Published Ahead of Print on August 1, 2023 as 10.1212/WNL.0000000000207662

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The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000207662

Clinical Reasoning: A Young Woman With Rapidly Progressive Weakness and Paresthesia

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Figure Count:
1

Table Count:
0

Search Terms:
[107] Secondary headache disorders, [138] Meningitis, [139] Bacterial infections, [181] Peripheral neuropathy, [294] Cranial neuropathy

Acknowledgment:
We would like to thank Editage (www.editage.com) and Scribbr (www.scribbr.com) for English language editing.

Study Funding:
The authors report no targeted funding.

Disclosure:
S. S. Alwakeel reports no disclosures relevant to the manuscript; A. Y. Alfaifi reports no disclosures relevant to the manuscript; F. A. Alabandi reports no disclosures relevant to the manuscript; S. Alshimemeri reports no disclosures relevant to the manuscript

Preprint DOI:

Received Date:
2022-12-14

Accepted Date:
2023-06-02

Handling Editor Statement:
Submitted and externally peer reviewed. The handling editor was Resident and Fellow Deputy Editor Katherine Fu, MD.

Abstract

A 24-year-old Middle Eastern female presented with a 2-month history of rapidly progressive, asymmetric weakness and paresthesia that began in her left lower extremity and progressed to involve both legs and arms. It was associated with overflow urinary incontinence and significant weight loss. Additionally, she complained of a constant occipital headache that worsened in the supine position and was associated with photophobia, tinnitus, nausea, vomiting, and horizontal binocular diplopia. She also had signs of meningismus, decreased left facial sensation, and right sensorineural hearing loss. As multifocal localization suggests a wide variety of possible differential diagnoses, this paper expands on the differential of a subacute multifocal process while highlighting the importance of identifying appropriate risk factors and performing a relevant yet focused diagnostic work-up.

Section 1

A 24-year-old Middle Eastern female presented with a 2-month history of generalized weakness prominent in the left lower extremity. Her symptoms began with proximal left leg heaviness, progressing to both legs. Weakness was associated with gradually worsening paresthesia and reduced sensation in the left lower limb, originating from the hip down to the foot. She also had lip and bilateral numbness in the distal upper limbs and complained of a gradual-onset constant occipital headache with pain radiating to the neck, worsening in the supine position, and not relieved by oral analgesics. Headache was associated with photophobia, tinnitus, nausea, vomiting, and horizontal binocular diplopia, which was exacerbated when looking at far objects. The patient also experienced overflow urinary incontinence. She reported a significant weight loss of 13 kg but had no fever or night sweats.

Her medical history was significant only for brucellosis, diagnosed 2 years ago with persistent high-grade fever, chills, sweating, and diffuse myalgia following ingestion of unpasteurized milk. Family and social histories were unremarkable.

On examination, the patient was afebrile with normal blood pressure. The patient showed positive meningismus signs, including nuchal rigidity, Kernig's sign, and jolt accentuation. Mental status and cognition remained intact. Cranial nerve examination revealed horizontal binocular diplopia with partially limited abduction of both eyes, impaired left facial sensation to pinprick and temperature, and right sensorineural hearing loss. The other cranial nerves were intact with normal fundi.

Motor examination revealed diffuse muscle wasting and decreased tone in the upper and lower extremities with no observable fasciculations. Her strength was 4/5 throughout the study period, except for the left lower extremity, which demonstrated foot drop and no antigravity strength. Reflexes were absent in the left biceps, brachioradialis, knee, and ankle. Hyporeflexia was observed on the right side. Plantar responses were flexor responses, and Hoffman test was negative.

Sensory examination revealed reduced sensation of light, touch, temperature, and pinprick over the first two fingers and lateral forearm of the left upper limb, along with the entire left lower limb. Vibration sensation was decreased in the left lower limb up to the knee level. The sensation of joint position in the toes was intact bilaterally. Systemic examination results were unremarkable, with no hepatosplenomegaly.

Questions for consideration:

1. What is the localization of this clinical presentation?
2. What are the possible differential diagnoses?

Section 2

The patient's symptoms were consistent with multifocal localization, including a lower motor neuron pattern and marked, asymmetric, generalized weakness in the left lower limb with left-sided areflexia, decreased tone, atrophy accompanied by sensory changes in the same limb, and overflow incontinence suggesting peripheral nervous system pathology, which potentially localized to the lumbar roots. Numbness of both arms and fingers, with dermatomal sensory loss, hyporeflexia, and a pattern of generalized weakness, indicated cervical polyradiculopathy. Perioral numbness with decreased left facial sensation suggested a lesion in the left trigeminal nerve involving the ophthalmic, maxillary, and mandibular branches, while hearing loss in the right ear suggested a lesion in the right vestibulocochlear nerve. Finally, occipital headache worsening in the supine position accompanied by photophobia, tinnitus, nausea, vomiting, and horizontal diplopia indicated increased intracranial pressure.

Polyradiculopathies along with cranial neuropathies suggested a multifocal leptomeningeal disease process, as these findings collectively localized to the brain and spinal cord meninges. Differential diagnoses of a subacute leptomeningeal process included bacterial and fungal infections, particularly tuberculosis and cryptococcosis, along with infections associated with raw milk ingestion and endemic infectious diseases of the Middle East such as brucellosis and listeriosis; neoplastic conditions such as leptomeningeal carcinomatosis and lymphoma; and rare inflammatory conditions such as sarcoidosis, IgG4, and histiocytosis.

Questions for consideration:

1. What investigations would you perform?
2. What is the final diagnosis?
3. What is the treatment for this patient?

Section 3

Laboratory tests revealed a normal leukocyte count of 4.8×10^9/L ($4.5–11.0 \times 10^9$/L) with relative lymphocytosis of 67% (20%–45%). Metabolic panel results were within the normal range, with unremarkable C-reactive protein levels and erythrocyte sedimentation rate.

Blood and acid-fast bacillus cultures and serological tests for *Mycobacterium*, various fungi, and *Brucella* were negative. However, the serum agglutination test revealed high blood anti-*Brucella* antibody titer of 1:320.

Cerebrospinal fluid (CSF) opening pressure was high at 370 mmH_2O. The fluid was yellow and turbid. The protein level was markedly high at 138 mg/dL (15–45 mg/dL), whereas the glucose concentration, 24.84 mg/dL (40–69.3 mg/dL), was markedly lower than that in the serum. The erythrocyte count was unremarkable. Leukocyte count (80 leukocytes/μL) revealed lymphocytic pleocytosis (90% lymphocytes and 10% polymorphonuclear leukocytes). CSF cultures were negative for bacteria, fungi, and mycobacteria. The anti-*Brucella* antibody titer in CSF was elevated to 1:80.

Brain MRI with contrast demonstrated multiple patchy subcortical, periventricular, and juxtacortical fluid-attenuated inversion recovery (FLAIR) white matter hyperintensities with no postcontrast enhancement. It also demonstrated diffuse cranial nerve enhancement involving the bilateral oculomotor, trigeminal, abducens, and right vestibulocochlear nerves (Figure 1A,B,C). Spinal cord MRI showed cauda equina nerve roots enhancement (Figure 1D).

Nerve conduction studies and needle electromyography showed normal sensory nerve action potentials and normal-to-low-normal compound muscle action potentials, with evidence of subacute-to-chronic cervical and lumbar radiculopathies.

In view of the endemic regional origin, neurological and constitutional manifestations, previous history of brucellosis and unpasteurized milk consumption, CSF lymphocytosis with increased protein and decreased glucose, combined with high levels of anti-*Brucella* antibody titer, neurobrucellosis was the final diagnosis.

On further reviewing of the patient's brucellosis history from two years ago, she reported stopping her antibiotics independently after 1 month of treatment due to pregnancy and improvement in symptoms.

The patient was treated with a 1-month course of intravenous ceftriaxone 2 g twice daily and a 4-month course of oral rifampicin 600 mg and doxycycline 100 mg. Her headache

markedly improved, and diplopia resolved within a few days following her admission. The patient regained control of urination. However, she continued to experience abnormal sensations and generalized weakness, requiring her to rely on a wheelchair.

The patient's condition improved after completing the antibiotic therapy. At follow-up 8 months after treatment initiation, she could walk and function independently. She had minor residual deficits on examination, including mild lower-limb weakness and right hearing loss.

Discussion

Brucellosis is the most common zoonotic infection worldwide. It is caused by *Brucella* species, which are gram-negative, aerobic, facultative intracellular coccobacilli that spread through contact with infected sheep, goats, cattle, and other animals. Brucellosis is frequently acquired via ingestion of unpasteurized milk or milk products,[1] and its incidence is highest in countries with suboptimal public and domestic animal healthcare programs. Endemic areas include countries in the Mediterranean basin, Middle East, Asia, Africa, Eastern Europe, the Caribbean, Mexico, and Central and South America.[2]

Brucellosis can lead to various complications, prolonged treatment, and repeated relapses. The symptoms of *Brucella* infection typically present within 2 months of bacterial exposure. With a wide range of clinical manifestations, patients may present with nonspecific symptoms such as fever, weight loss, and arthralgia. Hepatomegaly and splenomegaly are the most common physical findings.[1,3]

Neurological complications occur in 10% of cases.[1] Most patients with neurobrucellosis characteristically experience severe and constant headaches. Other common neurological symptoms include blurred vision, behavioral changes, agitation, muscle weakness, and neck rigidity. Cranial neuropathies are common and mostly affect the abducens, face, and vestibulocochlear nerves, resulting in facial paralysis and sensorineural hearing loss. Lumbosacral radiculopathy and elevated intracranial pressure have also been reported.[3,4]

Imaging findings are variable and may include inflammatory changes marked by granulomas; nodular lesions; abnormal enhancement of the cranial nerves, meninges, perivascular spaces, or lumbar nerve roots; white matter changes with diffuse, periventricular, or focal demyelinating appearance; and vascular insults such as lacunar infarcts, small hemorrhages, or venous thrombosis.[3,5] Therefore, this disease should be considered in the

differential diagnosis of other conditions, particularly multiple sclerosis. In contrast, neurobrucellosis white matter lesions have not been reported to show post-contrast enhancement and rarely involve the corpus callosum.[5]

In patients with laboratory-confirmed brucellosis based on either positive blood cultures or a serum agglutination test with a titer of ≥1:160, the following four criteria were proposed to diagnose neurobrucellosis: (1) symptoms and signs suggestive of the disease; (2) detection of *Brucella* spp. and anti-*Brucella* antibody titer in the CSF; (3) lymphocytosis with increased protein and decreased glucose levels in the CSF, and (4) the presence of suspicious imaging abnormalities.[4]

There is no consensus on an appropriate approach for neurobrucellosis treatment. Combining rifampicin, doxycycline, and either trimethoprim-sulfamethoxazole or ceftriaxone for 3–12 months, depending on the CSF response, has been recommended. Prednisolone is recommended to prevent long-term neurobrucellosis complications such as iritis, papilledema, myelopathy, polyneuropathy, or cranial nerve palsies.[3] One-fifth of the patients treated for neurobrucellosis experience long-term sequelae, most commonly persistent hearing loss and lower limb weakness.[1,3]

An additional paragraph discussing brucellosis relapse has been provided in the Supplement.

In summary, neurobrucellosis should be considered in the differential diagnosis of a subacute leptomeningeal process with constitutional findings when evaluating immigrant patients from endemic regions. This treatable condition should be suspected to ensure the early initiation of treatment and prevention of long-term sequelae.

Ethical considerations

The study participant provided written informed consent-to-disclose. This study was exempt from the need to obtain approval from an ethics board due to the study type.

WNL-2023-000458_sup --- http://links.lww.com/WNL/D20

References

1- Gul H, Erdem H. Brucellosis (Brucella Species). In: Bennett J, Dolin R, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Elsevier Health Sciences; 2020: 2753-2757

2- Areas at Risk. Centers for Disease Control and Prevention. Updated November 12, 2012. Accessed September 14, 2022. https://www.cdc.gov/brucellosis/exposure/areas.html

3- Bouferraa Y, Bou Zerdan M, Hamouche R, Azar E, Afif C, Jabbour R. Neurobrucellosis: Brief Review. Neurologist. 2021;26(6):248-252. Published 2021 Nov 4. doi:10.1097/NRL.0000000000000348

4- Guven T, Ugurlu K, Ergonul O, et al. Neurobrucellosis: clinical and diagnostic features. Clin Infect Dis. 2013;56(10):1407-1412. doi:10.1093/cid/cit072

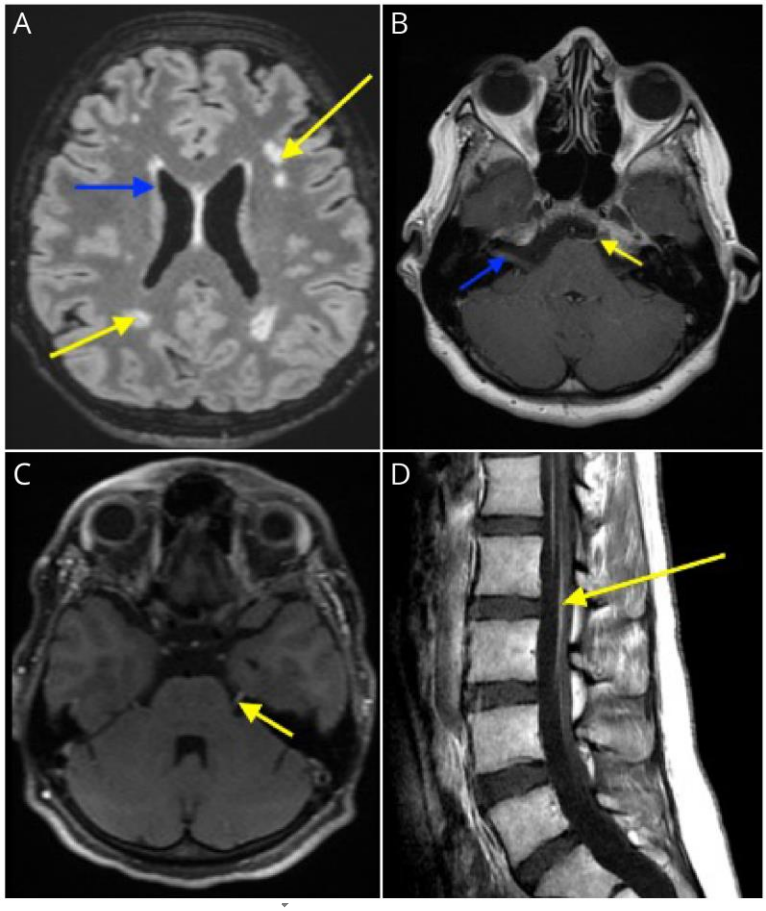
5- Kizilkilic O, Calli C. Neurobrucellosis. Neuroimaging Clin N Am. 2011;21(4):927-ix. doi:10.1016/j.nic.2011.07.008

References for the supplementary material have been listed in the eReferences in the Supplement.

Figure Legend

Figure 1: MRI of the brain and lumbar spine

(A) Axial fluid-attenuated inversion recovery (FLAIR) MRI demonstrating multiple bilateral subcortical and periventricular white matter lesions. (B-C) Axial T1-weighted gadolinium-enhanced MRI showing smooth enhancement in the left abducens (B), right vestibulocochlear (B), and left trigeminal nerves (C). (D) Sagittal T1-weighted gadolinium-enhanced MRI of the lumbar spine showing cauda equina nerve roots enhancement.



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