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Progress in the Pathological Mechanism and Treatment of Optic Neuritis

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Abstract

Optic neuritis (ON) is a kind of inflammatory disease characterized by optic nerve damage, which can lead to vision loss or even blindness. With the development of ON pathology, the medical community has gained a more comprehensive understanding of its immune-mediated complex processes. In addition, the treatment method has also developed from a single hormone therapy to a variety of treatment strategies including immunosuppressants, plasma exchange, immunoadsorption, etc., and the emerging therapy of stem cell transplantation has become the focus of attention. This review aims to explore the latest pathomechanisms of optic neuritis, comprehensively analyze the current therapeutic research advances, and provide a reference for future therapeutic directions.

Keywords

Optic Neuritis, Pathological Mechanism, Treatment Progress

1. Introduction

Optic neuritis (Optic Neuritis, ON) is an inflammatory disease that affects the optic nerve and can lead to vision loss and even permanent vision loss [1]. ON usually causes visual loss in one eye and is occasionally seen in both eyes. The main symptoms include central vision loss, central dark spots in the visual field, and color vision disorders, especially red-green vision abnormalities. Some patients will also experience pain during eye movements and papilledema [2]. The pathology of this disease is complex and involves multiple factors, including autoimmune responses, infection, and genetic liability [3]. In recent years, the deepening understanding of ON has promoted innovation and progress in treatment

methods. This review aims to explore the major pathomechanisms of ON and comprehensively analyze the progress of current therapeutic research, including medication, immunotherapy, and supportive therapy. It is hoped that through the elaboration of this paper, ophthalmologists and neurologist more insights will be provided with more effective treatment options for patients.

2. An Overview of the ON

2.1. Definition and Classification of the ON

ON is an inflammatory disease involving the optic nerve, and it is one of the most common blinding optic nerve diseases in young and middle-aged adults. Optic neuritis can occur alone or as one of the manifestations of other diseases. Currently, the international medical community usually divides ON into two types: typical and atypical [4], Typical ON is usually subacute monolateral, with painless, good prognosis, and atypical ON is usually bilateral, showing a high degree of visual loss and poor prognosis [5]. Typical ON is associated with multiple sclerosis (multiple sclerosis, MS), and it is the first episode symptom of MS in 20% to 42% of cases [6]. Furthermore, almost half of MS patients may develop ON at any time in the course of the disease [7]. The atypical ON is often associated with autoimmune diseases in MS, Especially, the antiaquaporin 4 (Anti-aquaporin-4 antibody, AQP 4) antibody disease or neuromyelitis optica spectrum disease (neuromyelitis optic spectrum disorder, NMOSD) and anti-myelinating oligodendrocyte glycoproteins (Myelin Oligodendrocyte Glycoprotein, MOG) antibody-related diseases (Myelin Oligodendrocyte Glycoprotein Antibody Disease, MOGAD) [8] [9]. Beyond traditional classification, medical research continues to reveal new mechanisms and disease entities associated with ON. Recently, a disease associated with antibodies against glial fibrillary acid protein, GFAP) (Glial Fibrillary Acidic Protein) has attracted much attention. This antibody-positive disease entity is often associated with inflammatory symptoms of the CNS such as meningitis, encephalitis, and myelitis [10]. In this type of GFAP astrocytic lesions, involvement of the visual system presents with asymptomatic bilateral optic disc edema and insidious inflammation of the optic nerve, which may lead to severe bilateral visual impairment, while conventional ON is relatively rare [11] [12].

2.2. Etiology and Epidemiology of ON

According to the existing studies, the main causes of ON include autoimmune factors, infectious factors, and genetic factors. Autoimmune factors are the most common cause of ON. Studies have found that autoantibodies against optic nerve antigens exist in ON patients, and these autoantibodies can cause inflammatory response and demyelination of the optic nerve [13]. A variety of infectious diseases may also lead to ON, including viral infections (such as influenza virus, varicella-zoster virus, cytomegalovirus, EB virus, etc.), bacterial infections (such as Neisseria meningitidis, Treponema pallidum, etc.), spirochete infections (e. g., Lyme disease), parasitic infections (such as Toxoplasma), etc. [14]. Autoimmune

diseases, such as systemic lupus erythematosus, Sjogrens syndrome, and IgG 4-related diseases, may also damage the optic nerve by generating an immune response against their own tissues [15]. It is worth noting that in a few cases, ON may occur after vaccination (e.g., influenza, COVID-19 vaccine), although the specific mechanism is not fully understood and may be related to the vaccine-inspired immune response [16]. ON in some cases where a definite cause cannot be found is called idiopathic ON.

The prevalence of ON varies between countries, with the UK report at about 4 to 8/100,000 person/year [17]. ON is common in young adults, and the age is 20 - 45 years old [18]. Especially in cases associated with MS, the prevalence was higher in women compared to men. According to the data reported by the ON treatment trial (Optic neuritis treatment trial, ONTT), among 455 patients with acute unilateral ON, the mean age was 31.8 years and women were 77.2% [19]. In the multicenter trial of the ON multicenter team (Optic Neuritis multicenter research group, ONMRG), the mean age of 70 ON patients was 36.3 years, 69% of whom were women [20]. In 2019, Ishikawa *et al* reported that 77.2% of 531 ON cases were negative for both AQP 4-Ab and MOG-Ab, and 63.7% were female, with a median age of onset of 47.5 years, reaching a peak onset in their 40s [21].

3. Pathological Mechanisms of 2 ON

3.1. Immunological Mechanisms

Normally, the immune system is tolerant to autoantigens of the central nervous system and does not trigger an immune response. However, in ON patients, this immune tolerance may be lost for unknown reasons, causing the immune system to mistakenly attack its own tissues. This loss of immune tolerance may be caused by multiple factors, including genetic susceptibility, environmental factors, and an immunomodulatory imbalance [22]. Because the immune system mistakenly recognizes the myelin components of the optic nerve as foreign antigens, triggering a cascade of inflammatory responses and tissue damage, especially autoantibodies against MOG and AQP 4, have been demonstrated to play a key role in the pathogenesis of ON [23]. In the immunological mechanism of ON, the activation and proliferation of immune cells also play an important role. For example, T cells recognize and respond to autoantigens presented by Antigen-presenting cells (APCs) through specific receptors, such as dendritic cells and macrophages that can effectively present neuroantigens to T cells, triggering a series of immune responses [24]. B cells differentiate into antibody-producing plasma cells, which can further activate T cells as APCs [25], Promoted the infiltration of inflammatory cells and the damage of the optic nerve. In addition, helper T cells, particularly the Th 1 and Th 17 subsets, amplify the inflammatory response by having secreted cytokines such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin-17 (IL-17). Studies have found that serum levels of Th 17-related cytokines and chemokines are significantly increased in ON patients associated with myelin oligodendroglial antibodies (MOG-IgG) and positively correlated with

serum titers of MOG-IgG, further highlighting the key role of Th 17 cells in MOG-IgG-induced neuroinflammation [26].

3.2. The Inflammatory Response

Following the activation of the autoimmune response, the activated immune cells and their secreted cytokines, such as IL-17 and IFN-*γ*, directly initiate the inflammatory response in the ON. This inflammatory response is not simply an extension of the immune response, but rather a complex pathological process involving the interaction of multiple inflammatory mediators and cells. It is some immunogenic and stimulated by the optic nerve, which leads to increased vascular permeability, which makes a large number of leukocytes and inflammatory factors penetrate into the optic nerve tissue [27]. Ulusoy *et al.* [28] found that the expression of IL-12 and IL-17 in peripheral blood of neuromyelitis optica (NMO) was significantly higher than that in healthy control group. These cytokines not only promote the recruitment of inflammatory cells, may also act directly on nerve cells, leading to neurological damage. Methylprednisolone shock therapy (methylprednisolone pulse therapy, MPPT) treatment reduced the levels of pro-inflammatory cytokines IL-12 and IL-18 in the peripheral blood of patients with acute ON, indicating that inhibiting the expression of inflammatory factors is one of the important mechanisms of ON treatment [29]. Koçak *et al.* [30] also found that patients with non-arteritic anterior ischemic optic neuropathy (NAION) had elevated levels of neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII). Abnormalities in these indicators may serve as potential biomarkers for assessing ON inflammatory activity and monitoring disease progression.

3.3. Mechanism of Nerve Injury

In the pathological process of ON, the mechanisms of nerve injury are multifaceted, involving multiple links such as immune-mediated direct attack, demyelination and axonal damage, excitotoxicity, oxidative stress, mitochondrial dysfunction, microcirculation disorders, and blocked nerve regeneration. In immune-mediated direct attack, cytotoxic T cells and B cells recognize and attack neural tissues including retinal ganglion cells (Retinal ganglion cells, RGCs), leading to cell damage or death through perforin and granzyme release of cytotoxic T cells or antibody-dependent cell-mediated cytotoxicity (Antibody-Dependent Cellular Cytotoxicity, ADCC) mechanisms [31]. Moreover, the demyelination process in ON not only leaves axons without their protective layer, but also makes them more vulnerable to inflammatory mediators and reactive oxygen species (Reactive oxygen species, ROS) released in the inflammatory environment, which can cause axonal degeneration and necrosis [32]. Excitotoxicity is caused by excessive neural activity, in which the accumulation of excitatory neurotransmitters such as glutamate can cause intracellular calcium overload and activate a range of cell death pathways, including mitochondria-mediated apoptosis [33]. Oxidative

stress and mitochondrial dysfunction further aggravate cell damage, leading to energy metabolism disorders, affecting the survival of the cell and function. In addition, microcirculation disorders can lead to reduced nutrient and oxygen supply to nerve cells, and the lack of nerve regeneration capacity limits the recovery of damaged nerves [34]. Taken together, these complex mechanisms contribute to visual dysfunction in ON patients.

4. Progress in the Treatment of the 3 ON

4.1. Drug Therapy

Drug therapy of ON mainly includes hormones and immunosuppressive agents. Acute phase hormonal therapy is preferred for ON, either intravenous or orally. However, for acute ON, pay attention to the time point of the application of hormonal shock therapy. Studies show that the earlier the hormone therapy starts, the greater the possibility of visual recovery. That is, intravenous methylprednisolone (Intravenous methylprednisolone, IVMP) started treatment within 4 days of onset with the best results; if the delay is more than 7 days, it may adversely affect vision [35]. For recurrent ON or refractory ON, such as ON positive for AQP 4 antibody, immunosuppressants may be combined. And Carnero and Correale [36] Currently, the commonly used immunosuppressors are tozumab, azathioprine, mycophenolate mofetil (banned in women during pregnancy), and azathioprine is often used as the first-line treatment of NMOSD. However, studies also indicated that the antitumor agent rituximab may be a better first-line treatment option. It is important to note that long-term immunosuppressants treatment for MS may lead to an increased risk of infection and tumors, thus requiring monitoring of patient response and regular examination of liver and kidney function to prevent drug-induced damage [37]. Moreover, some novel biological agents such as monoclonal antibodies also show therapeutic potential for optic neuritis. It has been shown that monoclonal antibodies have significant potential for the treatment of NMOSD. Specifically, agents such as rituximab, ecuzumab, inelizumab, and satilizumab have shown effectiveness in reducing disease relapse and improving symptoms by targeting specific immune cells or components of the complement system [38]. But as a whole, Hormonal therapy is still the basic treatment for ON, However, for the recurrent or refractory cases, Combination of immunosuppressive agents or novel biological agents may lead to better efficacy, However, the high recurrence rate of western medicine treatment alone remains, And the visual field defects, in recent years, With the gradual rise of traditional medicine, More and more TCM therapeutic prescriptions and rehabilitation therapies are gradually applied in clinical treatment, For example, traditional hormones combined with traditional Chinese medicine preparations and acupuncture in the treatment of ON, Some controlled trial clinical data found that, For conventional hormonal therapy alone, Combined with TCM treatment can more effectively improve the vision and visual field defects, While also improving the inflammatory response, To reduce the adverse effects, Thus reducing the recurrence

rate of patients. In this regard, in the field of drug therapy, the future treatment of ON can pay attention to the application of traditional Chinese medicine prescriptions and acupuncture therapy, which is of great significance to improve the quality of life of patients.

4.2. Plasmapheresis

Plasmapheresis (plasma exchange, PE) is a medical procedure that involves the separation of a patients blood into the plasma and blood cell components through a special separation device. In this process, harmful components from plasma are removed and subsequently replenished with equal amounts of fresh frozen plasma or albumin solution to treat a specific disease [39]. According to the guidelines issued by the European Neurology Union in 2010, early PE treatment is recommended for NMO patients not responding to hormonal therapy and immunosuppressive agents [40]. Studies have shown that PE treatment can reduce harmful molecules in the blood by two mechanisms: to reduce the concentration of these molecules and to completely replace the plasma containing these molecules. This treatment facilitates the removal of toxins and disease-initiating factors in the body while reducing the levels of pro-inflammatory cytokines. In this way, PE treatment helps to protect the optic nerve from the loss of the myelin sheath and may improve vision in patients with inflammatory demyelinating ON [41]. Similar to IVMP for ON, the start time of PE had a significant effect on the final outcome of the disease. A large cohort study noted that if PE treatment was delayed beyond 60 days, the possibility of improving vision would be greatly reduced [42]. It has also been found in clinical practice that PE is particularly suitable for the urgent treatment of those patients with NMO positive for AQP 4 antibodies. In the face of cases with suspected ON, even if all serological tests are negative, PE should be considered as an empirical treatment if IVMP fails [43]. However, PE treatment is not commonly used clinically due to its high cost, high plasma demand and potential risk of blood transfusion.

4.3. Immunoadsorption Treatment

Immunoadsorption (Immunoadsorption) is a blood purification technology that introduces a patients blood into an immunosorbent device through extracorporeal circulation, using specific antigens or antibody adsorbent to remove pathological immune components from the blood, such as autoantibodies, immune complexes or inflammatory mediators. This method can quickly reduce the concentration of these harmful components, thus reducing the disease [44]. This therapy and PE are alternative therapies for typical diseases such as ON that fail to hormone therapy. The results of a systematic evaluation and meta-analysis indicate that IA is effective and safe for ON in demyelinating diseases, highlighting the importance of early treatment initiation and finding significant improvements in response rates and indicators of visual function after treatment [45]. The results of Li *et al.* [46] showed that the effect of IA treatment was comparable to that of

PE treatment for NMOSD attacks without IVMP response. The results support the use of IA as a rescue treatment for NMOSD patients who are ineffective with initial steroid therapy. And Hoffmann *et al.* [47]'s research also showed that IA is suitable for treating IVMP refractory MS/NMOSD, effective in preventing recurrence, and is suitable for pregnant and lactating women. Although IA treatment offers a possible new treatment option for patients with optic neuritis, it is accompanied by several potential limitations and risks, including higher treatment costs, dependence on specific medical facilities, and possible side effects such as bleeding, infection, and allergic reactions during treatment. Moreover, due to the lack of large-scale clinical trial data, the long-term efficacy and safety of immunosorbent therapy still need further verification.

4.4. Intravenous Immunoglobulin

Intravenous immunoglobulin (intravenous immunoglobulin, IVIG), as a second-line treatment option for ON, is suitable for the treatment of recurrent ON, hormone-resistant ON, and NMOSD [48] [49]. Lin *et al.* [50]'s studies have shown that IVIG reduces the recurrence of NMOSD and is suitable as a rescue treatment. Ran Jianchuan *et al.* [51] Both PE and IVIG were found to improve vision, but IVIG was safer. The mechanisms of action of this therapy include neutralizing pathogenic autoantibodies, regulation of lymphocyte activity, interference with antigen presentation, and interaction with Fc receptors, cytokines, and the complement system [52]. IVIG is generally well tolerated and at lower risk compared to other treatments such as PE, but may also have some side effects such as headache, fever, nausea and anaphylaxis. Future studies may explore the combination of IVIG with other treatments and may tailor personalized treatment options based on the patients specific circumstances.

4.5. Stem Cell Transplantation Therapy

Despite the steady progress of hormones, immunosuppressive agents, and PE treatment strategies in the treatment of NMOSD, there is no cure, and the vast majority of patients can temporarily control the disease and need multiline therapy. Hematopoietic stem cell transplantation (Hematopoietic stem cell transplantation, HSCT) provides an alternative and potentially curative immunotherapy, and thus is an emerging field for ON therapy [53]. HSCT has the potential to etiologically cure those patients with refractory NMOSD who are refractory to conventional therapy. The process of HSCT involves myeloablative management to eliminate diseased immune cells in the patient, followed by the infusion of hematopoietic stem cells to restore the immune system [54]. The potential of HSCT for NMOSD has been demonstrated in several case reports and small clinical studies that show significant control of patient disease activity after treatment, and even achieve long-term disease-free survival in some cases [55] [56]. However, HSCT is a high-risk treatment that may be accompanied by severe short-and long-term side effects, including infection, graft-versus-host disease (GVHD), and other

transplant-related complications. Therefore, the patient selection criteria are very strict and the pre-treatment assessment is very detailed [57]. At present, the clinical research of stem cell therapy for ON is still ongoing, and more clinical evidence is needed to validate its efficacy and safety. In addition, the researchers are exploring other types of stem cell therapy, such as mesenchymal stem cells (Mesenchymal stem cells, MSCs), which have the potential for immune regulation and tissue repair, and may provide new directions for the treatment of autoimmune diseases such as NMOSD [58], On this basis, we can focus on the further research of new technologies such as stem cell drugs and therapies in the future, and increase the clinical trial data, which is of great significance to improve the long-term treatment effect of patients with immune diseases.

5. Summary

ON is a disease that severely affects vision with complex pathology mechanisms involving multiple immune-mediated injury processes. The current study has revealed a strong link between ON and diseases such as MS and highlights the importance of early diagnosis and treatment. Treatment approaches have been extended from traditional hormonal therapy to include multiple therapeutic strategies including immunosuppressive agents, biologics, and PE. Although existing treatments can alleviate symptoms and improve vision to some extent, existing treatment options still have limitations for refractory or recurrent ON. Therefore, to explore new treatment methods, such as immunoadsorption and HSCT treatment, combined with the optic nerve sheath lymphatic drainage pathway can induce brain protection immunity, development of optic nerve sheath lymphatic system treatment system, combined with the application of TCM rehabilitation treatment at the same time, to improve the treatment effect and improve the quality of life of patients is of great significance. Future studies need to focus on elucidating the detailed pathological mechanisms of ON, discovery of new biomarkers and development of more targeted therapies. Moreover, individualized treatment is an important direction for future treatment. According to the specific conditions of different patients, such as etiology, course of disease, immune status, etc., to develop personalized treatment plan, may achieve better treatment results. Meanwhile, the safety of the treatment and the long-term performance of the patient Prognosis is also a major concern for future research.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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