Kobak Joanna, Tyczyńska Magdalena, Forma Alicja, Dudek Iga, Maani Amr, Zembala Patryk, Baj Jacek. Optic nerve neuropathies – causative factors, methods of diagnostics, current and future possibilities of treatment. Journal of Education, Health and Sport. 2022;12(4):44-61. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2022.12.04.004
https://apcz.umk.pl/JEHS/article/view/JEHS.2022.12.04.004
https://zenodo.org/record/6423974

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).

Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

Received: 25.03.2022. Revised: 25.03.2022. Accepted: 08.04.2022.

Optic nerve neuropathies – causative factors, methods of diagnostics, current and future possibilities of treatment

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Abstract:
Introduction: Optic neuropathies are a broad group of diseases in which the dominant disturbance is damage to the optic nerve, often irreversible. Underlying causes of neuropathy are both genetic and environmental. Despite limited treatment options, much research is currently being done on substances that could improve optic nerve function and alleviate the clinical consequences of optic nerve damage.
Purpose: This article describes current findings in both the optic nerve neuropathy pathophysiology and diagnosis of the disorder, as well as treatment options and future perspectives.

State of knowledge: The pathogenetic cause of neuropathy is mainly demyelination within the neural sheath, often caused by inflammation. It is characterized by progressive loss of vision. The most common genetic cause of optic neuropathy is mitochondrially inherited Leber hereditary optic neuropathy (LHON) and is characterized by mostly sudden and painless loss of visual acuity. Toxic neuropathies are a group of diseases caused by heavy metals, pharmaceuticals, methanol and carbon monoxide. Nutritional neuropathy is mainly related to vitamin B1, B9 and B12 deficiency, and is a rare example of neuropathy that can be curable at the early stage of the disease. Another group of neuropathies is caused by ischemia and can be divided according to the place of the optic nerve affected – AION (anterior ischemic optic neuropathy) and PION (posterior ischemic optic neuropathy).
Conclusions: The therapeutic options in the treatment of optic neuropathy strictly depend on the causative factor. Nutritional deficiencies are treated with appropriate supplementation, so it is vital to truly determine the missing vitamins and elements.

Keywords: optic nerve; neuropathy; pathophysiology; diagnosis; treatment; alcohol use disorder; vascular disorder; toxic

1. Introduction

Optic neuropathy is a general term used to describe the damage of the optic nerve induced by numerous causes among which we can distinguish ischemia, inflammation, trauma, nutritional causes, toxins (including tobacco, ethambutol, amiodarone, ethylene glycol), as well as genetic background in form of hereditary optic neuropathies. Usually, optic neuropathies occur in elderly patients, however, due to a significant number of causes, it can technically occur in everyone regardless of age. Most common symptoms include loss of vision and impaired color vision with seeing flickering or flashing light during eye movement. Besides, patients quite often experience pain within the face, eye socket, and inside the eyes along with loss of peripheral vision.

2. Focus - pathogenesis of optic neuropathy

The common pathogenic basis for optic neuropathy is the inflammatory demyelination of the optic nerve. It shares a similar pathology with acute multiple sclerosis plaques in the brain, edema in the nerve sheaths, perivascular cuffing, and breakdown of myelin. Demyelination of the retinal vascular endothelium may be preceded by inflammation and in some cases manifests as retinal vein sheathing [1]. Loss of myelin exceeds the loss of axons.

It is worth mentioning that demyelination in optic neuropathy is mediated by the immune system. However, the exact mechanisms and the target antigens are not known. Activation of the systemic T cell may be identified at the onset of the symptom and usually occurs before cerebrospinal fluid changes [2]. There is an early normalization of systemic changes (within 2-4 weeks) compared to central changes. Activation of T cells triggers the cytokine release and the release of other inflammatory agents. Researchers have not observed activation of B cells against myelin basic protein in peripheral blood. However, this has been demonstrated in the cerebrospinal fluid of individuals with optic neuritis [3].

There are indications that some individuals may be genetically susceptible to optic neuritis. Evidence of this may be the over-representation of some human leukocyte antigens among individuals with optic neuritis [4-6].

3. Symptoms and diagnosis of optic neuropathy

The initial symptom is pain during eye movement, this is usually accompanied by a gradual worsening of eyesight. A 2012 study by Morrow and Wingerchuk [7] found that simultaneous onset of symptoms in both eyes occurs in only 0.4% of patients. Most patients may be able to date symptom onset to a specific day. However, individuals with optic nerve tumors do not have this capability. Images seen by patients may be unclear, dark, and has poor contrast. The colors may be pale or dirty. Visual acuity in patients continues to deteriorate after a subacute onset. If the disease is left untreated, visual acuity approaches its nadir within 1-2 weeks and improves again [7]. Some patients may perceive what is called *positive optic phenomena* [8]. Visual pain is usually so disturbing that the affected patient may not wait to see whether it will improve or not [7,8]. Moved by the pain, most patients consult their ophthalmologist early in the course of the disease. At least 8% of patients do not experience pain on eye movement. The inflammatory focus in this group of patients lies in the intracranial aspect of the optic nerve which is proximal to its mobile portion [7,8].

4. Diagnosis

Generally, the clinical diagnosis of optic neuropathy is based upon history and examination findings. The results from fundoscopic examination help in the differentiation of atypical optic neuropathies from typical cases. As such, an ophthalmologic examination must be carried out. It is worth mentioning that an ophthalmologic examination is an important feature of clinical evaluation. Diagnosis may be confirmed via magnetic resonance imaging study of the brain. Brain MRI also assesses the patient's risk of subsequent multiple sclerosis.

5. Differentiation between Leber hereditary optic neuropathy, alcohol-induced optic neuropathy, and ischaemic optic neuropathies

Leber hereditary optic neuropathy (LHON) is considered one of the most common mitochondrial (maternally inherited) diseases. It is characterized by acute, painless loss of vision that mostly affects young men, aged between 15 and 30 years. Though, the symptoms can occur at any time of life from early childhood to the seventh decade [9]. The prevalence of LHON is believed to estimate at 3.2:100 000 in the North East of England, 2.6:100 000 in the Netherlands, and 2:100 000 in Finland [10-12]. Ultimately, 90–95% of LHON patients have one of the three mtDNA point mutations in NADH dehydrogenase (ND) subunit genes m.3460G>A in MTND1, m.11778G>A in MTND4 or m.14484T>C in MTND6 gene [13-16]. Thus, both MTND1 and MTND6 can be called LHON hot spot genes [17-19]. Both incomplete penetrance of LHON and male predominance are still a great unknown. The probability that internal as well as external environmental factors could cause vision loss in predisposed patients with LHON has assumed that vision loss is linked to defects in oxidative phosphorylation. Systemic illnesses, immunologic factors, nutritional deficiencies, medications, or toxins, that stress or directly inhibit mitochondrial metabolism could introduce or increase manifestation of the phenotype in LHON disease [20].

Toxic substances, such as tobacco and alcohol, are assumed to have an impact on the penetrance, but only a few tobacco and alcohol abusers ultimately develop optic neuropathy. This fact leads to assumptions, that consider individual susceptibility. It has been suggested that predisposition may be due to LHON-associated mitochondrial mutations [21]. Later research, conducted by Kirkman investigated the role of smoking and alcohol abuse in the expression of visual loss in LHON. In its conclusion, smoking can be associated with an increased rate of visual loss and this relation might even be related to a dosage, furthermore, based on their results, the authors presumed that smoking has a consistent role in rising disease penetrance in LHON [22].

In summary, LHON is an infrequent disease without a typical presentation of pathognomonic factors. Although patients provided a good justification for toxic optic neuropathy, it is necessary to test them for other possible diseases [23].

Toxic neuropathy (TON) is portrayed as a bilateral visual loss, damage of papillomacular bundle, central or cecocentral scotoma, and worse colour vision [24]. TON is caused by the damage of the optic nerve via different toxins, including drugs, metals, organic solvents, methanol, and carbon dioxide, along with nutritional shortages, that contain B vitamins, folic acid, and proteins with sulphur-containing amino acids, which show a similar clinical picture to the ones induced by toxins [25]. The disorder is more prevalent in developing countries, because of people's greater exposure to harmful substances in both environment and food, alongside widespread malnutrition [26]. No racial, gender, or age-dependent predilections have been yet revealed in TON. The most widespread form of toxic optic neuropathy is associated with the chronic consumption of alcohol among heavy smokers, it is then followed by the types related to the usage of medication such as ethambutol, amiodarone, and chloroquine [27]. The pathophysiology of TON is unknown, but different substances probably affect the optic nerve in various ways. One generally accepted pathway, for at least some of the toxins, is mitochondrial injury and disparity of intracellular and extracellular-free radical homeostasis [28]. This might justify some similarities between TON and LHON. As the consumption of alcohol that leads to nutritional deficits is considered to be the main risk factor in TON, no substantial association concerning tobacco or alcohol use and vision loss was observed among patients with LHON mutations [29]. In conclusion, both tobacco and alcohol are not likely to promote vision loss in LHON [30]. As LHON and TON both have major similarities in their phenotypes, it is recommended to analyse the known LHON-associated mutations before establishing the TON diagnosis.

Ischaemic optic neuropathy (a disease in which vision loss is a result of ischemic optic nerve injury) can be divided into two types, with the conclusion of the different optic nerve segments: anterior (AION) and posterior (PION), the first relating to the optic nerve head (ONH) and the second to the rest of the said nerve [31,32]. Furthermore, a clinical division consisting of two forms can be made. The first one being arteritic AION (A-AION), that gives a picture of arteritis (specifically giant cell arteritis in older patients) and the second one being non-arteritic AION (NA-AION), which is caused by the smaller blood vessels damage, without the involvement of inflammation [33,34].

NA-AION is a disorder, that is more common between earlier mentioned types. Moreover, it is one of the most prevalent diseases, that disable vision in the groups of both middle-aged and elderly [35,36]. The disease is characterized by acute unilateral vision loss, painless eye movement, and optic disc swelling. Optic disc edema resolves within 4 to 8 weeks, resulting in optic atrophy [37]. NA-AION is a multifactorial illness, with many risk factors that participate in its development but none of them has been yet surely confirmed [38]. It is said that co-occurrence of cardiovascular system hazards with dense nerve structure and blood vessels in optic disc might be the cause [39-41]. Researchers believe that diabetes, higher cholesterol levels, "narrow" construction of optic disc, lower blood flow in optic disc play a great role in NA-ION advancement [42-44]. Additionally, arterial hypertension, anemia, and hepatic alcoholic disease are being considered and therefore remain a hot topic of scientific discussions [45].

Although NA-AION mostly affects one optic nerve, there are cases of bilateral impairment, that are considered to be caused by type C hepatitis, interferon treatment in said illness, occur during perioperative time or after liver transplant [46-50]. Though there is no known treatment for NA-AION, decrease of risk factors is important in reducing the chance of the second eye involvement as well as further incidents.

6. Differentiation between NAION and AION

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In comparison, Leber hereditary optic neuropathy (LHON), a rare mitochondrial illness, is described as an acute and painless loss of vision, mostly found among young men (age range from 15 to 30 years old). The incomplete penetrance of the disease, as well as male predominance, are still a great unknown. Moreover, LHON does not present typical pathognomonic factors, however, the assumption that vision loss is linked to defects in oxidative phosphorylation in predisposed patients allows to link the internal and external environmental factors with the said disorder [9,23].

7. Treatment options

The therapeutic options in the treatment of optic neuropathy strictly depend on the causative factor. The genetic basis of Leber's hereditary optic neuropathy significantly limits the methods of therapy. Mitochondrial DNA mutations impair the normal synthesis of ATP and contribute to the formation of oxygen free radicals, which in turn induce apoptosis of retinal ganglion cells (RGCs), causing clinical symptoms [51]. Therefore, treatment methods focus on preventing oxidative damage. To date, only one substance has been approved for the treatment of LHON - idebenone (Raxone). Due to its antioxidant properties, idebenone improves the energy supply of cells, which allows the regeneration of RGCs, preventing further clinical worsening of the disease and loss of vision [52-55]. Therapy should be introduced as soon as possible and be maintained for more than 24 months to maximize the effects [56]. In addition, many clinical trials concerning gene therapy have emerged in the last few years [55]. The vitreous body of the eye provides easy access to the administration of viral gene vectors. About 70% of people affected by LHON are carriers of m.11778G> A point mutation, which is associated with a low percentage of spontaneous cures (4%) [57]. The 1178G>A mutation affects the ND4 gene, which is only expressed in the mitochondrial genome. By the use of the allotropic expression, this gene can be delivered thanks to a special carrier called GS010 (rAAV2-ND4), which is a gene therapy product. The RESCUE and REVERSE studies, which consisted of a single intravitreal injection of rAAV2-ND4, showed that there is an improvement in vision in both eyes, also in the untreated eye [58,59]. A systematic review of 76 patients, including a group of RESCUE and REVERSE and their extension trial (CLIN06), have shown an improved vision for more than 4 years after rAAV2-ND4 injection [60]. The remaining therapeutic options for Leber's disease may become antioxidants such as EPI-743 and elamipretide, estrogen therapy, rapamycin or bone marrow-derived stem cells [61-65].

Regarding ischemic optic neuropathy, A-AION is well-known complication of temporal arteritis (giant cell arteritis). Giant cell arteritis (Horton's disease) is a rheumatological condition, in which the patient must meet at least three of the five criteria approved by the American College of Rheumatologists (ACR) such as 1) age of ≥50 at onset 2) new onset of localized headache 3) temporal artery tenderness or decrease pulse of artery 4) elevated erythrocyte sedimentation rate ≥50 mm/h 5) positive artery biopsy showing necrotizing arteritis [66]. Ischemic optic neuropathy in the form of A-AION accounts for only about 10-15% of all cases of ischemic damage, but it is important to make a differential diagnosis between A-AION and NA-AION as soon as possible as no suitable and effective treatment towards NA-AION has yet been found [67]. On the other hand, the lack of rapid implementation of therapy in the case of giant cell arteritis may lead to rapid involvement of both eyes and bilateral loss of vision, and the disease itself is also associated with serious consequences such as stroke or myocardial infarction [68]. Currently, according to the latest European EULAR and British recommendations, the mainstay of temporal arteritis therapy is prednisone administered orally in a dose of 40-60 mg daily [69,70]. The dose then decreases gradually, reaching 15-20 mg/day after 2-3 months and then ≤5 mg after a year. Thanks to the widespread introduction of corticosteroids into treatment over the past 55 years, it has been possible to reduce the onset and progression of vision loss among people with giant target arteritis [71]. Despite the limited and often contradictory information on the preferred route of steroid administration, both societies recommend an initial injection of 0.25-1 g of methylprednisolone intravenously for up to 3 days for patients with acute vision loss or amaurosis fugax [69,70,72-74]. In addition, the importance of the time of starting steroid therapy is clearly emphasized, indicating that the best effects are achieved with immediate drug administration, even before the results of the temporal artery biopsy [69,70,75,76]. As mentioned earlier, this may prevent the other, previously unoccupied eye from developing an ischemic condition as well [76,77].

To date, no recommendations have been developed regarding the treatment of NA-AION, which is much more common in the group of ischemic optic neuropathies, accounting for approximately 85% of all cases [77]. Initially, researchers focused on optic nerve decompression surgery (ONDS), which involved making several splits in the sheath of the optic nerve to facilitate the outflow of cerebrospinal fluid and reduce the pressure in the optic nerve [78-80]. Unfortunately, this method was claimed ineffective and dangerous in a large, randomized controlled trial called the Ischemic Optic Neuropathy Decompression Trial (IONDT) [81]. The treatment caused various side effects, most often pain and diplopia. Moreover, after surgery, patients had a higher risk of losing three or more lines of vision. Another substance that was studied to improve vision and prevent fellow eye involvement in NA-AION was aspirin. Due to the multifactorial etiology of NA-AION, which is not fully understood, it was assumed that if thrombosis is involved in the development of the disease, the antiplatelet properties of aspirin may be effective [82]. Although the study by Kupersmith et al. from 1997 [83] and Salomon et al. in 1999 [84] showed the effectiveness of aspirin in reducing the risk of involvement of the other eye, subsequent studies did not confirm this [85,86], including a randomized clinical trial on a larger group of 418 patients [87]. Currently, the use of aspirin is not recommended in NA-AION, arguing that this disease may be related not so much to thrombosis as to blood pressure drops that are not affected by aspirin [82,88]. Many researchers have focused on the role of steroids in the treatment of NA-AION by reducing disc optic edema, which occurs in this disease [89]. In 2008, a study was conducted on 613 patients, 312 of whom volunteered for oral prednisone therapy [90]. Within the group that took oral prednisone, both visual fields and visual acuity improved up to 6 months after the onset of NA-AION. However, this study had many limitations in performance, including no randomization, and the untreated group had more vascular risk factors [91]. Also, intravenous administration of triamcinolone, a fourth-generation steroid, showed no significant improvement in the course of the disease [92,93]. Intravitreal administration of triamcinolone may have some efficacy, but to this day no research that could popularize this

practice [94-96]. The latest randomized clinical trial and meta-analysis do not confirm the effectiveness of systemic steroid therapy in the treatment of NA-AION [97-98]. In addition to the above-mentioned therapeutic options that did not fulfill their role, the use of substances such as topically applied brimonidine [99], intravitreal bevacizumab [100], oxygen therapy [93], erythropoietin [101,102], or levodopa was also considered [103,104]. The substances tested so far in terms of their usefulness in the treatment of NA-AION are summarized in Table 1.

Type of treatment	Type of study	Results	Ref.
Optic nerve sheath decompression	Prospective, randomized, single-masked, multicenter trial	Risk of losing three or more lines of vision at 6 months	[81]
Aspirin	Retrospective cohort study	Little to no long-term benefit in reducing the risk of NA-AION in the fellow eye	[85]
	Retrospective case-control study	No improvement in the visual outcome	[86]
	Randomized clinical trial with observational cohort	No association between use of aspirin and new NA-AION in the fellow eye	[87]
Systemic steroids	Prospective, controlled, non-randomized study	Improvement in the visual field and visual acuity up to 6 months	[90]
	Prospective, non-randomized study	No benefits in visual and anatomic outcomes given in acute phase of NA-AION	[92]
	Retrospective, controlled, randomized clinical trial	No improvement in structural and functional outcomes	[93]
Intravitreal steroids	Retrospective, controlled, unmasked, non-randomized study	Improvement of visual field and visual acuity, during 6 months of the follow-up	[94]
	Prospective, unmasked, not controlled, non-randomized study	Improvement in visual acuity and color vision in all studied patients	[95]
	Prospective, controlled, unmasked, non-randomized study	Improved recovery in visual acuity, rapid resolution of the optic disc swelling, no changes in the visual field	[96]
Topical brimonidine	Prospective, double-masked, randomized, placebo-controlled trial	No significant advantages on visual acuity and visual field	[99]
Intravitreal bevacizumab	Prospective, controlled, non-randomized clinical trial	No improvement in visual acuity, visual field, or thickness of nerve layer	[100]
Oxygen therapy	Retrospective, controlled, randomized clinical trial	No improvement in structural and functional outcomes	[103]

Table 1. Substances currently researched for NA-AION.

PION was firstly described in 1981 [105]. It is divided into atretic PION, which coexists with giant cell arteritis, non-atretic PION, resembling NA-AION in a course, and surgical (postoperative) PION secondary to surgical procedures [106-107].

According to a cohort study by Sadda et al., the most common type of PION is non-atretic PION (53% of cases, n = 72) [107]. The treatment of A-PION is the same as the treatment of giant cell arteritis and involves the administration of large doses of systemic steroids [88,108] Surgical PION is characterized by a sudden unilateral or bilateral vision loss, usually present upon recovery from anesthesia [109]. The most common operation associated with the risk of PION development is spine surgery, with the most cases reported for the correction of scoliosis defect [110,111]. Since no proven methods of treating an already existing surgical PION, and the chances of spontaneous improvement of vision are low, one should focus on reducing the risk factors that contribute to the occurrence of this complication [112]. The etiology of PION is based on hypoxia of the optic nerve, so factors such as hypotension, intraoperative blood loss, anemia, and hemodilution will increase the risk of its occurrence [109]. It is important to maintain adequate hematocrit, transfuse colloids together with crystalloids to prevent hemodilution, and avoid the long Trendelenburg position, which reduces the venous pressure in the eyeball that contributes to the appearance of optic nerve edema.

Optic neuropathy, which arose based on nutritional deficiencies, is treated with appropriate supplementation, so it is crucial to accurately determine the missing vitamins and elements. The role behind the development of nutritional optic are nutrients that condition the proper function of mitochondria, mainly copper and B vitamins, with the greatest importance being vitamin B12 (cobalamin), vitamin B9 (folic acid), and vitamin B1 (thiamine) [113]. Recommendations of the British Society of Hematology recommend treating vitamin B12 deficiency with daily intramuscular injection of 1000 μg of hydroxocobalamin until improvement is achieved [114]. The therapy is then maintained with a single intramuscular injection of 1000 μg of hydroxocobalamin once every two months. The guidelines state that treatment should be instituted as soon as possible to avoid the persistence of neurological disabilities. When treatment is started, improvement usually occurs after 6 weeks to 6 months [115]. If a vitamin B9 deficiency is coexisting, it should be replaced first to prevent subacute degeneration of the spinal cord [115-116]. The therapeutic dose of vitamin B9 depends on the cause of its occurrence - the guidelines do not emphasize the exact supply in the case of neuropathy, while in the case of nutritional deficiencies and the occurrence of megaloblastic anemia, an oral intake of 5 mg of folic acid/day 4 months is recommended [114]. The appropriate daily amount of copper has not been accurately established, it fluctuates between 1.5-3 mg orally per day or higher doses which are gradually tapered down [247]. In a more severe course, intravenous therapy is also possible [117-118]. Vitamin B1 can be administered intravenously or intramuscularly in a dose of 100 mg daily for 2 weeks, then continued as an oral supplementation with a group B vitamin complex [119]. For Wernicke's encephalopathy, at least 500 mg of thiamine should be given three times a day for 2-3 days [120]. As for tobacco-alcohol optic neuropathy, it has a different prognosis depending on the degree and duration of exposure to alcohol and tobacco, the duration of vision impairment until diagnosis [27]. The most important thing, in this case, is to stop drinking alcohol and smoking, to eat a well-balanced diet, and to compensate for vitamin deficiencies. As mentioned earlier, methanol poisoning can lead to complete blindness. The effects of methanol poisoning are difficult to predict - some patients experience improvement in vision, while others experience worsening vision over time [121]. There are several human clinical studies suggesting the utility of recombinant human erythropoietin (EPO) either intravenously or in combination with systemic steroid therapy, where the addition of EPO significantly improved the treatment effect [122,123,124]. Erythropoietin is a hormone mostly produced by adult kidneys that has been shown to protect the cells of the retina from excessive oxidation and exposure to strong light. This hormone exhibits antioxidant, anti-inflammatory, neuroprotective, angiogenic, and antiapoptotic effects [125]. There is also a report that the

improvement in vision is only transient after intravenous administration of EPO in combination with methylprednisone, and a single study has shown that the efficacy of EPO in methanol induced optic neuropathy was not observed in the late cases of the disease [121,125,126].

Due to the multitude of medicinal substances capable of inducing TON, only ethambutol will be discussed in this publication, as it is the drug most often causing optic neuropathy and the incidence of this disease is up to 100,000 cases per year [127]. Ocular side effects are believed to be dose-dependent with most patients developing neuropathy at 60-100 mg/kg/day, although this is possible even at ≤ 15 mg/kg/day [128]. In addition, patients with kidney disease should not be treated with ethambutol as this drug is mainly excreted via the kidneys and accumulates in the body when the kidney disease is present [129]. Discontinuation of the drug usually results in visual improvement [130,131], although some reports indicate that visual disability persists [132,133], as well as progressive structural damage in the absence of clinical symptoms [134]. It is also noted that asymptomatic patients treated with ethambutol should undergo monthly screening of at least visual acuity and Amlser grid testing to detect impairments promptly [135].

8. Conclusions

Optic nerve neuropathy is a broad, heterogeneous entity that may be triggered or exacerbated by diverse factors ranging from malnutrition and vitamin deficiencies, toxic substances, including, inter alia, methanol, medications, heavy metals, organic solvents, carbon dioxide or hotly discussed in this review ethanol to vascular disturbances or genetic predispositions like in LHON. Pathogenetic mechanisms are mostly based upon inflammation followed by demyelination of the optic nerve. Due to poor divergences in clinical presentation and multiple similarities in phenotypes of particular types of optic neuropathy, each patient should encompass detailed differential diagnostics. Indeed, proper identification of the causative agent allows for the implementation of appropriate treatment; however, it is not always possible. Nevertheless, grasping the main cause of optic neuropathy may be intractable due to concomitance or overlapping abundant factors. In each, even the most compound case, the pivotal role plays responding to all possible causes, for instance, immediate removal or neutralizing toxic substances, supplementing nutritional and vitamin deficiencies, or administration of appropriate medications such as steroids in A-AION and A-PION or idebenone in LHON. Regarding NA-AION, so far there remains a paucity of available treatment options. It is worth mentioning novel therapies such as EPO administration in methanol poisoning or gene therapy in LHON that show very promising results.

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