Pearls & Oy-sters: Trigeminal Nerve Dysfunction as the Key Diagnostic Clue to Listeria Rhombencephalitis

Christopher Donald Hue, MD, PhD, Maria Bres Bullrich, MD, Victor Christopher Lam Shin Cheung, MD, Amit Kumar Sharma, MD, Asma Saba Syed, MD, FRCPC, Sachin Kishore Pandey, MD, FRCPC, Sarah Anne Morrow, MD, FRCPC, MS, and Derek Brian Debicki, MD, FRCPC, PhD

Correspondence
Dr. Hue
christopher.hue@lhsc.on.ca

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Pearls

- Listeria rhombencephalitis should be considered in patients with prodromal symptoms and asymmetric cranial nerve, long-tract, or cerebellar signs, even in the initial absence of fever or meningismus.
- Early trigeminal nerve involvement, causing ipsilateral facial hypoesthesia or hyperalgesia, can be the presenting clinical feature of listeria rhombencephalitis.

Oy-sters

- Listeria rhombencephalitis can present diagnostic challenges for neurologists, neurosurgeons, and neuroradiologists, particularly during initial stages of illness.
- Listerial brainstem invasion can mimic other brainstem lesions on neuroradiologic imaging such as cavernoma, hemorrhage, developmental venous anomaly, neoplasm, and embolic phenomenon.

A 69-year-old woman presented to the hospital with a 1-week history of cumulative neurologic symptoms beginning with periodontal and left-sided facial numbness, progressing over time to include nausea with vomiting, vertigo, gait unsteadiness, and hoarse voice. Her medical history was relevant for hypertension (prescribed perindopril/indapamide 8/2.5 mg oral daily), benign thyroid nodule, and endometrial ablation for leiomyoma. She used ibuprofen as needed for headache. A neurologic examination demonstrated hoarse voice with hypophonia, nystagmus (left-beating on leftward gaze and rotational on upward gaze), abnormal facial sensation (decreased sensation to pinprick in the ophthalmic and mandibular branches of left trigeminal nerve and hyperalgesia in the maxillary branch of left trigeminal nerve), depressed left palatal elevation, left hemi-body limb ataxia, and wide-based ataxic gait. There was no history of immunosuppressive therapy or substance abuse.

Initial CT of the head showed a small focus of acute hemorrhage in the left middle cerebellar peduncle (figure, A) with overlying linear enhancement (figure, B). Concurrent CT angiogram of head and neck vessels demonstrated no intracranial vessel occlusion or stenosis. Further evaluation with unenhanced MRI of the brain showed an ovoid susceptibility artifact in the left middle cerebellar peduncle surrounded by increased fluid-attenuated inversion recovery (FLAIR) signal extending into the left lateral pons, pontine tegmentum, posterolateral medulla oblongata, and posterolateral upper cervical spinal cord. Initial considerations included acute hemorrhage associated with cavernoma and developmental venous anomaly. A subsequent contrast-enhanced MRI of the brain 2 days later showed 2 rim-enhancing lesions in the brainstem with surrounding vasogenic edema, one located within the left middle cerebellar peduncle with linear enhancement extending along fibers of the trigeminal nerve (figure, C),

From the Department of Clinical Neurological Sciences (C.D.H., M.B.B., A.K.S., S.A.M., D.B.D.), Department of Medical Imaging (V.C.L.S.C., S.K.P.), and Division of Infectious Diseases, Department of Medicine (A.S.S.), Schulich School of Medicine and Dentistry, Western University; and Lawson Health Research Institute (S.A.M.), London Health Sciences Centre, Canada.

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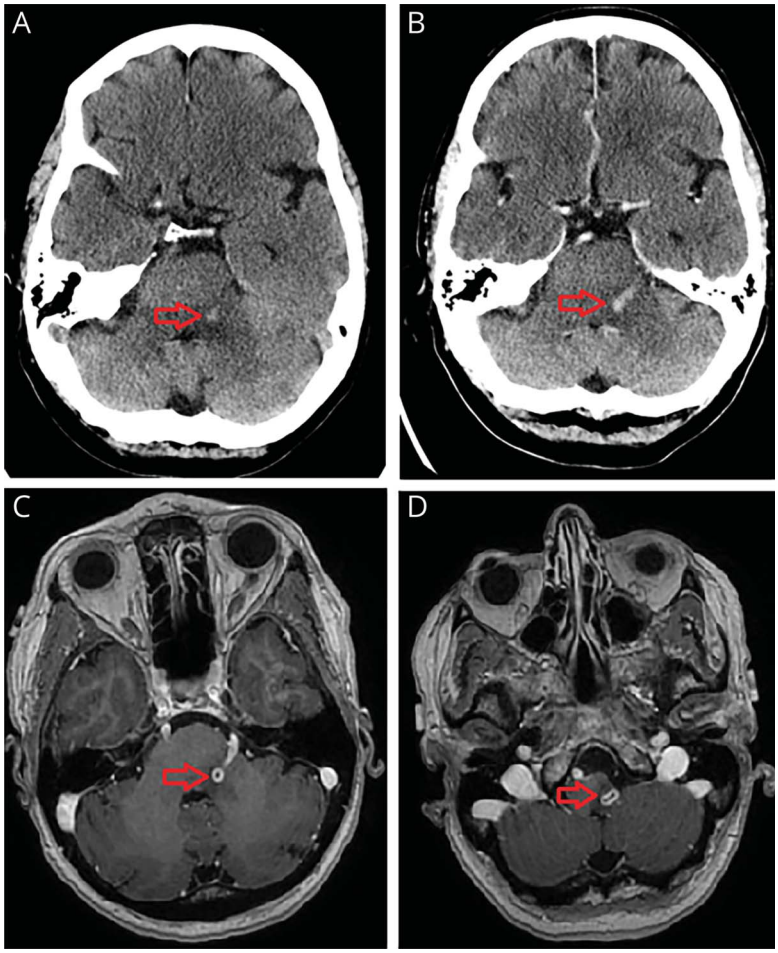
Figure Neuroimaging From Patient With Listeria Rhombencephalitis



Initial contrast-enhanced CT demonstrated (A) focus of acute hemorrhage in the left middle cerebellar peduncle (arrow) with surrounding vasogenic edema. (B) The contrast-enhanced sequence demonstrated overlying linear enhancement (arrow) extending from the area of hemorrhage to the cerebellopontine angle. Subsequent contrast-enhanced MRI of the brain demonstrated (C) a rim-enhancing lesion (arrow) in the left middle cerebellar peduncle with linear enhancement extending along fibers of the trigeminal nerve and (D) another rim-enhancing lesion (arrow) within the lateral aspect of the medulla and cervicomedullary junction.

and another within the lateral aspect of the medulla and cervicomedullary junction (figure, D). In addition, there was development of a new small focus of FLAIR hyperintensity, without diffusion restriction, in the anterior right frontal cortex. These findings raised the possibility of a disseminated infectious process. CT of the thorax, abdomen, and pelvis showed no evidence of malignancy. Transthoracic and transesophageal echocardiograms showed no vegetation or cardiac source of embolism.

CSF obtained from lumbar puncture showed elevated protein 494 mg/L, elevated nucleated cells 633 × 10^6/L (63% neutrophils, 37% lymphocytes), and normal glucose 3.6 mmol/L. *Listeria monocytogenes* was isolated from CSF and blood cultures.

Three days after admission, the patient became febrile (temperature 39.2°C). The patient's neurologic symptoms evolved with ongoing hypophonia, nystagmus (left-beating on leftward gaze and upbeating on upward gaze), binocular diplopia, hypoesthesia in all branches of left trigeminal nerve, hyperreflexia in the right upper extremity, and left-sided limb ataxia. She appeared drowsy, but maintained appropriate verbal responses and there was no nuchal rigidity. The patient received dexamethasone 10 mg IV once and 4 mg PO once to reduce vasogenic edema. Initial empiric treatment was with ceftriaxone and vancomycin (due to penicillin allergy), which was changed to meropenem after consultation with infectious diseases specialists. Upon isolation of *L monocytogenes*, the antibiotic treatment was further modified to ampicillin 2 g IV every 4 hours for 6 weeks and gentamicin 120 mg IV every 8 hours for 2 weeks.

The local public health unit was contacted, and no clear infectious source was identified. The patient denied consumption of any known contaminated food products, but wondered about developing symptoms after eating unpasteurized cheese. A local food vendor had also recalled deli meat products from the marketplace due to possible *L monocytogenes* infection near the time this case was diagnosed. In the hospital, the patient received a gastro-jejunostomy tube due to oropharyngeal dysphagia, but tolerated an oral diet by the time of discharge. Her functional status also improved as she was able to ambulate independently with a cane. The patient was discharged from the hospital approximately 4 weeks after admission.

Discussion

Listeriosis is a severe foodborne illness caused by *L monocytogenes* that occurs with a high global disease burden. Listerial brainstem encephalitis (rhombencephalitis) is estimated to occur in 17% of patients with listeriosis and is associated with lower survival rates and poor clinical outcomes.[1,2] Listeria rhombencephalitis develops in a biphasic course, characterized by an initial prodrome (5–15 days) of headache, fever, nausea, vomiting, and fatigue, followed by focal neurologic signs consisting of asymmetric cranial nerve, long-tract, or cerebellar signs.[3,4] In a series of 82 patients, confusion, hemiparesis, cerebellar ataxia, facial paralysis, and gait disturbance were frequent deficits, with over half of cases presenting with cranial nerve palsy.[5] Among another 123 cases of listeria rhombencephalitis, the most commonly involved CNS structures were cranial nerves VII, V, IX, X, medulla oblongata, cerebellum, and pons, in decreasing frequency.[6] In another 63 cases, pontomedullary abnormalities at initial presentation were common, representing 64% of patients.[4] Meningeal signs affected approximately 44%–55% of patients and normal mental status was found in 59% of patients.[4,6] Blood cultures were positive in 61% of cases and initial CSF cultures were positive for *L monocytogenes* in 33% of cases.[4] Early treatment with antibiotics was important for survival and reducing long-term sequelae. First-line treatment strategies, such as ampicillin monotherapy or with gentamicin, were associated with survival rates exceeding 75%.[4] If left untreated, mortality ranged from 32% to 51%.[4,6]

Early trigeminal nerve dysfunction was a distinguishing clinical feature in the presented case. Indeed, hypoesthesia and tingling sensation in the ipsilateral face is reported as a defining neurologic symptom at presentation of rhombencephalitis due to *L monocytogenes*.[6] These findings raise the possibility that *L monocytogenes* can invade the brainstem via the sensory trigeminal nuclei.[6] However, there is limited clinical evidence and understanding of the mechanisms by which *L monocytogenes* can infect the brainstem.

One possibility is that *L monocytogenes* can invade the brainstem from the cerebellopontine angle by retrograde intra-axonal transport along the trigeminal nerve into the brainstem nuclei and further along sensory tracts into the pons and medulla oblongata.[6] This was supported by MRI findings of contrast enhancement along the trigeminal sensory tract.[6] A contributing factor to these findings may be that among cranial nerves, the trigeminal nerve is relatively more conspicuously visualized on MRI due to its larger diameter.[7] Comparable to findings in the presented case, typical localizations of listerial lesions on cranial MRI include the brainstem, supratentorial white matter, cerebellum, and cerebellar peduncle, with MRI features that include T2 hyperintensity, contrast enhancement, and ring-enhancing lesions.[5] Neuropathologic human autopsy findings in 9 cases of listerial brainstem encephalitis demonstrated leukocyte infiltrations in multiple cranial nerves (including trigeminal) innervating the oropharynx, further supporting the possibility of retrograde invasion of the brainstem along cranial nerves.[8] Alternatively, brainstem invasion may be hematogenous in origin. A prospective cohort study (MONALISA) reported that blood cultures were positive for *L monocytogenes* in 63% of patients with neurolisteriosis, raising the possibility of persistent bacteremia leading to CNS dissemination.[2,6]

The results of CSF analysis in the presented case are consistent with those previously published for listeria rhombencephalitis. CSF can have a comparatively benign appearance in listerial brainstem encephalitis, with mean initial CSF leukocyte count of 237×10^6/L, as opposed to estimated mean of $1{,}000 \times 10^6$/L leukocytes in listerial meningitis.[4] The normal CSF glucose level in listeria rhombencephalitis is similar to that observed in listerial meningitis, but higher than expected in other bacterial meningitides.[4] A relatively lower CSF protein level (mean 850 mg/L) when compared with other bacterial meningitides,[4] was another feature similar to the presented case.

Early recognition of listeria rhombencephalitis is often delayed due to nonspecific prodromal symptoms and the absence of fever or meningeal signs at initial clinical presentation. Diagnosis can also be challenging because listeria rhombencephalitis occurs predominantly in healthy, immunocompetent adults,[4,6,7] as observed in the presented case. MRI head is crucial for early detection of brainstem involvement and accurate diagnosis,[9] although listerial invasion can mimic other brainstem lesions. The differential diagnosis for acute brainstem encephalitis is broad and can include other infectious (bacterial, viral, fungal, or parasitic), parainfectious, or noninfectious etiologies. Noninfectious etiologies include endocarditis, vasculitis, multiple sclerosis, central pontine myelinolysis, neurosarcoidosis, Behçet disease, Miller Fisher syndrome, neoplasms, and paraneoplastic syndromes.[1,4,7]

Early recognition of listeria rhombencephalitis presents a diagnostic challenge particularly during initial stages of the disease course. Brainstem encephalitis due to *L monocytogenes* should be considered as a diagnostic possibility in the setting of prodromal symptoms and asymmetric focal neurologic deficits even in the absence of fever or meningeal signs. In the presented case, early trigeminal nerve involvement was a key clinical feature leading to accurate diagnosis of listeria rhombencephalitis, and further supports a potential mechanism by which *L monocytogenes* can invade the brainstem.

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Appendix Authors

Name	Location	Contribution
Christopher Donald Hue, MD, PhD	Department of Clinical Neurologic Sciences, Schulich School of Medicine and Dentistry, Western University, London, Canada	Reviewed the case, drafted the first manuscript, reviewed the final version of manuscript for intellectual content
Maria Bres Bullrich, MD	Department of Clinical Neurologic Sciences, Schulich School of Medicine and Dentistry, Western University, London, Canada	Reviewed the case, reviewed the final version of manuscript for intellectual content
Victor Christopher Lam Shin Cheung, MD	Department of Medical Imaging, Schulich School of Medicine and Dentistry, Western University, London, Canada	Reviewed the imaging and final version of manuscript for intellectual content, drafted figure legends
Amit Kumar Sharma, MD	Department of Clinical Neurologic Sciences, Schulich School of Medicine and Dentistry, Western University, London, Canada	Reviewed the case, reviewed the final version of manuscript for intellectual content
Asma Saba Syed, MD, FRCPC	Division of Infectious Diseases, Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, Canada	Reviewed the case, reviewed the final version of manuscript for intellectual content
Sachin Kishore Pandey, MD, FRCPC	Department of Medical Imaging, Schulich School of Medicine and Dentistry, Western University, London, Canada	Reviewed the imaging and final version of manuscript for intellectual content
Sarah Anne Morrow, MD, FRCPC, MS	Department of Clinical Neurologic Sciences, Schulich School of Medicine and Dentistry, Western University, London, Canada	Reviewed the case, reviewed and edited the final version of manuscript for intellectual content
Derek Brian Debicki, MD, FRCPC, PhD	Department of Clinical Neurologic Sciences, Schulich School of Medicine and Dentistry, Western University, London, Canada	Reviewed the case, reviewed and edited the final version of manuscript for intellectual content

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