



The Transverse Myelitis Association

<http://myelitis.org>

We are pleased that you have found The Transverse Myelitis Association (TMA). The TMA is a not-for-profit international foundation dedicated to the support of children, adolescents, and adults with a spectrum of rare neuroimmunologic disorders, including Acute Disseminated Encephalomyelitis (ADEM), Neuromyelitis Optica (NMO), Optic Neuritis (ON), and Transverse Myelitis (TM). Founded in 1994 by family members and persons with these diagnoses, the TMA was incorporated on November 25, 1996 in the state of Washington and we became a 501(c)(3) organization on December 9, 1996. Membership of the TMA includes individuals with these rare disorders, their family members and caregivers, and the medical professionals who treat individuals with these disorders. The TMA currently has approximately 9,000 members from more than 80 different countries and has a large number of support groups across the United States and around the world.

Our Mission and Programs

Our mission is to support and advocate for individuals diagnosed with the rare neuroimmunologic disorders of the central nervous system and their families by promoting awareness, providing education, fostering clinician-scientists dedicated to these rare diseases through training, and advancing new knowledge through the support of basic science and clinical research. It is our goal to improve the quality of life of individuals with these rare disorders and to create a collaborative environment dedicated to the understanding of these disorders.

We provide numerous services for our members. Our web site offers a tremendous amount of information and creates a support network between persons with these disorders, including the development of local support groups. Our goal is to advance a comprehensive network dedicated to the care of our members through the development of professionals specializing in these rare disorders, centers of excellence focused on these disorders around the world, and our international community support system. Additionally, we are developing strategic research priorities with our Board of Directors and Medical Advisory Board to further the understanding of the causes of TM, ADEM, ON and NMO, and to develop new acute and regenerative therapies. To attract new clinicians and researchers into the rare neuroimmunologic disorder discipline, we have established the James T. Lubin Fellowship. We publish newsletters to update the community on current research and various community outreach events and opportunities.

We support and conduct various educational events through symposia and workshops involving clinicians, scientists, and individuals affected by these disorders for the exchange of information regarding research and treatment strategies. We also support a family camp for children with these disorders and their family members.

You can find a complete listing of all of our support groups on our web site, along with the contact information for our support group leaders. If you do not have access to our web site, we encourage you to contact us or your support group leader to be connected to other members of the Association and to get involved. It is a wonderful way to find support and information in your community, state or country. If there is no support group in your area, please consider starting one. To get started, all you have to do is get in touch with us. There are new support groups getting started all the time. Please also join us on Facebook to meet other members and engage in a dialogue through our website: <http://myelitis.org/get-involved/support-groups/>

In this packet we have included the latest publication of the TMA. All of the earlier versions of the journals and newsletters are archived on our web site and we urge you to read all of these

publications, as they are likely going to be your best source of information about the rare neuroimmunologic disorders. Please thoroughly review our web site for additional information including an excellent bulletin board system, videos of physician presentations from past workshops and symposia, and links to other sources of information, including the Johns Hopkins Transverse Myelitis and Neuromyelitis Optica Center and the TM and NMO Center at the University of Texas Southwestern in Dallas. Adults and children with ADEM and ON are also cared for at these centers.

There are no membership fees for the TMA; we operate exclusively on the basis of voluntary contributions. We urge you to support the TMA and to make us a regular part of your generous giving.

You are not alone. If we can be of any assistance, please feel free to contact us. We hope that you are doing well. Our best wishes to you and your family.

Sincerely,



Sanford J. Siegel
President



Chitra Krishnan
Executive Director

Contact The Transverse Myelitis Association

If you are interested in becoming a member of the TMA, or contributing to our efforts, please contact us at the information below. The efforts of the TMA are supported largely by our members and through charitable contributions and fund-raising events. Your support to help advocate for and bring awareness to these rare neuroimmunologic disorders through the TMA is greatly appreciated.

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Neuroimmunologic Disorders of the Central Nervous System: An Overview

We are grateful to Dr. Benjamin Greenberg, Director of the TM and NMO Centers at the University of Texas Southwestern in Dallas for this overview article.

The Transverse Myelitis Association advocates for people who have Transverse Myelitis (TM), Recurrent Transverse Myelitis, Neuromyelitis Optica (NMO), Acute Disseminated Encephalomyelitis (ADEM), and Optic Neuritis (ON) and their caregivers. The language used when diagnosing and describing these conditions can be quite confusing. This overview is meant to provide an introduction to these disorders and to the language used by physicians to describe them.

All of these conditions are immune-mediated disorders of the central nervous system (brain, spinal cord and optic nerves). The immune system is the body's defense against foreign invaders, such as viruses and/or bacteria. Normally, the cells that are a part of the immune system have the ability to distinguish an infectious agent from a person's body; however, sometimes some of these cells become 'confused' and mistakenly attack an organ within a person. This is known as autoimmunity. Health care providers sometimes use the term 'inflammation' to describe this occurrence. Inflammation refers to situations when immune cells invade human tissue. For example, if there is inflammation in a spinal cord, then immune cells have invaded the spinal cord. Inflammation can be normal, such as during an infection, or abnormal, such as during autoimmune attacks.

The neuroimmunologic disorders that are supported by the TMA occur when a person experiences an inflammatory attack at some location in their central nervous system. When the spinal cord is affected it is called Transverse Myelitis (TM), and when the optic nerve is affected it is called Optic Neuritis (ON). In Acute Disseminated Encephalomyelitis (ADEM) and Neuromyelitis Optica (NMO) there are various patterns of organ involvement, and in some disorders there is the potential for recurrent events. When the central nervous system is affected, there are multiple kinds of damage that can occur. The connections between the brain and body are like insulated electrical wires. During an immune mediated attack on the central nervous system, the insulation around the wire (myelin) or the wire itself (axon) can be damaged. When an inflammatory attack damages the insulation, the damage is referred to as demyelination.

When the myelin or axon of a neuron is damaged, it is unable to conduct a signal. The symptoms are dependent on which axons are affected. For example, if the wire that carries visual information from the eye to the brain (optic nerve) develops demyelination, then signals are not carried to the brain efficiently resulting in a person having blurred or lost vision (ON). If the demyelination occurs in the wires sending motor signals to a person's legs, then the person has weakness and difficulty walking.

Mechanism of Disease

Very little is understood about the disease mechanisms for these disorders. It is believed that a person who develops one of these rare neuroimmunologic disorders likely has a genetic predisposition to auto-immunity, and that there are environmental factors that interact with these genetics to trigger the disease. The specific genetics in each of these disorders is not completely understood and environmental factors have not been clearly identified. In the case of Multiple Sclerosis (MS), a relationship to decreased levels of vitamin D and diminished exposure to sunlight are being considered, but no other factors are suspected for these other neuroimmunologic disorders. It is believed that the immune system response could be to a viral, bacterial or fungal infection, and in the case of TM, a significant number of people have flu-like symptoms, a respiratory infection, or a child might have an ear infection preceding their attack. This immune response might explain why the immune system was revved up. However, it does not explain why the immune system becomes dysfunctional and attacks 'self.' Additionally, no one understands why some people have a good recovery from an attack, while others have no recovery.

The central nervous system is separated and protected from foreign agents by the blood brain barrier. For the immune system to attack anywhere in the central nervous system, cells from the immune system have to pass through this barrier. Thus, in the case of these disorders, not only does the immune system become confused, it also has to find a way to cross this protective barrier to get to the brain, the spinal cord and/or the optic nerves. These mechanisms are not very well understood.

Differential Diagnoses

Transverse myelitis (TM) is an immune-mediated inflammatory attack of a person's spinal cord. Sometimes the inflammation has no clear cause and is referred to as Idiopathic TM. The majority of these cases are probably post infectious events, but this can be difficult to prove. In general, individuals with Idiopathic TM do not have recurrences or future inflammatory events. At other times, TM is part of a larger autoimmune process, such as NMO, MS, Sarcoidosis, Sjogrens Syndrome, Lupus, or ADEM. When presenting with TM, clinical care should focus on reducing inflammation acutely and trying to determine if there is an underlying cause.

In rare cases, a person can have more than one inflammatory attack in their spinal cord; this is called **Recurrent transverse myelitis (RTM)**. In each unique episode, the inflammatory attack occurs only in the spinal cord. There is no brain or optic nerve involvement in any of the episodes. It is important in these cases that the inflammatory attack in the spinal cord be identified; the diagnosis cannot be based solely on clinical symptoms, as there can be a worsening of symptoms apart from a new attack in the spinal cord. It is also important that the attack be identified as a unique attack and not associated with an unresolved initial attack. For example, if a person experiences an inflammatory attack and then two weeks later, the inflammation worsens; this cannot be considered a second attack. The first attack must completely resolve over time and the next attack must occur after this resolution to be considered a subsequent attack. Everyone with recurrent TM must have NMO ruled out. There should also be a rule out of an underlying rheumatic disorder, discussed below.

Neuromyelitis Optica (NMO) involves immune-mediated inflammatory attacks in the spinal cord and/or the optic nerve. A person with NMO is at risk for multiple attacks of spinal cord inflammation or ON, or both. There is ordinarily no brain involvement, but this is not always the case. There is a blood test for NMO called NMO-IgG that is clinically available. If a person tests positive for NMO-IgG, they have NMO. In approximately 30% of cases, a person may test negative but still have NMO; thus a negative NMO-IgG does not definitively rule out NMO.

If a person with Transverse Myelitis presents with a lesion (inflammation) that extends to 3 vertebrae in length

or longer, they are at risk for multiple attacks, i.e., it is possible that the attack in the spinal cord is a first attack of Neuromyelitis Optica. This condition is called **Longitudinally Extensive Transverse Myelitis (LETM)**. Infants and young children seem to be the exception to this situation. Infants and young children tend to have very long lesions that may begin high in the cord (cervical region), and yet they do not seem to have the same risk for multiple attacks as adults with LETM. They have TM. As children can also have NMO, this remains an area that is in need of critical research focus.

Multiple Sclerosis (MS) involves an inflammatory attack that can occur anywhere within the central nervous system (i.e., brain, spinal cord and/or optic nerves). Brain lesions at the time of onset or early in the course of the disease are common. The lesions in the brain are ordinarily identified in a specific pattern; however, lesions may be present anywhere in the white matter. MS involves more than one episode (i.e., recurrent attacks), and the multiple episodes occur in different locations in the central nervous system.

Acute Disseminated Encephalomyelitis (ADEM) involves inflammation and demyelination in the brain and often involves inflammation in the spinal cord. In some instances, there can also be optic nerve involvement. ADEM may occur after a bacterial or viral infection (post infectious), or following an immunization (post vaccination). The demyelination in the brain is different than a demyelinating attack from MS; white matter lesions tend to be diffuse. ADEM is most often monophasic, although there are rare recurrent variants of ADEM. It can be characterized by headache or seizures and may involve vision loss. The spinal cord involvement is the same as TM, as are the associated symptoms. ADEM is more common in children than in adults.

Finally, **Optic Neuritis (ON)** ON involves a demyelinating attack of the optic nerve. In isolated ON, there is no brain or spinal cord involvement. An episode of ON may be a first attack of NMO or a first attack of MS. Working through a differential diagnosis is important. A person may have ON or Recurrent ON and never have an attack in the spinal cord or brain.

Diagnosis

Each of these neuroimmunologic disorders remain a challenge to diagnose. Only NMO has a distinct and defined marker and this auto-antibody is present in about 70% of cases that are diagnosed as NMO. The diagnostic criteria for the other disorders are neither entirely clear-cut nor universally accepted in medicine (i.e., there appear to be numerous exceptions to every rule). The relationships between each of these disorders are also not well understood (i.e., is each of these disorders a unique disease, or are some of them variants of the same disease?) To arrive at a diagnosis for any one of these disorders, an MRI will need to be done, with and without contrast agent, a spinal tap (lumbar puncture) should be performed, and brain scans will need to be done to rule out MS. If NMO is suspected (recurrent TM, ON, recurrent ON, or LETM), the NMO-IgG should be done.

Acute Treatments

Treatment for these disorders in their acute or early stages involves quieting down the immune system as quickly as possible, before damage is done. These treatments need to be considered in the context of the correct diagnosis and administered as quickly as possible. Time is critical. Unfortunately, there is very little research and almost no scientific evidence available as to the most effective treatments for any one of these disorders. It is important to be working with a physician who has good experience with these disorders, because acute treatment is going to involve primarily or exclusively clinical judgment. If your physician does not have this experience, it is important to ask your physician to consult with a physician who does. There are very few clinical centers with physicians who specialize in TM or NMO (e.g., University of Texas Southwestern, Johns Hopkins, Mayo Clinic, University of California San Francisco, Walton Centre - Liverpool, England), but there are numerous Multiple Sclerosis Centers associated with prominent medical

centers and medical schools. A specialist from one of these centers should be considered, as they have experience in demyelinating disorders of the central nervous system. The acute therapies most frequently used to treat an inflammatory attack include: high dose intravenous steroids (methylprednisolone), Plasmapheresis (Plasma Exchange or PLEX), Immunoglobulin Therapy (IVIG), and cyclophosphamide.

After the inflammation has begun to resolve and the person is medically stable, the next course of treatment for a person who has an inflammatory attack in their spinal cord (ADEM, NMO, MS or TM) involves intensive rehabilitation therapy. Centers devoted to spinal cord injury and disease or stroke offer comprehensive rehabilitation programs for people who have suffered significant spinal cord deficits from the inflammatory attack. The Christopher and Dana Reeve Foundation's web site (www.paralysis.org) provides excellent information regarding the factors that should be considered in selecting a rehabilitation hospital. Children and adults who have experienced significant muscle weakness or paralysis should be admitted to a specialized rehabilitation hospital, and the program should include an aggressive physical and rehabilitative therapy regimen (as opposed to an exclusive emphasis on independence training).

Most cases of ADEM and TM are considered monophasic. It is important to have regular appointments with a neurologist to monitor the progress of the disease, if any. Over time and depending on symptoms, a yearly exam might be sufficient for many people. The symptoms from these disorders can be quite challenging to manage and can change over time. Other specialists should be considered in consultation with a neurologist and general practice physician or pediatrician (e.g., urology, psychiatry, orthopedics, and physiatry).

People with NMO, Recurrent TM, or recurrent ADEM are at risk for multiple attacks and should be monitored more closely. People with these disorders will likely receive medication to either diminish the chance of another attack, or lessen its severity should it occur. It is important that a definitive differential diagnosis from MS be made by a physician. The MS treatments (i.e., Avonex, Betaseron, Copaxone, Gilenya, Rebif, and Tysabri) have not proven to be effective in the treatment of people with NMO or Recurrent TM and in some cases may cause more harm than good. Most often, people with Recurrent TM or NMO are considered for immune suppressant therapies. Which therapies a person is placed on is based entirely on the clinical judgment (experience) of the physician, combined with individual needs. Again, it is critically important to be working with a physician who has substantial experience with Recurrent TM and NMO. If it is not possible to be cared for by a physician from one of the centers that specialize in these disorders, we recommend that your neurologist consult with one of these specialists about a long-term therapy program.

The members of the TMA include people with idiopathic TM, ADEM, NMO, ON, recurrent TM, TM and NMO with HIV, people who have TM and NMO with an underlying rheumatic disorder (Lupus or Sjögren's syndrome), people who have Neurosarcoidosis, people with Lyme Disease and direct infections of the cord (i.e., meningitis), and people who have various myelopathies of the spinal cord, (such as radiation, spinal strokes or arteriovenous malformations), as well as the family members of people with these disorders.

While much about these disorders remains a mystery, there is much that is understood. Our great hope comes from the fact that there are excellent researchers and clinicians who are focused on the neuroimmunologic disorders and more is learned about the immune system and these disorders every single day. There is a great deal of information about each of these disorders on our web site (www.myelitis.org). We urge you to learn as much as you possibly can about your disorder and we hope that this will empower you to become the most effective advocate for your medical care.

Acute Disseminated Encephalomyelitis (ADEM)

Acute Disseminated Encephalomyelitis (ADEM) is a rare inflammatory demyelinating disease of the central nervous system. ADEM is thought to be an autoimmune disorder in which the body's immune system mistakenly attacks its own brain tissue, triggered by an environmental stimulus in genetically susceptible individuals. More often it is believed to be triggered by a response to an infection or to a vaccination. For this reason, ADEM is sometimes referred to as post-infectious or post-immunization acute disseminated encephalomyelitis.

Epidemiology

According to a study published in 2008, the estimated incidence in California is 0.4 per 100,000 population per year, and there are approximately 3 to 6 ADEM cases seen each year at regional medical centers in the US, UK, and Australia². ADEM is more common in children and adolescents than it is in adults, and there does not seem to be a higher incidence of ADEM among males or females, nor does there seem to be a higher frequency among any particular ethnic group.

Post-infectious In approximately 50-75 percent of ADEM cases, the inflammatory attack is preceded by a viral or bacterial infection. There have been a large number of viruses associated with these infections, including but not limited to: measles, mumps, rubella, varicella zoster, Epstein-Barr, cytomegalovirus, herpes simplex, hepatitis A, influenza, and enterovirus infections. A seasonal distribution has been observed showing that most ADEM cases occur in the winter and spring. The inflammatory attack and neurological symptoms often begin within a couple of weeks after the viral or bacterial illness.

Post-immunization Less than 5 percent of ADEM cases follow immunization². The association between an inflammatory attack following an immunization has been temporal and the direct connection between a vaccination and an immune attack has not been established. Post-vaccinial ADEM has been associated with immunization for: rabies, hepatitis B, influenza, Japanese B encephalitis, diphtheria/pertussis/tetanus, measles, mumps, rubella, pneumococcus, polio, smallpox, and varicella. Currently, the measles, mumps, and rubella vaccinations are most commonly associated with post-vaccinial ADEM. No infectious agent is isolated in most cases. The incidence of ADEM associated with the live measles vaccination is 1 to 2 per million. Neurologic symptoms typically appear 4 to 13 days after a vaccination.

Signs and Symptoms

The neurological signs from the inflammatory attack often begin with fever, headache, and vomiting. Encephalopathy (damage or malfunction of the brain) is a characteristic feature of ADEM and usually develops rapidly. This results in symptoms, such as altered level of consciousness, acute cognitive dysfunction, behavioral changes, and seizures in about a third of those diagnosed. The altered consciousness can range from lethargy to coma.

In addition to encephalopathy, other common neurologic signs of ADEM include: long tract pyramidal signs (decreased voluntary movement), acute hemiparesis (muscle weakness on one side of the body), cerebellar ataxia (decreased muscle coordination), and cranial neuropathies (damage of cranial nerves). ADEM is multifocal; meaning the inflammatory attack can occur in the brain, as well as occur as optic neuritis (ON) and/or transverse myelitis (TM). Thus, a child or adult with ADEM can have the symptoms of ON (i.e., impaired vision and eye pain), and/or all of the symptoms from an inflammatory attack in the spinal cord (TM). The TM symptoms depend on the severity and the level of the attack in the spinal cord. These can include: impaired breathing, bowel and bladder dysfunction, paralysis or muscle weakness, spasticity, paresthesias, or nerve pain. The inflammatory attack can go on for a few days or for a few weeks. The most severe symptoms are ordinarily reached within the first 4 to 7 days, and the first 2 to 4 weeks are the most

severe period.

Diagnosis

The diagnosis of ADEM is based on clinical and radiologic characteristics. Unfortunately, there is no specific biologic marker or confirmatory test to specifically identify the disorder, nor is there scientific, randomized, or controlled data on the diagnosis and treatment of ADEM. Decisions about the diagnosis and treatment of this disorder are based primarily on the opinions of experts. Since decisions will be based on clinical judgment, trying to connect to an expert is critically important.

An ADEM diagnosis is considered when individuals develop multifocal neurologic abnormalities with confusion, excessive irritability, or altered level of consciousness (encephalopathy), especially if the onset of symptoms occurs within 1 to 2 weeks after a viral/bacterial infection or a vaccination. Physicians must rule out that there is a direct infection of the central nervous system as opposed to an infection that subsequently triggered the immune system to cause the attack. Should a direct infection be suspected, one is often placed on an antibiotic and/or acyclovir (an antiviral drug) to fight the infection.

Laboratory studies include a complete blood count and cultures, and serologic studies are performed on blood and cerebrospinal fluid to detect bacterial and viral organisms. Additionally, viral cultures are obtained from nasopharynx and stool.

A lumbar puncture is also performed. This test is useful because evidence of inflammation is common in cerebrospinal fluid (CSF), with pleocytosis (increased white blood cell count) and/or increased protein concentration. While this is common, sometimes the CSF can be normal. Additionally, although oligoclonal bands are nonspecific and are more often associated with Multiple Sclerosis (MS), they are sometimes also present in ADEM.

An MRI of the brain and spine is important to establish a diagnosis of ADEM. Abnormalities are best defined by T2-weighted images, FLAIR sequences, and contrast-enhanced MRI with gadolinium. Abnormalities on MRI usually vary in location. Lesions associated with ADEM tend to be bilateral, but can also be asymmetric and are typically poorly margined. Multiple lesions in the deep and subcortical white matter are common, which is characteristic of demyelination (gray matter lesions sometimes accompany white matter lesions, especially among children). While the number varies, multiple brain lesions are usually present. ADEM lesions are typically large (though smaller ones have also been seen) with diameters ranging from <5 mm to 5 cm. Additionally, brainstem and spinal cord abnormalities on MRI are common in ADEM. In the spinal cord, there are typically large confluent intramedullary lesions that extend over multiple segments of the cord.

It is possible that the MRI may be normal early in the course of the disorder and may have to be repeated. Some physicians recommend repeating MRIs on follow-up to ensure there are no new lesions, which could change the diagnosis from ADEM to multiphasic ADEM (see below) or MS.

In a situation where nonspecific cerebrospinal fluid abnormalities and MRI evidence of white matter lesions are present, it is important that other inflammatory demyelinating disorders be considered. These include: MS, ON, TM, and Neuromyelitis optica (NMO).

Diagnostic Criteria An important paper was recently published by the International Pediatric Multiple Sclerosis Study Group, which proposed diagnostic criteria for ADEM in children.¹ The criteria are important for the purpose of arriving at better decisions about treatments and are meant to facilitate research on ADEM. The major criteria include:

A first clinical attack of central nervous system demyelinating disease with acute or subacute onset, polysymptomatic neurologic features, and encephalopathy

Brain MRI showing focal or multifocal lesions, predominantly involving the white matter, without evidence of previous white matter changes

Encephalopathy as a presenting symptom, with the onset of encephalopathy corresponding with the occurrence of the disease state (encephalopathy is defined to include behavioral changes, such as lethargy or irritability, or severe changes in the level of consciousness such as coma)

These features help distinguish ADEM from other clinically isolated syndromes, which have a greater risk for recurrence and subsequent diagnosis of MS.

The authors of the publication define three different categories of ADEM:

Monophasic ADEM is a one-time episode that can develop over a period for as long as three months. Any new or changing symptoms within this three month period is considered as one event. Symptoms that might occur during an oral steroid taper or within one month of the completion of the taper are also classified as one single episode. Recurrent and multiphasic ADEM episodes must occur more than three months after the initial event and more than one month after the completion of steroids.

Recurrent ADEM is defined as a subsequent attack that involves the same symptoms that occurred during the initial attack. The MRI findings tend to be similar to the initial attack, and there are no lesions, but there could be an enlargement of the lesions from the original episode.

Multiphasic ADEM is defined as an attack that involves new areas of the central nervous system from the initial or previous attacks. There must be signs of encephalopathy, but symptoms and neuroimaging findings are in different areas from the initial attack. There might be new lesions evident on MRI and there might also be evidence of partial or complete resolution of the lesions associated with the first episode.

The International Pediatric MS Study Group authors also provide an excellent comparison across a number of variables for making the differential diagnosis between ADEM and MS. ADEM more frequently occurs among younger age groups (<10 years) and there does not seem to be a higher incidence between boys or girls. MS occurs more frequently in adolescents and the incidence is higher for girls than for boys. A prior flu-like illness is typically the case in ADEM, while it is variable for MS. Encephalopathy is required to arrive at a diagnosis of ADEM while it is rare in the early stages of MS. Seizures are variable in ADEM and rare in MS. A single event in ADEM can fluctuate over the course of three months, while in MS a discrete event is separated by at least four weeks. Large lesions involving gray and white matter are frequently evident from MRI in ADEM and rare in MS. MRI frequently shows enhancement in both ADEM and MS. Over time, lesions typically appear to resolve in ADEM, while in MS, there is typically development of new lesions. CSF pleocytosis (presence of a greater number of cells than normal) is variable in ADEM and extremely rare in MS (white blood cell count almost always <50). Finally, the presence of oligoclonal bands in the spinal fluid is variable in ADEM and frequently found in MS.

Acute Treatment

All of the treatments for ADEM are based largely on opinions from respected authorities based on clinical experience, descriptive studies or reports of expert committees. Standard treatments recommended in acute ADEM are not confirmed from randomized, placebo-controlled trials.⁴

Since patients with ADEM usually present with fever, meningeal signs, acute encephalopathy, and evidence of inflammation in blood and CSF, it is important to first consider a treatment with antibiotics and/or acyclovir until an infectious cause is ruled out. A high dose of intravenous corticosteroids, for 3-5 days is the primary and most common first treatment of ADEM and the corticosteroids can be used concurrently with antibiotics and acyclovir. Plasma Exchange (PLEX) is recommended if there is no response to corticosteroids. Intravenous immunoglobulin (IVIG) is recommended if there is no response to PLEX.

The strength of evidence for the recommendation of corticosteroids and PLEX are graded as moderate. The strength of evidence for a recommendation of IVIG is poor. It should be noted that no studies have compared IVIG treatment with corticosteroids or plasma exchange, and there is debate over whether PLEX or IVIG should be used first when corticosteroids fail to work.

Prognosis and Management

The prognosis for most children with ADEM is good. The recovery is usually a slow process lasting from four to six weeks and the majority of children with ADEM make a full recovery. Between 60 to 90 percent are left with no neurological deficits. Those children who do have residual symptoms are reported to have symptoms from transverse myelitis (the spinal cord inflammatory attack), recurrent headaches, and behavioral problems. The location of lesions and the extent of inflammatory lesions do not appear to have any predictive value in regard to outcome. Typically, follow-up MRIs show complete or partial resolution of abnormalities in the majority of ADEM cases.

Long-term clinical follow-up and sequential imaging by MRI are normally required to confirm a diagnosis of ADEM. Should there be a development of a relapse with new lesions, it is not compatible with a diagnosis of monophasic ADEM, and depending on the clinical and imaging features, it likely suggests the correct diagnosis being either multiphasic ADEM or MS. Though there is no consensus, some physicians recommend that children receive follow-up MRIs for a period of up to five years to ensure that there is no new inflammatory activity after the initial ADEM attack; i.e., to confirm that the diagnosis is not MS.

Please be sure to read the symptom management strategies presented in the transverse myelitis article as these strategies will be the same for the symptoms that are present from an inflammatory attack in the spinal cord from ADEM.

References

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Neuromyelitis Optica (NMO) and NMO Spectrum Disorder

The Transverse Myelitis Association would like to thank Maureen A. Mealy, RN, MSCN, Clinical Program Manager at the Johns Hopkins Transverse Myelitis Center and Neuromyelitis Optica Clinic for writing this overview article.

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.

Intravenous Steroids:

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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Optic Neuritis (On)

The Transverse Myelitis Association would like to thank Dr. Benjamin Greenberg (UT Southwestern Medical Center) for his support in writing this article (which has been adapted from articles written by Dr. Laura Balcer, Hospital of the University of Pennsylvania).

Optic neuritis (ON) is an inflammatory demyelinating condition of the central nervous system that results in the loss of vision and is associated with eye pain, loss of color vision and visual field deficits. While ON can occur in isolation, it is often part of multiple sclerosis (MS), Acute Disseminated Encephalomyelitis (ADEM) or neuromyelitis optica (NMO or Devic's disease). ON can be the presenting feature of MS (15-20% of the time) and occurs in 50% percent of those diagnosed with MS at some point during their illness.² ON is typically monocular (affecting one eye), though it can also affect both eyes sequentially or simultaneously. Bilateral ON tends to be more common in children younger than 15 years old.²

The most common cause of ON is inflammatory demyelination of the optic nerve. The pathology (similar to that of acute MS) involves plaques in the brain, with perivascular cuffing, edema in the myelinated nerve sheaths, and myelin breakdown.² Similar to MS, a genetic susceptibility for ON is suspected, and it is believed that the demyelination in ON is immune-mediated. However, the specific mechanism and target antigen(s) are unknown.²

Epidemiology

ON is a rare condition. US studies estimate the annual incidence to be 6.4 per 100,000 in population.² The occurrence of ON tends to be the highest in populations located in higher latitudes (in the northern US and Western Europe), and is the lowest in regions closer to the equator.² ON is more common in women (predominance ratio of 3:1), and develops in most patients between the ages of 20 and 45.³ Additionally, ON typically occurs more frequently in Caucasians than African Americans.² It has been reported that whites with northern European descent develop ON eight times more frequently than blacks and Asians.³

Signs & Symptoms

The classic symptoms of acute ON consist of unilateral loss of vision (in 70 percent of individuals), periocular pain, and dyschromatopsia (color blindness or color vision deficiency).³ This typically comes on over the course of a few days and peaks within one to two weeks.² ON usually begins with decreased vision in one eye. Approximately 90 percent of diagnosed individuals also experience pain behind the eye which is usually exacerbated by eye movement.³ Visual loss can vary from mild reduction and minor blurring to no perception of light. Symptoms tend to exacerbate with increased body temperature.³ Other common signs and symptoms of acute ON include: visual field defects, swelling of the optic nerve, photopsias (the presence of perceived flashes of light), and an afferent pupillary defect always occurs in ON if the other eye is uninvolved.²

Another key aspect of ON is that vision and eye pain usually improve within 2 to 3 weeks after the onset of symptoms. More than 90 percent of individuals experience visual improvement within this timeframe regardless of treatment.³ Should symptoms persist for longer than 3 weeks, it suggests that it is either an atypical type of ON or is a different diagnosis.

Diagnosis

Generally, a clinical diagnosis of ON is based on the history and examination findings. Though demyelination is its most common identifiable cause, many other causes of optic neuropathy may resemble ON, and misdiagnosis is not uncommon.³ Diagnostic testing is typically directed toward excluding other causes of

visual loss in atypical cases, and assessing the risk of subsequent MS.² An early evaluation is essential to ensuring visual recovery has begun and to reconsider the diagnosis if it has not.

As mentioned, in typical cases of ON, visual improvement occurs within 2 to 3 weeks regardless of treatment. Thus, in typical cases, which show no additional clinical signs and symptoms of a systemic disease, the value of diagnostic testing is fairly low. However, if there are atypical signs and symptoms (i.e., bilateral presentation, younger than 15 years old, or possible infection) suggesting an alternative diagnosis, a complete assessment should be undertaken.³

MRI is used to take images of the brain and orbits to confirm the diagnosis of ON. However, the real value of MRI in typical ON is not to image the optic nerves, but rather to image the brain as a prognostic indicator for the future development of MS.³ Often the brain MRI shows white matter abnormalities, or lesions, which are characteristic of MS - ovoid, periventricular, and larger than 3 mm lesions which indicate a higher risk of developing MS.²

Lumbar puncture is usually not considered an essential diagnostic test in ON, but should be considered in atypical cases. Approximately 60 to 80 percent of ON diagnoses show nonspecific abnormalities in cerebrospinal fluid (CSF).² Additionally, 56 to 69 percent of individuals also show oligoclonal bands (OCB) in their CSF, which implies a higher risk of developing MS.² However, since OCB is closely associated with white matter lesions seen in MRI, the presence of OCB is not of high prognostic importance.²

Finally, optical coherence tomography (OCT) is also commonly used to detect ON. OCT measures the thickness in the retinal nerve fiber layer and detects thinning in 85 percent of patients with ON.² While lower values correlate with impaired visual outcome, its usefulness as a prognostic tool is limited due to the fact that abnormal values do not show up until early swelling disappears.² OCT is also important as a number of studies have found that a greater severity of optic nerve injury, seen on OCT, suggests NMO rather than ON associated with multiple sclerosis.²

Additional diagnostic tests used to detect ON or assess the risk of other conditions include: fluorescein angiography, visual evoked response, and Aquaporin-4-specific serum autoantibody to rule out NMO.²

Acute Treatment

Corticosteroids are the most common treatment for ON. They may be given intravenously or as high dose tablets. While corticosteroids have been effective in improving short-term visual recovery, they do not seem to affect the long-term outcome. Due to the lack of long-term benefit and the risk of potential side effects (including: insomnia, weight gain, and mood alterations), the use of corticosteroids is usually not advised.³ However, there are specific situations where they may be used to reduce the period of impairment and are usually considered when a more rapid recovery is required (such as patients with severe bilateral visual loss or those with occupations that require normal visual acuity).³ Unfortunately, there is currently no treatment that can reverse vision loss caused by ON.

Prognosis and Management

Most people recover well from ON. In approximately 80 percent of individuals, vision tends to recover by itself starting within 2–3 weeks from the onset of symptoms, usually stabilizing over months and continuing to improve for up to 1 year.³ According to a large clinical trial (the Optic Neuritis Treatment Trial), 1 year after the initial ON attack, 93 percent those diagnosed with ON had a visual acuity of 20/40 and 69 percent had visual acuity of 20/20.³ Additionally, the severity of initial visual loss does seem to affect final visual outcome and the best predictor of visual recovery is the baseline acuity at the time of the attack.³ On average, visual function is worse when ON is an early presentation of MS.³

Even though recurrences of ON can occur, the long-term outcome remains good. ON can recur either in the same or the contralateral eye. After ten years of follow-up in the previously mentioned Optic Neuritis Treatment Trial, 35 percent of participants experienced at least one documented recurrence.³ Long-term follow-up studies have shown that only two percent are left with significant visual impairment in both eyes.¹ Not surprisingly, recurrence is more common in those who are later diagnosed with MS.¹

In some cases, where there is no response to steroids (either intravenous or oral), plasma exchange is considered as a therapy. Long term immunomodulation and MS therapies (interferon beta-1a and interferon beta-1b) can be used to delay the progression or onset of MS in individuals who are likely to be diagnosed as MS.

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Transverse Myelitis

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Transverse myelitis (TM) is a rare inflammatory disease causing injury to the spinal cord with varying degrees of weakness, sensory alterations, and autonomic dysfunction (the part of the nervous system that controls involuntary activity, such as the heart, breathing, the digestive system, and reflexes). The first cases of acute myelitis were described in 1882 and were attributed to vascular lesions and acute inflammatory events. In England between 1922 and 1923 more than 200 postvaccinal cases were noted as complications of the smallpox and rabies vaccines. Later reports revealed that TM was post-infectious in nature, and agents including measles, rubella and mycoplasma were directly isolated from patient's spinal fluid. The term "acute transverse myelitis" was first used by an English neurologist in 1948 to describe a case of rapidly progressive paraparesis with a thoracic sensory level, occurring as a postinfectious complication of pneumonia. The Transverse Myelitis Consortium Working Group delineated diagnostic criteria for disease-associated TM and idiopathic TM along with a framework to differentiate TM from non-inflammatory myelopathies in 2002.

Epidemiology

TM has a conservatively estimated incidence of between 1 and 8 new cases per million per year, or approximately 1400 new cases each year. Although this disease affects people of all ages, with a range of six months to 88 years, there are bimodal peaks between the ages of 10 to 19 years and 30 to 39 years. In addition, approximately 25% of cases are in children. There is no gender or familial association with TM. In 75-90% of cases TM is monophasic, yet a small percentage experience recurrent disease especially if there is a predisposing underlying illness.

Signs and Symptoms

The spinal cord carries motor nerve fibers to the limbs and trunk and sensory fibers from the body back to the brain. Inflammation within the spinal cord interrupts these pathways and causes the common presenting symptoms. TM generally presents with rapidly progressing muscle weakness or paralysis, beginning with the legs and potentially moving to the arms with varying degrees of severity. The arms are involved in a minority of cases and this is dependent upon the level of spinal cord involvement. Sensation is diminished below the level of spinal cord involvement in the majority of individuals. Pain (ascertained as appreciation of pinprick by the neurologist) and temperature sensation are generally diminished and appreciation of vibration (as caused by a tuning fork) and joint position sense may also be decreased. Many report a tight banding or girdle-like sensation around the trunk and that area may be very sensitive to touch.

In most cases a sensory level is documented, most commonly in the mid-thoracic region in adults or the cervical region in children. Pain in the back, extremities, or abdomen is also common while paresthesias (e.g., tingling, numbness, burning sensations) are typical in adults. Sexual dysfunction is also the result of sensory and autonomic involvement. Increased urinary urgency, bowel or bladder incontinence, difficulty or inability to void, and incomplete evacuation of bowel or constipation are other characteristic autonomic symptoms.

Spasticity and fatigue are other symptoms common to transverse myelitis. Additionally, depression is often documented in TM patients and must be treated to prevent devastating consequences.

In some cases, symptoms progress over hours whereas in other instances, the presentation is over days. Neurologic function tends to decline during the 4-21 day acute phase, while eighty-percent of cases reach their maximal deficit within 10 days of symptom onset. At its worst point, 50% of individuals have lost all movements of their legs, 80-94% experience numbness, paresthesias or banding or girdling, and almost all have some degree of bladder dysfunction.

Diagnosis

Diagnosis of TM is based on clinical and radiological findings. Clinical characteristics of myelopathy are bilateral signs and/or symptoms of sensory, motor or autonomic dysfunction attributable to the spinal cord or a clearly defined sensory level. Evidence of inflammation either on MRI as gadolinium enhancement or on lumbar puncture as elevated white blood cells or IgG index is frequently observed.

If a myelopathy is suspected based on history and physical examination, a gadolinium-enhanced magnetic resonance imaging (MRI) of the spinal cord is first obtained to assess if there is a compressive or inflammatory (gadolinium enhancing) lesion as signs and symptoms may be alike. It is essential to rule out compressive myelopathy (compression of the spinal cord), which can be caused by a tumor, herniated disc, stenosis (a narrowed canal for the cord), hematoma or abscess. Identifying these disorders is critical since immobilization to prevent further injury and early surgery to remove the compression may sometimes reverse neurologic injury to the spinal cord.

Lumbar puncture is used to look for surrogate markers for inflammation in the cerebrospinal fluid (CSF). These include elevated white cell counts, elevated protein and an elevated IgG index. It should be noted, however, that a significant percentage of individuals with a clinical pattern that otherwise resembles TM do not meet these inflammatory features and, therefore, the absence of inflammatory markers does not rule out TM.

To identify the underlying cause of the inflammatory process, further tests are recommended to assess for the presence of a systemic inflammatory disease – such as Sjögren's syndrome, Lupus (SLE) and neurosarcoidosis. It is important to test for HIV infection, syphilis, vitamin B12 and copper levels to rule out possible causes of myelopathy.

A MRI of the brain is performed to screen for lesions suggestive of MS. If none of these tests are suggestive of a specific cause, the diagnosis is idiopathic transverse myelitis or parainfectious transverse myelitis (if there are other symptoms to suggest an infection).

In the absence of a systemic inflammatory disease, the regional distribution of demyelination within the CNS should be defined since several disorders (i.e. MS, NMO, or acute disseminated encephalomyelitis) may present with TM as the initial manifestation of a multiphasic disease. NMO involves primarily, but not exclusively, the optic nerve and the spinal cord, and new criteria define NMO based on longitudinally extensive lesions regardless of optic nerve involvement. A gadolinium-enhanced brain MRI and visual evoked potential should be obtained to look for these entities. The absence of multifocal areas of demyelination would suggest a diagnosis of isolated TM and lead to appropriate treatment measures.

Non-inflammatory myelopathies include those caused by arterial or venous ischemia (blockage), vascular malformations, radiation, fibrocartilaginous embolism or nutritional/metabolic causes and appropriate work ups under these situations might include aortic ultrasound, spinal angiogram or evaluation of pro-thrombotic risk factors.

Sub-Types of Myelitis (Longitudinally Extensive and Partial Myelitis)

Within the category of idiopathic TM, it may be of further value to distinguish between acute partial TM, acute complete TM and longitudinally extensive TM (LETM), since these syndromes present distinct differential diagnoses and prognoses.

Acute partial transverse myelitis refers to mild or grossly asymmetrical spinal cord dysfunction with an MRI lesion of less than 3 vertebral segments. Acute complete TM refers to complete or near complete clinical deficits below the lesion and an MRI lesion of less than 3 vertebral segments. LETM has a complete or incomplete clinical picture but an MRI lesion that is longer than or equal to 3 vertebral segments. By definition, a brain MRI is considered to be negative in this population. There is a lesser likelihood of presenting with oligoclonal bands (abnormal antibodies), or relapse with a second bout of myelitis, and a very low transition rate to MS (likely < 5 percent).

Potential Causes

The possible causes of transverse myelitis can be quite varied. Transverse myelitis may occur in isolation or in the setting of another illness. Idiopathic transverse myelitis is assumed to be a result of abnormal and excessive activation of an immune response against the spinal cord that results in inflammation and tissue damage.

TM often develops in the setting of viral and bacterial infections, especially those which may be associated with a rash (e.g., rubeola, varicella, variola, rubella, influenza, and mumps). The term *parainfectious* suggests that the neurologic injury associated with TM may be related to direct microbial infection and injury as a result of the infection, direct microbial infection with immune-mediated damage against the agent, or remote infection followed by a systemic response that induces neural injury. Approximately one third of individuals with TM report a febrile illness (flu-like illness with fever) in close temporal relationship to the onset of neurologic symptoms. In some cases, there is evidence that there is a direct invasion and injury to the cord by the infectious agent itself (especially poliomyelitis, herpes zoster, AIDS and Lyme neuroborreliosis). However, causality has not been established. A bacterial abscess can also develop around the spinal cord and injure the cord through compression, bacterial invasion and inflammation.

Experts believe that in many cases infection causes a derangement of the immune system, which leads to an indirect autoimmune attack on the spinal cord, rather than a direct attack by the organism. One theory to explain this abnormal activation of the immune system toward human tissue is termed **molecular mimicry**. This theory postulates that an infectious agent may share a molecule that resembles or **mimics** a molecule in the spinal cord. When the body mounts an immune response to the invading virus or bacterium, it also responds to the spinal cord molecule with which it shares structural characteristics. This leads to inflammation and injury within the spinal cord.

Although a causal relationship has not been established, TM has been anecdotally reported following influenza and booster Hepatitis B vaccinations. One theory suggests that it is possible that the vaccination may have excited an autoimmune process. ***It is critically important to bear in mind that extensive research has demonstrated that vaccinations are safe, and the potential link to TM may only be coincidental or at worst an exceptionally rare complication.***

As mentioned above, TM may be a relatively uncommon manifestation of several autoimmune diseases, including systemic lupus erythematosus (SLE), Sjogren's syndrome, and sarcoidosis. SLE is an autoimmune disease of unknown cause that affects multiple organs and tissues in the body. Sjogren's disease is another autoimmune disease characterized by invasion and infiltration of the tear and salivary glands by white blood cells with resultant decreased production of these fluids leading to dry mouth and dry eyes. Several tests can support this diagnosis: the presence of a SS-A antibody in the blood, ophthalmologic tests that confirm

decreased tear production and the demonstration of lymphocytic infiltration in biopsy specimens of the small salivary glands (a minimally invasive procedure). Neurologic manifestations are unusual in Sjogren's syndrome, but spinal cord inflammation (transverse myelitis) can occur. Sarcoidosis is a multisystem inflammatory disorder of unknown cause and manifested by enlarged lymph nodes, lung inflammation, various skin lesions, liver and other organ involvement. In the nervous system, various nerves, as well as the spinal cord, may be involved. Diagnosis is generally confirmed by biopsy, demonstrating features of inflammation typical of sarcoidosis.

Myelitis related to cancer (called a paraneoplastic syndrome) is uncommon. There are several reports in the medical literature of a severe myelitis occurring in association with a malignancy. In addition, there are a growing number of reports of cases of myelopathy associated with cancer in which the immune system produces an antibody to fight off the cancer and this cross-reacts with the molecules in the spinal cord neurons. It should be emphasized that this is an unusual cause of myelitis.

Vascular causes are noted because they present with the same problems as transverse myelitis. However, this is really a distinct problem primarily due to inadequate blood flow to the spinal cord instead of actual inflammation. The blood vessels to the spinal cord can close up with blood clots or atherosclerosis or burst and bleed. This is essentially a "stroke" of the spinal cord.

Acute Treatment

Intravenous Steroids

Intravenous steroid treatment is the first line of therapy often used in acute TM. Corticosteroids have multiple mechanisms of action including anti-inflammatory activity, immunosuppressive properties, and antiproliferative actions. Though there is no randomized double-blind placebo-controlled study that supports this approach, evidence from related disorders and clinical experience support this treatment. At the Johns Hopkins TM Center, the standard of care includes intravenous methylprednisolone (1000 mg) or dexamethasone (200 mg) for 3 to 5 days unless there are compelling reasons to avoid this therapy. The decision to offer continued steroids or to 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 initiated in moderate to severe TM (i.e., inability to walk, markedly impaired autonomic function, and sensory loss in the lower extremities) in individuals who show little clinical improvement after instituting 5 to 7 days of intravenous steroids, but may also be initiated at first presentation. PLEX is believed to work in autoimmune CNS diseases through the removal of specific or nonspecific soluble factors likely to mediate, be responsible for, or contribute to inflammatory-mediated target organ damage. PLEX has been shown to be effective in adults with TM and other inflammatory disorders of the CNS.

Other Immunomodulatory Treatment

If there is continued progression despite intravenous steroid therapy and PLEX, pulse dose intravenous cyclophosphamide (800–1000 mg/m²) is considered. Cyclophosphamide is known to have immunosuppressive properties. From the Johns Hopkins TM Center experience, it has been reported that PLEX provided an added benefit to steroids in patients who were not at a disability level of ASIA A and who did not have a history of autoimmune disease. For those who were classified at a disability level of ASIA A at their nadir, they showed a significant benefit when given combination therapy with steroids, PLEX and IV cyclophosphamide. (*Idiopathic transverse myelitis: corticosteroids, plasma exchange, or cyclophosphamide*. Greenberg BM, Thomas KP, Krishnan C, Kaplin AI, Calabresi PA, Kerr DA. *Neurology*. 2007 May 8; 68

(19):1614-7). Cyclophosphamide should be administered under the supervision of an experienced oncology team, and caregivers should monitor the patient carefully for hemorrhagic cystitis and cytopenias.

Chronic immunomodulatory therapy should be considered for recurrent TM. The ideal treatment regimen is not known and it is important for your neurologist to consult with a specialist who has significant experience in treating these rare, recurrent neuroimmunologic disorders.

Prognosis and Management

Recovery from TM may be absent, partial or complete and generally begins within 1 to 3 months after acute treatment. Significant recovery is unlikely, if no improvement occurs by 3 months. Subsequent to the initial attack, approximately 1/3 of individuals recover with little or only minor symptoms, 1/3 are left with a moderate degree of permanent disability and 1/3 have virtually no recovery and are left severely functionally disabled. Most show good to fair recovery. The rapid progression of clinical symptoms, the presence of back pain, and the presence of spinal shock, as well as para-clinical evidence, such as absent central conduction on evoked potential testing and the presence of 14-3-3 protein in the cerebrospinal fluid (CSF) during the acute phase are often indicators of a less complete recovery.

TM can be the presenting feature of MS. In individuals with acute partial transverse myelitis and normal brain MRI, about 10-33 percent develop MS over a five to ten year period. If the brain MRI shows lesions, the transition rate to clinically definite MS is known to be quite high, in the range of 80 to 90 percent within a few years. Those who are ultimately diagnosed with MS are more likely to have asymmetric clinical findings, predominant sensory symptoms with relative sparing of motor systems, MR lesions extending over fewer than 2 spinal segments, abnormal brain MRI, and oligoclonal bands in the CSF.

Although typically a monophasic disease, in a subset of cases that manifest a history of systemic autoimmune disease, TM can be recurrent. Recurrence can often be predicted at the initial acute onset based on multifocal lesions in the spinal cord, lesions in the brain, presence of anti-Rho antibody, underlying mixed connective tissue disease, the presence of oligoclonal bands in the cerebrospinal fluid, and/or NMO-IgG antibodies.

Long-Term Care and Management

After the acute phase, rehabilitative care to improve functional skills and prevent secondary complications of immobility involves both psychological and physical accommodations. There is very little written in the medical literature specifically dealing with rehabilitation after transverse myelitis. However, much has been written regarding recovery from spinal cord injury (SCI), in general, and this literature applies. The physical issues include bowel and bladder management, sexuality, maintenance of skin integrity, spasticity, activities of daily living (i.e., dressing), mobility, and pain.

It is important to begin occupational and physical therapies early during the course of recovery to prevent the inactivity related problems of skin breakdown and soft tissue contractures that leads to a decreased range of motion. Assessment and fitting for splints designed to passively maintain an optimal position for limbs that cannot be actively moved is an important part of the management at this stage.

The long-term management of TM requires attention to a number of issues. These are the residual effects of any spinal cord injury, including TM. In addition to chronic medical problems, there are the ongoing issues of ordering the appropriate equipment, reentry into school, re-socialization into the community, and coping with the psychological effects of this condition by the patients and their families. During the early recovery period, family education is essential to develop a strategic plan for dealing with the challenges to independence.

following return to the community.

Bladder function is almost always at least transiently impaired in patients with TM. Immediately after the onset of TM, there is frequently a period of transient loss or depression of neural activity below the involved spinal cord lesion, referred to as “spinal shock,” which lasts about 3 weeks. Following this period, two general problems can affect the bladder. The bladder can become overly sensitive, and empty after only a small amount of urine has collected, or relatively insensitive, causing the bladder to become over extended and overflow. An overly distended bladder increases the likelihood of urinary tract infections and, in time, may threaten the health of the kidneys. Depending on the dysfunction, treatment options include timed voiding, medicines, external catheters for males (a catheter connected to a condom), padding for women, intermittent internal self-catheterization, an indwelling catheter or electrical stimulation. Surgical options may be appropriate for some people.

Another major area of concern is effective management of bowel function. A common problem in spinal cord injury is difficulty with evacuation of stool, although fecal incontinence can also occur. The neurologic pathways for defecation are similar to those of the bladder. Many lacking voluntary control of the bowel may still be able to achieve continence by diet, strategic use of stool softeners and fiber, and the technique of rectal stimulation. Other aids include suppositories and oral medications. A high-fiber diet, adequate and timely fluid intake, and medications to regulate bowel evacuations are the basic components of success. Regular evaluations by medical specialists for adjustment of the bowel program are recommended to prevent potentially serious complications. There are some surgical options, although this is rarely necessary. Sexual dysfunction involves similar innervation and analogous syndromes as those found in bladder dysfunction. Treatment of sexual dysfunction should take into account baseline function before the onset of TM. Of the utmost importance is adequate education and counseling about the known physical and neurologic changes that TM has on sexual functioning. Because of the similarities in innervation between sexual and bladder function, patients with sexual dysfunction should be encouraged to empty their bladders before sexual stimulation to prevent inopportune incontinence. The mainstays of treatment of erectile dysfunction in men are inhibitors of cGMP phosphodiesterase, type 5, which will allow most of men with TM to achieve adequate erections for success in intercourse through a combination of reflex and/or psychogenic mechanisms. Although less effective in women, these same types of medications have been shown capable of enhancing a woman’s sexual functioning. The most commonly used oral erectile dysfunction drugs are Viagra (sildenafil), Levitra (vardenafil), and Cialis (tadalafil). Although sexual experience is impacted by spinal cord injury, sensual experience and even orgasm are still possible. Lubricants and aids to erection and ejaculation (for fertility) are available. Adjustment to altered sexuality is aided by an attitude of permissive experimentation, as the previous methods and habits may no longer serve.

Skin breakdown occurs if the skin is exposed to pressure for a significant amount of time, without sensation or the strength to shift position as necessary. Sitting position should be changed at least every 15 minutes. This can be accomplished by standing, by lifting the body up while pushing down on armrests, or by just leaning and weight shifting. Wheelchairs can be supplied with either power mechanisms of recline or tilt-in-space to redistribute weight bearing. A variety of wheelchair cushions are available to minimize sitting pressure. Redness that does not blanch when finger pressure is applied may signal the beginning of a pressure ulcer. Good nutrition, vitamin C, and avoidance of moisture all contribute to healthy skin. Pressure ulcers are much easier to prevent than to heal.

Spasticity is often a very difficult problem to manage. The goal is to maintain flexibility with a stretching routine using exercises for active stretching and a bracing program with splints for a prolonged stretch. These splints are commonly used at the ankles, wrists, or elbows. Also recommended are appropriate strengthening programs for the weaker of the spastic muscles acting on a joint and an aerobic conditioning regimen. These interventions are supported by adjunctive measures that include antispasticity drugs (e.g., diazepam, baclofen, dantrolene, tizanidine), therapeutic botulinum toxin injections, and serial casting. The therapeutic goal is to

improve the function of the individual in performing specific activities of daily living (i.e., feeding, dressing, bathing, hygiene, mobility) by improving the available joint range of motion, teaching effective compensatory strategies, and relieving pain.

Individuals with TM may find ordinary tasks such as dressing, bathing, grooming, and eating very difficult. Many of these obstacles can be mastered with training and specialized equipment. For example, long handled sponges can make bathing easier as can grab bars, portable bath seats and hand-held shower heads. For dressing, elastic shoe-laces can eliminate the need to tie shoes while other devices can aid in donning socks. Occupational therapists are specialists in assessing equipment needs and helping people with limited function perform activities of daily living. A home assessment by an experienced professional is often helpful.

Physical therapists assist with mobility. Besides teaching people to walk and transfer more easily, they can recommend mobility aids. This includes everything from canes (single point vs. small quad cane vs. large quad cane) to walkers (static vs. rolling vs. rollator) and braces. For a custom-fabricated orthotic (brace), an orthotist is necessary. Careful thought should go into deciding whether the brace should be an ankle-foot orthosis, whether it should be flexible or stiff, and what angle the foot portion should be in relationship to the calf portion. Some will benefit by a knee-ankle foot orthosis. Each person should be evaluated individually. The best results occur when a physician coordinates the team so that the therapists and orthotists are united on what is to be achieved. The physician best trained to take this role is the physiatrist.

Pain is common following transverse myelitis. The first step in treating pain effectively is obtaining an accurate diagnosis. Unfortunately, this can be very difficult. Causes of pain include muscle strain from using the body in an unaccustomed manner, nerve compression (i.e., compression of the ulnar nerve at the elbow due to excessive pressure from resting the elbow on an armrest continuously) or dysfunction of the spinal cord from the damage caused by the inflammatory attack. Muscle pain might be treated with analgesics, such as acetaminophen (Tylenol), non-steroidal, anti-inflammatory drugs such as naproxen or ibuprofen (Naprosyn, Alleve, Motrin), or modalities such as heat or cold. Nerve compression might be treated with repositioning and padding (i.e., an elbow pad for an ulnar nerve compression).

Nerve pain can be a significant challenge to find effective treatment. Nerve messages traveling through the damaged portion of the spinal cord may become scrambled and misinterpreted by the brain as pain. Besides the treatments listed above, certain antidepressants such as amitriptyline (Elavil), or anticonvulsants, such as carbamazepine, phenytoin, or gabapentin (Tegretol, Dilantin, Neurontin) may be helpful. Stress and depression should also be addressed since these conditions make pain harder to tolerate.

Individuals with TM should be educated about the effect of TM on mood regulation and routinely screened for the development of symptoms consistent with clinical depression. Warning signs that should prompt a complete evaluation for depression include failure to progress with rehabilitation and self-care, worsening fixed low mood, pervasive decreased interest, and/or social and professional withdrawal. A preoccupation with death or suicidal thoughts constitutes a true psychiatric emergency and should lead to prompt evaluation and treatment. Depression in TM is similar to the other neurologic symptoms patients endure, which are mediated by the effects of the immune system on the brain. Depression is remarkably prevalent in TM, occurring in up to 25% of those diagnosed at any given time, and is largely independent of the patient's degree of physical disability. Depression is not due to personal weakness or the inability to "cope." It can have devastating consequences; not only can depression worsen physical disability (such as fatigue, pain, and decreased concentration) but it can have lethal consequences. Suicide is the leading cause of death in TM. Despite the severity of the clinical presentation of depression in TM, there is a very robust response to combined aggressive psychopharmacologic and psychotherapeutic interventions. With appropriate recognition and treatment of TM depression, complete symptom remission is standard.

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