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

Joanna Kobak¹, Magdalena Tyczynska², Alicja Forma¹*, Iga Dudek¹, Amr Maani², Patryk Zembala³, Jacek Baj²

1. Department of Forensic Medicine, Medical University of Lublin, Jaczewskiego 8b, 20-090 Lublin, Poland, kobak.joanna@umlub.pl, formaalicja@gmail.com; iga.dudek6@gmail.com
2. Department of Human Anatomy, Medical University of Lublin, Jaczewskiego 4, 20-090 Lublin, Poland; m.tyczynska@onet.pl; amrmaanni@gmail.com; jacek.baj@umlub.pl
3. Department of Ophthalmology, Medical University of Warsaw, Warsaw, Poland; patrykx0@hotmail.com

*corresponding authors: formaalicja@gmail.com

ORCID:
Joanna Kobak: 0000-0003-2588-2436
Magdalena Tyczynska: 0000-0001-7754-9956
Alicja Forma: 0000-0001-8714-7627
Iga Dudek: 0000-0002-8101-074X
Amr Maani: 0000-0002-3687-8654
Patryk Zembala: 0000-0002-9050-4725
Jacek Baj: 0000-0002-1372-8987

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 have 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

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. Furthermore, a clinical division consisting of two forms can be made. The first one is arteritic AION (A-AION), which gives a picture of
arteritis (specifically giant cell arteritis in older patients), and the second one is non-arteritic AION (NA-AION), which is caused by the smaller blood vessels damage, without the involvement of inflammation.

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. NA-AION is a multifactorial illness, with many risk factors that participate in its development but none of them has been yet surely confirmed. It is said that co-occurrence of cardiovascular system hazards with dense nerve structure and blood vessels in optic disc might be the cause. Researchers believe that diabetes, higher cholesterol levels, “narrow” construction of optic disc, lower blood flow in optic disc play the great role in NA-AION advancement. Additionally, arterial hypertension, anaemia and hepatic alcholoe disease are being considered and therefore remain a hot topic of scientific discussions.

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 the perioperative time or after liver transplant. Though there is no known treatment for NA-AION, a decrease of risk factors is important in reducing the chance of second eye involvement as well as further incidents.

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 allotrophic 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.

References
1. Walter M, Gerhard U, Gerlach M, Weijers HG, Boening J, Wiesbeck GA. Cortisol concentrations, stress-coping styles after withdrawal, and long-term abstinence in alcohol dependence. Addict Biol. 2006; 11:157–62.
2. Lightman S, McDonald WI, Bird AC, et al. Retinal venous sheathing in optic neuritis. Its significance for the pathogenesis of multiple sclerosis. Brain 1987; 110 (Pt 2):405.
3. Roed H, Frederiksen J, Langkilde A, et al. Systemic T-cell activation in acute clinically isolated optic neuritis. J Neuroimmunol 2005; 162:165.
4. Söderström M, Link H, Xu Z, Fredriksson S. Optic neuritis and multiple sclerosis: anti-MBP and anti-MBP peptide antibody-secreting cells are accumulated in CSF. Neurology 1993; 43:1215.
5. Frederiksen JL, Madsen HO, Ryder LP, et al. HLA typing in acute optic neuritis. Relation to multiple sclerosis and magnetic resonance imaging findings. Arch Neurol 1997; 54:76.
6. Francis DA, Compston DA, Batchelor JR, McDonald WI. A reassessment of the risk of multiple sclerosis developing in patients with optic neuritis after extended follow-up. J Neurol Neurosurg Psychiatry 1985; 50:758.

7. Morrow MJ, Wingerchuk D. Neuromyelitis Optica. J Neuroophthalmol. 2012; 32:154–166.

8. Beck RW, Cleary PA, Anderson MM, et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. N Engl J Med. 1992; 326:581–588

9. Korkiamäki P, Kervinen M, Karjalainen K, Majamaa K, Uusimaa J, Remes AM. Prevalence of the primary LHON mutations in Northern Finland associated with bilateral optic atrophy and tobacco-alcohol amblyopia. Acta Ophthalmol. 2013 Nov;91(7):630-4. doi: 10.1111/j.1755-3768.2012.02506.x. Epub 2012 Sep 12. PMID: 22970697.

10. Spruijt L, Kolbach DN, de Coo RF, Plomp AS, Bauer NJ, Smeets HJ, de Die-Smulders CE. Influence of mutation type on clinical expression of Leber hereditary optic neuropathy. Am J Ophthalmol. 2006 Apr;141(4):676-82. doi: 10.1016/j.ajo.2005.11.007. PMID: 16564802.

11. Spruijt L, Hoogendijk JE, Hendrickx AT, de Coo IF, Doevendans PA, de Jong PT, Spriet WG, Kroes H, Smeets HJ. Additional mitochondrial DNA mutations may explain extra-ocular involvement in LHON. Am J Med Genet A. 2006 Jul 1;140(13):1478-81. doi: 10.1002/ajmg.a.31324. PMID: 16770803.

12. Puomila A, Hämäläinen P, Kivioja S, Savontaus ML, Koivumäki S, Huoponen K, Nikoskelainen E. Epidemiology and penetrance of Leber hereditary optic neuropathy in Finland. Eur J Hum Genet. 2007 Oct;15(10):1079-89. doi: 10.1038/sj.ejhg.5201828. Epub 2007 Apr 4. PMID: 17406640.

13. Wallace DC, Singh G, Lott MT, Hodge JA, Schurr TG, Lezza AM, Elsas LJ 2nd, Nikoskelainen EK. Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. Science. 1988 Dec 9;242(4884):1427-30. doi: 10.1126/science.3201231. PMID: 3201231.

14. Howell N, Bindoff LA, McCullough DA, Kubacka I, Poulton J, Mackey D, Taylor L, Turnbull DM. Leber hereditary optic neuropathy: identification of the same mitochondrial ND1 mutation in six pedigrees. Am J Hum Genet. 1991 Nov;49(5):939-50. PMID: 1928099; PMCID: PMC1683233.

15. Howell N, Kubacka I, Xu M, McCullough DA. Leber hereditary optic neuropathy: involvement of the mitochondrial ND1 gene and evidence for an intragenic suppressor mutation. Am J Hum Genet. 1991 May;48(5):935-42. PMID: 2018041; PMCID: PMC1683051.

16. Nikoskelainen E, Vilikki J, Huoponen K, Savontaus ML. Recent advances in Leber's hereditary optic neuroretinopathy. Eye (Lond). 1991;5 (Pt 3):291-3. doi: 10.1038/eye.1991.45. PMID: 1955049.

17. Chinnery PF, Andrews RM, Turnbull DM, Howell NN. Leber hereditary optic neuropathy: Does heteroplasmacy influence the inheritance and expression of the G11778A mitochondrial DNA mutation? Am J Med Genet. 2001 Jan 22;98(3):235-43. doi: 10.1002/1096-8628(20010122)98:3<235::aid-ajmg1086>3.0.co;2-o. PMID: 11169561.

18. Valentino ML, Barboni P, Ghelli A, Bucchi L, Rengo C, Achilli A, Torroni A, Lugaresi A, Lodi R, Barbiroli B, Dotti M, Federico A, Baruzzi A, Carelli V. The ND1 gene of complex I is a mutational hot spot for Leber's hereditary optic neuropathy. Ann Neurol. 2004 Nov;56(5):631-41. doi: 10.1002/ana.20236. PMID: 15505787.

19. Yu-Wai-Man P, Griffiths PG, Chinnery PF. Mitochondrial optic neuropathies - disease mechanisms and therapeutic strategies. Prog Retin Eye Res. 2011 Mar;30(2):81-114. doi:
10.1016/j.preteyeres.2010.11.002. Epub 2010 Nov 26. PMID: 21112411; PMCID: PMC3081075.

20. Amaral-Fernandes MS, Marcondes AM, do Amor Divino Miranda PM, Maciel-Guerra AT, Sartorato EL. Mutations for Leber hereditary optic neuropathy in patients with alcohol and tobacco optic neuropathy. Mol Vis. 2011;17:3175-9. Epub 2011 Dec 7. PMID: 22194643; PMCID: PMC3244475.

21. Cullom ME, Heher KL, Miller NR, Savino PJ, Johns DR. Leber's hereditary optic neuropathy masquerading as tobacco-alcohol ambylopia. Arch Ophthalmol. 1993 Nov;111(11):1482-5. doi: 10.1001/archoph.1993.01090110048021. PMID: 8240101.

22. Kirkman MA, Yu-Wai-Man P, Korsten A, Leonhardt M, Dimitriadis K, De Coo IF, Klopstock T, Chinnery PF. Gene-environment interactions in Leber hereditary optic neuropathy. Brain. 2009;132(Pt 9):2317-26.

23. Maass J, Matthê E. Bilateral vision loss due to Leber's hereditary optic neuropathy after long-term alcohol, nicotine and drug abuse. Doc Ophthalmol. 2018 Apr;136(2):145-153. doi: 10.1007/s10633-018-9622-5. Epub 2018 Jan 25. PMID: 29372350.

24. Nowomiejska K, Kiszka A, Maciejewski R, Jünemann A, Rejdak R. Central scotoma in tobacco-alcohol toxic optic neuropathy measured with semi-automated kinetic perimetry. Cutan Ocul Toxicol. 2018 Dec;37(4):319-323. doi: 10.1080/15569527.2018.1459666. Epub 2018 Apr 24. PMID: 29688089.

25. Baj J, Forma A, Kobak J, Tyczynska M, Dudek I, Maani A, Teresiński G, Buszewicz G, Januszewski J, Flieger J. Toxic and Nutritional Optic Neuropathies—An Updated Mini-Review. International Journal of Environmental Research and Public Health. 2022; 19(5):3092. https://doi.org/10.3390/ijerph19053092

26. Samanta SK, Fariduddin K, Mahapatra N, Bhunia J, Mondal P. Hooch blindness: a community study report on a few indoor patients of toxic optic neuropathy following consumption of adulterated alcohol in West Bengal. Nepal J Ophthalmol. 2012 Jan-Jun;4(1):162-4. doi: 10.3126/nepjoph.v4i1.5868. PMID: 22344014.

27. Chiotoroiu SM, Noaghi M, Stefaniu GI, Secureanu FA, Purcarea VL, Zemba M. Tobacco-alcohol optic neuropathy—clinical challenges in diagnosis. J Med Life. 2014;7(4):472-6.

28. Wang MY, Sadun AA. Drug-related mitochondrial optic neuropathies. J Neuroophthalmol. 2013 Jun;33(2):172-8. doi: 10.1097/WNO.0b013e3182901969. PMID: 23681241.

29. Grzybowski A, Holder GE. Tobacco optic neuropathy (TON) - the historical and present concept of the disease. Acta Ophthalmol. 2011 Aug;89(5):495-9. doi: 10.1111/j.1755-3768.2009.01853.x. Epub 2010 Mar 16. PMID: 20337605.

30. Kerrison JB, Miller NR, Hsu F, Beaty TH, Maumenee IH, Smith KH, Savino PJ, Stone EM, Newman NJ. A case-control study of tobacco and alcohol consumption in Leber hereditary optic neuropathy. Am J Ophthalmol. 2000 Dec;130(6):803-12. doi: 10.1016/s0002-9394(00)00603-6. PMID:11124301.

31. Hayreh SS. Ischemic optic neuropathy. Prog Retin Eye Res. 2009 Jan;28(1):34-62. doi: 10.1016/j.preteyeres.2008.11.002. Epub 2008 Nov 27. PMID: 19063989.

32. Obuchowska I, Mariak Z. Neuropatia niedokrwienna nerwu wzrokowego. Patogeneza, obraz kliniczny, diagnostyka i leczenie [Ischemic optic neuropathy. Pathogenesis, clinical features, diagnostics and treatment]. Klin Oczna. 2006;108(4-6):238-42. Polish. PMID: 17020004.

33. Hayreh SS. Risk factors in AION. Ophthalmology. 2001 Oct;108(10):1717-8. doi: 10.1016/s0161-6420(01)00738-2. PMID:11581036.

34. Hayreh SS, Podhajsky PA, Zimmerman B. Ocular manifestations of giant cell arteritis. Am J Ophthalmol. 1998 Apr;125(4):509-20. doi: 10.1016/s0002-9394(99)80192-5. PMID:9559737.
1. Pahor A, Pahor D. Klinische Befunde bei Patienten mit nicht arteritischer anteriorer ischämischer Optikusneuropathie (NAION) unter 50 Jahren [Clinical Findings in Patients with Non-Arteritic Anterior Ischemic Optic Neuropathy (NA-AION) Under 50 Years of Age]. Klin Monbl Augenheilkd. 2016 Jan;233(1):66-71. German. doi: 10.1055/s-0041-104773. Epub 2015 Oct 13. PMID: 26460575.

2. Hayreh SS, Zimmerman B. Visual field abnormalities in nonarteritic anterior ischemic optic neuropathy: their pattern and prevalence at initial examination. Arch Ophthalmol. 2005 Nov;123(11):1554-62. doi: 10.1001/archopht.123.11.1554. PMID: 16286618.

3. Wilhelm H, Beisse F, Rüther K. Die nicht arteritische anteriore ischämische Optikusneuropathie (NAION) [Non-Arteritic Ischemic Optic Neuropathy (NAION)]. Klin Monbl Augenheilkd. 2015 Nov;232(11):1260-9. German. doi: 10.1055/s-0035-1558170. Epub 2015 Nov 17. PMID: 26575534.

4. van Oterendorp C, Lagrèze WA, Feltgen N. Pathogenese und Therapie der nicht arteritiischen anterioren ischämischen Optikusneuropathie [Non-arteritic Anterior Ischaemic Optic Neuropathy: Pathogenesis and Therapeutic Approaches]. Klin Monbl Augenheilkd. 2019 Nov;236(11):1283-1291. German. doi: 10.1055/a-0972-1625. Epub 2019 Nov 11. PMID: 31711249.

5. Tesser RA, Niendorf ER, Levin LA. The morphology of an infarct in nonarteritic anterior ischemic optic neuropathy. Ophthalmology. 2003 Oct;110(10):2031-5. doi: 10.1016/S0161-6420(03)00804-2. PMID: 14522783.

6. Egan R. Prothrombotic and vascular risk factors in NAION. Ophthalmology. 2000 Dec;107(12):2116-7. doi: 10.1016/s0161-6420(00)00258-x. PMID: 11097559.

7. Salomon O, Huna-Baron R, Kurtz S, Steinberg DM, Moisseiev J, Rosenberg N, Yassur I, Vidne O, Zivelin A, Gitel S, Davidson J, Ravid B, Seligsohn U. Analysis of prothrombotic and vascular risk factors in patients with nonarteritic anterior ischemic optic neuropathy. Ophthalmology. 1999 Apr;106(4):739-42. doi: 10.1016/S0161-6420(99)90159-8. PMID: 10201595.

8. Reddy D, Rani PK, Jalali S, Rao HL. A study of prevalence and risk factors of diabetic retinopathy in patients with non-arteritic anterior ischemic optic neuropathy (NA-AION). Semin Ophthalmol. 2015 Mar;30(2):101-4. doi: 10.3109/08820538.2013.833262. Epub 2013 Oct 30. PMID: 24171808.

9. Pahor D, Gracner B. Weitsichtigkeit als Risikofaktor für Patienten mit nicht arteritischer anteriore ischämischer Optikusneuropathie [Hyperopia as a risk factor in patients with nonarteritic anterior ischaemic optic neuropathy]. Klin Monbl Augenheilkd. 2008 Dec;225(12):1070-4. German. doi: 10.1055/s-2008-1028000. Epub 2008 Dec 15. PMID: 19085788.

10. Hayreh SS, Zimmerman MB. Nonarteritic anterior ischemic optic neuropathy: clinical characteristics in diabetic patients versus nondiabetic patients. Ophthalmology. 2008 Oct;115(10):1818-25. doi: 10.1016/j.ophtha.2008.03.032. Epub 2008 May 27. PMID: 18502511.

11. Chang MY, Keltner JL. Risk Factors for Fellow Eye Involvement in Nonarteritic Anterior Ischemic Optic Neuropathy. J Neuropathol. 2019 Jun;39(2):147-152. doi: 10.1097/WNO.0000000000000715. PMID: 30300257.

12. Fodor M, Nagy V, Berta A, Tornai I, Pfiegl G. Hepatitis C virus presumably associated bilateral consecutive anterior ischemic optic neuropathy. Eur J Ophthalmol. 2008 Mar-Apr;18(2):313-5. doi: 10.1177/112067210801800226. PMID: 18320531.
47. Sinnreich M, Rossillion B, Landis T, Burkhard PR, Sztajzel R. Bilateral optic ischemic neuropathy related to chronic hepatitis C-associated anticardiolipin antibodies. Eur Neurol. 2003;49(4):243-5. doi: 10.1159/000070195. PMID: 12736543.

48. Brazis PW, Spivey JR, Bolling JP, Steers JL. A case of bilateral optic neuropathy in a patient on tacrolimus (FK506) therapy after liver transplantation. Am J Ophthalmol. 2000 Apr;129(4):536-8. doi: 10.1016/s0002-9394(99)00443-2. PMID: 10764869.

49. Yaghi C, Baz P, Koussa S, Daniel F, Haddad F, Sayegh R. Neuropathie optique ischémique antérieure aiguë compliquant un traitement par interféron alpha-2a et ribavirine pour hépatite aiguë virale C [Ischemic anterior optic neuropathy complicating interferon alpha-2a and ribavirin treatment for acute hepatitis C]. Gastroenterol Clin Biol. 2005 May;29(5):616-7. French. doi: 10.1016/s0399-8320(05)82144-x. PMID: 15980766.

50. Gupta R, Singh S, Tang R, Blackwell TA, Schiffman JS. Anterior ischemic optic neuropathy caused by interferon alpha therapy. Am J Med. 2002 Jun 1;112(8):683-4. doi: 10.1016/s0002-9343(02)01102-6. PMID: 12034426.

51. Chun, B. Y., & Rizzo, J. F. (2017). Dominant Optic Atrophy and Leber’s Hereditary Optic Neuropathy: Update on Clinical Features and Current Therapeutic Approaches. Seminars in Pediatric Neurology, 24(2), 129–134.

52. Heitz FD, Erb M, Anklin C, Robay D, Pernet V, Gueven N. Idebenone protects against retinal damage and loss of vision in a mouse model of Leber's hereditary optic neuropathy. PLoS One. 2012;7(9):e45182.

53. Gueven N. Idebenone for Leber's hereditary optic neuropathy. Drugs Today (Barc). 2016 Mar;52(3):173-81.

54. Zhao, X., Zhang, Y., Lu, L., & Yang, H. (2020). Therapeutic Effects of Idebenone on Leber Hereditary Optic Neuropathy. Current Eye Research.

55. Jurkute, N., Harvey, J., & Yu-Wai-Man, P. (2018). Treatment strategies for Leber hereditary optic neuropathy. Current Opinion in Neurology, 1.

56. Catarino CB, von Livonius B, Priglinger C, Banik R, Matloob S, Tamhankar MA, Castillo L, Friedburg C, Halfpenny CA, Lincoln JA, Traber GL, Acaroglu G, Black GCM, Doncel C, Fraser CL, Jakubaszko J, Landau K, Langenegger SJ, Muñoz-Negrete FJ, Newman NJ, Poulton J, Scoppettuolo E, Subramanian P, Toossy AT, Vidal M, Vincent AL, Votruba M, Zarowski M, Zernansky A, Lob F, Rudolph G, Mikazans O, Silva M, Liòria X, Metz G, Klopstock T. Real-World Clinical Experience With Idebenone in the Treatment of Leber Hereditary Optic Neuropathy. J Neuroophthalmol. 2020 Dec;40(4):558-565.

57. Zuccarelli M, Vella-Szijj J, Serracino-Inglott A, Borg JJ. Treatment of Leber's hereditary optic neuropathy: An overview of recent developments. Eur J Ophthalmol. 2020 Nov;30(6):1220-1227.

58. Newman NJ, Yu-Wai-Man P, Carelli V, Moster ML, Biousse V, Vignal-Clermont C, Sergott RC, Klopstock T, Sadun AA, Barboni P, DeBusk AA, Girmens JF, Rudolph G, Karanjia R, Taiel M, Blouin L, Smits G, Katz B, Sahel JA; LHON Study Group. Efficacy and Safety of Intravitreal Gene Therapy for Leber Hereditary Optic Neuropathy Treated within 6 Months of Disease Onset. Ophthalmology. 2021 May;128(5):649-660.

59. Yu-Wai-Man P, Newman NJ, Carelli V, Moster ML, Biousse V, Sadun AA, Klopstock T, Vignal-Clermont C, Sergott RC, Rudolph G, La Morgia C, Karanjia R, Taiel M, Blouin L, Burguèire P, Smits G, Chevalier C, Masonson H, Salerno Y, Katz B, Picaud S, Calkins DJ, Sahel JA. Bilateral visual improvement with unilateral gene therapy injection for Leber hereditary optic neuropathy. Sci Transl Med. 2020 Dec 9;12(573):eaaz7423.

60. Newman NJ, Yu-Wai-Man P, Carelli V, Biousse V, Moster ML, Vignal-Clermont C, Sergott RC, Klopstock T, Sadun AA, Girmens JF, La Morgia C, DeBusk AA, Jurkute N, Priglinger C,
Karanjia R, Josse C, Salzmann J, Montestrucc F, Roux M, Taitel M, Sahel JA. Intravitreal Gene Therapy vs. Natural History in Patients With Leber Hereditary Optic Neuropathy Carrying the m.11778G>A ND4 Mutation: Systematic Review and Indirect Comparison. Front Neurol. 2021 May;24:12:662838.

61. Sadun AA, Chicani CF, Ross-Cisneros FN, Barboni P, Thoolen M, Shrader WD, Kubis K, Carelli V, Miller G. Effect of epi-743 on the clinical course of the mitochondrial disease leber hereditary optic neuropathy. Arch Neurol. 2012;69(3):331–8.

62. Rustum Karanjia SGC, Garcia M, Sadun AA. Elamipretide (mtp131) topical ophthalmic solution for the treatment of leber’s hereditary optic neuropathy. Invest Ophthalmol Vis Sci. 2019;60:2266.

63. Pisano A, Preziuso C, Iommarini L, Perli E, Graziani P, Campese AF, Maresca A, Montopoli M, Masuelli L, Sadun AA, d’Amati G, et al. Targeting estrogen receptor beta as preventive therapeutic strategy for leber’s hereditary optic neuropathy. Hum Mol Genet. 2015;24(24):6921–31.

64. Yu AK, Datta S, McMackin MZ, Cortopassi GA. Rescue of cell death and inflammation of a mouse model of complex 1-mediated vision loss by repurposed drug molecules. Hum Mol Genet. 2017;26(24):4929–36.

65. Weiss JN, Levy S, Benes SC. Stem Cell Ophthalmology Treatment Study (SCOTS): bone marrow-derived stem cells in the treatment of Leber’s hereditary optic neuropathy. Neural Regen Res. 2016 Oct;11(10):1685-1694.

66. Hunder GG, Bloch DA, Michel BA, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990 Aug;33(8):1122-8.

67. Bernstein SL, Johnson MA, Miller NR. Nonarteritic anterior ischemic optic neuropathy (NAION) and its experimental models. Progress in Retinal and eye Research. 2011 May;30(3):167-187.

68. Morrow MJ. Ischemic Optic Neuropathy. Continuum (Minneap Minn). 2019 Oct;25(5):1215-1235.

69. Hellmich B, Agueda A, Monti S, et al 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Annals of the Rheumatic Diseases 2020;79:19-30.

70. Mackie SL, Dejaco C, Appenzeller S, Camellino D, Duftner C, Gonzalez-Chiappe S, Mahr A, Mukhtyar C, Reynolds G, de Souza AWS, Brouwer E, Bukhari M, Buttgeite F, Byrne D, Cid MC, Cimmino M, DiRuskeneli H, Gilbert K, Kermani TA, Khan A, Lanyon P, Luqmani R, Mallen C, Mason JC, Matteson EL, Merkel PA, Mollan S, Neill L, Sullivan EO, Sandovici M, Schmidt WA, Watts R, Whitlock M, Yacyshyn E, Ytterberg S, Dasgupta B. British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis. Rheumatology (Oxford). 2020 Mar 1;59(3):e1-e23.

71. Singh AG, Kermani TA, Crowson CS, Weyand CM, Matteson EL, Warrington KJ. Visual manifestations in giant cell arteritis: trend over 5 decades in a population-based cohort. J Rheumatol. 2015;42:309-315

72. Hayreh SS, Zimmerman B. Visual deterioration in giant cell arteritis patients while on high doses of corticosteroid therapy. Ophthalmology. 2003 Jun;110(6):1204-15.

73. Hayreh SS, Zimmerman B, Kardon RH. Visual improvement with corticosteroid therapy in giant cell arteritis. Report of a large study and review of literature. Acta Ophthalmol Scand. 2002 Aug;80(4):355-67.

74. Chan CC, Paine M, O’Day J. Steroid management in giant cell arteritis. Br J Ophthalmol. 2001;85(9):1061-1064.
75. González-Gay MA, Blanco R, Rodriguez-Valverde V, Martínez-Taboada VM, Delgado-Rodriguez M, Figueroa M, Uriarte E. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. Arthritis Rheum. 1998 Aug;41(8):1497-504.
76. Patil P, Williams M, Maw WW, Achilleos K, Elsideeg S, Dejaco C, Borg F, Gupta S, Dasgupta B. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. Clin Exp Rheumatol. 2015 Mar-Apr;33(2 Suppl 89):S-103-6.
77. El Chami S, Springer JM. Update on the Treatment of Giant Cell Arteritis and Polymyalgia Rheumatica. Med Clin North Am. 2021 Mar;105(2):311-324.
78. Sergott RC, Cohen MS, Bosley TM, Savino PJ. Optic Nerve Decompression May Improve the Progressive Form of Nonarteritic Ischemic Optic Neuropathy. Arch Ophthalmol. 1989;107(12):1743–1754.
79. Kelman SE, Elman MJ. Optic Nerve Sheath Decompression for Nonarteritic Ischemic Optic Neuropathy Improves Multiple Visual Function Measurements. Arch Ophthalmol. 1991;109(5):667–671.
80. Spoor TC, McHenry JG, Lau-Sickon L. Progressive and static nonarteritic ischemic optic neuropathy treated by optic nerve sheath decompression. Ophthalmology. 1993 Mar;100(3):306-11.
81. Optic nerve decompression surgery for nonarteritic anterior ischemic optic neuropathy (NAION) is not effective and may be harmful. The Ischemic Optic Neuropathy Decompression Trial Research Group. JAMA. 1995 Feb 22;273(8):625-32.
82. Egan, Robert A. ; Arnold, Anthony C. ; Lee, Andrew G. ; Van Stavern, Gregory P. / Should Aspirin Be Prescribed to Prevent Recurrence in Nonarteritic Anterior Ischemic Optic Neuropathy?. In: Journal of neuro-ophthalmology : the official journal of the North American Neuro-ophthalmology Society. 2020 ; Vol. 40, No. 3. pp. 428-433.
83. Kupersmith MJ, Frohman L, Sanderson M, Jacobs J, Hirschfeld J, Ku C, Warren FA. Aspirin reduces the incidence of second eye NAION: a retrospective study. J Neuroophthalmol. 1997 Dec;17(4):250-3.
84. Salomon O, Huna-Baron R, Steinberg DM, Kurtz S, Seligsohn U. Role of aspirin in reducing the frequency of second eye involvement in patients with non-arteritic anterior ischaemic optic neuropathy. Eye (Lond). 1999 Jun;13 (Pt 3a):357-9.
85. Beck RW, Hayreh SS, Podhajsky PA, Tan ES, Moke PS. Aspirin therapy in nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol. 1997 Feb;123(2):212-7.
86. Botelho PJ, Johnson LN, Arnold AC. The effect of aspirin on the visual outcome of nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol. 1996 Apr;121(4):450-1.
87. Newman NJ, Scherer R, Langenberg P, Kelman S, Feldon S, Kaufman D, Dickersin K; Ischemic Optic Neuropathy Decompression Trial Research Group. The fellow eye in NAION: report from the ischemic optic neuropathy decompression trial follow-up study. Am J Ophthalmol. 2002 Sep;134(3):317-28.
88. Hayreh SS. Ischemic optic neuropathies - where are we now? Graefes Arch Clin Exp Ophthalmol. 2013 Aug;251(8):1873-84.
89. Hayreh SS, Zimmerman MB. Optic disc edema in non-arteritic anterior ischemic optic neuropathy. Graefes Arch Clin Exp Ophthalmol. 2007 Aug;245(8):1107-21.
90. Hayreh, S.S., Zimmerman, M.B. Non-arteritic anterior ischemic optic neuropathy: role of systemic corticosteroid therapy. Graefes Arch Clin Exp Ophthalmol 246, 1029–1046 (2008).
91. Atkins EJ, Bruce BB, Newman NJ, BIousse V. Treatment of nonarteritic anterior ischemic optic neuropathy. Surv Ophthalmol. 2010 Jan-Feb;55(1):47-63.
92. Rebolleda G, Pérez-López M, Casas-LLera P, Contreras I, Muñoz-Negrete FJ. Visual and anatomical outcomes of non-arteritic anterior ischemic optic neuropathy with high-dose systemic corticosteroids. Graefes Arch Clin Exp Ophthalmol. 2013 Jan;251(1):255-60.

93. Pakravan M, Sanjari N, Esfandiari H, Pakravan P, Yaseri M. The effect of high-dose steroids, and normobaric oxygen therapy, on recent onset non-arteritic anterior ischemic optic neuropathy: a randomized clinical trial. Graefes Arch Clin Exp Ophthalmol. 2016 Oct;254(10):2043-2048.

94. Durbant E, Radoi C, García T, Denoyer A, Arndt C. Intravitreal triamcinolone injections in non-arteritic anterior ischemic optic neuropathy - A retrospective report. J Fr Ophtalmol. 2021 Jun;44(6):777-785.

95. Yaman A, Selver OB, Saatci AO, Soylev MF. Intravitreal triamcinolone acetonide injection for acute non-arteritic anterior ischaemic optic neuropathy. Clin Exp Optom. 2008 Nov;91(6):561-4.

96. Kaderli B, Avci R, Yücel A, Guler K, Gelisken O. Intravitreal triamcinolone improves recovery of visual acuity in nonarteritic anterior ischemic optic neuropathy. J Neuroophthalmol. 2007 Sep;27(3):164-8.

97. Saxena R, Singh D, Sharma M, James M, Sharma P, Menon V. Steroids versus No Steroids in Nonarteritic Anterior Ischemic Optic Neuropathy: A Randomized Controlled Trial. Ophthalmology. 2018 Oct;125(10):1623-1627.

98. Chen J, Zhu J, Chen L, Hu C, Du Y. Steroids in the treatment of nonarteritic anterior ischemic optic neuropathy: A PRISMA-compliant meta-analysis. Medicine (Baltimore). 2019 Nov;98(46):e17861.

99. Wilhelm B, Lüdtke H, Wilhelm H; BRAION Study Group. Efficacy and tolerability of 0.2% brimonidine tartrate for the treatment of acute non-arteritic anterior ischemic optic neuropathy (NAION): a 3-month, double-masked, randomised, placebo-controlled trial. Graefes Arch Clin Exp Ophthalmol. 2006 May;244(5):551-8.

100. Rootman DB, Gill HS, Margolin EA. Intravitreal bevacizumab for the treatment of nonarteritic anterior ischemic optic neuropathy: a prospective trial. Eye (Lond). 2013 Apr;27(4):538-44.

101. Modarres M, Falavarjani KG, Nazari H, et al Intravitreal erythropoietin injection for the treatment of non-arteritic anterior ischaemic optic neuropathyBritish Journal of Ophthalmology 2011;95:992-995.

102. Pakravan M, Esfandiari H, Hassanpour K, Razavi S, Pakravan P. The Effect of Combined Systemic Erythropoietin and Steroid on Non-arteritic Anterior Ischemic Optic Neuropathy: A Prospective Study. Curr Eye Res. 2017 Jul;42(7):1079-1084.

103. Lyttle DP, Johnson LN, Margolin EA, Madsen RW. Levodopa as a possible treatment of visual loss in nonarteritic anterior ischemic optic neuropathy. Graefes Arch Clin Exp Ophthalmol. 2016 Apr;254(4):757-64.

104. Johnson LN, Guy ME, Krohel GB, Madsen RW. Levodopa may improve vision loss in recent-onset, nonarteritic anterior ischemic optic neuropathy. Ophthalmology. 2000 Mar;107(3):521-6.

105. Hayreh SS. Posterior ischemic optic neuropathy. Ophthalmologica. 1981;182(1):29-41.

106. Hayreh, SS. Posterior ischaemic optic neuropathy: clinical features, pathogenesis, and management. Eye 18, 1188–1206 (2004).

107. Sadda SR, Nee M, Miller NR, Bioussse V, Newman NJ, Kouzis A. Clinical spectrum of posterior ischemic optic neuropathy. Am J Ophthalmol. 2001 Nov;132(5):743-50.

108. Athappilly G, Pelak VS, Mandava N, Bennett JL. Ischemic optic neuropathy. Neurol Res. 2008 Oct;30(8):794-800.
109. Wang MY, Brewer R, Sadun AA. Posterior ischemic optic neuropathy: Perioperative risk factors. Taiwan J Ophthalmol. 2020 Sep 11;10(3):167-173.

110. Patil CG, Lad EM, Lad SP, Ho C, Boakye M. Visual loss after spine surgery: a population-based study. Spine (Phila Pa 1976). 2008 Jun 1;33(13):1491-6.

111. Lee LA, Roth S, Posner KL, Cheney FW, Caplan RA, Newman NJ, Domino KB. The American Society of Anesthesiologists Postoperative Visual Loss Registry: analysis of 93 spine surgery cases with postoperative visual loss. Anesthesiology. 2006 Oct;105(4):652-9; quiz 867-8.

112. Fandino W. Strategies to prevent ischemic optic neuropathy following major spine surgery: A narrative review. J Clin Anesth. 2017 Dec;43:50-58.

113. Roda M, di Geronimo N, Pellegrini M, Schiavi C. Nutritional Optic Neuropathies: State of the Art and Emerging Evidences. Nutrients. 2020 Aug 31;12(9):2653.

114. Devalia V, Hamilton MS, Molloy AM; British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014;166(4):496–513.

115. Langan RC, Goodbred AJ. Vitamin B12 Deficiency: Recognition and Management. Am Fam Physician. 2017 Sep 15;96(6):384-389.

116. Hunt A, Harrington D, Robinson S. Vitamin B12 deficiency. BMJ. 2014;349g5226.

117. Rapoport Y, Lavin PJ. Nutritional Optic Neuropathy Caused by Copper Deficiency After Bariatric Surgery. J Neuroophthalmol. 2016 Jun;36(2):178-81.

118. Naismith RT, Shepherd JB, Weihl CC, Tutlam NT, Cross AH. Acute and bilateral blindness due to optic neuropathy associated with copper deficiency. Arch Neurol. 2009 Aug;66(8):1025-7.

119. Jefferis JM, Hickman SJ. Treatment and Outcomes in Nutritional Optic Neuropathy. Curr Treat Options Neurol. 2019 Feb 7;21(1):5

120. Sechi G, Serra A. Wernericke’s encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol. 2007;6(5):442–455

121. Zamani N, Hassanian-Moghadam H, Shojaei M, Rahimian S. Evaluation of the effect of erythropoietin + corticosteroid versus corticosteroid alone in methanol-induced optic nerve neuropathy. Cutan Ocul Toxicol. 2018 Jun;37(2):186-190.

122. Pakdel F, Sanjari MS, Naderi A, Pirmarzdashti N, Haghighi A, Kashkouli MB. Erythropoietin in Treatment of Methanol Optic Neuropathy. J Neuroophthalmol. 2018 Jun;38(2):167-171.

123. Pakravan M, Esfandiari H, Sanjari N, Ghahari E. Erythropoietin as an adjunctive treatment for methanol-induced toxic optic neuropathy. Am J Drug Alcohol Abuse. 2016;42(6):633-639.

124. Pakravan M, Sanjari N. Erythropoietin treatment for methanol optic neuropathy. J Neuroophthalmol. 2012;32(4):325-8.

125. Feizi, S., Alemzadeh-Ansari, M., Karimian, F., & Esfandiari, H. (2021). Use of erythropoietin in ophthalmology: a review. Survey of Ophthalmology.

126. Acar U, Kucuk B, Sevinc MK, Aykas S, Erdurmus M, Sobaci G. Intravitreal erythropoietin injection in late-stage optic neuropathy: a safety study on human. Int Ophthalmol. 2018 Jun;38(3):1021-1025.

127. Sadun AA, Wang MY. Ethambutol optic neuropathy: how we can prevent 100,000 new cases of blindness each year. J Neuroophthalmol. 2008 Dec;28(4):265-8.

128. Fraunfelder FW, Sadun AA, Wood T. Update on ethambutol optic neuropathy. Expert Opin Drug Saf. 2006 Sep;5(5):615-8.

129. Kanaujia V, Jain VK, Shrama K, Agarwal R, Mishra P, Shrama RK. Ethambutol-induced optic neuropathy in renal disorder: a clinico-electrophysiological study. Can J Ophthalmol. 2019 Jun;54(3):301-305.
130. Song W, Si S. The rare ethambutol-induced optic neuropathy: A case-report and literature review. Medicine (Baltimore). 2017 Jan;96(2):e5889.
131. Bouffard MA, Nathavitharana RR, Yassa DS, Torun N. Re-Treatment With Ethambutol After Toxic Optic Neuropathy. J Neuroophthalmol. 2017 Mar;37(1):40-42.
132. Lee EJ, Kim SJ, Choung HK, Kim JH, Yu YS. Incidence and clinical features of ethambutol-induced optic neuropathy in Korea. J Neuroophthalmol. 2008 Dec;28(4):269-77.
133. Tsai RK, Lee YH. Reversibility of ethambutol optic neuropathy. J Ocul Pharmacol Ther. 1997 Oct;13(5):473-7.
134. Addy LK, Harrison WW. Case Report: Long-term Structural and Functional Effects of Ethambutol Optic Neuropathy. Optom Vis Sci. 2020 Aug;97(8):555-560.
135. Chamberlain PD, Sadaka A, Berry S, Lee AG. Ethambutol optic neuropathy. Curr Opin Ophthalmol. 2017 Nov;28(6):545-551.