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The New Therapeutic Studies for Irreversible Optic Nerve Damages

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KEYWORDS

Optic neuropathy; optic nerve damage; retinal ganglion cells; Optic nerve damage therapies, Irreversible optic nerve damages current treatments; Types of optic nerve damages

ABSTRACT:

The irreversible optic nerve damages are known as optic neuropathies result in permanent loss of vision. The optic neuropathy usually affects the anterior optic nerve, leading to death of retinal ganglion cells (RGCs) and axonal loss. At present, there is no effective treatment to recover degenerated or damaged optic nerves because of their inability to regenerate themselves. The present essay has adopted a literature-based methodological approach to discuss epidemiological, pathophysiological, and clinical profile of the various optic neuropathies. The article traces the prevalence of optic neuropathies in Turkey and discusses the causes and effects of irreversible optic damage. Moreover, it reports on main rodent models used in the research conducted on optic neuropathy. In addition, the paper examined the current treatments used for the management of patients suffering from irreversible optic nerve damage and suggests options for future approach on introducing new treatments in the field. Thus, the dissertation holds significant implications as it helps advance the existing understanding regarding epidemiology, pathophysiology, and clinical types of optic neuropathies. Furthermore, it helps highlight the potential for new approaches in exploring treatments for irreversible optic nerve damage, which can guide future researchers in the area of activity.

1. Introduction

Optic nerve damage is caused by a number of disorders, which cause atrophy in the region due to the destruction of ganglion cells in retina and result in complete or partial visual loss (Sanz-Morello et al., 2021). Optic neuropathy (ON) is one of the leading irreversible optic nerve damage and it encompasses a group of optic nerve diseases, which result in temporary or permanent loss of vision (Margolin et al., 2022). Processes responsible for damaging the optic nerve include the increased pressure in the intraocular region, traumatic injury, ischemia, and compression, resulting in loss of sight. Currently, there is no well-established treatment to act towards these nerve destructions, therefore, they are referred to as irreversible optic nerve damage. It has long been recognized that patients suffering from irreversible optic nerve damage will never be able to regain their vision because the damaged nerves cannot be regenerated or repaired. Three assumptions have guided this belief: (1) an RGC in a mammal lacks the ability to recover itself once it has been injured; (2) a damaged RGC in a mammal cannot obtain a new axon; and (3) the regenerated axon cannot be integrated back in the system towards its destination area in the CNS (Miller & Tsai, 2023). Studies from the past two decades have been focused at identifying several strategies to enable regeneration of axons of RGCs along the region of the nerve. Some studies have reported a modest re-innervation of diencephalic and mesencephalic visual relay centers. Nonetheless, there are very limited options for treatment of this disorder to sustain the sight after irreversible damage or other neuro-degenerative conditions, such as glaucoma and ON. Furthermore, the role of local immune system in promoting the chance for surviving among the RGC and regeneration of axons has been highlighted. The research in this field is aimed at presenting effective clinical strategies to sustain the vision of patients suffering from irreversible optic nerve damage (Wong & Benowitz, 2022). The essay is aimed at reviewing the existing treatments for optic nerve damage and to explore future strategies for protecting and repairing the optic nerve. With the increasing prevalence of various optic disorders, there has been observed a growing need for eye care facilities in Turkey. This has led building of various eye care hospitals in Turkey, offering advanced ophthalmic diagnosis and treatment. As a result, the revenue in the eye care market in Turkey is expected to reach US$1.52m in 2024 (Statista, 2023). The present study focuses on Turkey due to the increasing prevalence of optic nerve damage among the Turkish people. For instance, Glaucoma, which leads to permanent optic nerve damage, has been threatening 2 million people in Turkey (Dünyagöz, 2023). There is a significant lack of studies exploring new treatments for irreversible optic nerve damage in the context of Turkey, which makes the present study immensely significant. A study conducted by Altındal and Kurt (2023) examined the causes of

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blindness and visual impairment among the people residing in the Mediterranean Coast District of Turkey. However, the study focused on easily curable diseases only. On the other hand, the present study focuses on the treatment for irreversible optic nerve damage.

2. Method

For this research paper, a secondary qualitative approach has been considered to explore new treatment studies for irreversible optic nerve damage. For this purpose, a systematic literature review approach (Lee et al., 2022), was taken into account which is supported by interpretivism philosophy and inductive access.

2.1. Data Collection Process

A list of keywords was formulated for selecting the required studies for this paper which include "Optic Nerve Damage;" "Irreversible Optic Nerve Diseases;" "Novel Therapies of ON"; "Novel Treatment;" "Clinical Types" and "Current Treatment." These keywords were instilled in different online databases including PubMed, Cochrane Library, EMBASE and other related sources for data collection.

To select the studies for this paper, an effective inclusion and exclusion criteria was formulated as presented below:

- **Inclusion Criteria**
- Research papers and journal articles, incorporating current and novel treatments regarding irreversible optic nerve damage
- Research papers and journal articles, published in 2020 to present
- Research papers, published in English language

- **Exclusion Criteria**
- Papers or journal articles published before 2020
- Papers or journal articles published in other languages, rather than English
- Chapter books and literature

Initially, about 50 papers and journal articles were considered. However, after implementing the selection criteria, only 34 papers and articles were utilized for this paper.

2.2. Data Analysis

In order to analyze the collected secondary qualitative data, content analysis (Mengist et al., 2020) was taken into account.

3. Irreversible Optic Nerve Damage

Damage to the optic nerve, referred to as optic neuropathy (ON), obstructs the flow of visual information, leading to eventual loss of vision. Optic nerve damage is regarded as irreversible as nerve fibers do not have the capability to regenerate or repair themselves once the damage has taken place. At present, the research on discovering clinical options for recovering the injured optic nerve is in its initial stages (Benowitz, 2022). ON can appear as the non-arteritic anterior ischemic optic neuropathy (NAION) and it can damage the optic nerve due to a change in the blood flow. It obstructs the reception of oxygen into the blood flow by interrupting the blood flow. This leads to degradation and eventual dysfunction of the optic nerve (Kraff, 2022). Optic neuritis is one of the most prevalent acute ON mostly affecting young adults. It involves an inflammation of the optic nerve and can be either idiopathic or an initial exhibition of demyelinating situations, of which multiple sclerosis is the most common in the Western hemisphere. In most cases, optic neuropathy is diagnosed as a hereditary condition (Miller & Tsai, 2023). However, some nutritional causes have also been associated with optic neuropathy. Margolin et al. (2022) highlighted the significant role of deficiencies of vitamin B12, folic acid, and copper in causing nutritional optic neuropathy. Moreover, the consumption of toxic medications as well as ingestion of toxins can also lead to optic neuropathy. For instance, Ethambutol, an anti-mycobacterial medication, is the primary cause behind toxic optic neuropathy, and has affected 100,000 patients globally as quoted in the study of Margolin et al. (2022). Glaucoma remains the most prevalent optic nerve neuropathy worldwide and the prevalent cause of irreversible blindness among people (Zhang et al., 2021).

3.1. Clinical Types

Since optic neuropathy encompasses a series of disorders created optic nerve atrophy, therefore, there are various clinical types of optic neuropathy. However, all of these nerve damages result from the death of RGCs, and lead to ultimate loss of vision (Buonfiglio et al., 2023; Sanz-Morello et al., 2021). Anterior ischemic optic neuropathies (AION), the most prevalent form of acute ON found in aged people, is characterized by visual loss due to swelling of optic disc as shown in Figure 3.1.

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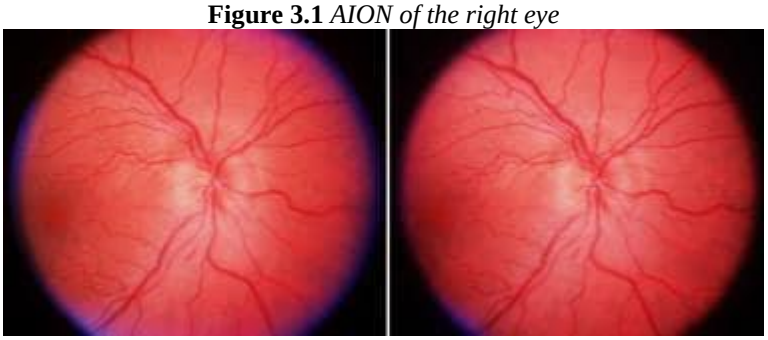
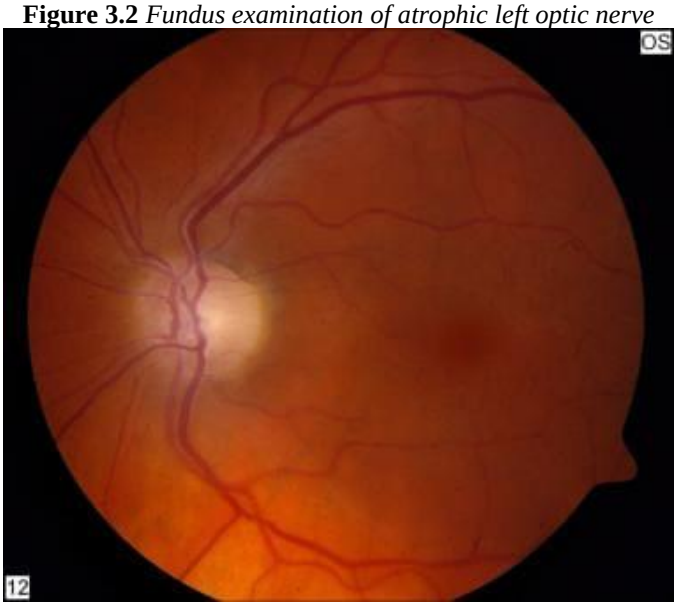
Figure 3.1 *AION of the right eye*



Note: Swollen pale disc as seen in a stereoscopic view
Source: *(Dahl, 2021)*

Furthermore, any internal or external compression along the optic nerve can lead to compressive optic neuropathy (CON), leading to reduced vision loss and ultimate optic atrophy (Rodriguez-Beato & De Jesus, 2020). Figure 3.2 shows the atrophic left optic nerve due to CON.

Figure 3.2 *Fundus examination of atrophic left optic nerve*



Note: The image indicates the atrophic optic nerve in the left eye of a 72-year-old man with a moderate loss of vision.
Source: *(Kanakamedala, 2023)*

Other clinical types of ON include "Glaucoma", "Leber's hereditary optic neuropathy (LHON)", "Optic neuritis", "Traumatic optic neuropathies", "Nutritional and toxic ON", and "Dysthyroid ON" (Buonfiglio et al., 2023).

3.2. Pathophysiology and Epidemiology

As a part of the CNS, the optic nerve in mammals lacks the capacity to regenerate and regrow its axon. In case of axonal damage, and injury to glial cells, the growth is inhibited. Furthermore, several inhibitory proteins of myelin, such as Nogo and glycoprotein obstruct the growth factors. In addition, the proximal damage to the eye, leads to a quicker apoptosis of RGCs, result in cell death along the optic nerve, also known as optic nerve atrophy. Furthermore, optic neuropathy is characterized by the compression of the vascular supply, which leads to ischemia of the optic nerve. This impairs the transmission of signals along the axons (Rodriguez-Beato & De Jesus, 2020). Furthermore, oxidative stress has a significant role in the pathophysiology of optic nerve neuropathies, such as "glaucoma," "LHON", and "AION". The lack of balance between the generation of the reactive oxygen species and reactive nitrogen species and the antioxidant mechanisms lead to their increased production, resulting in the deficiency of adenosine triphosphate, loss of RGCs, and irreversible nerve damage (Buonfiglio et al., 2023; Kang et al., 2021; Ruan et al., 2020; Sanz-Morello et al., 2021). The epidemiology of optic neuropathy depends on the type of nerve damage. The most cases of acute Optic neuritis, one of the most prevalent forms of ON, are diagnosed in females of the ages between 20 and 40 years. In Asian countries, the cases of optic neuritis are more commonly

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associated with the multiple sclerosis than in the American and European regions (Osborne & Balcer, 2023). Moreover, optic atrophy, which is an outcome of optic neuropathy, is more common among African American than in other ethnicities. However, there is no sex predisposition associated with this condition (Amula, 2022). On the other hand, the estimates of CON are 4 cases per 100k individuals as quoted in the study conducted by (Rodriguez-Beato & De Jesus, 2020).

4. Rodent Models

There are several rodent models of optic neuropathies, and researchers keep on developing new rodent models to conduct research on irreversible optic nerve damage and various clinical types of optic neuropathies. Researchers use these models to advance the existing studies on the pathophysiology of optic neuropathies and perform tests of potential treatments. Animal models help understand the etiology and pathogenesis of various immune responses and help develop various clinical strategies to treat optic diseases in human beings. Several studies have been conducted using rodent models to understand the underlying pathophysiology of ON (Redler & Levy, 2020). "Experimental Autoimmune Encephalomyelitis (EAE) Model" is the most popular rodent model to conduct experiments for studying optic neuropathies, particularly for optic neuritis. EAE is based on a complex system in which several immunological and neuropathological mechanisms intermingle and lead to inflammation, demyelination, and loss of axons (Redler & Levy, 2020). Other rodent models to study neuropathies include a new "MOG-specific TCR transgenic mouse", a 2D2 mouse developed by Bettelli et al. (2003). Almost 30 per cent of these mice show the symptoms of spontaneous ON upon immunization with subclinical levels of MOG peptide. Moreover, 56 per cent of these mice exhibit histological manifestation of EAE. Moreover, upon complete immunization, 80 per cent of the mice would develop optic neuropathy. It was established that the particularity of inflammation and demyelination was associated with the crucially increased concentration of MOG in the optic nerve than those in the spinal cord (Redler & Levy, 2020). Other examples of rodent models are the "crush injury model" for the study of TON, "ischemic optic neuropathy (ION) models", "Neuro-myelitis optica spectrum disorders optic neuritis (NMOSD-ON) model", "hereditary optic neuropathies models" for research of LHON and dominant optic atrophy and "toxic and deficiency optic neuropathies models" (Pozyuchenko et al., 2020). Recently, two new models were introduced, which are known as the "sonication-induced traumatic optic neuropathy (SI-TON) model" and "controlled orbital impact (COI) model." SI-TON is non-invasive and relies on the use of ultrasonic pulses for the creation of the injury. However, the major drawback of this model is that it scatters the ultrasonic energy from the primary site of injury and leads to potential harm to the contralateral optic nerve in rodents. In addition, the misplaced ultrasound micro-tip can cause tissue injury because of inaccuracy in target. The COI model causes minimum invasion compared with the old models of optic neuropathy. However, this model also has some limitations. For instance, this model requires a specialized equipment for setting up the platform and specialized software for adjusting the crucial parameters required for the application of the COI (Bastakis et al., 2019).

5. Current Treatment

Treatment options for Optic neuropathy are contentious, and there are currently no universal guidelines or tactics for their management. Since ON is so uncommon, there has been a dearth of large-scale randomized controlled trials, and there is also very little data available. Based on the specific pathophysiological mechanism, surgical optic canal decompression, observation (conservative management), steroid treatment, or a combination of the two are the four treatment options available to specialists for ON management.

Without the use of medication or surgery, patients are carefully watched during observation management. (Chen et al., 2022) is among the numerous studies that have surprisingly demonstrated that patients managed with observation can spontaneously show a recovery in visual acuity (VA) ranging from 30% to 60%. It is unclear what has led to this recovery.

Due to their unique pharmacological characteristics, corticosteroids may provide some advantages in the treatment of TON, according to some experts. It is suggested that the antioxidant, anti-inflammatory, and anti-apoptotic characteristics of corticosteroids help preserve ON axons and limit damage after trauma (Miller, 2021). Research conducted by (Au & Ma, 2022) demonstrated the effects of methylprednisolone, naloxone, trilazoids, and a placebo following acute spinal cord injury. The results indicated that administering methylprednisolone within 3-8 hours after the trauma greatly enhanced motor function and recovery. This encouraging finding regarding the effectiveness of steroids in treating neuronal trauma offered proof of the drugs' off-label use in treating ON.

Yet, other clinical and basic research studies (Bastakis et al., 2019) have found no difference or even negative effects of steroid usage after neuronal trauma.

Thirdly, ON can be treated by addressing the compression forces that may act on ON axons following trauma, such as edema or hemorrhage. (Nakazawa & Fukuchi, 2020) found little evidence that ON decompression surgery had a positive impact on TON in animal models and clinical trials. There is a lack of convincing evidence that surgical decompression is superior to alternative treatment options, and the majority of the published works on the topic are

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retrospective case series. It is already challenging to choose the best strategy, and the fact that various surgical procedures were used in these studies just makes things worse. (Lambiri & Levin, 2022) found no significant benefit from steroid treatment or decompression ON surgery in the prospective, multicenter International ON trauma study.

Finally, a treatment regimen for ON management has been suggested, which includes both decompression surgery and steroids. All patients were given steroids within eight hours of injury in this protocol. If there was no improvement, endonasal endoscopic decompression of the ON was done.

In order to prevent carriers from experiencing visual loss, the management of ON patients has centered on comprehending the disease's pathophysiology and potential triggers. When blindness begins in one eye, medical intervention is necessary. Researchers looked at medications with the potential to repair the electron transport chain in retinal ganglion cells' mitochondria. Gene therapy and free radical cell scavengers have both made great strides in the search for a cure for ON (Hage & Vignal-Clermont, 2021). Although promising, clinical trial results in halting the progression of visual loss have been inconsistent. We still do not know of an effective treatment that can restore vision in patients whose disease has persisted for more than a year.

A treatment that showed the most promise was one from the ubiquinone family. Coenzyme Q10 is a component of this, and it is responsible for transporting electrons from the mitochondrial ETC complex I to complex II. Although a small number of case reports indicated otherwise, coenzyme Q10 has not improved LHON, despite its usefulness in other IMDs where its insufficiency causes encephalomyelopathy (Hargreaves et al., 2020). Coenzyme Q10 has a big drawback when taken orally: it cannot pass the blood-brain barrier. This problem was solved by creating Idebenone, a synthetic hydro-soluble version of coenzyme Q10. In vitro, Idebenone protected retinal ganglion cells from death caused by complex I deficiency. Additionally, it enabled rotenone mice to regain their eyesight. The delivery of a gene to the RGC nucleus constitutes Gene therapy in ON. A protein is subsequently redirected into the mitochondria after being produced in either the cytoplasm or the ribosomes of the RGCs. The authors correctly deduced that the transfected cells had successfully restored complex I-dependent respiration because their ATP production was three times higher than that of the mock-transfected cybrids (Yu-Wai-Man et al., 2020).

6. Options for Novel Treatment

Published recently (Sreshta et al., 2021) are results from a multicenter, open-label, phase 3 semi-experimental trial that tested the efficacy of treating ON with the cytokine hormone erythropoietin (EPO). EPO is a hormone that is classified as a cytokine. It is a member of the superfamily and an essential cog in the wheel of erythroid lineage. The neuroprotective and anti-apoptotic effects of EPO in central nervous system (CNS) and peripheral nerves following injury, neurotoxicity, or ischemia have been demonstrated in various in vivo and in vitro studies (Ureña-Guerrero et al., 2020). In most cases, EPO's anti-apoptotic and neuroprotective effects are brought about by the phosphorylation of Janus kinase 2, which in turn activates the PI3-K, MAPK, and Stat5 pathways.

In addition, after NF-kB activation, proapoptotic factors (BAD) are reduced and anti-apoptotic factors (Bcl-xL, Bax) are increased (AlAsmari et al., 2021). Additionally, EPO lessens neuronal injury by reducing glutamate release and inhibiting Ca influx. EPO treatment following ON proved to be a safe and effective way to enhance color vision and best-corrected visual acuity (BCVA) without causing any negative side effects, thus making it a promising treatment option for ON (Lai et al., 2022). The ideal dosage range and treatment rounds need further investigation, though.

Spermidine is an additional molecule that helps ON axons survive damage. As a naturally occurring free radical scavenger, spermidine blocks the effects of reactive oxygen species (ROS). The following are known to increase post-neuronal injury: chemokine levels, p38, apoptosis signal-regulating kinase-1 (ASK1 (Basha et al., 2021) . Inducible Nitric Oxide Synthase (iNOS) upregulation in the mouse retina and suppression of the ASK-1-p38 pathway resulted in suppressed chemokine production in ONC mouse models when spermidine was administered orally once daily (Chen et al., 2021).

Crystalline is another class of molecules that may have neuroprotective and regenerative effects following ON trauma. There are three types of crystalline, which are the primary building blocks of mammalian lenses (Dimauro & Caporossi, 2022). These crystalline are members of the small heat shock proteins superfamily (sHSP). Apart from crystalline lenses, can be found in other ocular structures like cornea, retina, astrocytes, ON, Muller cells, and in many non-ocular tissues. In a study conducted by (Rajeswaren et al., 2022), it was demonstrated that administering a-crystallin intravenously to rats following an ONC improves RGC survival while simultaneously preventing the activation of retinal microglial cells.

The actions are enhanced by A-crystallin because it suppresses the RhoA/ROCK pathway and activates the regeneration process by increasing the expression of PKCα and suppressing the RAF/MEK/ERK pathway. In addition, (Rajeswaren et al., 2022)demonstrated that injecting a-crystallin intravenously into rats following an ON crush improves RGC survival while simultaneously preventing the activation of retinal microglial cells. As we've already established, the

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neuroprotective effects of crystallin release following lens injury extend to ON .Research has demonstrated that beta and gamma crystalline can enhance regeneration by activating CNTF expression in astrocytes (an action that is independent of macrophages) and the JAK/STAT3 signaling pathway that follows (Liu et al., 2022). The foregoing suggests that crystalline may one day make up a regenerative therapy for ON.

Some members of the family of (NGFs) that have been linked to neuroprotection following injury are (CNTF), (BDNF), and fibroblast growth factor-2 (FGF-2). Researchers have found that BDNF improves the survival of RGCs after injury. In addition, the survival of SMI-32+ large soma RGCs is enhanced when BDNF expression increase in the retinal tissue. This is because these cells are more prone to acute injury following ONC. In conclusion, a rat model of ON transaction demonstrated that RGC survival was enhanced when BDNF and the free radical scavenger S-PBN were administered together, but long-distance axon regeneration was not improved.

According to (Bennett et al., 2023), people who test positive for antibodies to myelin oligodendrocyte glycoprotein, AQP4, and CRMP5 may have more severe optic nerve atrophy and worse visual acuity recovery compared to people with typical optic neuritis caused by idiopathic or multiple sclerosis. By distinguishing between these conditions, important laboratory, imaging, and clinical findings help doctors narrow their diagnostic focus and provide the best acute and preventative care. The preservation of color vision, visual fields, and contrast sensitivity could be achieved through the prompt administration of high-dose corticosteroids and, in certain cases, plasmapheresis, which could be guided by the prompt and accurate diagnosis of optic neuritis subtypes. The understanding of autoimmune neurological disorders, the design of clinical trials, and the forefront of therapeutic innovation can all be enhanced by further progress in the diagnosis, treatment, and understanding of optic neuropathy.

7. Conclusion and Implications

In the past 20 years, numerous research groups have dedicated their efforts to finding new ways to treat the ON's currently incurable diseases. The understanding of demyelinating ON and TON in rats has grown thanks to recent advances in the field's models. Several therapeutic options have been identified through animal model studies and clinical trial results. These include both established pharmaceutical compounds and newer, more innovative drugs or stem cell therapies that are showing promise in slowing the disease's progression.

The wide variety of optic nerve pathologies, each with its own unique cause and degree of visual impairment, presents researchers and clinicians with a formidable array of obstacles. Mild to severe visual impairments, and in extreme cases, total unilateral or bilateral blindness, can be caused by optic neuritis and traumatic optic neuropathy, particularly the demyelinating form. It is crucial to find effective treatments that can alleviate symptoms and improve patient outcomes, since these diseases remain incurable despite substantial research. Both medical professionals and researchers are on the lookout for new and old treatments that can address the causes of optic nerve damage. Because these interventions must be administered soon after the insult, treatment is time sensitive. This review delves into the clinical and epidemiological profiles of optic nerve pathologies, illuminating their symptoms and prevalence. Additional aid in the development and testing of treatments is provided by rodent models that reproduce clinical features of these diseases.

As challenging as it is, present treatments try to lessen inflammation, safeguard the brain, and increase neural regeneration. The necessity for continuous research to enhance therapeutic tactics is, however, highlighted by a critical evaluation of current treatments. Complex optic nerve pathologies may be treatable with the use of emerging technologies and combination therapies. According to the papers were looked at, the optimal approach might involve a mix of pharmacological, cellular, and technological interventions. The translation of research into effective treatments for patients requires collaboration between pharmaceutical companies, medical professionals, and researchers. There is a scientific and humanitarian motivation to find the therapies for optic nerve pathology that will help people whose lives are severely impaired by these diseases.

8. Limitations and Future Research

There has been less study focused on optic nerve pathology, but there are still some caveats to think about. The results might be impacted by socio-cultural variables, diagnostic capabilities, and healthcare accessibility in the region. To overcome these limitations, future studies should investigate cultural differences in the way different populations react to optic nerve diseases. The generalizability of the research would be enhanced with a more extensive geographical scope that encompasses multiple countries. Additional research is needed on time-related factors, including intervention effects and longitudinal studies. If reliable, cross-cultural insights into optic nerve pathology is needed, Cross-verify of results in different healthcare structures should be done. All things considered, our knowledge will grow, and we will be able to develop treatments for optic nerve disorders that are both more universally applicable and more responsive to changes in time.

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