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Presenting Symptom(s): Left greater than right arm weakness and parathesias

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Disclosure: B Fuller, none; A Chiodo, none

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Appropriate Audience: Residents and practicing physicians.

Learning Objectives: After completing this educational activity, participant will be able to: (1) formulate a differential diagnosis of non-traumatic spinal cord injury; (2) summarize etiologies of acute transverse myelitis; and (3) administer treatment for acute transverse myelitis.

Level of Difficulty: Advanced

History

A 58 year old Caucasian female presented with a three week history of progressive left greater than right arm parathesias and weakness.

1. Prior to continuing, please develop a differential diagnosis and list each possible diagnosis in order of likelihood.
2. Is there any additional information regarding the clinical history that might be helpful in clarifying your differential list or changing its order of priority?

Commentary I

The differential diagnosis of a patient presenting with acute or subacute arm weakness and parathesias is protean. First, the clinician must determine if the cause is in the central nervous system, the peripheral nervous system, or something else. Peripheral causes could include cervical radiculopathy, brachial plexopathy (i.e. pancoast tumor), thoracic outlet syndrome, et cetera. Consideration of a cerebrovascular accident or cervical myelopathy should be the primary focus of an urgent neurological workup due to the serious morbidity and mortality. Other conditions that may present in this manner include Acute Inflammatory Demyelinating Polyneuropathy, and Multiple Sclerosis.

A detailed history should be obtained focusing on the presentation and acuity of symptoms as well as recent infection or vaccination, systemic inflammatory disease, cerebrovascular events, neoplasm, Multiple Sclerosis,



trauma, radiation therapy, visual deficits and bowel or bladder dysfunction. The specific symptoms of systemic infection or inflammatory disease that should be investigated include: rashes, night sweats, oral or genital ulcers, sicca syndromes, shortness of breath, pleuritic pain, and hematuria.

History, continued

The patient's medical history included Systemic Lupus Erythematosus cerebritis, Antiphospholipid Antibody Syndrome, sigmoid adenocarcinoma and idiopathic pulmonary fibrosis. She was on chronic coumadin therapy for a history of deep venous thrombosis and denied recent fevers, illness, vaccinations and foreign travel. The patient noted difficulty with voiding secondary to inability to sense her urine stream.

1. If necessary, revise your differential diagnosis based on the additional clinical history.
2. On which details of the physical examination should you focus at this point?

Commentary II

At this point the primary focus of the investigation should be on a possible cerebrovascular accident versus cervical myelopathy and urgent neuroimaging of the brain and cervical spinal cord followed by CSF and serology studies is mandatory.

Given the patient's history of Systemic Lupus Erythematosus involving the neuroaxis, the possibility of an Acute Transverse Myelitis or recurrent Lupus cerebritis must be entertained. The possible etiologies of Acute Transverse Myelitis are exhaustive and include: idiopathic, viral or infectious (Coxsackie virus, herpes simplex virus, polio, HIV, Syphilis, Lyme borelliosis, Leptospirosis, Ehrlichiosis, Babesiosis, and Mycoplasm Pneumonia), systemic inflammatory disease associated (Systemic Lupus Erythematosus, Antiphospholipid Antibody Syndrome, Bechets, sarcoidosis), spinal tumor, vasculitic, ischemic, hematomyelia, arterio-venous malformation, radiation myelopathy, epidural lipomatosis, fibrocartilaginous embolism, spinal cord necrosis secondary to arterial thrombosis, and vaccine myelitis (tuberculosis, hepatitis B vaccination).^(1,4)

Her history of Antiphospholipid Antibody Syndrome, colon cancer, and chronic anticoagulation therapy raises the specter of a cerebrovascular accident, thrombotic spinal cord infarct or metastases and hematomyelia respectively. The subacute time course makes the diagnosis of a fibrocartilaginous embolism or ischemic insult to the spinal cord unlikely. The absence of a history of radiation therapy, recent vaccination and systemic or gastrointestinal infection decreases the possibility of Acute Inflammatory Demyelinating Polyradiculopathy, infectious or post vaccination Acute Transverse Myelitis and radiation myelopathy.

The physical exam should focus on manual muscle testing and a thorough neurologic exam to ascertain if there is a discrete sensory level of the lesion. Signs of systemic inflammatory disease that should be investigated include: uveitis, retinitis, decreased lacrimation or salivation, skin rash (i.e. malar), oral or genital ulcers, adenopathy, pleuritic or pericardial friction rub and organomegally. Demonstration of a postural component to the symptoms may point to a dural arteriovenous malformation.

Physical Examination

In the emergency department manual muscle testing revealed in the left arm: shoulder abductors 2/5, elbow extensors 4/5, elbow flexors 2/5, finger extensors 3/5, and finger flexors 4/5. The right arm revealed: shoulder abductors 5/5, elbow extensors 5-/5, elbow flexors 3/5, finger extensors 4/5, and finger flexors 5/5. In both legs all muscles tested are 4/5 except left dorsiflexion is 5/5. Normal tone and muscle bulk is noted throughout.

The patient's neurological exam revealed a 3mm left pupil and a 5 mm right pupil with symptoms of a left Horner's syndrome. There was a mild ptosis on the left. No pronator drift was noted. Reflexes were 0/4 bilaterally at the biceps and brachioradialis, and 3/4 bilaterally at the patella. Babinski sign was absent bilaterally. Diminished light touch, proprioception and pinprick were found in the arms but not the trunk or legs. There was an absence of vibration sense in the arms and legs. Graphesthesia was noted in both palms and dysmetria in the right arm.

1. At this point, review your differential diagnosis and revise as appropriate.
2. Are there additional observations on physical examination that might be helpful in narrowing your differential list?

Commentary III

The physical exam findings of bilateral weakness, a discrete sensory level, and primarily upper limb opposed to lower limb findings suggest dysfunction at a specific spinal cord level. Although it is less common, multiple sclerosis can present with an initial attack to the spinal cord. Likewise, the involvement of the optic nerve and the spinal cord in neuromyelitis optica (NMO), may occur months or years apart. Therefore, the differential diagnosis must include at least multiple sclerosis, NMO, and transverse myelitis. The etiology of the patient's condition cannot be explained by history and physical exam findings alone. Neuroimaging and laboratory studies are still required.

Physical Examination, continued

She was admitted to neurology intensive care unit for monitoring of respiratory status after rapidly developing tetraplegia, dysarthria, dysphagia and respiratory insufficiency.

Her hospital course was complicated by: pneumonia, hypertension, respiratory insufficiency requiring BiPAP and CPAP, anemia secondary to a gastrointestinal bleed, hypotension requiring vasopressors, pneumoperitoneum secondary to perforated sigmoid colon requiring a transverse, left, and sigmoid colectomy with end right colostomy and Hartman pouch, thrombocytopenia, multiple compression fractures of the thoracic and lumbar spine requiring CASH brace, hyponatremia secondary to SIADH, incontinence of bladder, PEG tube placement, and neutropenia.

On admission to the acute rehabilitation service her manual muscle testing for the right upper limb revealed elbow flexors 3-/5, elbow extensors 2/5, wrist extensors 4/5, finger flexors and abductors 3/5. The manual muscle testing for the left upper limb revealed elbow flexors 3-/5, elbow extensors 2/5, wrist extensors 4-/5, finger flexors and abductors 3/5. Manual muscle testing of the right lower limb revealed right hip flexors 2/5, knee extensors, ankle dorsiflexors and plantar flexors 4/5. Manual muscle testing of the left lower limb revealed hip flexors 2/5, knee extensors, ankle dorsiflexors and plantarflexors 4/5.

Her neurologic exam revealed light touch and pinprick decreased beginning at the T2 level and including all dermatomes of the upper limbs, sacral sensation intact, rectal sensation intact and good rectal tone.

1. If necessary, revise your differential diagnosis based on the additional physical findings.

Clinical Impression

A cerebrovascular accident or cervical myelopathy of unknown etiology.

1. What diagnostic tests would you order at this time?

Commentary IV

Many clinicians believe that rapid diagnosis and treatment of an autoimmune mediated Acute Transverse Myelitis leads to a better patient outcome so urgent imaging and laboratory testing is of paramount importance.⁽²⁾

A diagnostic work up proposed by the Transverse Myelitis Consortium Working Group includes: an urgent MRI of the brain and spinal cord with gadolinium enhancement to rule out a vascular or compressive lesion and check for inflammation. If no cause of a compressive myelopathy is found then a lumbar puncture is required to evaluate for inflammatory markers such as CSF pleocytosis and elevated IgG index. If clinical features of a systemic illness are present then the next step is to obtain: CSF gram stain and culture, Venereal Disease Research Laboratory, AFB, TB culture, India ink stain, fungal cultures, parasite serology, Antibodies for HSV, VZV, HLTV-1, and anti-Borrelia burgdorferi, viral PCR studies (HSV, VZV, CMV, HIV) and serum rapid plasma regain. If a systemic inflammatory



disease is suspected, as in this case, then serologic studies should include: ESR, serum angiotensin converting enzyme levels, ANA, Anti-ds DNA antibody, SS-A (Ro), SS-B (La), Sm (Smith), RNP, PTT, Russel Viper Venom time, anticardiolipin antibody, lupus anticoagulant, b2 glycoprotein and complement levels.⁽⁶⁾

Another serologic marker to test for is NMO IgG for Neuromyelitis Optica.^(7, 8, 9)

If the above are negative then the patient likely has an idiopathic Acute Transverse Myelitis. Visual evoked potentials, an EMG as well as CSF IL-6 and 14 3-3 levels should be obtained to determine extent of injury and prognosis.^(1, 7, 8)

Test Results

The patient's MRI with and without gadolinium contrast of the brain revealed multiple scattered foci of abnormal T2 and FLAIR hyperintensities throughout the periventricular and subcortical white matter bilaterally, likely due to multiple sclerosis. Her MRI of the spine with and without gadolinium contrast revealed: extensive signal abnormality that was low on the T1-weighted images and high on the T2-weighted. The central portion of the cord showed more severe signal changes within the gray matter of the cord, which may have been related to severe spinal cord edema and/or syrinx formation. This area of signal abnormality extended from the lower medulla to the superior T7 level. Striking enhancement of the cord substance was noted extending from the C2 body level to the T4 vertebral body level. This area of abnormal enhancement was predominantly peripheral in location. Inferior to the T7 level, the spinal cord appears normal.

1. If necessary, augment or change the clinical impression based on the test results.

Commentary V

A proposed criteria for diagnosis of Acute Transverse Myelitis by the Transverse Myelitis Consortium Working Group proposes as inclusion criteria: sensory, motor or autonomic dysfunction attributable to the spinal cord, bilateral signs and symptoms, a discrete sensory level, exclusion of compressive lesion by neuroimaging, inflammation within the spinal cord demonstrated by CSF pleocytosis or elevated IgG index or gadolinium enhancement, and progression to nadir between four hours and 21 days.⁽⁶⁾

Exclusion criteria for an idiopathic Acute Transverse Myelitis suggested by the Transverse Myelitis Working Group includes a history of spine radiation, anterior spinal artery thrombosis, arteriovenous malformation in the spinal cord, serologic evidence of a connective tissue disease, central nervous system manifestations of syphilis, Lyme disease, HIV, HLTV-1, Mycoplasma Pneumonia, and other viral infections. Neuroimaging consistent with multiple sclerosis and history of optic neuritis are also exclusion criteria.⁽⁶⁾

White matter degeneration of the spinal cord is the most common pathologic MRI change found in Acute Transverse Myelitis but the gray matter may also be involved.⁽³⁾ Some clinicians believe that if demyelination on MRI is unifocal then the likely diagnosis is idiopathic or disease associated acute transverse myelitis. Small multiple enhancing lesions of the spinal cord maybe associated with Systemic Lupus Erythematosus induced Acute Transverse Myelitis or Multiple Sclerosis. Extensive multilevel lesions maybe associated with the vasculitis found in Antiphospholipid Antibody Syndrome.⁽⁴⁾ Patients whose spine MRI reveals longitudinal lesions greater than three vertebral body segments, especially with concurrent NMO antibodies, are more likely to have a relapsing myelitis.⁽¹⁰⁾ While the traditional definition of transverse myelitis demanded involvement of the optic track and the spinal cord alone, it has recently been recognized that some patients who have optic nerve and spinal involvement, and who have NMO antibodies, may also have brain lesions. It has been proposed that these patients be included in the definition of NMO.

In this case the patient presented with three weeks of impaired sensation and motor function of the bilateral arms, a sensory level at the upper thorax, an absence of a compressive lesion on MRI but inflammation of the spinal cord from C2 to T4 as evidenced by gadolinium enhancement. This patient's MRI also had findings of extensive multilevel lesions involving both gray and white matter of the spinal cord.

1. What additional diagnostic testing would you order?

Commentary VI

CSF and serology studies are required.

Test Results, continued

Her pertinent laboratory values were: CSF clear with protein 180, glucose 76, RBC 56, WBC 4, HSV negative, no evidence for monoclonal B cell population, culture negative, AFB negative, no evidence of oligoclonal bands, CMV PCR positive titer, anti nuclear antibody positive with titer 1:1280 and homogeneous, IgG index 0.63, Anti-ds DNA 24.6, INR 1.6, Anti-cardiolipin negative (previously reported positive), b2 glycoprotein negative, C3 183, C4 33, ESR 27, Anti-SM negative, Anti-RNP negative, Anti-RO/Anti-SSA negative, Anti-LA/Anti SSB negative. Unfortunately, NMO IgG was not tested.

1. What is the impact of the additional test results on the final diagnosis?
2. Considering all the data from the history, physical examination and laboratory studies, what is/are your final diagnostic impression(s)?

Final Diagnostic Impression

Systemic Lupus Erythematosus and Antiphospholipid Antibody associated Acute Transverse Myelitis.

Commentary VII

The patient's history and physical exam coupled with the MRI findings of extensive inflammatory lesions of the spinal cord and serologic evidence of Systemic Lupus Erythematosus and Antiphospholipid Antibody Syndrome support this diagnosis of Acute Transverse Myelitis. The positive CMV PCR titer could support a diagnosis of a viral myelitis, but in light of the other evidence this is much less likely. The serologic evidence supportive of Systemic Lupus Erythematosus associated Acute Transverse Myelitis includes her positive ANA and mildly elevated IgG index for age. Her history of positive Anticardiolipin antibody supports the diagnosis of Antiphospholipid Antibody Syndrome associated Acute Transverse Myelitis and it is known that previously positive Antiphospholipid antibody titers can become negative.⁽³⁾

Acute Transverse Myelitis is a rare event with an incidence estimated to be 1-4/million with approximately 1400 new cases per year in the United States. It has a bimodal age distribution of 10-19 and 30-39 years with 28% percent of cases occurring in children of which many are associated with recent immunization. Thirty to sixty percent of idiopathic Acute Transverse Myelitis cases report an antecedent infection.⁽¹⁾ Systemic Lupus Erythematosus associated Acute Transverse Myelitis is an extremely rare condition. A recent review article by Kovacs found only 91 cases in the medical literature between 1974 and 1999 with antiphospholipid antibodies being detected 64 percent of these cases.⁽⁵⁾

Acute Transverse Myelitis is a medical emergency and expeditious treatment is associated with a more favorable outcome. The pathophysiology of Systemic Lupus Erythematosus associated Acute Transverse Myelitis is uncertain though vasculitic and thrombotic causes are postulated.⁽⁵⁾ In the infectious etiologies of Acute Transverse Myelitis superantigen mediated activation of T lymphocytes is thought to play a role.⁽¹⁾

The prognosis of Acute Transverse Myelitis is variable. Generally one third have a good recovery, one third have moderate deficits and one third have a poor recovery.⁽⁶⁾ In the literature review by Kovacs of patients with Systemic Lupus Erythematosus associated Acute Transverse Myelitis fifty percent had a complete recovery, twenty nine percent a partial recovery and twenty one percent worsening or no recovery.⁽⁵⁾ Most patients have only one event but in up to twenty percent of patients recurrent episodes occur. This is more likely if the patient has MRI findings of multifocal lesions in the spinal cord and brain, oligoclonal bands in CSF, a history of a mixed connective tissue disease or detection of serum autoantibodies.⁽¹⁾

1. What treatment would you now initiate for this patient?

Commentary VIII

Treatment for this patient's Systemic Lupus Erythematosus associated Acute Transverse Myelitis treatment included: pulse steroids, monthly pulse intravenous cyclophosphamide, low dose mycophenolate mofetil, rituximab and anticoagulation.

The patient's response to treatment was good and on discharge from acute rehabilitation she was ambulating fifty feet with a rolling walker minimum assist, her wheelchair mobility was five hundred feet modified independent and stair climbing was total assist. Her activities of daily living were: transfers minimum assist, toilet transfers moderate assist, tub transfers total assist, eating set up, grooming moderate assist, bathing moderate assist, dressing upper extremities moderate assist, dressing lower extremities moderate assist, and toileting maximum assist.

Recently, NMO IgG has been found to be an important prognostic marker for subsequent development of Neuromyelitis Optica in patients with transverse myelitis and longitudinally extensive lesions. ^(7, 8, 9) MRI findings also guide treatment and prognosis. Ninety percent of patients with Acute Partial Transverse Myelitis and cerebral lesions as well as ten percent that present instead with a Complete Transverse Myelitis and asymmetric short cord lesions may convert to Multiple Sclerosis. ⁽¹⁰⁾ This is of import as Neuromyelitis Optica is more responsive to immunosuppression therapy and Multiple Sclerosis to immunomodulatory treatments. ⁽⁷⁾

Early diagnosis and aggressive treatment is associated with better functional outcomes. ⁽²⁾ A treatment regime suggested by the Johns Hopkins Transverse Myelitis Center includes: intravenous methylprednisolone 1000 mg or dexamethasone 200 mg for 3-5 days with a decision to continue based on follow up MRI. If symptoms persist despite steroid treatment then pulse IV cyclophosphamide 500-1000 mg/m² or plasma exchange may be required. ⁽¹⁾ In the subgroup of patients at risk for recurrent Acute Transverse Myelitis, seropositive for NMO-IgG with extensive MRI lesions, chronic immunomodulatory therapy for up to two years with azathioprine 150-200 mg/day or methotrexate 15-20 mg/wk or mycophenolate 2-3 g/day or oral cyclophosphamide 2 g/kg/day may be beneficial. ^(1, 7) Patients with Antiphospholipid Antibody Syndrome may benefit from anticoagulation. ⁽²⁾

Early rehabilitation with physical and occupational therapy to prevent skin breakdown, contracture as well as promoting strength and mobility is of the utmost importance. Other rehabilitation interventions include: splinting, spasticity management once spinal shock has resolved, a bowel and bladder program and medical management of neuropathic pain. ⁽¹⁾

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