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Optic Neuritis: A Model for the Immuno-pathogenesis of Central Nervous System Inflammatory Demyelinating Diseases

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Abstract

Evidence for the tenuous regulation between the immune system and central nervous system (CNS) can be found with examples of interaction between these organ systems gone awry. Multiple sclerosis (MS) is the prototypical inflammatory disease of the CNS and is characterized by widely distributed inflammatory demyelinating plaques that can involve the brain, spinal cord and/or optic nerves. Optic neuritis (ON), inflammatory injury of the optic nerve that frequently occurs in patients with MS, has been the focus of intense study in part given the readily accessible nature of clinical outcome measures. Exploring the clinical and pathological features of ON in relation to other inflammatory demyelinating conditions of the CNS, namely MS and neuromyelitis optica, provides an opportunity to glean common and distinct mechanisms of disease. Emerging data from clinical studies along with various animal models involving ON implicate innate and adaptive immune responses directed at glial targets, including myelin oligodendrocyte glycoprotein and aquaporin 4. Resolution of inflammation in ON is commonly observed both clinically and experimentally, but persistent nerve injury is also one emerging hallmark of ON. One hypothesis seeking evaluation is that, in comparison to other sites targeted in MS, the optic nerve is a highly specialized target within the CNS predisposing to unique immunologic processes that generate ON. Overall, ON serves as a highly relevant entity for understanding the pathogenesis of other CNS demyelinating conditions, most notably MS.

Keywords

Demyelination; multiple sclerosis; neuro-immunology; optic neuritis; pathogenesis

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

INTRODUCTION

From a clinical and pathological perspective, multiple sclerosis (MS) is often considered the archetypal inflammatory disease of the central nervous system (CNS). To date, the etiology and pathogenesis of MS remain elusive. A trend in the classification of inflammatory demyelinating diseases of the CNS has operated on the premise that a considerable overlap exists between MS and other conditions such as neuromyelitis optica (NMO) and acute disseminated encephalomyelitis (ADEM) [1]. Optic neuritis (ON), inflammatory demyelination of the optic nerve, can be a clinical manifestation of each of these diseases. ON is a common component of MS and in fact is frequently the first presentation of disease, termed clinically isolated syndrome (CIS) prior to development of any other inflammatory episodes. ON is an appealing system for studying the immuno-pathogenesis of CNS demyelinating diseases for several reasons. First, structural and functional changes in the visual system occur in the majority of MS patients, often at the earliest stage of disease [2]. Second, ON is a highly defined and discrete clinical entity [3]. Third, the structure and function of the visual system can be quantified and analyzed *via* a number of different methods, including structural, psychophysical and electrophysiologic testing [4]. Fourth, the immune mechanisms of inflammatory demyelination of the optic nerve are readily explored using a variety of experimental animal models.

The objective of this review is to briefly highlight some of the current data reflecting the immuno-pathogenesis of ON as it pertains to MS. Our own interest in this topic stems from work on the animal model experimental autoimmune encephalomyelitis (EAE) that has been used to isolate specific anatomic pathways of inflammatory demyelinating disease, including the optic nerves, to enable experimental traction for questions relating to the immunopathogenesis of MS. Interestingly, there is mounting evidence that ON may exhibit features distinct from MS that are important considerations for the basis of immune targeting of the CNS. Our current studies, as with many highlighted in this review, take advantage of the utility of isolating the anterior visual system for examining the response and mechanisms involved in CNS demyelination. In this vein, exploring the unique features of ON along with the commonalities with MS offers a valuable opportunity to identify critical features involved in the pathogenesis of CNS demyelinating diseases.

CLINICAL AND PATHOLOGICAL FEATURES OF ON

Patients with ON typically present with central vision loss that is often accompanied by pain with eye movement and a relative afferent pupillary defect on examination [3]. A variety of patterns of vision loss can be observed, however, patients may report associated phosphenes and/or Uhthoff's phenomenon [5]. Usually only one eye is affected, although in one modest study simultaneous bilateral involvement was seen in 6% of a cohort of ON patients [6]. Improvement over several weeks is a hallmark of the disease, and ultimate recovery of vision is expected. 94% of ON patients demonstrated recovery to 20/40 or better at five years after onset and over two-thirds of patients exhibited full recovery to 20/20 acuity 15 years after ON [7, 8]. Two-thirds of patients will have retrobulbar disease, which is not associated with disc edema. When disc swelling is present, it is typically mild and not associated with hemorrhages. It should be noted that much of our current understanding of

ON is derived from a seminal study on the natural history of ON, the Optic Neuritis Treatment Trial (ONTT) [9] and current reviews on the clinical nature of ON are abundant [10–12].

Multiple outcome measures are successfully employed to identify and quantify the features of visual dysfunction associated with ON. Low contrast letter acuity testing is highly sensitive to visual dysfunction in MS [13], and other measures of visual function are routinely employed to determine the clinical effect of ON, including high contrast letter acuity, color vision, and visual field testing. Because the optic nerve head is the only CNS tissue accessible for direct inspection, ophthalmoscopy and optical coherence tomography (OCT) are especially valuable for the assessment of injury. OCT has been used to expose the extent of anterior visual pathway involvement in MS (see below). Thus, structural injury within the optic nerve and anterior visual pathway is readily assessed by highly accessible outcome measures.

Characterization of the immuno-pathology expressly of ON has not been widely recounted, as post-mortem analyses of optic nerves are not typically generated, particularly in the acute stage of disease. Presumably the same features of inflammatory demyelination characterizing active MS plaques [14] are shared with ON, in which perivascular infiltrates are the source for inflammatory cells targeting myelin within the parenchyma of the nerve. Some unique features of the anterior visual pathway are important to consider in deciphering the immune mechanisms of inflammatory injury to the optic nerve. The lamina cribrosa, a fibrous mesh composed of collagen beams, serves as a physical barrier between both the retina and scleral wall of the globe and the optic nerve. Nerve fibers within the lamina cribrosa are unmyelinated, and oligodendrocytes are found only posterior to this divide in humans. This physical distinction between the retina and optic nerve may indeed be a key for posterior compartmentalization of inflammation to the optic nerve during ON, as retinal inflammation is not typical of ON [15]. Experimentally, this concept was tested using New Zealand rabbits. In this strain of rabbit, the axons of the optic nerve are myelinated over a long distance into the retina. Following immunization with cow myelin and adjuvant, rabbits received an intravitreal injection of myelin basic protein (MBP). Extensive inflammatory lesions were observed in the myelinated fibers within the retina [16]. Further historic studies provide evidence that inflammation in ON is restricted to the nerve proper. Acute optic nerve lesions were characterized in great detail using a monkey model of MS during fulminant disease [17, 18]. Optic disc edema and inflammation of tissue surrounding the nerve, both features of ON in humans, were consistently observed. However, inflammatory infiltrates were excluded from the optic nerve head or the retina adjacent to the lamina cribrosa. These studies support the concept that acute inflammatory destruction of myelin in human ON is anatomically compartmentalized.

The neuroanatomy of the eye and optic nerve deserves some consideration when addressing the elusive basis for restriction of inflammation to the optic nerves in ON. The immunologically specialized nature of the CNS is a function of its unique lymphatic drainage and antigen presenting cell (APC) populations, as well as the presence of the blood-brain barrier (BBB) [19, 20]. Differential access by peripheral immune cells to the optic nerve relative to the remainder of the CNS is unlikely. For example, the subarachnoid

space around the optic nerve is in communication with the intracranial subarachnoid space [21]. In addition, the vasculature of the optic nerve share the same blood-brain barrier features that exist throughout the rest of the CNS [22, 23]. Overall, despite its unique anatomy, the optic nerve is likely targeted in similar fashion as other brain and spinal cord tissue in MS.

While reports on acute optic nerve lesions are scant, chronic ON lesions in humans have been examined in more detail. The pathology of established ON lesions greatly resembles chronic inactive MS plaques [24, 25]. In a systematic study by Jennings and Carroll [25] eight optic nerves from four patients with MS were analyzed, encompassing 22 non-contiguous ON segments. Each lesion exhibited features of long-standing injury, with the defining characteristic being astrogliosis. Additionally, quantification of cellular subsets within the optic nerve revealed reduced numbers of microglia, oligodendrocytes and oligodendrocyte precursor cells. Some cases, however, were noted to have more features of remyelination than others. As with MS [26], injury and loss of axons that comprise the optic nerve are also prominent features of chronic ON [24]. The characterization of inflammatory damage in ON is highly informative and serves as the basis for the investigation into mechanisms of immune-mediated damage to myelin in the optic nerve.

ASSOCIATION OF ON WITH MS AND NMO

Isolated ON often heralds the clinical onset of a relapsing-remitting course typical of MS, and has been referred to as a *forme fruste* of MS [27]. It is estimated that from 20–40% of MS patients will initially present with a clinical episode of ON and that up to 80% of patients with MS experience ON at some point during the course of their illness [10, 28]. Interestingly, studies employing OCT have demonstrated that companion eyes show evidence of axonal loss [29]. These results confirm the original observation noted by the ONTT in which abnormalities in asymptomatic fellow eyes were noted, particularly on perimetry [27]. Thus it appears that ON is a very frequent event in MS, in part due to the fact that the fraction of MS patients reporting clinical ON is an underestimate of patients that have actual optic nerve injury.

NMO is an inflammatory demyelinating disease preferentially affecting the optic nerves and spinal cord. It is important to note that other regions of the CNS can be affected in NMO, including midline cerebral structures and the brainstem [30]. A more common feature of ON with NMO is the bilateral nature of optic nerve involvement. Furthermore, whereas the majority of patients with ON in MS will recover a substantial fraction of vision, patients experiencing ON in NMO are more likely to experience persistent deficits with greater disability [31]. While an inclusion of ON was historically obligatory for the diagnosis of NMO, recent revisions to the diagnostic criteria, and expansion of NMO into a spectrum of disorders, has been proposed [32]. This has been largely based on the identification of antibodies targeting aquaporin 4 (AQP4) that are associated with NMO [33]. In addition to re-defining the clinical nature of NMO, identification of anti-AQP4 antibodies has facilitated investigation into the immunopathophysiology of inflammatory demyelinating diseases of the CNS.

The pathophysiologic implications of anti-AQP4 antibodies to ON and MS are tremendous. Theories have naturally arisen in support of the concept that NMO – and by extension ON – is a humoral disease. Detailed pathological assessment supports a pathogenic role of humoral immunity in NMO, including substantial deposition of complement in active lesions of the spinal cord [34]. Further, a recent case-control study revealed that CSF levels of the B cell development and survival factors BAFF and APRIL, as measured by ELISA, are higher in NMO than in MS patients or controls [35], suggestive of aberrant B cell physiology. Peripherally circulating anti-AQP4 levels were associated with worsened clinical and radiologic disease activity in NMO patients [36, 37], suggesting the production of antibodies directly results in CNS damage. The humoral component of NMO pathogenesis is bolstered by the observation that a sizeable fraction of anti-AQP4 negative NMO patients harbor antibodies to the myelin protein, myelin oligodendrocyte glycoprotein (MOG) [38, 39]. Hence, at least two autoantibodies are associated with CNS inflammatory demyelination that frequently targets the optic nerves.

However, selective targeting of the optic nerves by antibodies that recognize proteins widely distributed throughout the CNS has not been fully explained. It is conceivable that antibody targeting of the optic nerves is a function of the distribution of target antigens. This hypothesis is supported by the elevated expression of AQP4 and MOG target antigens in the optic nerves [40]. Because AQP4 is concentrated at astrocyte end-foot process, it is possible that the distribution of astrocytes within the optic nerve, particularly in proximity to the lamina cribrosa, predisposes to disruption of metabolic function after anti-AQP4 antibodies disturb their metabolic and barrier qualities near the nerve head [41]. Because astrocytes are arranged throughout the nerve extensively (one report noting astrocytes compose half of the tissue volume of optic nerves [42]) and astrocyte processes extend throughout the optic nerve, antibodies against AQP4 are likely to impact the entire nerve and not just the anterior portion [42]. In terms of MOG, frequent mention is found in the literature that it serves as a prime target for antibodies in spite of its relatively low abundance in myelin due to its location on the outer surfaces of the myelin sheath [43]. Overall, the optic nerve may be particularly targeted by the humoral autoimmune response in NMO based on its distribution of cellular and molecular targets.

The cellular immune contribution to the pathogenesis of NMO has not been overlooked. For example, one report found that on average, 40% of T cells exhibited reactivity towards an AQP4 peptide in NMO patients both sero-positive as well as sero-negative for anti-AQP4 antibodies [44]. Additionally, Zamvil and colleagues recently found that T cells from NMO patients respond to the second extracellular domain of AQP4. Although healthy controls also are capable of exhibiting this response, fine mapping the epitope targeted by T cells revealed reactivity to peptide residues 63–76 of AQP4. Interestingly, cross-reactivity between T cells recognizing this region of AQP4 with the adenosine triphosphate-binding cassette transporter permease of Clostridium species *C. perfringens* was detected. This important observation implies that T cell responses in NMO could be generated by molecular mimicry. Furthermore, T cells reactive to AQP4 from patients with NMO favor Th17 polarization [45]. The elevation in IL-17-producing T cells in NMO patients may provide a mechanistic link to the production of auto-antibodies given that Th17 cells are highly capable of eliciting

antibody secretion from naïve B cells [46]. Thus, T cells, long considered central to the pathogenesis of MS, are likely to also be instrumental in the pathogenesis of NMO.

ANIMAL MODELS OF ON

Animal models have long been utilized to explore the pathogenesis of MS and related diseases, and several systems designed to specifically explore ON have been reported. Perhaps unheeded is the fact that ON is typically a prominent feature of EAE, an experimental model frequently employed to explore the immunopathogenesis of MS. In susceptible animals, EAE is used to mimic certain aspects of autoinflammatory demyelination that is common to both ON and MS [47]. EAE is readily induced in certain mouse and rat strains by immunization with CNS proteins or peptides along with suitable adjuvants [48]. This instigates inflammatory demyelination that in many models typically targets the spinal cord, resulting in ascending paralysis. Common CNS antigens used as immunogens include MOG, MBP, proteolipid protein (PLP), and various peptide epitopes derived from these proteins.

Historically, Rao and colleagues were amongst the first to focus on the optic nerve in EAE, using a guinea pig model [49]. These studies were in agreement with subsequent reports on EAE induced in guinea pigs [50] and by immunization of SJL mice with PLP [51] which defined basic properties of acute ON, including neutrophil and monocyte infiltration in submeningeal and intraparenchymal space. Several important features of inflammatory demyelination of the optic nerve can be elucidated from murine EAE. For example, immunizing SJL mice with residues 139–151 of PLP results in a relapsing-remitting EAE with severe inflammation of the optic nerve and retinal ganglion cell (RGC) degeneration [52]. This particular EAE model is useful for studying the kinetics of ON and has been used to demonstrate that inflammation occurs prior to neuronal loss, offering the potential to characterize the immune cell and neuronal processes that drive retinal ganglion cell (RGC) loss in ON. Recovery of inflammation within the optic nerves is a common occurrence with several models of EAE, including ON induced by immunization of SJL mice with PLP. However, immunization of C57BL/6 mice with MOG or the immunodominant T cell epitope within MOG, residues 35–55 ($MOG_{35–55}$) typically involves chronic, persistent inflammation, although the level of inflammation may be reduced at chronic stages [53]. Notably, a recent report has suggested that the amount of antigen used for EAE induction leads to different disease outcomes with regards to day of onset, intensity of inflammation, number of infiltrates, and amount of demyelination on the optic nerve [54]. The findings of this report are highly relevant to the utility of autoimmune models of ON, but first compel confirmation by additional studies.

Spontaneous CNS demyelination has also been generated in mice with the SJL genetic background using T cell receptor (TCR) transgenic technology. These mice, with T cells specific for residues 92–106 of MOG, develop spontaneous relapsing-remitting lesions within the CNS that are spatially diverse and can involve the optic nerves [55]. The expansion of MOG-specific B cells in these mice is notable given the potentially important contribution of antibodies to CNS demyelination. A different transgenic approach was used to demonstrate that CD8 T cells are also capable of eliciting inflammatory demyelination

within the optic nerves. Mice on a BALB/c background in which the influenza hemagglutinin protein is expressed in cells expressing MOG were crossed to a TCR transgenic mouse in which CD8 T cells are highly specific for hemagglutinin [56]. Without transfer of pre-activated hemagglutinin-specific T cells, injury to the CNS did not develop, indicating the sequestered nature of CNS myelin antigens that contributes to 'ignorance' of potential myelin targets. However, optic nerve inflammation was observed as early as five days following transfer of stimulated T cells; in fact, optic nerve inflammation preceded inflammation within the spinal cord. The susceptibility of the optic nerve and timing of damage relative to the remainder of the CNS are provocative. Notably, approximately eight weeks following delivery of ON-inducing CD8 T cells only mild diffuse T cell infiltration was observed alongside features suggestive of remyelination, emphasizing the tendency for ON recovery in various animal models.

A remarkable advance toward understanding the immuno-pathogenesis of ON was achieved with the creation of a transgenic mouse on the C57BL/6 background that spontaneously develops inflammation within the optic nerves. Kuchroo and colleagues engineered a mouse on the C57BL/6 background, termed the 2D2 mouse, that has transgenic T cell receptors capable of recognizing $MOG_{35–55}$ presented on MHCII molecules [40]. Approximately 30% of these animals spontaneously develop isolated ON. Immunization with $MOG_{35–55}$ in complete Freund's adjuvant (CFA) and two subsequent doses of pertussis toxin induces severe EAE concurrent with ON in 2D2 mice. Conveniently, immunizing these transgenic animals with sub-optimal levels of MOG peptide in CFA consistently stimulates inflammation and damage to optic nerves with much higher incidence without signs of EAE. An extensive assessment of the 2D2 mouse by Talla, *et al.* verified the isolated nature of ON and normal features of spinal cord [57]. This system is exceedingly useful for studying ON pathology and disease progression separate from, or simultaneous with, EAE. Again notable is the recovery from ON that is observed in 2D2 mice (Wu, unpublished observation). Interestingly, T cells from 2D2 mice don't recognize only $MOG_{35–55}$, as spontaneous EAE can develop in the absence of MOG expression [58] and T cells from 2D2 mice have been shown to recognize a neurofilament contained within axons [59]. To date, there is no satisfactory answer regarding the preferential targeting of the optic nerve in 2D2 mice. Kuchroo and colleagues, in their original description of the 2D2 mouse, postulated that the specificity of inflammatory demyelination is related to the relatively greater abundance of MOG within the optic nerve compared with the rest of the CNS. In fact, they assayed protein expression of MOG and PLP within the optic nerve and spinal cord and showed that the former has a significantly elevated quantity per weight in the optic nerves compared to the spinal cord, whereas there was equal expression in both tissues for the latter [40]. Our own work has capitalized on the spontaneous nature of ON in the 2D2 mouse. We examined the role for different APCs in the generation of spontaneous inflammatory demyelination within the CNS. We found that in spite of being sufficient for prototypical EAE, dendritic cells (DCs) were not capable of independently driving spontaneous ON mediated by 2D2 cells [60]. Overall, the potential to examine and manipulate inflammatory demyelination isolated to the optic nerves in transgenic mouse models is a highly valuable resource for neuroimmunology research.

Reports of an ‘optico-spinal’ EAE model for NMO were received with much enthusiasm in 2006 when two groups independently generated double transgenic mice by crossing 2D2 mice with IgH^{MOG} mice that express a transgene for the immunoglobulin heavy chain specific for MOG [61, 62]. IgH^{MOG} mice express a large proportion of MOG-specific B cells (approximately up to a third). Severe spontaneous inflammatory demyelination of the optic nerves and spinal cord develops in the 2D2×IgH^{MOG} mice on a C57BL/6 background with high frequency. Immunoglobulin class-switching is observed in this model, indicating that cognate B and T lymphocyte interactions may coordinate spontaneous lymphocyte auto-reactivity and reflect a key humoral aspect observed in NMO. Additionally, one group observed eosinophilic infiltrates in a portion of optico-spinal lesions in addition to CD4 T cells and macrophages [62]. Of note, no distinctions between pathological characteristics of optic nerve and spinal cord lesions were described. This chronic EAE model has been used to demonstrate key factors influencing lesion distribution and severity within the CNS. However, caution must be maintained in making comparisons between the 2D2×IgH^{MOG} model and NMO. It is important to note that the murine model does not fully recapitulate the features of NMO, in particular those most relevant to the pathological nature of CNS injury. For example, AQP4-specific antibodies were not detected in the 2D2×IgH^{MOG} mouse [62]. Additionally, pathological features intrinsic to NMO, including complement deposition and necrotic lesions, are not features of 2D2×IgH^{MOG} mice with disease. Essentially, the 2D2×IgH^{MOG} mouse is remarkable more for developing spontaneous EAE, with coincident ON that is typically associated with EAE, rather than for revealing pathophysiologic mechanisms of NMO.

To more fully explore the immune mechanisms involved in NMO, additional rodent models have been pursued. In particular, several studies have made attempts to demonstrate that anti-AQP4 antibodies are directly pathogenic. For example, intracerebral injection of IgG from a patient with NMO together with human complement resulted in astrogliosis and leukocyte infiltration. This pathology was not widespread and did not affect the optic nerves or spinal cord, but rather was focused along the injection site [63]. In another study, induction of injury proved equally as difficult, even with specific targeting of the optic nerves by direct injection of anti-AQP4 antibodies along with complement. Not until continuous infusion of anti-AQP4 antibody with complement into the region around the optic chiasm did features of NMO develop, including inflammatory demyelination with recruitment of macrophages and loss of AQP4 and GFAP immunoreactivity [64]. Several additional studies, in agreement with ongoing human trials described above, emphasize the role of cellular immunity in NMO models. For example, transfer of AQP4 antibodies magnified T cell-mediated EAE severity and produced features of NMO pathology [65, 66]. Overall, while a model of NMO with high conformity to features of the human disease has yet to be created, the cooperation between B cells and T cells seen in CNS autoimmunity suggests it is likely that T cells are a critical component to the pathogenesis of NMO.

Several infectious models involving ON have been described. One system involving neurotropic strains of mouse hepatitis virus (MHV) has been employed for many years as an infectious model of MS [67, 68]. Similar to most autoimmune models of CNS demyelination, demyelination in the optic nerves of MHV infected mice is largely mediated by activated microglia and infiltrating macrophages without significant involvement of B

cells. However, in contrast to EAE, there is minimal T cell localization to the optic nerve after MHV infection [69, 70]. MHV-induced ON is rapid, developing within five days, and although persistent loss of myelin is detected over an extended period, resolution of inflammation is relatively brisk as well [69]. The reproducibility of this model has facilitated exploration of factors involved in injury to axons as well as responses to various treatments for ON [71]. In a different infectious model, ocular infection with a recombinant strain of HSV-1 engineered to express IL-2 can induce demyelination within the optic nerves of a variety of mouse strains [72]. As opposed to a direct cytotoxic effect on cells of the optic nerve [72], IL-2 is prone to alter the host-pathogen balance locally. Murine infection with the nematode *Angiostrongylus cantonesis* represents an entirely different model of ON. This helminth is neuro-invasive and is capable of causing meningitis, encephalitis, and/or myelitis in humans with an eosinophilic inflammatory response [73] and is also recognized as a cause of optic neuritis in humans [74]. *A. cantonesis* has recently been used as an infectious trigger for ON in BALB/c mice. Intravascular infection with larval stage *A. cantonesis* produced demyelination of the optic nerve along with RGC loss [75]. These studies raise the possibility that systemic or ocular infections could predispose to ON. Crucially, each model system provides additional resources to tackle the complex processes involving immunologic responses in the eye that contribute to ON.

NERVE INJURY IN ON

ON is highly suited for the study of neuronal and axonal responses to inflammatory demyelination within the CNS. In particular, the availability of clinical testing modalities favors ON as a paradigm for the pursuit of neurodegeneration and repair mechanisms in MS. Working under the premise that optic nerve injury and loss - which can be captured using outcome measures such as evoked potentials and OCT - mirrors how the rest of the CNS contends with injury in MS, a tremendous amount of effort has been devoted recently to characterizing the timing and effect of RGC and axonal loss in ON. Several key findings have lent support to the concept that neurodegeneration within the retina and optic nerve is an early consequence of focal inflammatory optic nerve injury as well as a diffuse process affecting the remainder of the CNS in MS. In particular, axonal loss in the optic nerve can be captured by quantifying the thickness of the retinal nerve fiber layer (RNFL) using OCT. Reduced thickness of the RNFL in patients with MS has been repeatedly observed [29, 76, 77]. However, it is important to note that axonal loss, as revealed by OCT, is under-appreciated by clinical report. Specifically, evidence of optic nerve injury is prominent in companion eyes from patients with ON in addition to patients who have not presented with ON [77–79] and even eyes in patients with MS without a history of ON [29, 78]. The timing of axonal injury within the optic nerve is important when considering the relevance to nerve loss and initiation of therapy. A recent two year longitudinal study involving 135 MS patients without recent ON found significant thinning of the ganglion cell layer that progressed over the course of observation [80]. Interestingly, while a difference in RGC loss was apparent between eyes with a history of ON and fellow eyes, decline in thickness over time was not different in each eye, indicating that a diffuse process affecting both eyes contributes to nerve degeneration in MS. Subtler changes within the retina have been explored using OCT. Several studies have found microcystic abnormalities and macular

edema in MS and NMO patients in eyes with a prior history of ON. In MS patients, microcystic macular edema was observed more commonly in eyes with prior history of ON (50%) compared to eyes without prior ON (27%) [81], while in NMO patients retinal microcystic inner nuclear layer pathology was exclusively found in eyes with a prior history of ON [82]. While the role of OCT in clinical practice is still evolving, these studies highlight how innocuous axonal and neuronal injury of the optic nerve can be and how sensitive the anterior visual pathway is to CNS-wide MS damage.

Mechanistic studies using animal models have further supported the concept that nerve loss occurs early during ON. In a guinea pig model of EAE, axonal swelling and neurofilamental alterations were prominent features of ON [83]. Using autoradiography to follow tritiated leucine delivered intra-vitreally, follow up studies revealed that axonal transport is disrupted as early as six hours after the induction of disease [84]. Remarkably, over 30 years later portions of these results were substantiated using non-invasive MRI with manganese contrast injected into the vitreous humor. Specifically, axonal transport rate was decreased at the onset of optic neuritis in C57BL/6 mice with EAE [85]. To explore the impact of inflammatory demyelination on axonal injury and eventual nerve loss, Shindler and colleagues used the SJL mouse model of EAE involving ON. Inflammation was found to begin earlier (day 9 post-immunization) in the nerve compared to the loss of RGCs (approximately day 14 post-immunization). While caution is advised when interpreting outcomes from EAE-associated ON because of one study suggesting that there may be strain differences in neurodegeneration after ON [86], similar findings were observed in ON resulting from $MOG_{35–55}$-induced EAE in C57BL/6 mice [87]. Using the 2D2 system with isolated ON on the commonly employed C57BL/6 background, a systematic attempt to identify serologic biomarkers of neurodegeneration in ON was made [57]. Elevated levels of phosphorylated neurofilament H were detected in mice with ON compared with unaffected littermates, suggesting that an axonal injury may produce a serum biomarker of disease for use in clinical practice. What remains to be uncovered is the mechanistic pathway or pathways for axonal and neuronal injury in ON. Several valid suspects under scrutiny in MS include inflammatory mediators such as cytokines [88], oxidative and proteolytic stress [89], glutamate excitotoxicity [90], metabolic derangements such as mitochondrial dysfunction [91], and the consequences of demyelination itself that impairs trophic interactions between axons and myelin [92]. Determining which factors contribute to axonal and neuronal damage in ON will be central to applying therapeutics during the optimal window identified by current studies.

FURTHER CONSIDERATIONS AND CONCLUSIONS

Non-biased genetic approaches to the etiology of MS and autoimmune diseases have furthered the understanding of their etiology. Interestingly, recent genetics studies have identified commonalities between MS and autoimmune diseases that target tissues outside of the CNS [93]. Yet genetic underpinnings to ON deserve particular mention, as it remains feasible that there is a unique signature to the etiology of ON compared with MS. For example, when Mowry and colleagues queried whether certain genetic susceptibility variants identified for MS were associated with attacks in various regions within the CNS, they found that a polymorphism within the CD6 gene conferred reduced odds of ON [94]. While this

study does not define whether ON patients are a unique sub-group of MS, it raises possibilities of specific immune mechanisms for ON in MS. Another genetic association with ON comes from the identification of a possible familial form of NMO. Based on a small study, occurrence of NMO amongst family members is more frequent than would be expected based on the prevalence of this disease [95]. Finally, in terms of genetic risks for ON, the dependence on genetic background for animal models of ON and EAE is well recognized [96]. Interestingly, it is principally immune genes that have been identified as influencing susceptibility in murine model systems as well as in MS using genome-wide association studies. Thus, genetic influences may contribute to the immunologic bias toward inflammatory demyelination within the optic nerves, suggesting that future genetic studies examining patients with ON in isolation may be of additional benefit.

In sum, ON represents one of the most tractable clinical entities available to gain insight into the pathogenesis of MS and demyelinating conditions of the CNS. Clinical measures, along with animal models that capture relevant features of ON, are highly useful tools to continue the investigation into its etiology and pathogenesis. There is no question that signature qualities are shared between ON and MS, including entry of leukocytes through the BBB, T and B cell targeting of myelin components, and axonal injury. However, why ON is such a common clinical entity with regard to inflammatory CNS demyelination is unclear. Presumably a disabling exacerbation such as ON is more likely to prompt clinical evaluation than lesions in other regions of the CNS. Yet this cannot be the sole explanation for the disproportionately high frequency of optic nerve involvement with inflammatory CNS demyelination, as studies such as those utilizing OCT reveal an even greater proportion of subclinical optic nerve involvement. Furthermore, several experimental models exist that specifically target the optic nerve as outlined above. Perhaps frequent involvement of the optic nerve by inflammatory demyelination is related to the number of myelinated axons per oligodendrocyte, with the optic nerve having a high ratio relative to spinal cord [97]. Moreover, whether there are unique features that are specific to ON that distinguish it from MS and/or NMO remains to be conclusively demonstrated. Genetic, experimental and immunologic data need to be expanded before this conclusion is reached. Overall, several aspects of ON make it appealing to study as a model system for inflammatory processes that lead to CNS injury.

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Biography

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