

Chronic Inflammatory Demyelinating Polyradiculoneuropathy Associated with Rare Autoimmune Conditions

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Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune mediated disorder affecting nerve roots and peripheral nerves. Patients usually present with symmetric proximal and distal weakness, large-fiber sensory deficits and diffusely reduced reflexes. While the disease progression usually lasts for at least eight weeks, CIDP course can be relapsing-remitting, chronic progressive, or stepwise progressive.¹⁻² The immunopathogenesis of CIDP includes abnormalities in the innate and adaptive immune systems including cellular and humoral responses but the triggering events and precise interaction between these systems are still not entirely elucidated.²⁻³ There have been many case reports of polyautoimmunity in CIDP patients including concurrent myasthenia gravis, systemic lupus erythematosus, autoimmune hepatitis, and many others.³⁻¹⁰ The identification of polyautoimmunity in some CIDP patients suggests a possible common immunopathogenic mechanism.¹¹ Here we report three cases of CIDP that were associated with autoimmune conditions including primary sclerosing cholangitis, immune mediated thrombocytopenia, and postpartum with positive antinuclear antibody (ANA).

Patient 1

A 63-year-old male with a remote history of primary sclerosing cholangitis (PSC) and ulcerative colitis status post colon resection presented with subacute onset of numbness and tingling in his face, hands and feet, and bilateral hand weakness. Muscle strength testing was graded as follows (right/left, Medical Research Council grade): first dorsal interossei 4/4, abductor digiti minimi 4/4, and abductor pollicis brevis 4/4. Strength examination of the

remaining muscle groups was normal. Sensory nerve conduction studies (NCS) revealed absent bilateral median and ulnar sensory nerve action potentials (SNAPs) and intact right sural SNAP. Motor NCS showed compound muscle action potentials (CMAPs) with reduced amplitudes and prolonged distal latencies in the right peroneal (fibular), right tibial, bilateral median and bilateral ulnar nerves, and prolonged F-wave latencies. No clear conduction block or temporal dispersion was observed. On needle electromyography (EMG), scattered fibrillations and long-duration motor unit potentials were observed in muscles from the right upper and lower extremities. The study was interpreted as an acute to subacute sensorimotor polyneuropathy with predominantly demyelinating features. Over the next two months, his weakness and paresthesia worsened, with the development of significant weakness in his bilateral facial muscles, and muscles in the bilateral proximal upper and lower extremities. His speech became dysarthric and he was unable to ambulate. Cerebrospinal fluid (CSF) showed elevated protein at 122 mg/dL (normal 15-45 mg/dL) with 1/ μ L mononuclear cell (normal 0-5/ μ L). A right sural nerve biopsy showed loss of myelinated axons without inflammation, amyloid deposit or granuloma formation.

Laboratory analysis revealed elevated sedimentation rate at 95 mm/hr (normal <15 mm/hr) and C reactive protein (CRP) at 5 mg/dL (normal <0.9 mg/dL). The following abnormal liver function results were observed: aspartate aminotransferase (AST) of 132 U/L (normal 14-40 U/L), alanine aminotransferase (ALT) of 87 U/L (normal 10-54 U/L), alkaline phosphatase of 378 U/L (normal 38-113 U/L) and total bilirubin of 6.7 mg/dL (normal 0.2-1.3 mg/dL). Finding of active PSC were confirmed via computed tomography of the abdomen and endoscopic retrograde cholangio-pancreatography (ERCP).

Intravenous immunoglobulin (IVIG) was administered, leading to minimal improvement. Oral prednisone at 40mg daily was initiated, and he also received 5 sessions of plasma exchange. His common biliary ducts were dilated via ERCP. These treatments led to significant improvement in all of his symptoms, signs and serological findings. At month five, his speech became normal, and he ambulated independently. Muscle strength exam showed no weakness. Repeat sedimentation rate and liver function tests were all normal. Prednisone dosage was reduced to 10 mg daily.

Patient 2

A 76 year-old-male presented with subacute onset of numbness and tingling of hands and feet, and weakness

of bilateral lower extremities. He had been hospitalized a few weeks prior to presentation for acute cholecystitis and pneumonia. During that admission he was found to have newly developed thrombocytopenia with platelet count of $39 \times 10^3/\mu\text{L}$ (normal $150\text{--}450 \times 10^3/\mu\text{L}$) and anemia with a hemoglobin of 8.8g/dL (normal 14–18g/dL). Muscle strength examination revealed the following (right/left): shoulder abductors 4/4, elbow flexors 4/5, elbow extensors 4/4, wrist extensors 3/4, first dorsal interossi 3/3, abductor digiti minimi 3/3, abductor pollicis brevis 3/3, hip flexors 3/2, knee flexors 2/2, knee extensors 3/3, dorsiflexors 3/2, and plantar flexors 3/3. Reflexes were diffusely absent. Sensory exam showed absent pinprick up to the distal shins and reduced vibration sensation up to the knees. On sensory NCS, the left sural, superficial peroneal, median, ulnar and radial SNAPs were absent. Motor NCS showed slow conduction velocities in the left peroneal, tibial, median and ulnar nerves, prolonged distal latencies in the left median and ulnar nerves, and presence of conduction block in the left ulnar nerve. CSF showed elevated protein at 68mg/dL and mononuclear cell count at $3/\mu\text{L}$. MRI of the lumbar spine showed mild cauda equine root enhancement.

Hematology was consulted for further workup of anemia and thrombocytopenia. Hemoglobin quickly improved, but platelet count further reduced to $17 \times 10^3/\mu\text{L}$. There was no evidence of hemolysis. A bone marrow biopsy showed no evidence of lymphoproliferative disorder. A skeletal survey was negative for lytic lesions. Computed tomography (CT) chest, abdomen and pelvis showed no evidence of malignancy or organomegaly. There was no evidence for POEMS, immune thrombocytopenic purpura (ITP) or Evans syndrome. No clear etiology for thrombocytopenia was found despite extensive workup.

He was treated with monthly IVIG and oral prednisone which led to steady improvement in his neuromuscular status. At month 48, his strength examination was normal while on prednisone monotherapy of 5 mg daily. In parallel with the improvement in muscle strength, there was a steady improvement in the platelet count which became gradually normalized at month 35. It was thought that he suffered from a combination of CIDP and immune-mediated thrombocytopenia.

Patient 3

A 39-year-old female presented with progressive numbness and tingling of hands and feet, radicular leg pain, and difficulty with gait requiring assistance at two months after an uncomplicated cesarean section. Muscle strength

exam revealed the following: shoulder abductors 4/3, elbow flexors 3/3, elbow extensors 3/3, wrist flexors 3/3, wrist extensors 4/4, abductor digiti minimi 4/4, first dorsal interossi 4/4, abductor pollicis brevis 4/4, hip flexors 2/2, knee flexors 2/2, knee extensors 1/2, dorsiflexors 2/3, and plantar flexors 2/2. A sensory exam revealed reduced pinprick up to distal legs and vibration sensation at the toes. Laboratory results showed a positive ANA at 1:2560 that was normalized two months later. CSF studies showed elevated protein at 409mg/dL with mononuclear cell count at $6/\mu\text{L}$. An MRI of the cervical and lumbar spine showed diffuse nerve root enhancement, more prominent in the lumbar than the cervical region. Sensory NCS revealed reduced right sural but intact right median and right ulnar SNAPs. On motor NCS, the right peroneal and right tibial CMAP amplitudes were reduced, the right tibial H-reflex was absent, and the right tibial, median and ulnar F-waves all had prolonged latencies. EMG revealed scattered presence of fibrillation potentials and neurogenic recruitment of normal appearing motor unit potentials. A right sural nerve biopsy showed mild loss of axons without clear evidence of inflammation or demyelination. A salivary gland biopsy was essentially normal. The patient was evaluated by rheumatology, and no evidence of a connective tissue disorder was found.

She was treated with intravenous methylprednisolone at 1 gram per day for five days, IVIG at 2 gram per kilogram of body weight, and seven sessions of plasma exchange with no improvement. At week nine, her muscle strength continued to deteriorate, and she became bedridden. She was started on oral prednisone at 60mg daily which led to noticeable improvement in her strength in one week. For the subsequent five months, she was treated with repeated monthly IVIG and prednisone at weaning dosages, which led to steady and significant improvement in her strength and sensory exam, and she regained ambulatory status. Subsequently she was treated with oral prednisone alone. Repeat MRI of lumbar and cervical at month seven showed reduction in nerve root enhancement. A repeat electrodiagnostic study at month 14 showed normal nerve conduction studies except an absent right tibial H-reflex. At month 48, the patient had a normal neurological exam off immunosuppression.

Discussion

The co-occurrence of CIDP with other autoimmune diseases has been previously described in several case reports.³ Here we described three patients presenting with CIDP with rare autoimmune conditions. The first patient

had a remote history of primary sclerosing cholangitis and ulcerative colitis status post colon resection. He had not received medical treatment for either condition, furthermore, his liver function tests were normal for the prior few years. Coinciding with the onset of CIDP, there was a recurrence of his PSC.

To date, there have been no prior reports of co-occurring CIDP and PSC. Murata et al. described a 36-year-old woman with an 18-month history of progressive numbness and clumsiness of the limbs who was diagnosed with CIDP as well as primary biliary cirrhosis (PBC). PBC is clinically similar to PSC, however, PBC causes inflammation and destruction of only septal and intralobular bile ducts and spares extrahepatic ducts.¹² One proposed mechanism for co-occurrence of CIDP and PSC is that there may be common antigens associated with biliary epithelial cells and Schwann cells.¹³ Prior studies have shown myelinated fibers in CIDP express the major histocompatibility complex II along with B7 family of co-stimulatory molecules which are also expressed on biliary epithelial cells.¹³⁻¹⁴

Patient two had a combination of CIDP and thrombocytopenia. There have been a few prior reported cases of CIDP in association with ITP or Evans syndrome.¹⁵⁻¹⁸ However, hematological evaluation of our patient did not suggest a diagnosis of either ITP or Evans syndrome which manifests as a combination of hemolytic anemia and thrombocytopenia. The thrombocytopenia noted in our patient worsened and improved in parallel with his CIDP which suggested an immune-mediated mechanism. Platelets have also been implicated in a variety of active immune functions, thus suppression of platelet function could potentially stimulate the development of other autoimmune conditions.¹⁹

The onset of CIDP in patient three occurred two months postpartum with transient, but significant, elevation of ANA. There have been few reported cases of CIDP worsening during the postpartum period, but new onset CIDP in the postpartum period has not been described.²⁰ Pregnancy creates a relative immunosuppressed state in which T helper type 2 (Th2) and Th3 cells are increased and Th1 cytokines are suppressed.²¹ During the postpartum period there is a shift towards Th1 cytokines which may heighten the proinflammatory response leading to development or exacerbation of other autoimmune conditions.²¹ Prior studies have shown that active and remitting CIDP have a higher percentage of Th1 cells in CSF with upregulation of type I cytokines compared to other noninflammatory neurologic diseases.²²

Conclusion

Other autoimmune diseases, even rare autoimmune conditions, can co-occur with CIDP, and the presence of such coexisting conditions can help make a diagnosis of CIDP. The identification of polyautoimmunity in some CIDP patients supports the idea of a common immunopathogenic mechanism.^{3,11}

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