Post-treatment Lyme Disease or Neuroborreliosis? A Case Study

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Abstract

Lyme disease is a tick-borne infection caused by *Borrelielia burgdorferi* endemic to Manitoba. This infection can cause long lasting nonspecific symptoms that can affect the day to day function of Manitobans for months to years after initial Lyme infection. Presented is a complicated case of a patient with multiple tick-borne infections who subsequently developed trouble with memory and cognitive function. The lack of diagnostic criteria for post-treatment Lyme disease, and poor diagnostic measures for neuroborreliosis, results in possible underdiagnoses of chronic Lyme syndromes and infections.

Case History

A 55 year old man presented to Selkirk emergency on July 12 2015 with a two day history of fever, pounding frontal headache, myalgia and significant fatigue. Over the last four weeks the patient had spent considerable time outside working on his cottage in Buffalo Point, Manitoba and had noticed a tick bite approximately four weeks ago. He had not travelled recently or been in contact with anyone who had traveled. His past medical history was unremarkable other than low blood pressure which had been noted by his family physician. He had been previously healthy and worked in a machine shop, which he owned. At triage he was hypotensive (86/57 mmHg), and febrile (38.5C oral). While in triage, the patient experienced two episodes of syncope and was transferred to resuscitation where he recovered and was able to self-ambulate. He was noted to be alert and orientated, diaphoretic, pale and dehydrated on exam. There were no rashes. The patient denied photophobia and nuchal rigidity. Chest X-ray was clear. Computer tomography uninfused of the head scan was normal and urine analysis showed trace protein but was otherwise normal. ECG was normal. Blood work showed a decrease of white cell count (1.9 x 10E9/L), decreased platelets (49 x 10E12/L), decreased hemoglobin (135 g/L) and an increase of AST (118 U/L), ALT (103 U/L), lactate dehydrogenase (1038 U/L) and GGT (63 U/L). West Nile virus and Lyme serologies were ordered. Differential diagnosis included West Nile Virus, Lyme disease, and heat exhaustion. The patient was discharged with a 10 day course of 100 mg BID Doxycycline and told to return the next day for repeat blood work and reassessment.

The following day he was afebrile (36C) but continued to be hypotensive (82/59) with low white cell count, hemoglobin, platelets and high AST, ALT, GGT, and LD. He was diagnosed with pancytopenia and referred to Cancer Care Manitoba Hematology. He was never seen by Cancer Care as his pre-appointment blood work showed normal white cell count, hemoglobin, lactate dehydrogenase and platelet levels. The peripheral blood film had been relatively normal but had a slight increase in reticulocyte count. Hematology recommended that viral illness such as EBV, Hepatitis B and hepatitis C be ruled out as the cause of acute insult.

Anaplasma phagocytophilum IgG antibody titer from a December 4th 2015 collection was 128. Titers equal or greater than 64 are consistent with infection with *A. phagocytophilum*. *A. phagocytophilum* IgG IFA was positive as well. The patient had shown clinical and laboratory evidence of anaplasmosis infection, which was resolved with doxycycline.

The following summer on Aug 14, 2016, the patient presented to Selkirk emergency with a 2-3 day history of generalized weakness, fever, and right sided neck pain and stiffness after being at his cottage in Buffalo Point Manitoba. His temperature was 39.5C and he was discharged with the diagnosis of fever not-yet-determined. On Aug 17, 2016 he returned to the emergency department with continual malaise, fever, neck stiffness and a 5-6 cm target lesion on his anterior chest with central clearing. He had taken two doses of doxycycline at this time. He was diagnosed with Lyme disease and discharged with instructions to complete a 6 week course of doxycycline. Serology show negative results for *B. burgdorferi* IgG and IgM, negative for West Nile Virus and a positive titre from his previous Anaplasmosis infection.

The patient slowly improved while taking doxycycline but unfortunately developed residual and persistent symptoms of brain fog, stiffness, aching, clumsiness, dizziness and poor memory. He described himself as feeling like “an old man”. He also experienced a sensation of twitching of the muscles on the left side of his face, which suggested possible facial nerve involvement. His neurological exam remained unremarkable. His cognitive symptoms prevented him from working an 8-hour work day, when previously he could work more than 12 hours. The patient eventually sold his machine shop business, due to his inability to manage complex tasks. The patient continues to struggle with cognitive impairment to this day.

In November 2017 it was questioned whether or not the patient was suffering from neuroborreliosis. His Lyme serology had been negative in August 2016, but he was treated with doxycycline early, so it is possible that he did not seroconvert. A lumbar puncture was performed January 17, 2018, sixteen months after the second acute episode of fever and fatigue. Cerebrospinal fluid analysis was abnormal but did not suggest neuroborreliosis. Protein count was slightly elevated at 0.42 g/L (Normal 0.20 to 0.40 g/L). The cell concentration was normal, but 12% of the cells were neutrophils, while normally cells should be 100% mononuclear cells. *B. burgdorferi* antibodies were not tested for in CSF as there were no detectible antibody in serum to compare. It was concluded that the patient did not have neuroborreliosis. The patients residual cognitive issues remain a complicated diagnosis and the cause is yet to be determined.

Literature Search

A literature search was performed using Pubmed with the MeSH terms: Neuroborreliosis: blood, CSF, Diagnosis, Drug Therapy, Epidemiology. Lyme Disease: blood, diagnosis.

Discussion

There are three tick-borne diseases endemic to southern Manitoba: Anaplasmosis, Babesiosis and Lyme disease. All of which are carried by the tick species *Ixodes scapularis,* more commonly known as the deer tick or black-legged tick. The black-legged tick is found in pockets around southern Manitoba (Figure 1) Buffalo point is located in the most southeastern corner of Manitoba on Lake of the Woods, an area that has one of the highest incidence rates of Anaplasmosis and Lyme disease cases in Manitoba. Reported cases of all three tick-borne diseases have increased over the last several years. Lyme disease is the most common tick-borne disease in Manitoba with 64 cases being reported in 2016.[1]

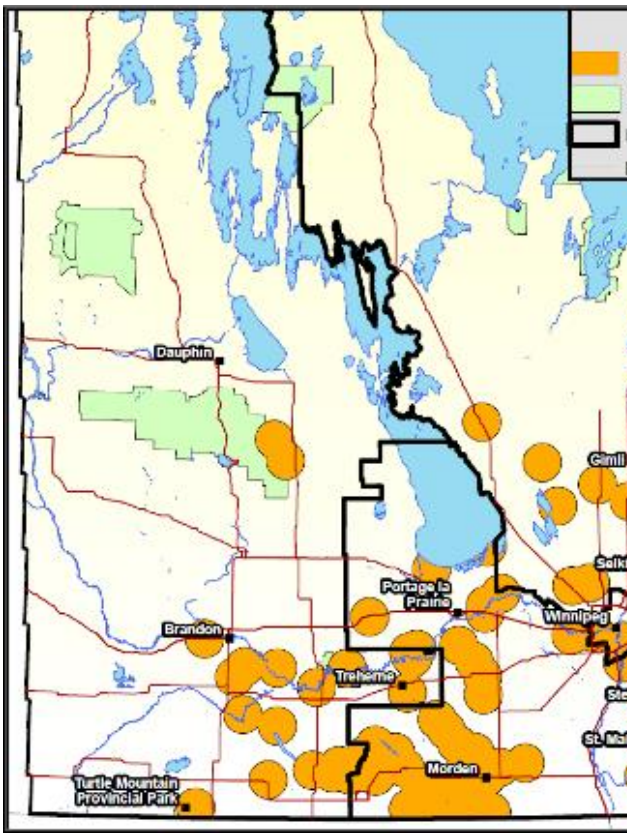

Figure 1
Areas where the disease-bearing tick; *Ixodes scapularis* can be found in Manitoba[1]

Lyme disease in North America is most commonly caused by the spirochete *Borrelielia burgdorgeri.* There are three clinical stages of the disease: Early localized, characterized by the erythema migrans rash. Early disseminated, characterized by multiple erythema migrans rashes and neurologic, and cardiac involvement. As well as Late Lyme disease, characterized by arthritis and possible neurologic involvement. Acute infection of Lyme may present with the following symptoms: Fatigue (54 percent), anorexia (26 percent), headache (42 percent), neck stiffness (35 percent), myalgias (44 percent), arthralgias (44 percent), regional lymphadenopathy (23 percent), and less commonly fever (16 percent)[10]. Anaplasmosis, caused by *Anaplasma phagocytophilum,* is less common with seventeen cases reported in Manitoba in 2016[1]. Anaplasmosis is an acute febrile illness and presents with symptoms of malaise, myalgia, headache and chills and uncommonly nausea, vomiting, arthralgias and cough. Rash and neurological symptoms are uncommon. Laboratory findings of anaplasmosis include significant leukopenia and elevated plasma serum lactate dehydrogenase and liver enzymes[11].

Generally, with prompt treatment, an acute Lyme infection should resolve. However, residual and persistent symptoms may occur lasting months to years[12]. Anaplasmosis may also cause residual constitutional symptoms[2]. Two culprits of persistent Lyme symptoms include Post-treatment Lyme disease syndrome and Nervous system Lyme disease. Post-treatment Lyme disease syndrome is the occurrence of symptoms such as cognitive issues, fatigue, and joint swelling after clearance of *B. burgdorferi* infection. Studies suggest 10 – 15% of Lyme patients will develop persistent nonspecific symptoms after successful treatment[3]. This syndrome is *not* a chronic or persistent infection of *B. burgdorferi,* rather is suggested to be prolonged inflammatory processes residual from acute disseminated infection. There is no evidence that *B. burgdorferi* can persist latently in tissue concurrently or after antibiotic treatment[4]. Unlike active Lyme disease which is diagnosed by measuring seroconversion, post-treatment Lyme disease syndrome cannot be objectively measured. Clinical diagnostic criteria has not been standardized. One example mentioned by the Infectious Disease Society of America defines post-treatment Lyme disease syndrome as:

> "Widespread musculoskeletal pain, cognitive complaints, radicular pain, paresthesias, or dysesthesias provided the symptoms interfered with the ability to function. The symptoms also had to begin within 6 months after the initial diagnosis and treatment of *B. burgdorferi* infection and had to persist for at least 6 months."[4]

Additional antibiotic treatment for post-treatment Lyme disease syndrome is not recommended[5]. Significant cognitive slowing can be attributed to post-treatment Lyme disease syndrome (termed encephalopathy), and is not a sign of Lyme neuroborreliosis[6]. Up to 92% of post-treatment Lyme disease syndrome patients report cognitive changes. Specifically; memory impairment, attention, decreased reaction time and decreased information processing time[3].

Rarely, (3-15% of cases) the peripheral or central nervous system may be involved in active *B. burgdoferi* infection, known as neuroborreliosis. This can present as meningitis, facial nerve palsy amongst other cranial nerve palsies (specifically cranial nerve 8 and 12[7].) and radiculoneuritis. Inflammation of the brain parenchymal tissue is very rare[8]. Fortunately, the infection is responsive to ceftriaxone treatment, yet any damage to neural structures may be permanent[12]. Post-treatment Lyme disease syndrome is higher in patients with neuroborreliosis which incidences of 12-59%[7]. Cerebrospinal fluid analysis is used to diagnose CNS involved neuroborreliosis. CNS infection causes CSF pleocytosis, elevated protein levels and most importantly, a higher concentration of IgG to *B. burgdorferi* in CSF relative to antibody levels in serum. This may represent local humoral activity in the CSF. CNS neuroborreliosis may be underdiagnosed. Sensitivity of CSF analysis for neuroborreliosis has been suggested to be as low as 50%[8]. To increase sensitivity, a concordant analysis of levels of chemokine CXC13 in CSF can be completed. CXC13 is a chemoattractant for B-cells and has been shown to be reliably elevated in Neuroborreliosis[9].

Conclusion

Persistent constitutional or cognitive symptoms are not uncommon in Lyme disease. Residual syndromes are poorly defined and are often confused with direct neural involvement in Lyme infection. Furthermore, there is potential for Neuroborreliosis to be underdiagnosed. The patient presented here represents a complicated case in which tick-borne infections may or may not have contributed to his residual complaints of decreased cognitive function. Though he did not seroconvert for Lyme disease, he presented with characteristic symptoms of infection in 2016 and developed a clinical picture of post-treatment Lyme disease that meets the proposed diagnostic criteria outlined above. However, his CSF analysis was abnormal as well. CSF protein was elevated with an abnormal proportion of

neutrophils. It was ultimately determined that he did not have neuroborreliosis, yet his *B. burgdorferi* CSF antibody was not measured, because he was seronegative. As a result, a final definitive diagnosis was not reached. The lack of standardzed diagnostic criteria for post-treatment Lyme disease and low sensitivity laboratory tests for Neuroborreliosis leaves room for controversy of an increasingly common, and potentially debilitating disease in Manitoba.

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