A 79-year-old woman presented with a 3-month history of confusion, memory decline, fatigue, and difficulty completing her activities of daily living. Her comorbidities included hypertension (on lisinopril), hyperlipidemia (on atorvastatin), anxiety (on sertraline), and migraine headaches (on verapamil). She also described a 1-month history of constant, unilateral facial numbness; tingling in her left cheek; and holoccephalic headaches that were worse than her typical migraines. Review of systems was remarkable for a 1-month history of a nonpruritic pink chest rash. She denied fevers, chills, vision changes, scalp tenderness, jaw claudication, abdominal pain, dysuria, arthralgia, myalgia, and mood changes. The patient lived in rural Minnesota on a wooded property. She denied any recent travel, pet, or animal exposure.

Upon evaluation, she was afebrile and hemodynamically stable. Physical examination revealed mild left anterior cervical lymphadenopathy and diffuse pink ovoid-shaped patches without central clearing on her upper chest. No focal neurologic deficits were present including nuchal rigidity, tremors, rigidity, or gait abnormality. Her Kokmen mental status test was 34 of 38 (−1 attention, −1 information, −2 recall). Electrocardiogram demonstrated normal sinus rhythm. Laboratory work-up was significant for the following (reference ranges provided parenthetically): hemoglobin, 12.3 g/dL (11.6 to 15.0 g/dL); platelets, 305 x 10^9/L (157 to 371 x 10^9/L); white blood cells, 11.1 x 10^9/L (3.4 to 9.6 x 10^9/L); serum glucose, 95 mg/dL (70 to 140 mg/dL); serum creatinine, 0.71 mg/dL (0.59 to 1.04 mg/dL); erythrocyte sedimentation rate (ESR), 51 mm per hour (3 to 28 mm per hour); C-reactive protein (CRP), 39.9 mg/L (≤8.0 mg/L). Peripheral blood smear, liver-function testing, thyroid stimulating hormone, HIV immunoassay, rapid plasma reagin (RPR), vitamin B9, vitamin B12, and urinalysis results were unremarkable. Magnetic resonance imaging of the brain with contrast demonstrated mild chronic lacunar infarctions with associated diffuse cerebral volume loss but no findings suggestive of infectious or inflammatory encephalopathy.

Further questioning revealed that the patient’s spouse recently had a tick bite and rash that was treated with oral antibiotics. However, the patient did not recall any tick or insect bites and denied outdoor exposure other than gardening in her backyard.

1. Which of the following pathogens is the most likely cause of this patient’s symptoms?
   a) Borrelia burgdorferi
   b) Borrelia garinii
   c) Herpes simplex virus (HSV)
   d) Varicella zoster virus (VZV)
   e) West Nile virus

   B. Burgdorferi is the most common pathogen causing Lyme disease in the United States, particularly in the Northeast and upper Midwest, and most frequently involves the skin, joints, and nervous system. Lyme disease involving the nervous system is termed Lyme neuroborreliosis and manifests as radiculoneuropathy, cranial neuropathy, meningitis, and encephalopathy. B. garinii also causes Lyme disease but is found primarily in Europe and Asia. This patient did not have any significant travel history. Herpes simplex virus may present as encephalitis or aseptic meningitis, characterized by rapid onset of fever, focal neurologic signs,
headache, and altered consciousness. The patient’s lack of fever, reassuring neurologic examination, and unremarkable magnetic resonance imaging (MRI) scan did not support a diagnosis of HSV encephalitis. Varicella zoster virus may manifest as herpes zoster-associated encephalitis, which typically presents as altered mentation following herpes zoster vesicular eruption. This patient’s chest rash was characterized as diffuse ovoid-shaped patches rather than vesicles or bullae, and she had no history of herpes zoster, making herpes zoster-associated encephalitis unlikely. West Nile virus is the most common arboviral disease in the United States and is primarily transmitted via mosquitoes. Manifestations include fever and neuroinvasive disease such as encephalitis, meningitis, or acute flaccid paralysis, albeit most individuals infected with West Nile virus are asymptomatic. The patient’s lack of fever, muscle weakness, or flaccid paralysis did not support this diagnosis.

The most likely pathogen causing this patient’s symptoms was B. burgdorferi. Historical and examination clues that suggested Lyme disease included her spouse’s history of recent tickborne illness, residence in an endemic B. burgdorferi region (upper Midwest United States), lack of travel history, anterior chest rash representing erythema chronicum migrans (although they lacked the classic “bulls-eye” appearance), normal blood counts, and normal peripheral blood smear. Although Minnesota is endemic for other tickborne illnesses such as anaplasmosis, babesiosis, and ehrlichiosis, rash is most strongly associated with Lyme disease. The lack of hemolytic anemia, jaundice, and dark urine also made babesiosis less likely. Testing for coinfection by anaplasmosis, babesiosis, and ehrlichiosis is recommended in patients with Lyme disease who have persistent fever while on appropriate therapy or characteristic laboratory abnormalities (eg, anemia, hyperbilirubinemia, and elevated lactate dehydrogenase).

Two-stage Lyme disease testing was performed, which revealed a positive first-tier Lyme antibody-screening test. Second-tier Western immunoblot demonstrated 3 of 3 significant protein bands for serum immunoglobulin (Ig) M against B. burgdorferi (positive: ≥2 bands) and 8 of 10 significant protein bands for serum IgG (positive: ≥5 bands). Serum serologies for anaplasmosis, babesiosis, and ehrlichiosis were negative. The patient was diagnosed with early disseminated Lyme disease.

2. What is the most likely etiology of this patient’s constant left-sided facial numbness and tingling?
   a) Cranial neuropathy
   b) Giant cell arteritis
   c) Postherpetic neuralgia
   d) Temporomandibular joint (TMJ) syndrome
   e) Trigeminal neuralgia

Cranial neuropathy is strongly associated with Lyme neuroborreliosis. This patient’s symptoms likely represented trigeminal neuropathy, characterized by unilateral facial numbness or tingling, in the setting of her Lyme disease diagnosis. Although classically associated with facial nerve palsy, Lyme disease may affect other cranial nerves and present bilaterally. Other symptoms that suggest Lyme-associated cranial neuropathy include ophthalmoplegia, diplopia, vertigo, hearing loss, and balance disturbance.

Giant-cell arteritis usually presents in patients >50 years of age with findings including headache, visual disturbances, scalp tenderness, jaw claudication, fever, anemia, and elevated ESR and CRP. Although this patient had a 3-month history of headache and elevated inflammatory markers, she lacked visual symptoms, scalp tenderness, and jaw claudication. Postherpetic neuralgia is persistent neuropathic pain in a well-defined dermatomal distribution after herpes zoster. The patient denied previous vesicular rash on her face, making this diagnosis unlikely. Temporomandibular joint syndrome causes dull, unilateral constant facial pain and may present with headache, decreased range of mandibular motion, and intermittent jaw locking. Examination may elicit tenderness in the muscles of mastication and mandibular condyle; these findings were not present on this patient’s
examination. Trigeminal neuralgia is characterized by recurrent brief episodes of lancinating pain in the trigeminal nerve distribution, most commonly caused by compression of the trigeminal nerve root but may be caused by secondary etiologies such as brainstem lesions or herpes zoster. The patient did not report episodic lancinating pain.

Given this patient’s encephalopathy, headaches, and trigeminal neuropathy, lumbar puncture was performed owing to concern for Lyme neuroborreliosis.

3. Which test on cerebrospinal fluid (CSF) studies would most likely yield this patient’s diagnosis?
   a) B. burgdorferi IgG serology
   b) B. burgdorferi polymerase chain reaction (PCR) antigen testing
   c) CSF bacterial culture
   d) Lyme CSF:serum IgG antibody index
   e) Venereal disease research laboratory (VDRL) test

Cerebrospinal fluid studies are obtained when assessing for Lyme neuroborreliosis and typically demonstrate modest lymphocytic pleocytosis, normal glucose, and mildly elevated protein. B. burgdorferi IgG serology is imperative to obtain; however, positive CSF B. burgdorferi IgG serology alone does not confirm Lyme neuroborreliosis because passive IgG transfer may occur through the blood–brain barrier. Cerebrospinal fluid PCR-detectable B. burgdorferi antigens may be present in early cases of Lyme neuroborreliosis; however, false-positive and false-negative results are common. Therefore, negative CSF PCR antigen testing cannot be used to exclude the diagnosis; rather, its utility lies in confirming the diagnosis in known seropositive patients. Cerebrospinal fluid bacterial culture is important to obtain to rule out bacterial meningitis, but its value is limited in diagnosing Lyme neuroborreliosis because <10% of CSF bacterial cultures are positive for Borrelia species. Lyme CSF:serum IgG antibody index, in which samples of CSF and serum serologies are simultaneously obtained and compared, is the best study to confirm the diagnosis of Lyme neuroborreliosis. Elevated Lyme CSF:serum IgG antibody index confirms intrathecal antibody production rather than passive IgG transfer that may occur through the blood-CSF barrier alone. Of note, Lyme CSF:serum IgG antibody index may be negative if duration of symptoms is <6 weeks and may remain positive for years even after treatment. Finally, CSF VDRL testing should be obtained to rule out neurosyphilis in patients with suspected Lyme neuroborreliosis, which could confound Lyme serologic testing because of cross-reactive antibodies. Nonetheless, neurosyphilis is unlikely given this patient’s negative serum RPR.

This patient’s CSF studies were significant for clear gross CSF appearance, normal opening pressure, total nucleated cells of 8 per microliter (0 to 5 per microliter) with mild lymphocytic predominance, glucose of 50, and total protein of 33 mg/dL (0 to 35 mg/dL), indicating the absence of significant meningitis. No organisms were seen on Gram stain. B. burgdorferi CSF PCR antigen testing, CSF bacterial culture, CSF VDRL, and CSF meningitis-encephalitis PCR pathogen panel results were negative. Lyme CSF:serum IgG antibody index was 3.1 (0.6 to 1.2), confirming the diagnosis of Lyme neuroborreliosis.

4. What is the best treatment of this patient’s condition?
   a) Amoxicillin (oral)
   b) Azithromycin (intravenous)
   c) Ceftriaxone (intravenous)
   d) Cefuroxime axetil (oral)
   e) Prednisone (oral)

Empiric antimicrobial therapy should be initiated before definitive laboratory confirmation of Lyme disease. Amoxicillin is an acceptable alternative agent in early localized Lyme disease when doxycycline is contraindicated. However, this patient has disseminated disease. Azithromycin may be used as second-line therapy for early, localized Lyme disease in patients who cannot tolerate doxycycline or beta-lactams, but macrolides notably have lower efficacy. Ceftriaxone is
appropriate in patients with neurologic manifestations of Lyme disease, particularly if there is parenchymal involvement of the brain or spinal cord, as well as in those with Lyme carditis. In patients with Lyme neuroborreliosis without brain or spinal cord parenchymal involvement, other appropriate agents include cefotaxime, penicillin G, or oral doxycycline. Cefuroxime axetil is an acceptable alternative for early, localized Lyme disease, when doxycycline is contraindicated and would not be appropriate in this case given the patient’s disseminated involvement. An early short-term course of prednisone is indicated for facial nerve palsy, including when caused by Lyme neuroborreliosis. However, this patient presented with trigeminal neuropathy rather than facial nerve palsy. There is no evidence of suggest the use of glucocorticoids in the management of this patient’s Lyme-associated trigeminal neuropathy.

Given this patient’s diagnosis of Lyme neuroborreliosis, the most appropriate therapy was ceftriaxone. The patient was treated with a 21-day course of intravenous ceftriaxone, 2 grams daily, with excellent clinical response. Her encephalopathy, headaches, facial numbness and tingling, and rash resolved by the end of her treatment course.

5. How would you counsel the patient regarding prevention of future recurrence of disease?
   a) Lyme disease vaccination
   b) Pre-exposure prophylactic cefuroxime
   c) Pre-exposure prophylactic doxycycline
   d) Use of acaricides (tick pesticide) on house property
   e) Use of N-Diethyl-meta-toluamide (DEET) repellant and permethrin-treated clothing

Reinfection with *B. burgdorferi* is possible, and prevention strategies are focused on reduction of exposure. Lyme-disease vaccination is not commercially available currently. In 1998, the Food and Drug Administration approved a recombinant lipoprotein outer surface A vaccine for Lyme disease; however, vaccine production was terminated in 2002 because of public concerns for autoimmune response to the vaccine, antivaccine sentiment, and low demand. Pre-exposure chemoprophylaxis with cefuroxime or doxycycline is not recommended to reduce the risk Lyme disease. However, postexposure chemoprophylaxis with a single dose of doxycycline of 200 milligrams is indicated if given within 72 hours of a high-risk tick bite: defined as a tick bite from a confirmed *Ixodes* tick, occurrence in an endemic area, and tick attachment for $\geq 36$ hours. If a tick bite cannot be confirmed as high risk, watchful waiting is recommended. Tick pesticides, such as acaricides, are effective at terminating ticks and may be encouraged by public health officials in endemic areas; however, tick pesticide barrier sprays do not reduce household risk of tick exposure or incidence of tickborne disease. Tick repellants, including DEET ($\geq 20\%$) and insecticides such as permethrin, are recommended to reduce risk of tickborne illness in addition to using personal protective measures and removal of attached ticks, once identified.

The patient and her spouse were counseled to use DEET insect repellent on exposed skin and permethrin-treated clothing when outdoors, particularly given their history of tick exposure and living in a region in which Lyme disease is endemic.

**DISCUSSION**

Lyme disease is classified into three stages: early localized disease (days after tick bite), early disseminated (weeks to months), and late disease (months to years). Early localized disease is characterized by a single erythema migrans lesion and may include flu-like symptoms. Early disseminated disease manifestations include multiple erythema migrans lesions, neck pain or stiffness, cranial neuropathy, radiculoneuropathy, and flu-like symptoms. Late disease involves multifocal neuropathy; monoarticular or oligoarticular arthritis, classically involving the knee; acrodermatitis chronica atrophicans; and flu-like symptoms. This case of Lyme neuroborreliosis in an elderly woman who presented with encephalopathy, headaches,
trigeminal neuropathy, and erythema chronicum migrans demonstrates a presentation of early disseminated Lyme disease and highlights its often nonspecific symptoms. Lyme neuroborreliosis manifesting with the triad of painful radiculopathy, neuropathy, and CSF lymphocytic pleocytosis is termed Bannwarth syndrome.9

The differential diagnosis for this patient’s altered mental status included urinary tract infection, toxic-metabolic encephalopathy, vitamin deficiency, HIV, syphilis, giant-cell arteritis, depression, structural brain lesions, and primary neurocognitive disorder. Key historical and examination features that suggested the diagnosis of Lyme disease included family history of recent tickborne illness, residence in an endemic B. burgdorferi region (Minnesota), lack of travel history, presence of rash, normal hemoglobin, and peripheral blood smear. Diagnosing Lyme disease may be challenging given its broad spectrum of clinical manifestations including rheumatologic, cardiac, and neurologic symptoms. Only one-third of patients recall tick bites. In this case, the patient did not recall a tick bite. Only one-half of patients with Lyme neuroborreliosis remember having a skin rash and one-quarter have a rash at time of presentation.10 This patient did have erythema chronicum migrans, manifesting as diffuse nonpruritic pink ovoid patches on her chest, although they lacked the classic circular “bulls-eye” appearance. It is important to note that erythema migrans does not always have central clearing and may have alternative appearances such as solid lesions, blue-purple hues, crusting, and blistering.11 Other nonspecific Lyme-associated findings this patient presented with included fatigue (seen in 54% of Lyme neuroborreliosis cases), headache (42%), and regional lymphadenopathy (16%).7 Laboratory work-up may reveal nonspecific findings such as leukocytosis; elevated inflammatory markers; and mildly elevated liver function tests,4 consistent with this patient’s nonspecific laboratory work-up. No imaging findings are specific for Lyme neuroborreliosis, although nonspecific frontal cortex white matter changes may be seen.12

The diagnosis of Lyme disease involves two-tier Lyme serum serology testing: a first-tier enzyme immunoassay or immunofluorescence assay, which detects the presence of antibodies and serves as an exclusionary test, followed by a confirmatory second-tier Western immunoblot, in which ≥2 of 3 IgM significant protein bands and ≥5 of 10 IgG significant protein bands are considered positive results. Serologic confirmation of early localized or early disseminated disease is generally unnecessary in patients who present with erythema migrans rash and have a history of living in or traveling to endemic areas. These patients may be diagnosed clinically and treated empirically, as false-negative results on serologic testing are common within 2 weeks of exposure.1 Two-tier serologic Lyme testing is indicated in patients with early, localized or early, disseminated Lyme disease without erythema migrans, late disseminated disease, and those with rare manifestations including rheumatologic, cardiac, and neurologic involvement. Additional testing to consider includes CSF analysis for neuroinvasive Lyme disease (as illustrated by this case presentation); diagnostic arthrocentesis with PCR testing of joint fluid for Lyme-associated septic arthritis; or electrocardiogram to assess for atrioventricular block in patients who may have Lyme carditis, which may present with chest discomfort, dyspnea, syncope, peripheral edema, or palpitations.

The differential diagnosis of altered mental status in the geriatric patient population is broad. Tickborne diseases, such as Lyme disease, should be considered in those presenting with infectious symptoms and unexplained clinical manifestations, even if the patient has no known history of tick exposure. Risk factors for tick exposure include living in endemic regions, illness during tick season (generally April to September), living near wooded areas, and pet or animal exposure. If clinically suspected, appropriate therapy should be promptly initiated before laboratory confirmation to prevent progression of disease.
POTENTIAL COMPETING INTERESTS
The authors report no competing interests.

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REFERENCES

CORRECT ANSWERS: 1. a. 2. a. 3. d. 4. c. 5. e