of selected heavy metals) and mutations of selected genes. These are very important aspects, which in the future can be used to determine the causes of glaucoma. Genes that allow determining the occurrence of glaucoma in recent years, the interest concerning the origin of many diseases, including glaucoma, has increased. Various techniques of molecular biology and genetics are used for this purpose. Development of the latter field had an impact on the understanding of genes, determination of their location, as well as insight into the types of mutations, which result in glaucoma. Studies aimed at finding the answer to the following question: what is the etiology of glaucoma, are very important, and this answer may become the basis for the rapid detection of this disease and it may create the foundation for searching anti-glaucoma medications, which would work more effectively [1].

3. INFLUENCE OF MYOC AND WDR GENES

Recently, numerous studies aimed at understanding the cause of glaucoma are conducted, especially concerning open-angle type of glaucoma. So far, 29 loci were

identified, where mutations occur that lead to the various types of glaucoma. They have their locations in three genes: MYOC, OPTN and WDR36 [3]. MYOC Gene Mutations in MYOC gene are responsible for the creation of myocilin protein - hence the name of the gene. However, there is an alternative form of this gene – TIGR (Trabecular meshwork inducible glucocorticoid response). It's identified in the open-angle glaucoma [4]. This gene has been identified as the gene responsible for the creation of glaucoma, as the first one out of all that have been so far discovered. The first mention about it appeared in 1997 [3]. Stone et al. [5] performed a mapping of genes and concluded that three fragments lead to mutations and cause the creation of open-angle glaucoma. They also proved that the identification of genes responsible for the creation of this disease may lead to the understanding of the pathophysiology of glaucoma [5].

The product of TIGR gene mutation is a protein consisting of 504 amino acids (56,972 kDa). Loci are located on the long arm of chromosome 1 [3]. Some of the most recent studies indicate that there are many mutations. One of them is the change of proline to serine at position 341 in the myocilin protein. Such change causes a disturbance in the secondary structure of the protein, which results in the change of physical and chemical properties of the protein. 13 mutations of MYOC are already known for the primary open-angle glaucoma (POAG) in the population living in the area of China [4]. Kumar et al. [3] also indicate that the causes of glaucoma creation should be sought in the third exon of myocilin. Ser341Pro mutation was discovered recently and it requires deeper and more detailed studies, which will allow answering the following question: what are the exact mechanism and the impact of mutation on the formation of POAG [4].

WDR36 Gene WDR36 gene is located on GLC1G locus and its mutation is also responsible for the creation of primary open-angle glaucoma - POAG. The protein that is encoded by this gene consists of 951 amino acids (105,322 kDa) [3,5]. WDR36 gene is located on the long arm of chromosome 5 and it contains 23 exons. It's also detected in the tissues of the eye, including the lens, iris, sclera, ciliary muscles and optic nerves [3]. Mookherjee et al. [2] selected 10 SNPs, i.e. they observed 10 cases of variability of DNA sequence, which consist of changing at least one nucleotide between individuals of the given species. They marked them with the following symbols: rs1971050, rs1993465, rs12153937, rs10038177, rs11241095, rs10043631, rs10038058, rs10491424, rs17553936, rs13186912. The change that they've noticed in rs10038177 turned out to be the most significant and it concerned the change of cytosine to thymine.

They've determined that this change of the nucleotide with symbol rs10038177 is responsible for the increased risk of developing glaucoma. Silicon analysis carried out by the researchers did not show new SNP variants with number rs10038177 in patients with glaucoma. However, the results of these studies show a strong connection between the single SNP marked as rs10038177, which occurs in WDR36 gene, and the changes of glaucomatous type in patients suffering from glaucoma [2].

Other studies also indicate the occurrence of correlation between mutations in WDR36 gene and the incidence of glaucoma. Studies conducted by Taher et al. [5] indicate that mutations causing the disease are also dependent on the ethnic groups. So far, the mechanism of action of WDR36 gene in the case of risk of developing primary open-angle glaucoma was not determined, however it is assumed that it has a big role in the pathophysiology of glaucoma [3].

4. INFLUENCE OF SOME METAL AND NONMETALS IONS

Oxidative stress play important role in increasing intraocular pressure (IOP) and development of glaucoma. The high concentrations of reactive oxygen species (ROS) causes in release of cytochrome C. This changes the expression and structure of the proteins, modify lipids and damage DNA. In effect, damages in affected cells lead to their apoptosis [6]. Toxic metals causes oxidative stress in two ways. Metal ions such as Fe, Cr and Cu take part in redox reactions and increase ROS production. In other way Cd, Pb and Ni ions reduces numbers of antioxidant cells, which leads in accumulation of ROS in insufficient neutralization [7]. Retinal pigment epithelial melanosomes accumulate metal ions, this prevents neural retina from their harmful influence [8]. RPE cells can bind Zn, Fe, Pb, Al, and Se ions. Binding strength depends to their atomic weight and size [9].

4. 1. Mercury (Hg)

This element accumulates in multiple tissues in the body, also in cornea and lens [10]. Firstly Hg ions attach to cell membrane, because this element has high affinity to sulfhydryl groups (-SH). Then, Hg creates complexes with proteins and enzymes, it can effectively block all enzymatic pathways in the cell [11]. Previous studies have confirmed that high Hg levels in serum may correlates with the development of glaucoma [12]. In vivo studies with monkeys have shown, that Hg penetrates blood-retinal barrier. In acute poisoning it led to damage of the visual cortex, vision problems and to blindness [13].

4. 2. Manganese (Mn)

Studies from 2015 were conducted on Korean population, showed that reduced Mn levels in serum, correlates with the development of glaucoma [12]. Also Mn and Zn can prevent harmful accumulation and toxic impact of Cd in the RPE. Mn and Cd have the same affinity to the transport proteins (e.g. Zinc transporter ZIP14), so high Mn levels reduces absorption and accumulation of Cd. But higher concentrations of Mn, associated with the excessive supply, may cause neurotoxicity [13].

4. 3. Arsenium (As)

This element attach to sulfhydryl groups (-SH), blocks proteins and enzymes. As also can react with thiols, especially with glutathione [14]. Central nervous system is the target organ for As, Pb and Hg. Therefore, the effects of arsenic poisoning are numerous and varied neuropathies [15]. In 2016 pilot studies showed where mice drink water with sodium arsenate. In effect As levels in eyes tissues were higher than in liver, lungs or even in brain [16].

4. 4. Cadmium (Cd)

Liver and kidneys are target organs for Cd. It is because in liver this element induces production of metallothioneins (Mt), which binds Cd (II) ions and create complexes Cd-MT. Next in kidneys this complexes are filtered, resorbed and degrade, in this last stage Cd ions are released and damaging kidneys structure [17]. Prolonged exposure to Cd causes accumulations in eye tissue, this increase oxidative stress and it may lead to the development of different eye disease, also glaucoma [18,19].

4. 5. Lead (Pb)

This element is harmful for rods, photoreceptors, bipolar cells and photoreceptors even in very low concentrations [20]. As other heavy metals Pb induces oxidative stress, which causes lipid peroxidation, DNA damages and weakens the cellular antioxidant defense mechanisms [21]. Studies from 2009 provides that high Pb level in women serum with Primary Open Angle Glaucoma (POAG) is important risk factor for glaucomatous optic neuropathy without increasing intraocular pressure IOP [22].

4. 6. Iron (Fe)

This element is absorbed, but is removed only during menstruation or other blood loss. Therefore, the concentration of Fe in the macula increases with age. Fe acts important role in the phototransduction cascade in the retina [23]. However, divalent Fe cation is strong generator of free radicals and may cause retinal degeneration. This ion leads to production of hydroxyl radical, in Fenton reaction, which is the most reactive oxygen species that causes lipid peroxidation, DNA damages and degradation of biomolecules [24]. All reactions may cause degradation of retinal ganglion cells and increase of IOP, which can lead to the development of glaucoma [25,26]. Studies from 2012 showed that Fe supplementation in higher level than 18 mg per day, correlates with increase development of glaucoma [27].

4. 7. Calcium (Ca)

Studies confirmed that disturbance in the economy of calcium can lead to many neurodegenerative diseases, such as a glaucoma [28]. Later studies showed that daily supplementation with doses higher than 800 mg correlates with increase development of glaucoma. Because Ca in high concentrations also may case oxidative stress [29].

4. 8. Copper (Cu) and Zinc (Zn)

Cu ions, released from storage proteins, are responsible for creation of ROS and increased oxidative stress [30]. Patients with glaucoma have high Cu and low Zn levels in the aqueous humour. It may be due from abnormalities in the secretion of aqueous humor, its impeded drainage through the Schlemm's canal and damage to the blood-aqueous humor barrier. Violation of this barrier may lead to the influx plasma proteins to the anterior chamber of the eye and cause the concentration of copper [31]. Zn ions are also part of complex, which protect eye structures from harmful effects of light and oxidative stress. That is why also low levels of this element can correlates with eye diseases [32].

4. 9. Selenium (Se)

This nonmetal can create deposits around the melanosomes, but the role of Se in glaucoma is not fully understood. Studies confirmed that supplementation and high Se serum levels can increase the development of glaucoma. Probably the excess of Se saturated pool of selenium-dependent enzymes and causes cell damages [33]. But selenium also is part of glutathione peroxidase, enzyme, which protects against oxidative stress. This shows, that also low levels can lead to accumulations of free radicals [34].

5. CONCLUSIONS

Toxic metals (Cd, Hg, Pb and others) influent on the development of glaucoma [13,18,22]. In our studies we want to show that patients with glaucoma will have higher toxic metals levels (Pb, Cd, Hg, As). We also suppose that their higher concentrations will occur frequent in the residents of larger cities, which we combine with greater environmental degradation. It is possible that our studies will confirm previous experiments about adaptation to environmental pollution. This type of resistance to pollution, and pollution, has been repeatedly described [35-37]. On the other hand, low concentrations of Se, Mn, Zn make the antioxidant protection is insufficient and it may promote the development of glaucoma [13]. However, too high concentrations of the protective elements, in result of supplementation, also cause glaucoma [33]. Therefore, we speculate that among patients with glaucoma protective metal concentrations will be lower than in the healthy control group. In addition, we expect that glaucoma will develop as a result of insufficient antioxidant protection more than as a result of excessive selenium supplementation. We also hypothesize that the greater the deficiencies Mn, Se and Zn will be in the residents of the large cities.

As showed earlier studies [27], excessive Ca and Fe supplementation is associated with the development of glaucoma as a result of oxidative stress. We believe that in the population of Polish people with glaucoma will be characterized by higher concentrations of these elements. We suspect, that people from larger cities will have higher levels of Fe and Ca in the blood. The results of genetic studies show that many patients with glaucoma is characterized by mutations in the genes MYOC [3] and WDR36 [2]. In our study, we focus on the new discovered Ser341Pro polymorphisms [4] within the MYOC and WDR36 GLC1G locus on chromosome 5 [6,3].

These new discovered changes that have not been studied in the Polish population. We want to see are these polymorphisms occur in our country. If we will observe this changes what, we want to check how often they occur and how they correlate with the concentrations of metal ions in the blood. Our research focus on the detection of new glaucoma markers and better understanding of the a etiology of this disease.

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(Received 24 September 2016; accepted 10 October 2016)