

The Transverse Myelitis Association

...advocating for those with acute disseminated encephalomyelitis, neuromyelitis optica, optic neuritis and transverse myelitis



NEUROIMMUNOLOGIC DISORDERS OF THE CENTRAL NERVOUS SYSTEM: AN OVERVIEW

The Transverse Myelitis Association would like to thank Dr. Benjamin Greenberg (UT Southwestern Medical Center) for writing 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. 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 **Long 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)** 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. 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.