

Current options for the treatment of optic neuritis

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Abstract: Optic neuritis can be defined as typical (associated with multiple sclerosis, improving independent of steroid treatment), or atypical (not associated with multiple sclerosis, steroid-dependent improvement). Causes of atypical optic neuritis include connective tissue diseases (eg, lupus), vasculitis, sarcoidosis, or neuromyelitis optica. In this manuscript, updated treatment options for both typical and atypical optic neuritis are reviewed. Conventional treatments, such as corticosteroids, therapeutic plasma exchange, and intravenous immunoglobulin therapy are all discussed with commentary regarding evidence-based outcomes. Less commonly used treatments and novel purported therapies for optic neuritis are also reviewed. Special scenarios in the treatment of optic neuritis – pediatric optic neuritis, acute demyelinating encephalomyelitis, and optic neuritis occurring during pregnancy – are specifically examined.

Keywords: optic neuritis, optic neuropathy, treatment, neuroophthalmology

Introduction

Acquired optic neuropathy can occur from a myriad of causes, including compressive (optic nerve sheath meningioma), genetic (Leber's hereditary optic neuropathy), infiltrative (lymphoma), nutritional (thiamine deficiency), traumatic (shear injury), paraneoplastic (collapsin response mediator protein-5 antibody), or toxic (amiodarone) etiologies. Optic neuritis (ON) is a term used when the pathophysiologic basis of optic neuropathy is inflammation. A primary infection (Lyme's disease, toxoplasmosis, human immunodeficiency virus) can cause injury to the optic nerve, but usually ON is associated with noninfectious inflammation, such as multiple sclerosis (MS), neuromyelitis optica (NMO), or other systemic diseases like lupus or sarcoidosis. This review will identify the major causes of noninfectious, inflammatory ON and report on the current state-of-the-art knowledge regarding ON treatment.

Demyelinating ON

Typical ON implies demyelinating ON, and is frequently associated with MS. In typical ON, vision loss is at its worst within several days after onset, and recovery begins within several weeks, independent of steroid treatment.¹ Atypical ON is defined by having features different from this MS-associated demyelinating ON, and is discussed separately below.

Clinical overview of demyelinating ON

Demyelinating ON is generally unilateral. Visual acuity at nadir ranges from normal to no light perception.¹ Pain is typical, occurring in >90% of cases, and worsens with

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eye movement. Photopsia, dyschromatopsia, and various visual field defects (central, paracentral, arcuate) may all occur. Disc swelling is usually diffuse, but the appearance can mimic nonarteritic ischemic ON.¹ Unlike the vast majority of nonarteritic ischemic ON eyes, however, contrast enhancement of the optic nerve on magnetic resonance imaging (MRI) will occur in up to 94% of cases of demyelinating ON.²

Demyelinating ON is retrobulbar two-thirds of the time, the remainder of cases showing papillitis. In either situation, between 3–6 months after ON, optical coherence tomography confirms retinal nerve fiber layer (RNFL) loss.³ If initially present, optic nerve edema does not persist, and if it does, this would signify an atypical course. The diagnosis of ON is usually made clinically, but earlier diagnosis has been shown to be possible with multifocal visual evoked potentials or functional MRI.⁴ More comprehensive features regarding diagnosis, epidemiology, and detailed clinical characteristics of demyelinating ON are beyond the scope of this review, but can be found in several other manuscripts.^{1,4,5}

Corticosteroids for treatment of acute demyelinating ON

Corticosteroids were found to show benefit after neurological injury in both animal and human models.^{6,7} This formed the basis for clinical trials, and in 1988, Spoor and Rockwell evaluated high-dose intravenous (IV) steroids in a trial for ON treatment and reported excellent outcomes.⁸ In the wake of this report, and in part because of the variability in how ON was treated, the ON Treatment Trial (ONTT) was launched. The ONTT was designed to help answer whether treatment with oral or IV steroids resulted in improved vision or faster recovery of vision after acute ON, and if there were adverse effects of therapy.⁹

Results from the ONTT showed that 3 days of high-dose IV methylprednisolone did not change overall outcomes of visual acuity after 6 months, but did hasten visual recovery after ON. Lower-dose oral steroids increased the incidence of recurrent ON for reasons that remain unclear. Treatment with steroids was found in the ONTT to be safe, with minimal adverse events;¹⁰ however, one patient had acute pancreatitis and another had acute transient depression.¹¹

More recently, a Cochrane review evaluated the effects of corticosteroids on visual recovery in patients with acute ON.¹² Authors searched all randomized trials for any form of corticosteroids between 1950 to February 2012, and determined that six trials with a total of 750 subjects met criteria for analysis. Of these, the ONTT carried the most weight. Their conclusion was that there was no benefit for either

oral or IV steroids on the outcome of visual acuity, contrast sensitivity, or visual fields.

Corroborating the limitations of steroids for ON, another study showed that in a rat model, despite administration of either low- or high-dose steroids, there was no improvement in visual evoked potential, electroretinogram testing, or viable retinal ganglion cells when compared to controls.¹³

Despite these results suggesting lack of efficacy by steroids to change overall visual outcomes, other factors exist that support steroids after ON. As mentioned, the ONTT did confirm that IV methylprednisolone hastens visual recovery time after ON. Also, high-dose steroids delayed the onset of clinically definite MS, although this trend does not continue over time.¹⁴ Furthermore, in the ONTT, contrast sensitivity, visual fields, and color vision showed persistent improvement over placebo after 6 months in the IV methylprednisolone group.¹¹

It may be that timing of administration of high-dose steroids is more important than realized, and corticosteroids might show higher efficacy if used more promptly. Statistical improvements may only appear if steroids are given in a much shorter window after ON onset than previously suspected.

Basic science support for earlier steroid treatment is evidenced by one report in which rats were given steroids prior to onset of experimental autoimmune encephalomyelitis, the investigational rat model of MS. In these rats, early steroids suppressed development of ON, and when ON did occur, there was relative preservation of retinal ganglion cells.¹⁵ Of course, it is impossible to predict exact onset of ON. However, Plant et al examined eight patients with a history of prior ON who reported onset of typical pain suggestive of hyperacute ON, but without yet having vision loss.¹⁶ In five of these patients, MRI confirmed the incipient ON. The authors determined that steroids given very early in the course of ON resulted in excellent outcomes, and may better prevent vision loss than if given later.

In summary, for acute demyelinating ON, the two main first-line therapeutic options are to give at least 3 days of high-dose steroids as early as possible, or to not treat with steroids.¹⁷ This decision can be made on an individual basis after discussing options with the patient.

In addition to the fundamental question of whether or not to use steroids after ON, there remains no consensus regarding type, route, or dose of steroids.

Although not an arm of the ONTT, high-dose oral steroids may hasten vision recovery time similar to the IV formulation.¹⁸ This route may be an option when IV access is problematic or the inconvenience of IV steroids makes it unobtainable.

In the IV methylprednisolone subgroup of the ONTT, an oral steroid taper (1 mg/kg/day for 11 days) was given after completion of the IV doses. There was no arm which used IV methylprednisolone without oral steroids. Some physicians use the taper to control withdrawal side effects, but there is no evidence that efficacy is a reason to use the oral taper. In one retrospective analysis, a low-dose steroid taper following IV methylprednisolone had no effect on Expanded Disability Status Scale (EDSS) score or relapse recovery versus IV methylprednisolone alone, although visual recovery from ON was not specifically measured in that study.¹⁹ For patients with diabetes, hypertension, osteoporosis, and other relative contraindications to steroids, the possible risks of prolonged exposure should be taken into consideration prior to prescribing a steroid taper.

Although methylprednisolone is generally used as the steroid formulation for high-dose corticosteroid use, one study did compare clinical and biochemical parameters for IV methylprednisolone versus IV dexamethasone in patients with acute ON.²⁰ Three months after using 3 days of roughly equivalent doses of each corticosteroid (1 mg dexamethasone \approx 5 mg methylprednisolone), there was no difference in any of the tested endpoints, suggesting that IV high-dose dexamethasone was not inferior to IV methylprednisolone and can be used if needed.

Although not a steroid itself, adrenocorticotropic hormone induces natural release of steroid hormone, and may have effects beyond steroids.²¹ Adrenocorticotropic hormone is available in a prolonged release intramuscular or subcutaneous form, and is approved for acute ON as an option for patients who do not tolerate or have had side effects from methylprednisolone.

How is ON treated in the real world? In the United States, 48.4% of surveyed ophthalmologists recommend 3 days of high-dose IV methylprednisolone for most patients with ON, while 32.9% would usually recommend no treatment. This is in contrast to 87.3% of neurologists, who would treat acute ON with IV methylprednisolone most of the time. In the United States and Canada, roughly 15% of both ophthalmologists and neurologists would treat acute ON with a low-dose oral prednisone taper.²² This subgroup is less likely to know the results of the ONTT.²³

Therapies for preventing exacerbations in MS

ON is the presenting feature of clinically definite MS in 15%–20% of patients. The choice for treatments to prevent future relapses in MS, including future attacks of ON, is

controversial, but it is evident that the presence of other demyelinating lesions on brain MRI after ON increases the risk of clinically definite MS. An update on current treatment algorithms and novel treatments for MS therapies can be found in several reviews.^{24,25}

Treatment of steroid-refractory demyelinating ON

As mentioned, one feature of typical ON is visual improvement within 2–3 weeks after onset.²⁶ At times, otherwise typical demyelinating ON associated with MS does not improve as expected. A search for atypical causes of ON should be sought in these patients, but if the diagnosis remains the same, these cases can be termed steroid-refractory demyelinating ON.

Treatments for steroid-refractory demyelinating ON may include a second round of 3–5 days of high-dose steroids, or alternatively, using therapeutic plasma exchange (TPE), immunoadsorption, or IV immunoglobulin.

TPE is indicated as a first-line treatment for various neurological conditions, including myasthenia gravis, Guillain–Barre syndrome, and chronic inflammatory demyelinating polyneuropathy. Acute central nervous system demyelinating syndromes have also been shown to improve after TPE, giving this therapy a role in treatment of cases not improving after steroids.²⁷

Briefly, TPE works by separating the patient's plasma from whole blood by various means. The separated plasma is discarded, and a replacement solution is infused into the patient in its place. TPE removes about 2500 mL of plasma volume per session. For neurological conditions, TPE sessions are usually repeated three to five times on consecutive or alternating days.²⁸ The mechanism of action of TPE for treating ON or MS is unclear, but may involve the removal of pathogenic circulating immunoglobulins or complement from plasma.²⁹

TPE has been studied for use in ON. Timing of when to start TPE is not strictly defined, but earlier treatment is probably better, and treatment started more than 6 weeks after onset of ON has inferior results.²⁹ The largest case series of using TPE for steroid-refractory ON involved 22 patients with either known MS or clinically isolated demyelinating syndromes, along with one who had NMO (see below).³⁰ All patients received two cycles of IV methylprednisolone, and TPE was offered if vision had not recovered by at least 50% on visual acuity testing. Of patients receiving TPE, 30% did not show any benefit, 26% recovered 85% or more, with the remaining somewhere in between. Although this was not a

placebo-controlled trial, it does provide evidence that TPE is associated with occasional good outcomes.

Immunoadsorption is a process similar to TPE. The difference is that in immunoadsorption, once plasma is filtered, instead of being discarded and replaced with an albumin solution, it is passed through an immunoadsorber, which clears the plasma of immunoglobulins. The cleared plasma is then passed back into the patient. Supposed benefits of immunoadsorption over TPE are the decreased chances of adverse events such as allergic reactions or infection,²⁸ although either immunoadsorption or TPE can be associated with catheter-based adverse events such as thrombosis or site infections. Fewer reports of immunoadsorption treatment for ON are available, but do appear to suggest that immunoadsorption is an option in place of TPE for steroid-refractory ON.³¹

The efficacy of IV immunoglobulin has had both negative and positive results. One report found that in patients with ON and vision 20/400 or worse after corticosteroids, 78% of those receiving IV immunoglobulin improved to 20/30 or better, compared to only 12.5% of controls.³² IV immunoglobulin was given within 3 months of ON onset, and with a dose of 0.4 g/kg/day for 5 days with monthly 0.4 g/kg each month to a total of 4 g/kg. Prior studies with negative results had used either less IV immunoglobulin, or time to treatment was longer.

Treating ON associated with acute widespread fulminant demyelination

Rarely, ON will occur in the setting of a more dangerous life-threatening demyelinating emergency. This results from either widespread, active demyelination, or from a tumefactive area of demyelination producing a mass effect. Examples of this entity include Balo's concentric sclerosis or the Marburg variant of MS, although neuromyelitis optic, acute demyelinating encephalomyelitis (ADEM), or MS can all present acutely in this manner. Any of these processes can result in increased intracranial pressure with potential herniation. If these situations also include concomitant ON, the treatment of the widespread demyelination will also be therapy for the ON, and there is no separate treatment regimen for the ON component.³³ The remission-inducing therapy of these emergencies is similar to treatment of ON (albeit with a greater level of urgency and supportive care): high-dose corticosteroids, often followed by either plasma exchange or IV immunoglobulin, as discussed above.^{34,35} There are no trials using concomitant steroids and IV immunoglobulin, or of using combined steroids and TPE (giving

the steroids after each session of TPE), but the authors have either used or seen these approaches used.

Other purported therapies for acute demyelinating ON

At present, although corticosteroids are the main first-line therapy for acute demyelinating ON, there is interest in the use of agents with other potential mechanisms of action. Although none of these have undergone rigorous clinical trials, preliminary data is available.

3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) are commonly prescribed for treatment of hypercholesterolemia. Based on positive preliminary brain MRI data, one study randomized 64 persons within 4 weeks of ON to treatment with either a statin or placebo. The primary outcome was improvement in contrast sensitivity, which was met; however, visual acuity, color vision, and MRI metrics did not improve. Both visual evoked potential amplitude and latency were better in the statin group, as was patient-reported visual outcome.³⁶ None of the patients received steroids for ON as they are not standard treatment in Denmark, where the study took place.

Another agent proposed to have positive effects on neurological injury is erythropoietin. Fewer brain MRI lesions have been reported in MS patients given erythropoietin,³⁷ and at the 2011 European and Americas Committees for Treatment and Research in MS, preliminary data was released where 40 patients with a first episode of ON were randomized to either methylprednisolone or 33,000 IU of IV erythropoietin. Results showed that mean RNFL thickness was significantly preserved in the erythropoietin group.³⁸ Despite these positive results, potential adverse effects such as polycythemia and venous sinus thrombosis need to be evaluated in larger trials.

A heat-killed extract of *Mycobacterium w* is approved as an immunomodulator in India. Based on its relatively low cost and good safety profile, it was studied in eight patients with steroid-refractory ON. All six who completed follow-up showed visual improvement in this uncontrolled trial,³⁹ and further research into this therapy has been suggested.

Two newer agents recently failed to show positive results in preliminary studies of optic nerve damage.

Fingolimod is an oral agent approved for the prevention of relapses in MS. The mechanism of action is proposed to be via lymphocyte segregation in lymph nodes, preventing movement into the central nervous system. Fingolimod was studied in a rat model of ON. Although it showed anti-inflammatory effects, there was no improvement in visual function as measured by visual evoked potential, nor

was there increased survival of retinal ganglion cells in the fingolimod-treated group.⁴⁰

Memantine is an N-methyl-D-aspartate receptor antagonist which has shown evidence of possible neuroprotection in a glaucoma model. In one study, memantine and placebo were given to patients with ON after treatment with steroids. Optical coherence tomography analysis was performed after 3 months, and results showed that although overall RNFL thickness was greater in the memantine-treated group, there was no improvement in visual function or in thickness preservation of the temporal quadrant of the disc.⁴¹

In conclusion, treatment of typical ON can include high-dose steroids or observation at onset, with other therapies such as IV immunoglobulin or TPE in cases which do not improve as expected.

Atypical ON

What is atypical ON? If typical ON is defined as being associated with MS and having features seen in demyelinating ON, then atypical ON means either ON associated with a disease other than MS, or ON having features not commonly seen with demyelinating ON (Table 1). Because a number of persons with otherwise typical demyelinating ON may have an atypical clinical feature, here atypical ON is defined as: (1) not associated with MS, and (2) requiring continued immunosuppression to maintain remission.⁴²

It follows that atypical ON represents a relatively smaller proportion of patients.^{43,44} Atypical ON may be an indication of an underlying systemic disease such as collagen vascular disease, vasculitis, or sarcoidosis.⁴⁵⁻⁴⁷ Patients with ON who have laboratory evidence of autoimmunity but lack clinical signs of collagen vascular disease are said to have isolated autoimmune optic neuropathy. Patients with

Table 1 Features considered atypical for demyelinating optic neuritis

Features considered atypical for optic neuritis
Aged <15 years or >50 years
No relative afferent pupillary defect
Aquaporin-4 (neuromyelitis optica) antibody positivity
Immediate and dramatic response to steroids
Bilateral or chiasm involvement
Severity – no light perception or hand motion vision
Progressive vision loss after several weeks
Painless
Presence of a macular star (inferring neuroretinitis)
Lack of recovery over time
Steroid dependence (worsening of vision with steroid tapering)
Optic atrophy at presentation
Anterior or posterior uveitis

steroid-dependent ON without having systemic disease have been defined as having chronic relapsing inflammatory optic neuropathy.⁴⁸

ON associated with systemic autoimmune disease, vasculitis, or sarcoidosis

Determining the etiology of ON in someone who has autoimmune disease can be difficult, as many cases also harbor brain MRI lesions similar in appearance to MS, or have other concomitant autoimmune diseases or antibodies, like the anti-NMO antibody (see below).

The prognosis and pathophysiology of optic neuropathy in autoimmune diseases like lupus is different than MS.⁴⁹⁻⁵⁴ Small vessel vasculitis and thrombosis associated with hypercoagulability may cause ischemic optic neuropathy. Inflammatory ON in these conditions is characterized by pain on eye movement, and enhancement on MRI. Regarding treatment, without having a large study like the ONTT, there are only case series reports to help guide management. Probably the most common treatment option is to use high-dose steroids (3–5 days of 1000 mg IV methylprednisolone) at onset. The earlier steroids are started in lupus-associated ON, the better the visual outcome.⁵⁵ Unlike MS, in atypical ON, a slower steroid taper (even months) is recommended to prevent ON recurrences.⁵⁶ As an alternative to high-dose steroids, cyclophosphamide has been reported as more effective than methylprednisolone in lupus-associated ON in several studies.^{57,58}

Autoimmune-associated ON can occur in a patient already on immunosuppression. In a retrospective review of patients in Taipei with ON, eight patients had systemic lupus erythematosus.⁵⁵ Five of those patients had stable systemic lupus erythematosus managed by oral steroids (5–15 mg/day) at the time of onset of ON. The other three patients initially presented with acute vision loss.

Goodwin provides a cursory review of patients with ON from vasculitis (microscopic polyarteritis, Wegener's granulomatosis, and Henoch–Schönlein purpura) or collagen vascular disease (systemic lupus erythematosus and Sjogren syndrome) in whom steroid therapy with and without immunosuppressive therapy was given.⁵⁹ In Wegener's granulomatosis, the optic nerve may be affected by contiguous orbital spread of sinonasal disease or by occlusive vasculitis.⁶⁰ Wegener's granulomatosis-associated ON often has an unfavorable prognosis, yet some patients show a positive response to steroids.⁶⁰ Huchzermeyer et al presented a report of a patient that after a period of initial control with

high-dose steroids, ultimately required a more complex regimen to induce remission: a combination of rituximab, steroids, and cyclophosphamide.⁶¹ It is possible that the divergent responses to steroids are due to distinctive pathological mechanisms and/or promptness of treatment. The early occlusive vasculitis can be treated successfully via rapid diagnosis and aggressive anti-inflammatory therapy.⁶²

Optic neuropathy can occur with neurosarcoidosis, and inflammation from ON is one of several mechanisms. The refractory nature of the ON often mandates a slow steroid taper. Treatment of sarcoidosis refractory to steroids may include immunosuppressive agents (eg, azathioprine and cyclosporine) and antimetabolites (cyclophosphamide, chlorambucil, and methotrexate).⁶³ It is noteworthy to mention that infliximab has shown promise in the treatment of systemic sarcoidosis.⁶⁴ However, one should exercise caution with routine use of tumor necrosis factor- α antagonists to treat inflammatory conditions with neurological manifestations, as they have been associated with demyelinating attacks.⁶⁵

Myers et al reported ten patients over 7 years with atypical ON (steroid-dependent ON not associated with demyelinating disease).⁶⁶ The authors also performed a Medline search finding 38 comparable patients in the literature treated with steroid-sparing therapy. Combining the two pools of patients, 17 patients had systemic lupus erythematosus, twelve had sarcoidosis, three had other ocular or systemic conditions, and the remaining 16 had no known other systemic disease. Steroid-sparing treatments given to these patients included cyclophosphamide (n = 19), azathioprine (n = 16), chlorambucil (n = 10), cyclosporine (n = 5), methotrexate (n = 8), and mycophenolate mofetil (n = 5) (some patients were treated with multiple agents). Clinical benefit was defined by the authors as meeting two or three of the following criteria: (1) ability to reduce systemic steroids to a daily dose of ≤ 10 mg oral prednisone; (2) clinically reduced inflammation; (3) stabilization or improvement in visual acuity or symptoms such as pain; and (4) tolerance of drug-related side effects. From the total pool of 48 patients, 38 (79%) showed clinical benefit. It was determined that for patients with steroid-dependent ON unrelated to demyelinating disorders, immunosuppressive therapy was shown to be not only efficacious, but also helpful to avoid debilitating side effects of long-term corticosteroid use.

Corticosteroid-dependent ON without systemic disease

Chronic relapsing inflammatory optic neuropathy is a term given to isolated ON that requires chronic steroids or

immunosuppression to prevent relapse. This type of ON is usually more painful and results in worse vision than demyelinating ON. Frisen et al described two patients with this clinical picture, and biopsy confirmed a granulomatous optic neuropathy, although the patients had no evidence of systemic sarcoidosis after 1 year and 7 years of follow-up.⁶⁷ Kidd et al described 15 patients with a similar clinical picture as the Frisen patients, in which there was no systemic disease, with recurrences of ON occurring without evidence of systemic granulomatous disease after a median of 8 (2–26) years.⁴⁸ All patients in Kidd's report exhibited a rapid response to systemic steroid treatment in terms of pain relief and visual function. However, relapse was common upon steroid taper, requiring chronic immunosuppressive therapy. The steroid-dependent nature of chronic relapsing inflammatory optic neuropathy may owe to the inflammatory nature of the pathological mechanism, which involves nerve infiltration and subsequent granuloma formation.^{68,69}

The question arises, not only in chronic relapsing inflammatory optic neuropathy, but in all cases of so-called "isolated" optic neuropathy, as to whether disease processes in these patients are truly limited to focal involvement, or if systemic signs will manifest themselves given enough time. How pathophysiological mechanisms differ in isolated versus systemic disease has yet to be clearly elucidated. Certainly, studies to further define these mechanisms will be indispensable in guiding therapeutic direction more precisely.

The importance of early diagnosis cannot be overemphasized for patients presenting with ON. One must consider various causes of atypical ON in the differential, as successful treatment of atypical ON depends on timely initiation of therapy. Also, one must also take caution interpreting studies of ON done prior to 2004, as there was no routine testing for the antibody associated with NMO, potentially including some of these patients in the study group.

In conclusion, for patients with atypical ON, a slower steroid taper with immunosuppression should be considered.

ON from NMO

NMO, also known as Devic's disease, is an inflammatory disease of the central nervous system characterized by ON and myelitis. Epidemiological evidence suggests a female predominance with a median age of onset in the mid to late 30s.⁷⁰ Although classically described as monophasic, >80% of patients suffer a relapsing-remitting course,^{70,71} with disability accumulating after each attack. Fifty percent of patients become wheelchair-dependent, and 62% are functionally blind after 5 years.^{71,72} As the clinical course

for NMO tends to be worse than MS, and with more severe attacks, early diagnosis and implementation of treatment are paramount.

The discovery of a specific antibody to the aquaporin-4 water channel, NMO-immunoglobulin G,⁷³ shaped the development of new diagnostic criteria for NMO in 2006,⁷⁴ which aided in differentiating NMO from MS. The target of the antibody is a water channel present in the foot processes of astrocytes at the blood–brain barrier, widely expressed in the optic nerves and spinal cord. NMO-immunoglobulin G has been found in 50%–70% of patients,⁷³ and when applied as a diagnostic feature, the antibody is associated with 77%–91% sensitivity and 94%–100% specificity for NMO.^{74,75}

MS is less prevalent in Asia. Because of this, a greater number of cases of Asian ON are atypical. A study by Lai et al examined 20 Chinese patients with isolated atypical ON.⁷⁶ Criteria required one of the following: (1) visual loss progressing for >2 weeks since onset, (2) no visual recovery over 3 weeks after onset, or (3) worsening of vision over one line of acuity after withdrawal of corticosteroids. Additionally, the following two criteria were required: (4) no diagnosis of a defined collagen vascular disease or neurological autoimmune disease at onset, and (5) neuroophthalmologic follow-up for at least 12 months. While most of the patients responded favorably to initial steroid treatment, 55% of patients incurred relapses that were steroid-resistant, and most of these had aquaporin-4 antibodies. Indeed, the disease known as optospinal MS, so prevalent in Asia, may actually be NMO.

Treatment of acute NMO-related ON

Evidence for the best choice of treatment for acute attacks in NMO is limited. First-line treatment typically involves high-dose IV methylprednisolone (1 g/day for 3–5 days). In MS, RNFL thickness as measured by optical coherence tomography can be correlated with visual function. Recent reports have demonstrated a greater loss of RNFL thickness in NMO, consistent with the greater loss of function in these patients.^{77–79} Nakamura et al showed that early treatment (particularly ≤ 3 days after onset of ON) with high-dose IV methylprednisolone was associated with preservation of RNFL thickness.⁸⁰ Moreover, in contrast to the ONTT results (described earlier) stating that the final visual acuity is not affected in MS patients receiving steroid treatment, the Nakamura study reported improved visual outcomes in NMO patients receiving early IV methylprednisolone therapy. Consequently, it is imperative to

distinguish MS from NMO in the acute stage. In cases where IV methylprednisolone is ineffective, TPE is often utilized. Evidence for the effectiveness of TPE comes from several case reports,^{81–84} and its success may depend on how early treatment is initiated.⁸³ Currently, no evidence supports the use of IV immunoglobulin in acute NMO treatment. These treatment concepts mirror those recognized by the European Federations of Neurological Societies.⁸⁵

Concepts in NMO relapse prevention

Since disability in NMO is directly associated with relapses, attack prevention is the core strategy to inhibit cumulative loss of function. As it had been previously thought that NMO shared pathological mechanisms with MS, it is not surprising that many of the therapies used for treating MS have been tried in NMO. Many of these drugs fall into two categories: immunomodulatory and immunosuppressive therapies. In recent years, the principal method of relapse prevention has been via the latter group, and these drugs are reviewed below. A brief review of the former can be found in Collongues and de Seze.⁸⁶

Azathioprine to prevent relapses in NMO

Azathioprine is a prodrug that is converted to 6-thioguanine which acts as inhibitor of DNA synthesis. It is commonly used in the prevention of organ transplant rejection and has been utilized in the treatment of autoimmune diseases including rheumatoid arthritis and MS.

In a study of seven newly diagnosed NMO patients, treatment with azathioprine plus prednisone led to a reduction in EDSS; furthermore, patients were followed for at least 18 months and had no relapses during that time. IV methylprednisolone was given for 5 days, followed by oral prednisone (1 mg/kg/day) daily for 2 months. The dose of azathioprine was 2 mg/kg/day, which was started on week three. Two months later, this was followed by steroid taper to 10 mg/day and azathioprine doses of 75–100 mg/day.⁸⁷

A retrospective study by Costanzi et al evaluated 70 patients with at least 12 months of follow-up that had been diagnosed with NMO or NMO spectrum disorders and treated with azathioprine from 1994–2009.⁸⁸ Efficacy of treatment was measured in terms of annualized relapse rates (ARR), EDSS, and visual acuity scores. ARR was significantly reduced in those treated with azathioprine with or without prednisone. This reduction was consistent with that seen in a study of Brazilian patients with NMO by Bichueti et al.⁸⁹ Those patients were similarly treated with azathioprine with or without prednisone.

With regard to dose, although a linear regression model showed no significant differences, Costanzi et al noted that patients treated with at least 2 mg/kg/day had lower posttreatment ARR compared to patients treated with less than that dose.⁸⁸ They recommend a target dose of 2.5–3.0 mg/kg/day.

An additional consideration when deciding on a drug for a particular patient may be cost. One year of azathioprine treatment has been estimated to cost approximately \$2100 versus \$27,000 per year for rituximab, as an example.

Corticosteroids as relapse prevention in NMO

Although steroids have been used in the treatment of ON associated with MS, relatively few studies have thoroughly examined the clinical efficacy of steroids in NMO. A study by Mandler et al involved patients treated with prednisone and azathioprine.⁸⁷ In a retrospective analysis of Japanese patients with NMO, low-dose steroid monotherapy was associated with a significant decrease in ARR in eight out of nine patients.⁹⁰ The median ARR during steroid treatment periods was 0.49/year (0–0.93/year) compared to 1.48/year (0.65–5.54/year) during periods without low-dose steroids. Furthermore, it was noted that most relapses occurred when steroids were tapered to a dose of ≤ 10 mg/day.

Rituximab for relapse prevention in NMO

Rituximab is a chimeric human-murine antibody against human CD20 and, therefore, selectively targets B-cells. Its mechanisms of action include complement-dependent cytotoxicity and antibody-dependent cellular toxicity. Rituximab was originally used to treat B-cell malignancies, but has been utilized in the prevention of transplant rejection and treatment of autoimmune disorders.

No standards for dosing regimens currently exist. Some studies have used a fixed dose of 1000 mg given every 6 months. Others have used 375 mg/m² each week for 4 weeks of induction therapy and two 1000-mg infusions given 2 weeks apart for maintenance therapy. Kim et al employed a slight variation to this protocol: induction consisted of 375 mg/m² once weekly for 4 weeks, or 1000 mg infused twice, with a 2-week interval between infusions, for maintenance therapy; 375 mg/m² was given whenever the frequency of CD27+ memory B-cells was $>0.05\%$ in peripheral blood.⁹¹ Another study used this approach of dosing based on cell counts (CD19 $> 2\%$) rather than based on time.⁹²

Multiple studies from the United States, Europe, and Asia have shown benefits of rituximab therapy in NMO patients in terms of reduction of relapses and either stabilization

or improvement of neurological function (per EDSS).^{93–95} In contrast, other studies have shown mixed results with rituximab therapy. In a retrospective review of nine patients treated by Lindsey et al, while three patients had no relapses (in 22 months for two of the patients, or 42 months for the third patient), the other six patients continued to have relapses.⁹⁶ Similarly, in an Italian study of two patients, one patient improved while the other suffered a spinal cord relapse with a new, enhancing MRI lesion.⁹⁷ Why these variations are seen across studies with rituximab remains unclear. One possible explanation may relate to the natural progression of NMO. Lindsey et al suggest that rituximab may have better efficacy in treating patients with long-standing NMO as opposed to those that have more recently developed symptoms.⁹⁶

Another possible explanation for lack of response to treatment in some patients is related to the pathophysiology of NMO. Recent studies have pointed toward aquaporin-4 antibodies and, more generally, the humoral arm of the immune system as likely playing a central role in the disease process of NMO. In this light, reports have demonstrated a correlation between aquaporin-4 antibody levels and clinical response,⁹⁸ while another report failed to show this relationship.⁹⁰ It is important to point out that some patients have relapses despite very low circulating B-cell counts;⁹⁶ in a report by Greenberg et al, patients that incurred relapses while their CD19 counts were $<2\%$ were classified as “rituximab nonresponders.”⁹² Recurrent myelitis may over time illicit inflammatory responses from the cellular arm of the immune system as well.⁹⁹ Further elucidation of this aspect of the pathological process in NMO is necessary.

Other therapies for relapse prevention in NMO

Other drugs have also been explored in the treatment of NMO and currently have a minimal amount of data to characterize their efficacy. A case report of a 9-year-old girl with relapses of NMO after azathioprine treatment was in remission for 2 years following mycophenolate mofetil therapy.¹⁰⁰ In a retrospective study of 24 patients (15 with NMO and nine with NMO spectrum disorders), a median dose of 2 g/day mycophenolate mofetil resulted in decreased disability and relapse rates.¹⁰¹

Data for cyclophosphamide are predominantly from case reports of patients with NMO and another autoimmune disease, showing both positive¹⁰² and negative¹⁰³ results. In the report by Jarius et al, a patient with lone NMO had a dramatic reduction in relapses after cyclophosphamide treatment (50 mg/day).⁹⁸

Natalizumab is a monoclonal antibody that binds to the $\alpha 4$ subunit of $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins. It is approved for use in relapsing MS. In a study of five patients who were considered to have relapsing-remitting MS but were later diagnosed with NMO, natalizumab was given as the patients had progressive disease after their initial treatment regimens.¹⁰⁴ Unfortunately, relapse frequency was unchanged; furthermore, patients had severe exacerbations during and after treatment in addition to having new MRI lesions during relapses.

Future treatments for relapse prevention in NMO

The next generation of anti-CD20 antibodies and molecules targeting the complement pathway are among those that may have a potential role in the treatment of NMO. These and other future therapeutic possibilities are reviewed elsewhere.⁸⁶

In conclusion, because the vision loss in NMO is more profound, treatment of ON is relatively aggressive. Additionally, therapies to prevent attacks are highly recommended.

Special scenarios in the treatment of ON

Special scenarios in the treatment of ON include pediatric ON, ADEM, and ON occurring during pregnancy. These topics will all be discussed below.

The spectrum and treatment of pediatric ON

Pediatric ON is not the same as ON in adults. The etiology, clinical features, and prognosis of pediatric ON are all different. Acute treatments, however, are quite similar to adult ON, although duration of recommended treatment in pediatric ON is longer.

ON has been reported in patients as young as 21 months.¹⁰⁵ The etiology of pediatric ON may be as an isolated post-infectious process, or it may be associated with MS, NMO, or ADEM. Up to 66% of children may have a prodromal viral illness.¹⁰⁶ Although MS is not an uncommon comorbid diagnosis in pediatric ON, the rate of MS that is pediatric is low – only 3%–5%.¹⁰⁷

Pediatric ON is more likely than adult ON to have papillitis and be bilateral.¹⁰⁸ This bilaterality historically was considered a negative predictor of conversion to MS,¹⁰⁹ but in a meta-analysis, while abnormal MRI made conversion to MS 25-fold higher in risk, it did not appear that bilaterality made it less likely.¹¹⁰

The severity of pediatric ON is variable, ranging from 20/15 to no light perception,¹⁰⁹ although in general, pediatric ON is considered to have more severe vision loss at presentation than in the adult counterpart,¹⁰⁸ and in one study 84% had 20/200 or worse at presentation.¹¹⁰

Treatment of pediatric ON, whether it is isolated or in association with MS, NMO, or ADEM, is similar. However, there is no class I evidence regarding any treatment of pediatric ON. Nevertheless, treatments may include high-dose steroids, IV immunoglobulin, and TPE. IV methylprednisolone is given on a weight-based regimen (4–30 mg/kg/day)¹⁰⁸ up to 1 g for 3–5 days, although for ON caused by NMO, treatment up to 7 days has been described.¹¹¹ One difference between adults and pediatric ON is that in a higher number of pediatric ON cases, there may be worsening if steroids are tapered too quickly. For this reason, some advocate a slow oral steroid taper in pediatric ON, with a dose of 1 mg/kg prednisone to start with a taper over 4–6 weeks.¹⁰⁸ Recovery periods after ON are dependent on cause, but in one study, the mean recovery period from vision nadir to 20/40 was 2.3 months,¹¹² and it is considered that pediatric ON has an overall worse prognosis compared to adult ON.

As in adult ON, select cases of pediatric ON may benefit from the use of IV immunoglobulin or TPE. There have been reports of IV immunoglobulin showing good outcome in pediatric ON.¹⁰⁶ The dose of IV immunoglobulin in children for ON is 2 g/kg/day spread out over 1–5 days.¹⁰⁸

Pediatric ON associated with NMO has been treated with IV methylprednisolone for up to seven courses or IV immunoglobulin at 2 g/kg total, or may be treated with up to seven sessions of TPE.¹¹¹ There are no approved guidelines, however, and these cases are often comanaged by neurologists, neuroimmunologists, and pediatricians.

ON from ADEM – description and treatment

Similar to the above section on acute fulminant demyelination associated with ON, ADEM is a diffuse demyelinating process which may have associated ON. In these cases, ON may be severe and bilateral, but it would be uncommon for the ON to be an isolated, or even the most pronounced, clinical entity. Similar to above, treatment of the ADEM in general constitutes treatment of the ON.

ADEM is a heterogeneous clinical entity, which does not have a specific biomarker.^{113,114} It has a continuum with MS in some cases, although they are at heart distinct entities. ADEM is considered mainly a disease of children. It is usually associated with a viral or postvaccination febrile prodrome,

followed by an afebrile period, and then an acute, rapidly presenting neurologic deterioration, usually associated with altered mental status and seizure, both of which differentiate it from MS. Also, unlike MS, ADEM often produces a cerebrospinal fluid pleocytosis and lack of oligoclonal bands. Widespread central, and often peripheral, nervous system damage can occur in ADEM, of which ON is often present, usually bilaterally. Patients with ADEM are often sick enough to require the intensive care unit.

Treatment of ADEM is similar to other acute demyelinating disease, although there are no clinical evidence-based guidelines for management. Treatment is usually IV methylprednisolone 30 mg/kg/day for 30 kg body weight or 0.5–1 g/day for >30 kg body weight for 3–5 days,¹¹⁵ followed by a taper, which may last for 6 weeks; a taper of 3 weeks or less has been associated with increased risk of relapse.¹¹⁶ For those who require it, a second course of IV methylprednisolone, IV immunoglobulin, or plasma exchange should be considered.^{116,117} The alternative treatment for children in whom corticosteroids are contraindicated or ineffective is 2 g/kg IV immunoglobulin over 2–5 days.¹¹⁸

Treatment of MS-associated ON exacerbations in pregnancy

Treatment of ON associated with pregnant patients in the setting of known or suspected MS is often conducted with the assistance of an obstetrician, usually specializing in high-risk pregnancies. The third trimester is considered to be protective against MS attacks, but attack risk increases in the postpartum period. Immunomodulatory medications are usually discontinued prior to planned conception, so patients may not be on MS medications during pregnancy.

If a patient develops ON during pregnancy, questions include: is treatment efficacy different because of the pregnancy, and is treatment safe during pregnancy?

Steroids are not contraindicated in pregnancy. Methylprednisolone is a pregnancy category C drug, but this risk is considered low, and IV methylprednisolone is generally regarded to be relatively safe for pregnancy.¹¹⁹ Risks are considered low since steroids are metabolized prior to reaching the fetus.¹²⁰ Nevertheless, because (as noted above), there are no long-term benefits to treating ON with steroids, if ON occurs during pregnancy, there may be more of a reason not to treat with high-dose steroids. There are no trials of high-dose steroid efficacy in pregnant women to know if they have the same response in decreasing duration of symptoms.

One trial did look into IV immunoglobulin as a preventative treatment during pregnancy. Patients were given

2 g/kg within the first 2 months of pregnancy, then 0.4 g/kg every 6 weeks until 12 weeks postpartum. These patients had less relapses than those not treated, with no adverse effects of IV immunoglobulin during the pregnancy. Another group started on IV immunoglobulin postpartum had a decreased relapse rate in the postpartum period.¹²¹ However, it is noted that the protocol was retrospective and not randomized, with imbalance as to prepregnancy relapse rate.¹²² Although this study did not look at IV immunoglobulin as a treatment of attacks or of ON, it does deserve mention.

TPE has not been studied in ON during pregnancy, but immunoabsorption has been used in other diseases and was found to be safe and well tolerated during pregnancy.¹²³

Pregnancy appears to be less protective for attacks than MS for NMO.¹²⁴ Also, the postpartum period produces an increase in NMO relapses.¹²⁵ Attacks of ON occurring from NMO may be more severe than in MS, and therefore, treatments may be more warranted. Steroids have been used safely in NMO attacks,¹²⁶ but information is lacking on specific recommendations. The treating physician needs to consider data on steroids, IV immunoglobulin, and plasma exchange in pregnancy for other conditions.

Conclusion

The treatment of ON requires first that the physician determine the etiology and comorbidities of the affected patient. Only then can a proper therapeutic plan be implemented.

Disclosure

The authors report no conflicts of interest in this work.

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