NEUROMYELITIS OPTICA (NMO) AND NMO SPECTRUM DISORDER

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OVERVIEW

Neuromyelitis Optica (NMO) is a rare relapsing autoimmune disorder that preferentially causes inflammation in the optic nerve and spinal cord. It is characterized by longitudinally extensive transverse myelitis (LETM, myelitis which is 3 vertebral segments in length or greater), which can leave one quite debilitated at presentation, and unilateral or bilateral optic neuritis. It was once thought of as a variant of Multiple Sclerosis (MS), and is still oftentimes misdiagnosed as MS. However, several factors differentiate it from MS: 1) it does not often involve the brain, especially early in the disease, 2) the severity of attacks is more robust as compared to MS, and 3) the pathophysiology differs from MS – whereas MS is thought to largely be a T-cell mediated disease, NMO is mediated by anti-aquaporin 4 antibodies. Blood testing includes an anti-aquaporin-4 antibody (NMO-IgG) test, which is highly specific (>99%) and its sensitivity ranges from 48-72%, depending on the assay used.[1,2] Treatment for this disease involves acute management with therapies, including IV methylprednisolone and plasma exchange (PLEX), and prevention of future attacks with immunosuppressants, including mycophenolate mofetil or rituximab, and aggressive rehabilitation.

EPIDEMIOLOGY

NMO can affect children as young as 3 years and adults as old as 90 years. While MS is more prevalent among Caucasians, NMO disproportionately affects those of African descent.[3] It is more common in women, particularly the relapsing form of NMO. Seventy percent of NMO patients have relapses after their initial symptoms. The onset of NMO varies from childhood to adulthood, and the age of onset is about 40. In a more recent study published by Mealy et al, of the cohort of 187 patients from three academic centers in the United States, there were 14 patients with onset as a minor, with only 5-8 being pre-menses in their development.[3] Children are more likely to be NMO IgG seronegative. Typically, the average age of onset is about 10 years later than that of MS.

SIGNS AND SYMPTOMS

Most symptoms are related to optic nerve and spinal cord dysfunction, and include:

- Loss or blurring of vision in one or both eyes

- Loss of color vision
- Paralysis (no motor function) of a limb or limbs
- Paraparesis (weakness) of a limb or limbs
- Loss of sensation
- Loss of bladder or bowel control
- Profound bladder retention
- Intractable nausea and vomiting
- Intractable hiccups

DIAGNOSIS

In 2006, revised diagnostic criteria were proposed by Dean Wingerchuk, MD, MSc.[4] These guidelines include two absolute criteria, as well as the need for fulfillment of at least 2 out of 3 supportive criteria in order to be diagnosed with NMO. These criteria are as follows:

Absolute criteria

- Optic neuritis
- Myelitis

Supportive criteria

- Brain MRI not meeting criteria for MS diagnosis
- Positive NMO-IgG test
- LETM on T2-weighted imaging on MRI

Sometimes, if one does not meet these criteria, a diagnosis of NMO spectrum disorder is given at the discretion of the practitioner, because of the pattern and severity of their attacks, response to immunomodulatory agents, MRI evidence, or the high specificity of the NMO-IgG. An NMO spectrum diagnosis is highly likely to become clinically definite NMO. Regardless of the diagnosis of clinical definite NMO or NMO spectrum disorder, the standard of care for acute and maintenance therapy is the same.

ACUTE TREATMENT

While not all individuals present alike, the following are possible treatments in the management of an acute event.

<u>Intravenous Steroids:</u>

Although there are no clinical trials that support a unique approach to treat patients experiencing Transverse Myelitis (TM) or Optic Neuritis (ON), it is well recognized as a

standard of care to give high-dose intravenous methyl-prednisolone for suspected acute myelitis, generally for 5 days, unless there are compelling reasons not to. The decision to offer continued steroids or add a new treatment is often based on the clinical course and MRI appearance at the end of 5 days of steroids.

Plasma Exchange (PLEX):

PLEX is often recommended for moderate to aggressive forms of TM and ON, as is very often the case with NMO, if there is not much improvement after being treated with intravenous steroids. There have been no clinical trials that prove PLEX's effectiveness in NMO but retrospective studies of TM treated with IV steroids followed by PLEX have shown a beneficial outcome. PLEX also has been shown to be effective in other autoimmune or inflammatory central nervous system disorders. Early treatment is beneficial - PLEX is typically started within days of administering steroids, very often before the course of steroids has finished. Particular benefit has been shown if started within the acute or sub-acute stage of the myelitis or if there is continued active inflammation on MRI.

Other Acute Treatments:

In cases of no response to either steroids or PLEX therapy and continued presence of active inflammation in the spinal cord, other forms of immune-based interventions may be required. The use of immunosuppressants or immunomodulatory agents may be required. One of those approaches is the use of intravenous *cyclophosphamide* (a chemotherapy drug often used for lymphomas or leukemia). Initial presentation with aggressive forms of myelitis, or if particularly refractory to treatment with steroids and/or PLEX, aggressive immunosuppression with cyclophosphamide is recommended. It is very important that an experienced oncology team be involved in the administration of this drug, and individuals should be monitored carefully as potential complications may arise from immunosuppression. As with all medications, risks versus benefits of aggressive immunosuppression need to be considered and discussed with the clinical care team.

The use of IV immunoglobulin (IVIG) has not been tested and its use in the management of acute or sub-acute NMO is not supported.

MANAGEMENT OF NMO

In NMO, the likelihood of recurrence of disease activity is greater than 90%.[5] As mentioned, attacks in NMO are devastating, and about 50% of those diagnosed with NMO and untreated are dependent on a wheelchair and functionally blind by 5 years. Therefore, it is generally thought that ongoing treatment with medications that suppress the immune

system is necessary. There are no FDA-approved medications for maintenance in NMO, so anything prescribed is done off-label. The three primary therapies used in the US are mycophenolate mofetil (CellCept), rituximab (Rituxan), and azathioprine (Imuran).

All of these medications carry a risk of infections, particularly upper respiratory infections and urinary tract infections (UTIs). Good hygiene and hand washing are important if on immunosuppressants, as is having a good urologist if at risk for UTIs. There is also the risk with any of these medications of the development of a rare brain infection called progressive multifocal leukoencephalopathy, or PML. PML is an infection caused by the reactivation of a virus, called the JC virus, which lives in the kidney. In someone who is immunosuppressed, this virus can escape the kidney, cross the blood-brain barrier, and enter the brain, causing profound inflammation. Although it can be treated, it is very devastating, and sometimes fatal. It is important to know that exposure to these medications in NMO has not led to a known case of PML. The known rate of incidence of PML if on Rituxan is 1 in 25,000 and the rate in CellCept is 1 in 6,000 based on data from use of these medications for immunosuppression for other purposes. The manufacturer of Imuran cautions about a risk of PML with Imuran as well, but the incidence of PML on Imuran is not documented. Clinical diligence and early intervention are important if PML is suspected.

Chronic immunosuppression requires regular skin exams with a dermatologist since our immune system is our best defense against cancer cells developing, and any of these treatments can interfere with its normal functioning.

Mycophenolate mofetil and azathioprine are both twice daily pills which broadly suppress the immune system. Both medications were originally FDA approved for organ transplant rejection prophylaxis, although azathioprine now is indicated in rheumatoid arthritis and both have been widely used in several autoimmune disorders. These medications require frequent blood draws upfront, then generally twice yearly to monitor for liver toxicity and to ensure optimal immunosuppression (absolute lymphocyte count around 1 and total white blood cell count between 3 and 4).

Azathioprine is the medication that has been around the longest, and, over the years, has been used most widely in NMO. However, while the annualized relapse rate seems to be low on azathioprine, one complication with this medication involves the fact that some are not able to stay in remission on azathioprine alone and have to be on steroids in addition(these complications will be discussed below). Additionally, a long-term study of azathioprine found that the risk of lymphatic-proliferative cancers was reported to be 3%. Common side effects include gastrointestinal upset, and this may manifest as bloating, constipation, nausea, diarrhea, and may vary throughout the course of one's time on the

medication. Azathioprine is contraindicated in pregnancy, so pregnancy planning is very important. It is FDA Category D (which means don't take this drug during pregnancy unless it's life-saving) and is associated with an increased risk of miscarriages, 7% rate of congenital problems, and high rate of bone marrow suppression that recovers after birth. It is the cheapest of the medications.

Mycophenolate mofetil has a similar effect on the gastrointestinal system, though many report that the symptoms are milder with mycophenolate as compared with azathioprine. Additionally, some complain of headaches with mycophenolate, particularly in the beginning; these tend to wane with ongoing use. Generally, mycophenolate seems to be quite robust in its ability to keep individuals in remission, and, what's more, while lymphoma may be a risk of this medication, there have been no cases reported in NMO patients while on this medication so the risk is likely low. Mycophenolate is also contraindicated in pregnancy, so, again, planning is imperative. It is also an FDA Category D (don't take this drug during pregnancy unless it's life-saving), and carries a 45% chance of miscarriage. Of those that do not miscarry, 22% have congenital defects mostly in the face (mouth, ears).

Rituximab is an intravascular infusion which works differently from the other two agents listed above. Rather than being a broad immunosuppressant, rituximab completely depletes one particular type of white blood cell called B-cells, which has downstream effects on the rest of the immune system. Though protocols are slightly different, in general, it is given two times twice a year (4 infusions total), and is given in an outpatient infusion center. This is because of a 30% risk of an infusion reaction without pre-medication with some cocktail of methylprednisolone, diphenhydramine and perhaps acetaminophen. The medication is quite well-tolerated. There are generally no side effects to the medication. There is no lymphoma risk with this medication. Also, because it works differently than the other medications, it is often recommended if there is no response to the other immunosuppressants mentioned above, and vice versa; it is quite infrequent for a person to be unresponsive to both rituximab and mycophenolate/azathioprine when each of the medications are dosed appropriately. There is a monthly blood test to monitor the B-cell CD20 expression. Rituximab is safer in pregnancy than the other two previously described, (Category C; may be toxic in animals or no human data) -- there are no official FDA reports of birth defects in cases of pregnancy with rituximab but babies are born with no CD20 cells. It does not appear to increase risk of infection in babies as the cells re-populate within 6-18 months. In monkey studies performed by the manufacturer, there was no toxicity on the fetus and monkey babies were born with no CD20 cells, again with no infection risks. In the largest case series published in February 2011, out of 153 women who became pregnant on rituximab, there were 4 post-natal infections and two congenital abnormalities (1 club foot, 1 heart defect) but these women were also on other

immunosuppressant medications during the pregnancy, including azathioprine and mycophenolate. They concluded that rituximab does not increase the risk of congenital malformations above the natural rate of 1-2%. Planned pregnancy is still recommended.

Low-dose prednisone is used as well, more often in other parts of the world. As noted above, some clinicians also use it in combination with azathioprine for those who continue to relapse on azathioprine alone. Its use is oftentimes not favored in the US for maintenance therapy due to the potential complications associated with long-term steroid use, including diabetes, osteoporosis, weight gain, mood instability, hypertension, skin changes, etc.

LONG TERM CARE

Rehabilitative care is essential to prevent secondary complications of immobility and to improve functional skills. It is important to begin therapy early during the course of recovery to prevent inactivity-related problems (like skin breakdown and soft tissue contractures) that lead to loss of range of motion.

Depression

During the early recovery period, family education is essential to develop a strategic plan for dealing with the challenges to independence following return home. Ongoing problems typically include ordering the appropriate equipment, dealing with re-entry into school, work, and community, and coping with the psychological effects of this condition on both those diagnosed with NMO and their families. While it is an appropriate response to be saddened by the idea of having to adjust to an altered way of living as a result of residual complications of NMO, inability to move past this grief in a reasonable period of time such that it interferes with relationships and functional living, it needs to be addressed and treated. Many fear that depression reflects on oneself as an inadequate ability to cope with their diagnosis and feel weak. But it is not a personal strength issue, and depression is very much a physiological manifestation and treatable. Both talking to a psychiatrist / psychologist and medication management can have benefit, and some studies indicate a synergistic effect of combining the two. Depression can rebound and can at times become more resistant to treatment.

Spasticity and immobility/paralysis

Spasticity means stiffness or muscle spasms, and is often a very difficult problem to manage. Some stiffness in our muscles is necessary in order to control our movement, but when they become too tight, the result can range from slightly bothersome stiffness

(particularly upon wakening) to uncontrollably painful spasms. When the latter occurs, small triggers such as changes in position, temperature, humidity, or presence of infections can cause this painful spasticity. The key goal is to remain flexible with exercise, a daily stretching routine, and a bracing program with splints, as needed. These splints are commonly used at the ankles, wrists or elbows. Medication options to relieve spasticity can be used in conjunction to these techniques, as well as therapeutic botulinum toxin injections and serial casting. The therapeutic goal is to improve function in performing specific activities of daily living (i.e., feeding, dressing, bathing, hygiene, mobility) through improving the available joint range of motion, teaching effective compensatory strategies, and relieving pain. Left untreated, severe spasticity can lead to shortening of the affected muscle or joint called contractures, further impacting mobility, rehabilitation, and independence.

An appropriate strengthening program for the weaker of the spastic muscle acting on a joint and an aerobic conditioning regimen are also recommended. Assessment and fitting for splints designed to maintain an optimal position for limbs that cannot be actively moved is an important part of the management at this stage. The effects on mobility as a result of NMO can vary widely, however, from paralysis to mild weakness. Either way, physical therapy is instrumental in returning function. Because physical therapists deal with many different types of injuries and diseases, it is ideal to work with one who has a particular interest in spinal cord rehabilitation when possible. Assistive devices may be necessary for weakness – it can be difficult and oftentimes humbling to take the necessary step of using an assistive device, but when faced with the alternative of broken hips, heads, and the downstream effects of lost wages or jobs, it is an important and sometimes indispensable step in maintaining independence. It is also always very important to remember to exercise, as tolerated, in order to maintain physical health and stamina.

Managing bowel and bladder complications

Another major area of concern is effective management of bowel and bladder function. Constipation is the most common bowel elimination issue. A high fiber diet, adequate and timely fluid intake, medications to regulate bowel evacuations, and regular exercise are all important contributors in helping with gastrointestinal motility. Common bladder problems include incontinence, frequency, nocturia (frequent urination at night), hesitancy, and retention. Treating incontinence, frequency, and nocturia is often easier than treating hesitancy and retention, where clean intermittent urinary catheterizations are the basic component to success. Working with a good urologist is imperative to prevent potential serious complications, particularly one who understands spinal cord disease. Urodynamic testing is necessary to determine urine retention to check risk for urinary tract infections, particularly if there is a history of UTIs to guide the urologist in terms of the best

management.

Fatigue

Fatigue is the lack of mental and/or physical energy. Fatigue can be a direct result of a disease process (primary fatigue) or an indirect result (secondary fatigue). In NMO, fatigue is more often thought to be a result of secondary fatigue. Examples of secondary fatigue include fatigue from medications, depression, stress, poor sleep patterns, infections, or changes in walking, which increase energy requirements. The key is to try to identify the underlying cause of the fatigue – for example, if one is not sleeping well because of pain, bladder dysfunction, or depression, this needs to be identified and addressed; not getting consistent sleep will worsen every other aspect of NMO! If too much energy is exerted due to changes in walking, physical therapy can help identify better body mechanics that will help conserve energy. When nothing else can be identified as contributing to fatigue, REST is recommended! Conserving energy such that activities are planned and paced can allow for these activities to be more enjoyable rather than stressful. Also, reorganizing home and office can help to reduce the amount of wasted energy exerted so that energy can be saved up for activities that are enjoyable. Also, exercise routines incorporated in the day can actually help build stamina and reduce fatigue in the long-run – it's also a great stress reducer! Pilates, yoga, and swimming are great, but the key is to find something enjoyable and not overdo it.

Neuropathic Pain

Changes in sensation often occur and can manifest as lack of sensation, or numbness, as well as painful sensations called neuropathic pain. This pain is described in many different ways, including burning, squeezing, stabbing, or tingling. Having the sensation of pain means the nerve signal is getting through, but in an inappropriate way. While this can get better over time, there is a long list of medications to treat these symptoms. The same medication doesn't work for everyone, so the trial and error of finding the right medication can be frustrating. Alternative therapies such as acupuncture and meditation have also been utilized, with varying success.

While the body is constantly working toward repair, once damage is done to the central nervous system, there will always be evidence of this damage, usually evidenced on an MRI. Clinical fluctuations of old symptoms, particularly in the setting of infection, stress, heat, menstrual cycle, or anything that increases core body temperature or throws the body off of its normal course are also possible. It is important to note that this is not inflammatory driven and therefore in no way represents worsening of the condition.

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