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CLINICAL VIGNETTE

Sjogren's Ganglionopathy

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A 73-year-old right-handed woman presented to neurology for evaluation of inability to use her hands. Her past medical history is significant for chronic lymphocytic leukemia (CLL) diagnosed 25 years ago. This was incidentally discovered on routine blood work. The diagnosis was confirmed by bone marrow biopsy and she has remained asymptomatic and watchful monitoring. She also has a history of migraines which were unchanged.

She was recently hospitalized for mini-strokes. At the time she had fallen recurrently and developed diplopia with a 6th cranial nerve palsy. She was treated with heparin drip and then transitioned to dabigatran with resolution of diplopia. Her hospitalization was complicated by herpes simplex meningitis which was successfully treated with intravenous acyclovir. After extensive physical therapy, she was able to return home. She was able to walk on her own and was quite strong. Two weeks later, she worsened and could not walk or rise from a sitting to standing position. Her hands were stiff and felt cold. Her fingers moved in a claw-like fashion and she was not able to utilize her hands for fine motor movements. She needed special utensils to hold her food properly, and described a sensation of "electricity", pins and needles and numbness involving her hands. She also experienced difficulty washing, combing her hair and difficulty buttoning and tying things. Her family reported memory issues and difficulty sleeping.

She was started on gabapentin which was initially titrated to 900mg per day and later decreased to 600mg/day for worsening dry mouth. The gabapentin provided some relief but did not resolve the symptoms completely.

On physical exam the patient was well-developed, well-groomed woman who appeared her stated age. Her vital signs were stable. Her skin exam was normal without Gottron's papules, shawl sign, heliotrope, or mechanic's hands. Her cardiopulmonary exam was normal. Her optic discs were sharp. Her speech was fluent and coherent. Memory, attention, and ability to follow commands were intact. Her visual fields were full. Pupils were equally round and reactive to light. Extraocular movements were intact. Facial sensation was intact. There was no face, jaw, palate, or tongue weakness or atrophy, nor temporal wasting. Hearing was grossly intact. Shoulder shrug was normal. Her motor exam was normal except for her thumb flexion, abduction, finger flexion, extension, abduction and adduction revealed 4 out of 5 strength. Dysmetria on finger-nose-finger and slightly reduced rapid alternating hand

movements were noted. She was not able to walk independently on heels, on toes or tandem. Proprioception testing was abnormal (up was mistaken for down on the right big toe). Her physical exam also revealed positive Romberg test and significantly reduced vibratory sensation at the toes and moderately reduced at the ankles. Reflexes were absent except for 2+ brachioradialis on the right.

Laboratory testing included normal A1C (5.5), positive Anti-Nuclear Antibody (ANA) but negative dsDNA, SM, RNP, SSA/SSB, centromere, scleroderma-70, Rheumatoid factor, anti-CCP, ANCA antibodies and negative antiphospholipid antibodies (Anti-Cardiolipin and Beta-2- Glycoprotein antibodies and lupus anticoagulant). Her inflammatory markers, ACE and complement levels (C3, C4) were normal. Her infectious testing included negative RPR, HIV, Hepatitis B and C antibodies, MTB Quantiferon gold and Cocci serologies. She had a monoclonal IgG kappa gammopathy, without monoclonal bands seen on serum and urine protein electrophoresis. Serum paraneoplastic panel, autoimmune sensorimotor panel, Anti-MAG antibodies, and Acetylcholine receptor antibodies were negative. Lumbar puncture revealed normal cell counts but elevated protein at 75, less than 45 is considered normal.

Colonoscopy was normal 2 years prior. Computer tomography of the chest, abdomen, and pelvis did not reveal any abnormalities. MRI of the brain revealed chronic bilateral cerebellar infarctions and L frontal infarctions and generalized volume loss. MRI of the L spine without contrast revealed moderate right foraminal narrowing at L5-S1 due to a disc bulge and facet hypertrophy. EMG/NCS showed predominantly sensory abnormalities without any electrodiagnostic evidence of demyelination.

Altogether, the sensory-predominant findings, non-length dependent paresthesia (hands > feet in terms of onset and intensity), large-fiber sensory loss (areflexia, sensory ataxia, vibratory sensation loss, and absent proprioception, pseudo-athetosis, Romberg sign), and the electrodiagnostic findings all support the diagnosis of a disorder of sensory ganglionopathy. She had dysmetria and intention tremor on exam which was attributed to cerebellar strokes.

The differential diagnosis of a sensory ganglionopathy includes paraneoplastic, post-infectious and autoimmune related sensory polyganglionopathies. The serum paraneoplastic panel and ganglionic AChR antibodies returned negative. Her CLL was

deemed to be in remission and mammogram and colonoscopy were both negative. Though she was a former smoker, CT chest did not reveal any masses. Infectious causes were also considered. HIV and Hepatitis panel returned negative. A post-infectious reaction to the recent HSV infection was also considered. Lastly, given her neurological findings, abnormal nerve conduction study and dry mouth, Sjogren's was suspected. Although her Sjogren's serologies were negative, minor salivary gland biopsy revealed multi-focal lymphocytic sialadenitis with a focus score of >1 . This met the revised histopathologic criterion for Sjogren's syndrome.

Primary Sjogren's Syndrome (SS) is an autoimmune disease that primarily involves the exocrine glands leading to structural damage and functional impairment, causing sicca syndrome of mucosal surfaces. It affects about 1% for the population and is more common in women.¹ Though dry eyes and dry mouth are the most common symptoms, extra-glandular manifestations are common and include inflammatory arthritis, involvement of the skin, kidneys, heart, lung and intestines.² Inflammation of the nerves is also another complication of Sjogren's Syndrome. Patients usually present with hypergammaglobulinemia, positive ANA, of which anti-SSA and anti-SSB are more specific. The main characteristic finding on minor salivary gland biopsy is focal lymphocytic infiltration.³

Neurological manifestations are quite rare in SS however these can be quite debilitating as it can affect the peripheral and central nervous systems (CNS). Central nervous system involvement is much less common (2-25% of patients).⁴ Some of the CNS manifestations include cognitive disorders, aseptic meningitis, epileptic seizures, headache, transverse myelitis, optic neuritis, disseminated encephalopathy and lesions in the CNS similar to multiple sclerosis.⁴ Peripheral neuropathies such as sensory axonal neuropathy and painful small fiber neuropathy are the most frequent neurological manifestations.⁴ Other peripheral neuropathies include mononeuropathy multiplex, multiple cranial neuropathies, trigeminal neuropathy, autonomic neuropathy, and radiculopathy and sensory ataxic neuropathies (also known sensory ganglionopathy).⁵ Though rare, sensory neuropathies (SN) or ganglionopathies lead to the most significant disabilities. Their prevalence is unknown.⁶ The prevalence of peripheral neuropathies associated with Sjogren's syndrome increases with age.²

Sensory ganglionopathies are pure sensory neuropathies caused by dorsal root ganglia neuronal destruction. This process results in a multifocal pattern of sensory deficits which is different from the usual length-dependent pattern found in axonal neuropathies.⁶ The pathogenesis is unknown though many mechanisms have been proposed, such as genetic susceptibility, drug-related toxicity, infectious agents, and autoimmune damage.⁶ Primary SS and celiac disease are two autoimmune diseases that are frequently involved.⁶

Symptoms

The symptoms of SN include paresthesia, ataxia, difficulty with fine motor movements due to impaired proprioception leading to ataxia, reduced vibration sense and reduced or absent reflexes and abnormal Romberg's test. Motor strength is usually not affected.⁶ Autonomic dysfunction may also be present with hypohydrosis or anhidrosis, tachycardia and orthostatic hypotension.⁷ Sensory neuropathy in SS tends to be asymmetrical and predominately affects the upper extremities.⁶ There is also loss of kinesthesia, difficulty with fine motor skills, and pseudoathetosis, an inability to localize the extremity in space.⁷ The neurological symptoms can precede the onset of sicca symptoms. Progression tends to be chronic, insidious and, despite treatment, can be quite debilitating.

Diagnosis

Electrophysiological studies reveal widespread reduction of sensory potential amplitudes, without a distal worsening toward the legs.⁶ Motor nerve conduction studies are generally normal. Somatosensory evoked potential may also show abnormal central conduction times which can be attributed to degeneration of dorsal root columns in the spinal cord.⁶ For patients who have long standing disease, MRI can reveal hyperintense T2-weighted lesion at the posterior columns and volumetric reduction in cervical area resulting from dorsal root degeneration.⁶ Excisional biopsy of dorsal root ganglion is the gold standard but rarely ever performed due to the complications associated with the procedure.^{6,8}

Treatment

Due to the lack of long-term studies, there are no validated treatments to guide SN management. Randomized clinical studies are needed but difficult to perform due to the rarity of SN. The recommended first line treatment is corticosteroids and IVIG. Case reports have also shown that corticosteroids in conjunction with other immunosuppressive treatments, namely mycophenolate mofetil have shown positive results.⁶ Other studies have shown a benefit to pulse cyclophosphamide.⁷ Several reports have also shown success with rituximab but results have been quite mixed.⁷ Other therapies include hydroxychloroquine, tacrolimus, azathioprine, plasmapheresis, and infliximab.⁷

Interestingly, her repeat serologies years later revealed a positive ANA at a higher titer and positive SSA further supporting a diagnosis of Sjogren's Syndrome. SSB and Rheumatoid factor remained negative. Our patient was treated with prednisone at 1mg per kilogram daily and subsequently tapered over 8 months. Given her history of recent strokes, IVIG was avoided due to the increased risk of clots. Patient deferred rituximab due to fear of side effects and instead treated with cellcept. While her symptoms improved significantly, these did not fully resolve.

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