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A 2-Year-Old Boy With Difficulty Waking After Bone Marrow Transplantation

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We report a 2-year-old boy who was evaluated for difficult waking during prolonged intensive care unit admission associated with bone marrow transplant for Wiskott-Aldrich syndrome. Neurologic examination was found to be abnormal, with nuchal rigidity initially, then decreased extremity movement and areflexia developing over several days. Electromyogram showed length-dependent, axonal, sensorimotor polyneuropathy. Cerebrospinal fluid showed albuminocytologic dissociation suggestive of Guillain-Barre syndrome or acute motor and sensory axonal neuropathy variant. The patient was treated with immunotherapy and slowly showed signs of motor recovery over several months. A review of Wiskott-Aldrich syndrome, Guillain-Barre syndrome, immune-mediated complications of bone marrow transplantation, and acute weakness in the intensive care unit is provided in this case report.
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A 2-year-old boy with a history of allogenic bone marrow transplant for Wiskott-Aldrich syndrome (WAS) 1 year prior was referred for concerns of decreased responsiveness and difficulty weaning from ventilator.

At the time of consultation, he was in the pediatric intensive care unit (ICU) for an episode of culture-negative sepsis (characterized by fever, respiratory failure, and hypotension requiring pressor support) and had been intubated for 1 week; he had been in the hospital for over 9 months at this point. The primary team became concerned that although he was now hemodynamically stable, he was not yet as alert and ready for extubation as expected (based on previous similar ICU admissions). His posttransplant course had been complicated by intestinal graft vs host disease (GVHD) treated with infliximab; cytomegalovirus and Epstein-Barr virus viremia, thrombotic microangiopathy treated with eculizumab; as well as multiple episodes of sepsis. Engraftment studies during this time showed 100% engraftment.

His medication list at this time was extensive including analgesics (morphine), multiple anti-infective agents, intravenous immunoglobulin (IVIG) weekly, daily steroids (hydrocortisone and methylprednisolone), total parenteral nutrition, and multiple antihypertensives for hypertension secondary to the thrombotic microangiopathy. He had a family history of WAS in a sibling, and his WAS manifest with scattered petechiae on day of life 5. Genetic testing was consistent with WAS. His initial treatment included IVIG, steroids, rituximab, and plasmapheresis. He underwent an allogenic bone marrow transplant at the age of 17 months.

On initial neurologic examination, he was intubated and sedated but easily awakened; he was breathing spontaneously. He did look toward the examiner and toward his mother, but did not follow any commands, which was not unusual for him during this hospitalization. Facial appearance and movement were normal as much as could be assessed. He grimaced and withdrew all extremities to noxious stimuli, and he had normal reflexes. Tremulousness was observed in all extremities, and he had nuchal rigidity on passive neck range of motion.

The initial assessment was a waxing or waning encephalopathy with concerns for central nervous system (CNS) infection or injury. Initial evaluation included an electroencephalography that showed generalized slowing, but no epileptiform discharges and no seizures. He underwent a head computed tomography that was unremarkable. Initial blood work showed only anemia and elevated transaminases, both of which had been persistent over the preceding weeks. He then underwent a lumbar puncture to evaluate for possible CNS infection: cerebrospinal fluid (CSF) results showed white blood cells = 2/mm^3 (reference range: 0-4 mm^3),

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red blood cells = 1/mm^3 (reference value = 0/mm^3), glucose = 76 mg/dL (40-70 mg/dL), and protein 106 mg/dL (15-45 mg/dL). An magnetic resonance imaging with contrast was done to further characterize CNS involvement and showed dural enhancement, thought to be secondary to the lumbar puncture. Over the course of the next 2 days, the patient had fewer spontaneous movements, such that by the third day of the consultation, he continued to grimace but could no longer withdraw from noxious stimuli, and was arreflexic; he remained ventilator dependent taking fewer spontaneous breaths. An electromyogram (EMG) or nerve conduction study (NCS) was obtained to further characterize peripheral nerve injury; he had absent motor and sensory responses to testing in bilateral upper and lower extremities consistent with a severe axonal sensory or motor peripheral neuropathy. Vitamin B12 levels checked at this time were normal.

With the results of the EMG and CSF studies, a diagnosis of transplant-associated Guillain-Barre syndrome (GBS), acute motor and sensory axonal neuropathy (AMSAN) variant was made. He was treated with IVIG and plasmapheresis. The hematology team added belimumab to his immunosuppression regime, as he had elevated B-cell activating factor levels. Over the next 2 months, he demonstrated some gradual improvement; he was able to turn his head side-to-side and wiggle his fingers, but remained ventilator dependent. He eventually underwent tracheostomy placement; slowly over time he was weaned from full respiratory support to bilevel positive airway pressure. He was slowly regaining antigravity strength in upper and lower extremities at last neurologic examination (4 months after diagnosis).

Discussion

This patient presents an opportunity to review WAS, GBS, and peripheral neurologic involvement in GVHD, and causes of acute weakness in the ICU.

Wiskott-Aldrich Syndrome

WAS is an X-linked disorder of hematopoietic cells, with defects in lymphocytes and platelets; it is 1 of 3 WAS-related disorders (WAS, X-linked thrombocytopenia, and X-linked congenital neutropenia) caused by different genetic variants.[1] The WAS gene, located at Xp11.23, encodes the WASP protein, which is involved at the cell-actin cytoskeleton interface, in activating white blood cells, triggering motility, and adhesion to other cells and tissues. Female carriers of WAS are usually asymptomatic but rare reports of symptomatic girls with skewed X-inactivation can be found in the literature. WAS usually presents in infancy with early complications including bleeding, eczema, and recurrent infections; outside of infancy, these patients are at high risk for developing autoimmune conditions such as rheumatoid arthritis, vasculitis, immune thrombocytopenia, or neutropenia. They also are at increased risk of developing lymphoma, especially if they have been exposed to Epstein-Barr virus. Hematopoietic cell transplant is the only curative treatment, and is considered early in life, before autoimmune conditions or malignancy develop. Neurologic autoimmunity has not been frequently described in WAS patients; there is 1 report of a patient with WAS developing GBS that responded to IVIG.[2] Additionally, Lambert-Eaton myasthenic syndrome has been reported in a girl with an Xp11.22 duplication, a region that includes the WAS gene among others.[3]

Guillain-Barre Syndrome

GBS is commonly encountered by the pediatric neurologist, as it is the most common cause of acute flaccid paralysis in healthy children; the incidence increases with age. It is generally a postinfectious process whereby immune stimulation causes an abnormal autoimmune response directed toward peripheral nerves and spinal roots. There are demyelinating or axonal forms that can affect motor, sensory, or autonomic nerves, and are named accordingly: acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy, and AMSAN. GBS is an humorally mediated process with demyelinating and axonal forms.[4] In demyelinating forms, the immune reaction is against epitopes in Schwann cell surface membrane or myelin. In axonal forms, the immune reaction is against epitopes in the axonal membrane, due to molecular mimicry between the axolemma and microbial surface molecules. Antibody binding then causes complement fixation, macrophage recruitment, and membrane attack complexes to deposit along the axolemma, disrupting nerve structure and function, either temporarily (until myelin can be repaired or regenerated) or permanently, if axonal injury is extensive.

Diagnosis of GBS is based initially upon clinical suspicion, typically with rapid (days to weeks) progression of symmetric ascending weakness and areflexia, and can be supported via several testing modalities.[5] CSF studies show elevated protein levels with normal-to-mildly elevated white blood cell counts (usually <10 cells/mm^3 but always <50 cells/mm^3), the so-called albuminocytologic dissociation. CSF opening pressure can be normal or elevated. Electrophysiologic studies (EMG or NCS) may be normal early in the course, but over days to weeks become abnormal, showing an acute polyneuropathy with either predominantly demyelinating or axonal features, depending on the form (AIDP, acute motor axonal neuropathy, or AMSAN). Abnormal F waves, a measure of conduction through the proximal nerve regions, are often found early in the course of AIDP. As the CSF and nerve conduction studies may be normal early in the course, imaging of the neuroaxis is often undertaken to rule out other etiologies of ascending weakness (transverse myelitis, etc). Magnetic resonance imaging of the brain and spinal cord can show nerve root enhancement. Symptoms progress for days to a month, stabilize and recover over weeks to months, though if axonal injury is throughout the length of the nerve, there may be permanent nerve damage.[6]

Immunomodulatory treatments, IVIG, or plasmapheresis, have been shown to be effective and are more helpful if implemented early, when initial testing (CSF or NCS) may still be normal. Steroids are not helpful in GBS. Eculizumab, a monoclonal antibody that binds to complement, which had