Transverse Myelitis Plus Syndrome and Acute Disseminated Encephalomyelitis Plus Syndrome
A Case Series of 5 Children

Allen DeSena, MD, MPH; Donna Graves, MD; Michael C. Morriss, MD; Benjamin M. Greenberg, MD, MHS

IMPACTANCE Classically, transverse myelitis and acute disseminated encephalomyelitis are considered central nervous system demyelinating conditions. In both conditions, the spinal cord is involved to varying degrees, and there is a variety of presentations, usually involving some degree of progressive paralysis of the upper and/or lower extremities. Treatment usually consists of high-dose intravenous steroids in addition to plasma exchange and/or intravenous immunoglobulin. In some cases, immunosuppressive medications, such as intravenous cyclophosphamide, have been used with variable success. Cases with atypical features on examination, imaging, or with neurophysiological studies may be helpful in shedding light on the etiology and/or pathophysiology because many of these patients have permanent disabilities despite appropriate treatment.

OBSERVATIONS This case series presents 5 pediatric cases observed from 2009-2012 at our medical center, Children’s Medical Center Dallas. These cases were notable because they provided evidence of autoimmune events affecting the central nervous system but with additional peripheral axonal pathology.

CONCLUSIONS AND RELEVANCE We describe these cases with respect to findings that suggest a variant of these conditions that have concomitant nerve-root involvement. These patients had worse outcomes than typical patients with transverse myelitis/acute disseminated encephalomyelitis, and these observations build on previous work by other investigators that highlighted persistent flaccid paralysis and electrophysiological evidence of axonal loss portending a poorer prognosis. Furthermore, these cases suggest a potential role for approaching how we classify subtypes of transverse myelitis and acute disseminated encephalomyelitis.

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Report of Cases

Children’s Medical Center Dallas institutional review board approval was obtained, allowing for retrospective medical record review; patient consent was waived.

Case 1
A 13-year-old girl presented in late September 2009 with an ascending paralysis over the course of 48 hours. On initial presentation, she was noted to have severe flaccid weakness in both of her lower extremities, with her left lower extremity affected more than her right lower extremity. Her reflexes were absent at her patellars and ankles bilaterally, and she had a downgoing plantar response bilaterally. She had a sensory level on the right at the T10 dermatome. Sensation was impaired to pin, temperature, and light touch, although it was normal in...
her lower extremities distally to vibration and proprioception. She had an MRI of her spinal cord that showed intramedullary increased T2 signal from T11 to L2, predominantly affecting the gray and white matter of the anterior spinal cord bilaterally, without contrast enhancement on postcontrast T1-weighted images. She had a white blood cell (WBC) count of 0 μL and red blood cell (RBC) count of 0 μL in her cerebrospinal fluid (CSF) and normal CSF glucose and protein levels. The workup findings were negative for enterovirus, herpes simplex virus (HSV), Epstein-Barr virus (EBV), fungal and acid-fast bacilli infections, syphilis, neurosarcoidosis, and neuromyelitis optica. The IgG synthesis rate and index were normal. Despite not meeting typical criteria for idiopathic TM, the patient received 5 days of high-dose steroids, with no clear response, followed by 5 rounds of plasma exchange, with some improvement. Approximately 2 weeks after her initial presentation, a repeat MRI of the spinal cord was performed, and the patient was noted to have developed diffuse contrast enhancement of ventral nerve roots. A nerve conduction study (NCS)/electromyogram (EMG) was not obtained acutely, although NCS/EMG obtained approximately 8 months later showed severely decreased amplitudes in the left peroneal motor responses with a normal distal latency and conduction velocity. And she had EMG findings consistent with active and chronic denervation and reinervation in all L4-L5 muscles of the left leg and absent motor units in her left tibialis anterior. Although initially nonambulatory, she was able to improve substantially with near-normal strength in her right lower extremity (at least 4/5 in all muscle groups) and more severe weakness in her left hip flexors (4−/5) and left dorsiflexors (2/5). She currently is able to ambulate with unilateral support for short and moderate distances, and her urinary retention present on initial admission has resolved (Figure 1).

Case 2

A 14-year-old boy presented in June 2009 with a rapidly progressive flaccid paralysis and burning pain involving both lower extremities over approximately 72 hours along with severe urinary retention. He was presumptively treated with intravenous immunoglobulin (IVIG) owing to initial concern for Guillain-Barré syndrome. After failure to improve, he was transferred to our facility and was noted to have weakness in all muscle groups in his lower extremities, rated as a 2/5 in large muscle groups in both legs, and absent reflexes in his patellars and ankles bilaterally. On initial assessment, he said he had pain in his lower extremities, with some decrease to pain and light touch noted only in his feet bilaterally. His spinal cord was imaged by MRI, revealing increased intramedullary T2 signal...
within the anterior spinal cord from T11 to the conus medularis and diffuse enhancement of his ventral nerve roots on contrast-enhanced T1-weighted images. An NCS/EMG revealed findings consistent with an acute motor axonal neuropathy. A repeat of this study approximately 12 months later again showed decreased amplitudes, consistent with an axonal neuropathy, in bilateral tibial and peroneal nerves, which was worse on the right side. Analysis of the CSF showed a WBC count of 8/μL, RBC count of 0/μL, an elevated CSF protein level to 148 mg/dL, and a normal CSF glucose level. The workup results were negative for EBV, varicella zoster (VZV), HSV, West Nile (WN) virus, cytomegalovirus (CMV), Lyme disease with negative antibody testing results for ganglioside antibodies, Sjögren syndrome antigen A (SS-A), Sjögren syndrome antigen B (SS-B), ribonucleoprotein (RNP), Scl-70 antibodies, and antinuclear antibody (ANA). The patient was subsequently treated with high-dose steroids for 5 days, intravenous (IV) cyclophosphamide (1000 mg/m²) and plasma exchange. He minimally improved in his lower extremity weakness and now only ambulates with bilateral support, requiring a wheelchair for longer distances. His urinary retention also improved, obviating the need for intermittent catheterization, although he continues to have urinary urgency and occasional incontinence.

**Case 3**

A 9-year-old girl presented in late August 2012 with pain in her right lower extremity followed by weakness and sensory changes. Her tone was noted to be reduced on initial examination, with mild weakness in the bilateral lower extremities that was worse on the right (about 4−/5 in proximal muscles), although the examination was limited by pain. She had absent reflexes in the bilateral patellars and ankles and a downgoing plantar response. She had no noted sensory level, and sensation to light touch, pin, temperature, vibration, and proprioception were normal in both lower extremities. She was suspected to have Guillain-Barré syndrome, although an MRI obtained shortly after hospitalization showed increased T2 signal in her spinal cord from T10 to T12, predominantly within the dorsal spinal cord. There was diffuse postcontrast enhancement of her cauda equina. Findings from an NCS/EMG obtained about 4 to 5 days after the onset of her symptoms were normal. A lumbar puncture revealed a WBC count of 10/μL and RBC count of 10/μL in the CSF, with normal CSF glucose and protein levels. Laboratory testing results were negative for WN virus and all other arboviruses; varicella zoster; mycoplasma; Lyme disease; human T-cell lymphotropic virus type 1; human immunodeficiency virus; HSV; hepatitis viruses A, B, and C; CMV; and EBV. Results from antibody testing for double-stranded DNA, ANA, RNP, SS-A, SS-B, and Scl-70 antibodies were also negative. She had minimal response to high-dose steroids for 5 days and was given IVIG, with good improvement. She initially presented requiring unilateral support but was able to ambulate without difficulty and had a complete recovery at the time of her 3-month follow-up after rehabilitation.

**Case 4**

An 8-year-old boy presented in September 2012 to our emergency department after awakening with complete flaccid paraparesis and occasionally incontinence. Urinary retention also improved, obviating the need for bilateral support, requiring a wheelchair for longer distances. His voluntary movements were normal. Approximately 2 weeks following his initial presentation, a repeat spinal MRI was performed demonstrating diffuse ventral nerve-root enhancement, with mild improvement in the enhancing intramedullary spinal cord lesions. In addition, an NCS/EMG showed a mild decrease in amplitude of his left tibial motor response only, with all other nerves tested having normal amplitudes, distal latencies, F-wave responses, and conduction velocities, as well as normal needle EMG testing of all muscles tested in his lower extremities. He was then treated with IVIG for 5 days followed by IV cyclophosphamide (1000 mg/m²). Following the IVIG and IV cyclophosphamide, he modestly improved, although he still required bilateral support to stand and cannot walk. His NCS/EMG finding was similar when he was tested approximately 4 weeks later, despite his modest improvements (Figure 2).

**Case 5**

A 29-month-old girl presented in September 2012 following a febrile illness with an unsteady gait that progressed over 48 hours to refusal to walk. Her strength, reflexes, and sensation to light touch and pain were assessed to be normal on examination initially, although later examinations resulted in difficulty in assessing her strength, coordination, and sensation owing to fussiness. Magnetic resonance imaging of the brain and spine was performed that showed multifocal cerebral, cerebellar, and dorsal spinal cord T2 hyperintense lesions without contrast enhancement. However, there was diffuse cauda equina enhancement along the nerve roots of her lower spinal cord. She initially responded well to steroids, with near-complete resolution of symptoms. However, she presented again within a week with more extensive brain and spinal cord
lesions. She was treated at that time with steroids and plasma exchange followed by IVIG and IV cyclophosphamide owing to the continued radiologic and clinical progression. During this admission, because of persistent fussiness, her examination continued to be challenging, although her reflexes were noted to be absent in her lower extremities approximately 4 weeks after her initial presentation. Her inability to ambulate well was her most notable finding, but she also developed visual loss consistent with optic neuritis later in her course—this corresponded to the radiologic progression for which we escalated therapy. Coupled with her prior nerve-root enhancement, an NCS/EMG was obtained and was noted to be normal. Following the IVIG and cyclophosphamide therapy, she clinically responded well and subsequently had a near-complete recovery 4 weeks following discharge. Her CSF showed a WBC count of 2 μL, RBC count of 1178 μL, and normal CSF glucose and protein levels. Additional testing results for CMV, varicella zoster, HSV, Lyme disease, WN virus and other common arboviruses, parvovirus B19, human herpes virus-6, and EBV were negative. Test results for anti-aquaporin-4 antibodies, RNP, SS-A, SS-B, Scl-70 antibodies, and ANA were negative; a positron-emission tomographic scan demonstrated no findings suggestive of neoplasm or sarcoidosis. She had 0 oligoclonal bands and a normal IgG synthesis index and rate. Despite an initial good response at our first clinic visit, she deteriorated following completion of her steroid taper approximately 6 weeks after her initial discharge, with new enhancing lesions on her brain MRI, requiring re-escalation of steroids and another dose of IV cyclophosphamide (Figure 3).

Discussion

An acute myelitis with features of peripheral nerve involvement has been described with WN virus, polio, or poliolike viruses, certain vaccinations, and Lyme disease. Our case series illustrates that ventral nerve-root inflammation or diffuse cauda equina inflammation may be found in patients presenting with clinical and MRI features of idiopathic TM (as in patients 1-3), idiopathic TM with brainstem extension (as in patient 4), or ADEM (as in patient 5). Of note, all of these patients presented in the mid to late summer, suggestive of a common, yet unidentified, viral or other microbial etiology. All of the patients had incomplete recoveries and/or particularly aggressive disease courses, and the patients with isolated ventral root enhancement had the most residual disability. The findings on imaging were time dependent (delayed from initial presentation); thus, it is unknown whether the frequency...
Figure 3. Magnetic Resonance Imaging for Case 5

Initial magnetic resonance imaging of the brain and spine in case 5 show a subtle increased T2 signal in the cervical spinal cord (A, arrowhead) and diffuse enhancement in the roots of the cauda equina (B, arrowhead). C, There are multifocal demyelinating lesions on the fluid-attenuated inversion recovery axial images of the brain. Magnetic resonance imaging studies performed 4 weeks later demonstrated progression of the size of the lesions in the spinal cord (D, arrowhead) with the development of intense enhancement (E, circle). F, Lesions in the brain had also progressed in size and number.

of proximal root involvement in idiopathic TM is simply underestimated or these cases may represent a distinct pathophysiologic mechanism. Whether the enhancing nerve roots on MRI represent antigen-driven inflammation or blood-brain barrier breakdown relative to neuronal degeneration is unknown, but this finding has been described in a number of infections that can affect anterior horn cells. All of the patients presented with flaccid paralysis, and 3 of the patients had evidence of possible axonal loss, indicated by decreased amplitudes of affected areas. Other investigators have noted
the involvement of nerve roots in certain patients with TM, and our findings are also in agreement with previous findings that persistent flaccid paralysis and evidence of axonal loss, either by NCS or by T1 hypointensities in the cord, are likely associated with a higher risk for incomplete motor recovery.9-13 Extensive neurophysiological work done by Kalita and colleagues14-16 also noted this association and further postulated that weakness, as evident on NCS/EMG, may indicate a particular threshold of anterior horn cells has been lost. In their work, they found a high correlation between abnormal NCS and prognosis.14-16 In addition, the fact that these patients can present with marked flaccid paralysis and areflexia, making them clinically indistinguishable from acute inflammatory demyelinating polyradiculoneuropathy, is notable. Many of these TM plus cases may be missed and could account for patients with acute inflammatory demyelinating polyradiculoneuropathy who are labeled as nonresponders.

Because of the diagnostic implications of TM, we argue that neuroimaging should be considered in all cases of acute inflammatory demyelinating polyradiculoneuropathy. In patients diagnosed as having TM, follow-up imaging of the spinal cord should be considered in patients not responding to therapy. The finding that some, but not all, of our patients demonstrated abnormal findings on NCS/EMG is intriguing, and we feel these patients were either etiologically and/or pathophysiologically distinct from TM and ADEM with pure central nervous system involvement. It has been our practice to treat these patients more aggressively because of our concern about their overall prognosis, although we recognize that further research may uncover findings that would refute this approach. Our observations build on those of previous investigators, and we argue that these patients, many of whom have suboptimal outcomes, should also be a focus for study and/or should have their own classification under the TM rubric.