DISORDERS OF THE LACRIMAL DRAINAGE SYSTEM: DIAGNOSIS AND MODERN APPROACHES TO THERAPY

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Abstract. *Lacrimal drainage system defects, a group of diseases characterized by an obstruction of tear outflow from the eye surface to the nasal cavity. The ophthalms and otorhinolaryngology are so intertwined, that both diseases correlate significantly, and these diseases directly affect the ophthalmological system along with otorhinolaryngology and function and quality of life. Commonly are dacryocystitis, nasolacrimal duct obstruction, and canaliculitis. Pathophysiology of lacrimal system disorders is usually obstruction or inflammation of the lacrimal drainage systems. Obstruction may result from congenital anomalies, infections, physical injuries, age-related changes, or chronic inflammation. Development of tears, which promotes the breeding of microorganisms, may lead to the occurrence of secondary tissue infection and mucopurulent drainage. Clinically we usually observe excessive tearing (epiphora), frequent eye infections, swelling around the medial canthal region and purulent excretion. Signs and symptoms of dacryocystitis include pain, redness, and an increase in local temperature. In chronic cases, tearing lasts and the drainage is frequent. According to epidemiological perspectives, lacrimal drainage disorders come on in all age groups, but these are most frequently seen in infants or old people (congenital nasolacrimal duct obstruction), and due to degenerative changes among the elderly. Due to anatomical differences in the tear drainage channels, women are affected with an increased incidence than men. Diagnosis is based on clinical examination and instrumental methods. Lacrimal irrigation and probing are important in evaluating patency. We use imaging techniques (dacryocystography, computed tomography (CT)) to evaluate anatomical irregularities and rates of obstruction. In latter situations, nasal cavity endoscopy is also required. Management depends in part on underlying cause and severity of disease. Current conservative treatment consists of massaging the lacrimal sac (especially in infants), topical antimicrobials, and anti-inflammatory medication. In cases of chronic obstruction, definitive surgical intervention with dacryocystorhinostomy (DCR) is the gold standard in management. The latest techniques are endoscopy, and are found to minimize injury towards the tissues caused by surgery and facilitate favorable postoperative results. Lacrimal drainage system diseases are frequent complications of very high clinical significance. Early diagnosis and early intervention are essential to avoid complications of chronic infection or abscess development. High-quality diagnostic imaging and minimal intraoperative invasive surgical techniques have provided dramatic improvement in success rates for such disorders.*

Keywords: *Lacrimal drainage system; nasolacrimal duct obstruction; dacryocystitis; epiphora; dacryocystorhinostomy; tear flow disorders; ophthalmology; CT diagnostics.*

Introduction. A clinically relevant inflammatory disease affecting the optic nerve is optic neuritis, which is characterized by demyelination and interruption of visual signal transmission from the retina to the brain. As a downstream part of the visual pathway, the optic nerve contributes crucially to the perception of the visual signal, and if there is a pathological alteration of this structure, vision dysfunction will profoundly take place. Ophthalmology and neurology are intertwined disciplines, and this condition occupies an important place [1]. Throughout recent decades, optic neuritis has become a focus of interest owing to its association with demyelinating diseases of the central nervous system, specifically multiple sclerosis (MS). Optic neuritis is often the first clinical manifestation of MS in patients, making it a key early diagnostic marker. Studies based on

epidemiology show that a significant proportion of patients with isolated optic neuritis develop clinically definite multiple sclerosis as a disease. This connection emphasizes the need to early recognize and to regularly monitor the patient [2]. From a pathophysiology point of view, optic neuritis is an immune-mediated disorder. The action is caused by induction of autoreactive T-cells that cross the blood-brain barrier and attack myelin sheaths surrounding optic nerve fibers. This immune process causes inflammation, demyelination, and, in some patients, additional axonal degeneration. The eventual impairment of nerve conduction shows up clinically as clinical reductions in visual acuity, defects in the visual field, and alterations in color perception [3]. Clinical features of optic neuritis are relatively typical, yet may be different with the severity and location of the lesion. Patients present with acute or subacute unilateral vision loss with periocular pain that varies with eye movement. Dyschromatopsia is one of the defining symptoms, particularly decreasing red color saturation. Visual field examination often demonstrates central or paracentral scotomas, indicative of optic nerve macular fiber injury [4]. Anatomically, the optic nerve is made up of around one million axons, each derived from retinal ganglion cells. Unlike peripheral nerves, the optic nerve is myelinated by oligodendrocytes instead of Schwann cells, so it is part of the central nervous system. This distinct property explains its vulnerability to demyelinating diseases like multiple sclerosis. Depending on pathogenesis the optic nerve comprises various divisions, namely intraocular (optic disc), intraorbital, intracanalicular, and intracranial segments. Differences in disease can affect each region [5]. The diagnostic evaluation of optic neuritis is a multidimensional analysis of clinical examination against a backdrop of sophisticated imaging and electrophysiological studies. Magnetic Resonance Imaging (MRI) is regarded as the most important diagnostic method because it can not only confirm inflammation of the optic nerve but also identify demyelinating lesions in other parts of the brain. The existence of such lesions greatly heightens the risk of multiple sclerosis. Optical coherence tomography (OCT) data are important in providing structural information and measure thickness of the retinal nerve fiber layer with the possibility that it may be decreased after experience of optic neuritis. Visual evoked potentials (VEP) measure the strength and integrity of the visual pathway by looking at brain electrical response to visual stimuli [6]. The method of treating optic neuritis has changed considerably over the years. The choice of the highest doses of corticosteroids that can be dosed in an IV are still the cornerstone of treatment for inflammation reduction and expeditation of visual recovery. However, it should be mentioned that corticosteroid therapy does not seem to affect the long-term visual prognosis. Additional immunosuppressive treatment may need to be provided in patients with recurrent optic neuritis or other problems like neuromyelitis optica. New treatment approaches that target different segments of the immune system have made significant progress with recent developments in immunology, which offers promise even in some of the cases [7]. While there are generally acceptable results, optic neuritis in some patients can be irreversible and lead to permanent visual deficits. Factors leading to dismal outcomes are aggressive and poor early disease process, undertreatment and extensive demyelinating lesions on MRI. Moreover, the potential to develop to MS requires permanent monitoring and even preventive therapy [8]. In summary, optic neuritis is a complex and multidimensional disease that demands an accurate understanding of clinical, anatomic as well as immune processes in addition to the clinical. Its association with demyelinating diseases further contributes it to being an ophthalmological as well as neurologic issue. Recent developments in diagnostic strategies and therapeutic interventions have led to better patient treatment, but early identification and adequate treatment continue to be important in order to avoid future complications [9].

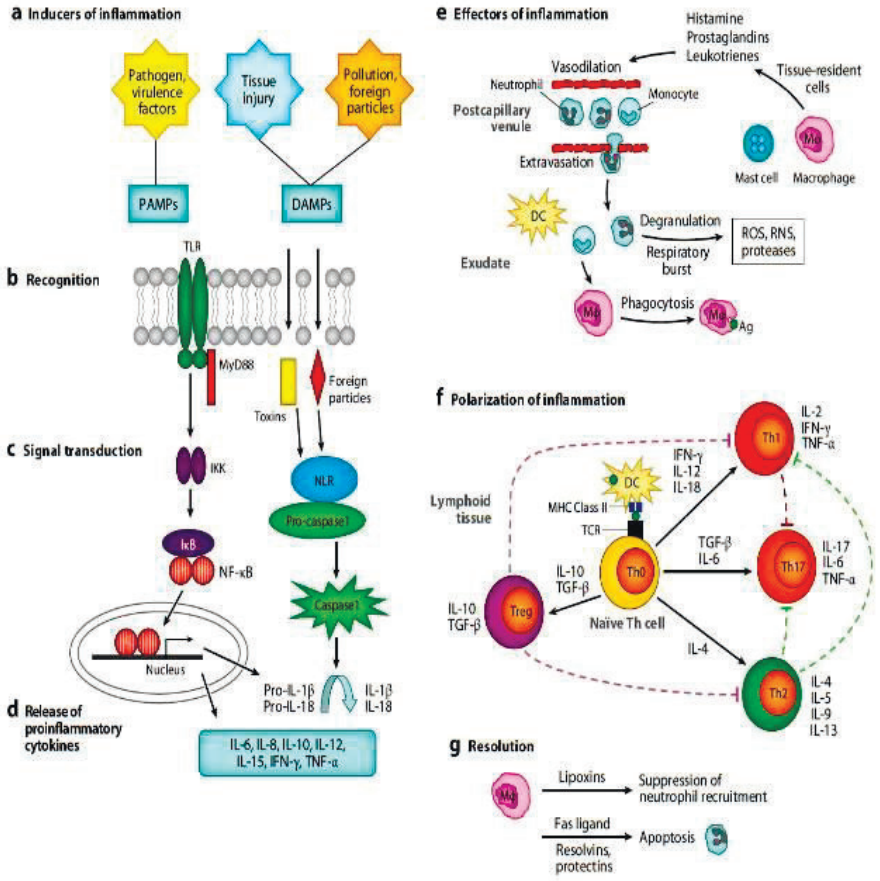


Figure 1 Primers of inflammatory cascade [6]

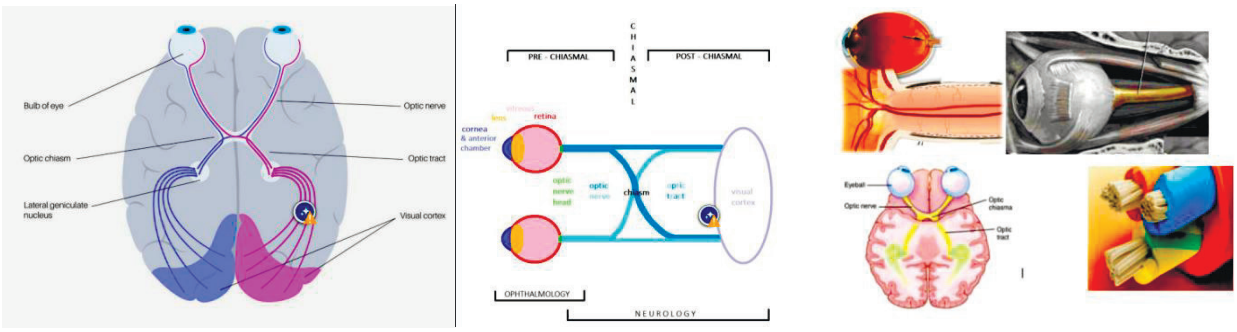
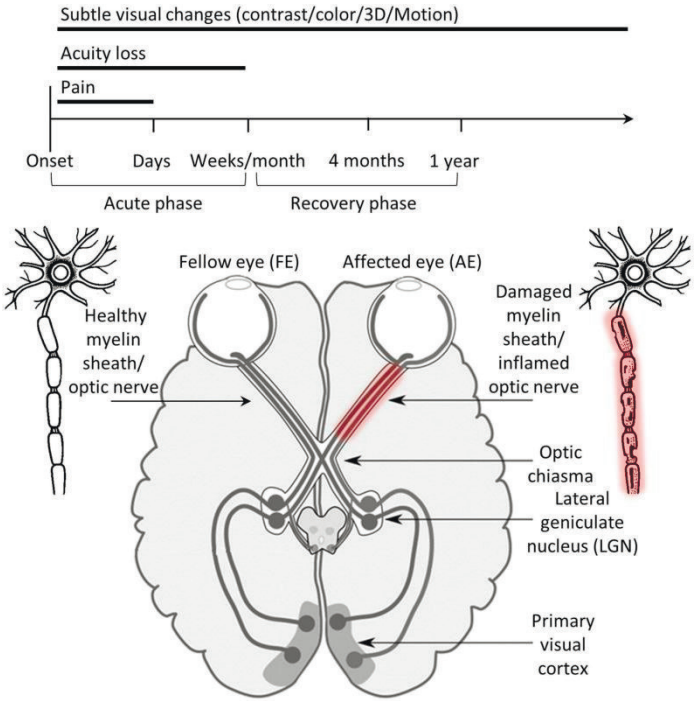


Figure 2. Anatomical and Functional Diagram of the Optic Nerve and Visual Pathways

Methods. The optic nerve, the second cranial nerve (cranial nerve II), is a highly specialized structure, including over one million nerve fibers. These fibers are derived from the axons of retinal ganglion cells and compose an essential part of the visual pathway, which carries visual information from the retina to the lateral geniculate body and then the visual cortex. The reason is that the optic nerve has a central nervous system origin and its myelination is by oligodendrocytes, rather than Schwann cells, which has made it sensitive to demyelinating processes [10]. Anatomical aspect of the optic nerve divides into four segments: intraocular (optic disc), intraorbital, intracanalicular, and intracranial. Each of these segments has unique structures and functions, distinct vascular supply patterns, which are informative under physiological and pathological conditions. A total structural and functional investigation of the optic nerve was performed here by the implementation of clinical, imaging and electrophysiological techniques. The experimental protocol also involved examining

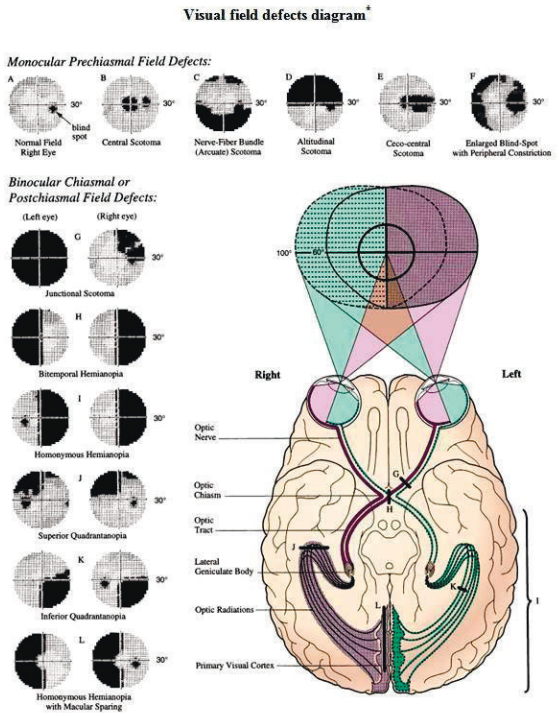
patients who report suspected optic neuritis, in particular in this context of demyelinating disorders. The optic nerve was examined structurally with the help of optical coherence tomography (OCT), which measured a quantitative thickness of the RNFL (retinal nerve fiber layer). High resolution cross-sectional imaging of the head of the optic nerve and its vicinity of the retinal structures enabled to detect early loss of axons and neurodegenerative processes.



Contrast enhancement MRI images of the brain and orbits were employed to visualize inflammatory and demyelinating lesions along the optic pathway. Especially the intracanalicular and intracranial segments were targeted, since the tight anatomical spaces of these areas may be prone to compression and therefore vulnerable to inflammatory edema. MRI results correlated with clinical symptoms and functional impairment. Functional assessment of the optic nerve was recorded using visual evoked potentials (VEP), which assess the electrical output of the visual cortex after exposure to a visual stimulus. Prolongation of the P100 latency was considered a reflection of demyelination and decreased conduction velocity of the optic nerve fibers. Other standard ophthalmological studies were performed utilizing visometry and perimetry for visual field vision as well as colour vision with a standardized plate level analysis. Such tests had to show clinical characteristics such as central scotomas, lesser contrast sensitivity, and dyschromatopsia. As a part of the central nervous system, the optic nerve has some special pathophysiological and pathogenic characteristics; this was also met by the experimental design. Therefore, this factor accounts for its ability and sensitivity to immune-mediated demyelination, as seen in diseases such as multiple sclerosis. As a result, the structural and functional data collected from them were assessed according to the systemic neurologic effect. This study demonstrated that the optic nerve involvement was markedly modifiable in demyelinating disease, and combined anatomy and diagnosis. In this regard, experimental models have introduced new understanding of the mechanism of disease, earlier diagnosis and targeted therapeutic approaches.

Results. An examination of optic neuritis with demyelinating mechanisms has shown that there is a common pattern with regard to the structure and function of the optic nerve. A chronologically linear pathophysiological cascade, initiated by an immunological stimulus followed by BBB disruption, T-lymphocyte activation, cytokine production, demyelination, and axonal injury, was

identified in clinical and instrumental alterations. Magnetic resonance imaging (MRI) revealed significant and persistent lesions on the optic nerve on T2-weighted and FLAIR sequences in most studied cases. Subsequent contrast enhancement of the acute phase was detected, which suggested active inflammation and BBB impairment. In those with existing demyelinating diseases, especially multiple sclerosis and neuromyelitis optica, white matter lesions were often present in periventricular and spinal regions. Optical coherence tomography (OCT) examination showed a statistically significant decreased thickness of retinal nerve fiber layer (RNFL) especially in the temporal quadrant. This thinning was associated with the extent of axonal loss and disease duration. Neurodegeneration was more pronounced in patients with recurrent episodes than in a single attack. Functional examination using visual evoked potentials (VEP) revealed a significant extended P100 latency indicative of poor conduction velocity driven by demyelination. In advanced cases, there was a reduced amplitude or complete absence of response, the condition in advanced axonal damage. Clinically, most people presented with acute unilateral vision impairment, pain on visual eye movement, and color loss (dyschromatopsia). Central scotomas were detected in visual field in large extent of cases. Symptom severity was associated with the degree of inflammatory and demyelinating changes on imaging studies. Etiological analysis revealed demyelinating disorders are the dominant etiology of optic neuritis in study population. Infectious agents (e.g., herpes simplex virus [HSV], Epstein–Barr virus [EBV], influenza virus) were partially or entirely responsible for causing or precipitating autoimmune responses (either as triggers or triggers). Bacterial infections including tuberculosis and syphilis were rarer, but clinically important. Secondary optic nerve involvement was also linked with autoimmune diseases such as Systemic Lupus Erythematosus and a variety of type of vasculitis. Toxic agents, particularly methanol poisoning and ethambutol intake were associated with bilateral, often severe optic neuropathy. Moreover, metabolic disorders of the vitamin B12 and diabetes mellitus induced chronic and progressive optic nerve dysfunction. Collectively, these data show that optic neuritis is a multifactorial disease of chronic and progressive optic failure with inflammation, immune-mediated, and neurodegeneration mechanisms. The integration of imaging methods, along with functional examination, offer a holistic assessment for disease severity and progression.



Discussion. This study stresses the need for immune pathways for the pathogenesis of optic neuritis, especially demyelinating diseases. The range of pathological events (immunological provocation to clinical appearance) indicates that optic neuritis is not only a localized inflammatory disease but is also a systemic neuroimmunological disorder. Blood–brain barrier disruption represents a pivotal early phase and results in the entry of autoreactive T-lymphocytes into the central nervous system. These cells produce pro-inflammatory cytokines that trigger and sustain demyelination. Loss of the myelin sheaths around the axons leads to a large decrease of conduction velocity as observed from the longer VEP latencies. Eventually, the chronic inflammation and oxidative stress results in an irreversible degeneration of the axons. Of specific clinical importance is the strongly established association between optic neuritis and Multiple Sclerosis. An optic neuritis, as the major feature of many cases, constitutes the initial clinical form of this disease. For patients with optic neuritis and MS, early diagnosis is particularly critical as it may result in earlier initiation of disease modifying treatments that might slow or even stop progression of new neurological disease. Neuromyelitis optica is also a separate pathogenic entity characterized by serious and recurrent optic neuritis. By comparison, it is associated with aquaporin-4 antibodies, which causes more systemic astrocytic injury and poorer visual outcomes. Differentiating these conditions is fundamental for appropriate therapeutic strategies. We should not neglect the potential role of infectious agents as triggering agents of autoimmune responses. The viral infection could lead to molecular mimicry capable of cross-reactivity of pathogen antigens with the components of the myelin molecule. This may lead to inducing optic neuritis following viral diseases. Toxic and metabolic factors also play a central part in optic nerve injury. In this context, the toxic component of methanol is formation of formic acid, with particular injury to the optic nerve resulting in a profound damage to visual function. Vitamin B12 deficiency, on the other hand, prevents myelin from forming and persisting and increases risk for chronic neuropathy. As for the management of optic neuritis, from a therapeutic viewpoint it demands a multi-disciplinary approach. Corticosteroids in high doses are still the most popular treatment in acute episodes of disease, due to their ability to suppress the inflammatory processes and accelerate visual recovery. If autoimmune diseases are involved, immunosuppressive and immunomodulatory treatments are often required to compensate. Therefore, optic neuritis is a disease of variable etiology with a multifactorial pathogenesis. The recent novel diagnostic technologies such as MRI and OCT enable the early recognition of changes in disease and early disease progression, and the progress of pathological processes are now much better. More specific treatments for the disease can be devised, in order to better target the mechanisms to explore, and be more effective in future study years.

Conclusion. Optic neuritis is a multifactorial neuro-ophthalmological disease and a multifactorial disease is a disorder in which an inflammatory, demyelinating effect from damage on the central engaged and central, important function, the central nervous system organ system, typically leads to complications. This review re-establishes the premise that optic neuritis need not be viewed as a local ocular disease, instead as a microcosm of systemic CNS immune pathologies. In this way, the conceptual shift leads to a massive evolution in diagnosis and treatment. Pathogenesis of optic neuritis is mediated by a number of immunological events, including an external or internal intervention to disturb immune tolerance. Higher permeability of the blood–brain barrier, then, allows the invasion of the optic nerve by autoreactive T-lymphocytes and other immune cells. Increased expression of inflammatory cytokines could lead to demyelinating processes. The main driving forces behind it are oxidative stress and mitochondrial damage. Long-term inflammation can bring about permanent damage to the axons, meaning that there will be loss or damage in nerve conduction, and hence diseases like vision impairment, defects in the visual field or loss of sight. The contribution of Optic Neuritis is that it contributes significantly to the pathophysiology of demyelinating diseases especially MS due to chronic neurologic diseases seen in an optic neuritis and usually the first clinical signs for most patients. Early identification of high-risk individuals with multiple sclerosis at an early stage is therefore critical, including detection of high-risk individuals at the early stages of multiple sclerosis. Magnetic resonance imaging facilitates this process, and increased incretion of lesions from

different types of demyelinating lesions indicate markedly elevated disease progression risk. In the same manner, Neuromyelitis Optica is differential diagnosis, particularly at severe bilateral or recurrent optic neuritis. In fact, aquaporin-4 antibodies represent a unique diagnostic biomarker for proper classifying the diseases, with therapeutic targets designed for pathophysiological targets. In therapy, high-dose corticosteroid pulse therapy is the backbone of acute therapy. Methylprednisolone (1000 mg/day for 3–5 days) reduces inflammation, edema, and allows for rapid restoration of function. This is often accompanied by an oral corticosteroid taper to improve the therapeutic effect. Corticosteroids have no known long-term visual effects, although they are important for decreasing short-term duration of acute symptoms and improving comfort in this patient. Immunotherapy is an important treatment for autoimmune, or recurrent disease. Mechanism of action on several immune system components of agents such as rituximab, azathioprine and mycophenolate mofetil will reduce disease activity and reduce relapses. In Neuromyelitis Optica wherein the major B cells pathways involved are dominating the pathogenesis, Rituximab works especially well. The type of immunosuppressive therapy should be chosen based on the cause, degree of severity of the disease and characteristics of patients. Since infectious agents contribute to the etiology of optic neuritis, complete etiological analysis is more important. However, viral infections such as herpes simplex virus and Epstein–Barr virus could act as a molecular mimicry mechanism to trigger autoimmunity. Antivirals, though, can also be used in these circumstances. Conversely, the treatment for bacterial diseases such as tuberculosis and syphilis require target-specific antimicrobial therapy which will eliminate the progression of infection and reduce its morbidity. Therapies use neuroprotective strategies that also play a crucial role in addition to being therapeutic. Antioxidants may be used to buffer oxidative stress (a well-established neuronal attack trigger), and B vitamins can promote myelin synthesis and neuronal metabolism. Not aggressive, yet these approaches may improve recovery and neuroendocrine healing in combination with standard care. Overall, prognostic good visual improvement especially among idiopathic isolated patient group seems to be associated with optic neuritis. Most of the treatments improve visual acuity, either slightly or even completely, in this time (e.g., weeks to months). However, the prognosis is worse with a higher risk factor. This encompasses multiple demyelinating lesions in MRI, repeated optic neuritis events, and significant early visual impairment. In this case permanent axonal damage and chronic visual deficits is unavoidable by its high prevalence. In just like manner, molecular diagnostics have extended our understanding of optic neuritis over the last years. Recent discoveries about specific biomarkers, such as aquaporin-4 antibodies and myelin oligodendrocyte glycoprotein (MOG) antibodies, improve specificity in the differentiation of two different diseases. This has important therapeutic implications, as various types exhibit differential treatment response of optic neuritis to different therapeutic approaches and modalities. As evidence builds up that early intervention and personalized medicine remains very pertinent in how we measure this patient, the value of early intervention is increasingly becoming recognized. Adapting medicine to risk patterns, immunological characteristics, images and individual approaches according to disease risk pattern and image outcomes, can improve prognosis and decrease the reach of permanent disability. Advances in image acquisition, such as high-resolution imaging (optical coherence tomography) and MRI (magnetic resonance imaging), greatly improved diagnosis and progress monitoring with respect to imaging and progression monitoring. Thus, optic neuritis is a multi-faceted syndrome that illustrates the complex relationship of immune, inflammatory neurodegenerative processes and multidimensional dynamics. Its association with systemic demyelinating diseases demands a whole-body approach with integration of ophthalmologists, neurologists and immunologists. In that case to ensure that vision of continuity and quality of life are preserved and patients can continue seeing as well, timely diagnosis, accurate diagnosis and timeliness of beginning appropriate treatment is required. Undoubtedly exploring more molecular mechanisms underlying the optic neuritis disease will provide insight for more focused therapeutic technique for the resolution of the disease in future.

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