

TRANSVERSE MYELITIS

The Transverse Myelitis Association would like to thank Drs. D. Joanne Lynn (The Ohio State University), Charles Levy (North Florida/South Georgia Veterans Health Service), Adam Kaplin (Johns Hopkins Medical Center) and Douglas Kerr (Biogen-Idec) for their assistance in writing this article. Drs. Lynn, Levy, Kaplin and Kerr serve on The Transverse Myelitis Association Medical Advisory Board. The Transverse Myelitis Association is solely responsible for the content of this article.

OVERVIEW

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.

