Case Report

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Rhombencephalitis due to *Listeria monocytogenes* infection with GQ1b antibody positivity and multiple intracranial hemorrhage: a case report and literature review

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Abstract

Listeria monocytogenes is a Gram-positive facultative intracellular bacterium that causes central nervous system infection. We report a case of rhombencephalitis caused by *L. monocytogenes* infection, which mimicked Bickerstaff's brainstem encephalitis, and GQ1b antibody positivity and multiple intracranial foci were observed. A 68-year-old male patient presented with a nonspecific prodrome of faintness, forehead tightness, and walking instability. This was followed by progressive cranial nerve palsies, limb weakness, cerebellar signs, hyperpyrexia, and impaired consciousness. Brain imaging showed multiple abnormal brainstem and cerebellar signals that were accompanied by blood infiltration without any lesion enhancement. Serum GQ1b antibody positivity led to an initial diagnosis of Bickerstaff's brainstem encephalitis, which was treated with immunosuppressive therapy with limited efficacy. A pathogen examination helped confirm *L. monocytogenes* infection. A combination of meropenem and trimethoprim-sulfamethoxazole therapy was applied and the patient recovered without sequelae. The symptoms and imaging of *Listeria* rhombencephalitis are nonspecific. Accurate diagnosis and prompt treatment of this condition are essential. Whether *Listeria* infection triggers an autoimmune response remains unclear.

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Introduction

Listeria monocytogenes is a Gram-positive facultative intracellular bacterium that can cause human listeriosis via food contamination. Previous studies have indicated that the incidence of listeriosis is approximately three to six patients per million each year globally.[1–3] However, a rising incidence of listeriosis has been reported in many countries recently with high case-fatality rates of approximately 20% to 30%.[1–3] This disease primarily affects elderly people, pregnant women, newborns, immunodeficient patients, and even healthy individuals.[4,5] Infections can cause a range of symptoms from mild gastroenteritis to bacteremia, and in some cases, malignant central nervous system (CNS) compromise. We report a case of rhombencephalitis associated with *L. monocytogenes* infection that mimicked Bickerstaff's brainstem encephalitis (BBE) with GQ1b antibody positivity and multiple intracranial foci.

Case presentation

A 68-year-old man presented to our emergency room complaining of slight faintness and forehead tightness, walking instability, emotional agitation, and insomnia over the preceding 9 days. The walking instability progressed to a drunken gait, accompanied by persistent left-sided numbness of the face and an intractable hiccup. Brain computerized tomography (CT) showed lacunar cerebral infarction and ischemic white matter lesions. The patient refused in-patient observation and returned home. Two days later, the patient experienced drowsiness, restlessness, frequent vomiting, dysphagia, hiccupping, expectoration of white mucosal sputum, and dysuria, accompanied by fever (maximum temperature of 39.7°C). The patient presented to our emergency room again and was admitted to the ward. Prior conditions included chronic obstructive pulmonary disease for over 10 years and long-term use of the inhalants Spiriva and Seretide, and no history of immunosuppressive diseases.

A physical examination showed the following: drowsiness, dysarthria, ptosis of the upper eyelids, insufficient abduction of the right eye, right-sided horizontal nystagmus, absence of bilateral pharyngeal reflexes, Grade IV muscle strength in all four limbs, unstable bilateral finger-to-nose tests and heel–knee–shin tests that were much worse on the left side, decreased tendon reflexes of the upper and lower limbs, equivocal left-sided Puusepp's sign, and negative meningeal irritation.

Blood panels showed a high leukocyte count (12.55×10^9/L) and neutrophil percentage (91%), with low potassium (3.0 mmol/L) and sodium (120 mmol/L) levels. The patient's 24-hour urine volume was 3.50 L, urine potassium level was 35.7 mmol/L, urine sodium level was 102.0 mmol/L, and urine chloride level was 127.0 mmol/L (Table 1). Serum ganglioside antibody testing was positive for GQ1b immunoglobulin (Ig) M antibodies. There were no abnormalities for serum liver, kidney, coagulation, and thyroid

Table 1. Laboratory examination results.

Items	Results	Normal values
Blood leukocyte count	12.55×10^9/L	$3.5–9.5 \times 10^9$/L
Blood neutrophils	91%	40%–75%
Blood potassium, mmol/L	3.0	3.5–5.3
Blood sodium, mmol/L	120	137–147
Urine potassium, mmol/L	35.7	0–20
Urine sodium, mmol/L	102	130–260
Urine chloride, mmol/L	127	170–250

function, C-reactive protein levels, the erythrocyte sedimentation rate, procalcitonin levels, 1,3-β-D-glucan levels, cysticercus antibody, *Brucella* as shown by the tiger red pate agglutination test, Lyme disease antibody, *Leptospira* antibody, *Toxoplasma gondii* IgM + IgG antibody, *Leishmania donovani* antibody, rheumatism immunity series, tumor markers, paraneoplastic syndrome-related antibody, and autoimmune encephalitis-related antibodies.

Brain magnetic resonance imaging (MRI) showed a previous lacunar cerebral infarction in the right frontal lobe, and there were many artifacts due to restlessness during imaging. Chest CT showed bilateral emphysema and bullae, chronic inflammatory changes, and pleural thickening in the left oblique fissure. An abdominal CT plain scan suggested a fatty liver, multiple small liver cysts, and left-sided kidney stones.

Cerebral spinal fluid (CSF) could not be obtained because the patient was unable to cooperate with lumbar puncture. Based on the clinical manifestations and auxiliary examination findings, the possibility of brainstem encephalitis, syndrome of inappropriate secretion of antidiuretic hormone, and pulmonary infection were considered. The patient was treated with intravenous immunoglobulin (0.4 g/kg/day), meropenem (0.5 g every 8 hours), and electrolyte correction therapy. After 5 days, clinical symptoms slightly improved and methylprednisolone (1 g for 3 days, 500 mg for 3 days, followed by tapering to a lower dosage) was added to the treatment. Following glucocorticoid pulse therapy, the patient's disordered consciousness and limb weakness improved and body temperature returned to normal. However, electrolyte imbalance, ptosis, nystagmus, dysarthria, dysphagia, hiccupping, abdominal distention, and ataxia remained. Re-examination of brain MRI showed multiple abnormal signals in the midbrain, pons, medulla oblongata, left cerebellar hemisphere, and cerebellar vermis, accompanied by blood infiltration without any lesion enhancements (Figure 1a–e). Brainstem and cerebellum hemorrhagic signals were observed on brain CT (Figure 1f). Lumbar puncture performed at this stage showed normal CSF pressure, but a high amount of leukocytes (40×10^6/L with mononuclear cells accounting for 70% and polynuclear cells accounting for 30%) and a high protein level (0.6 g/L). When methylprednisolone 500 mg was used on the third day, results from next-generation sequencing of CSF showed *Listeria* infection (200 sequences of the genus *Listeria* and 172 sequences of the species *L. monocytogenes*), which was confirmed by subsequent CSF culture. Serum was positive for anti-*L. monocytogenes* 1/2a antibody IgM and IgG, while CSF was negative for anti-*L. monocytogenes* 1/2a antibody IgM and weakly positive for IgG. We modified the diagnosis to listeriosis of the CNS and immediately changed the patient's antimicrobial therapy. Because the patient was positive for penicillin allergy by a skin test, we treated him with 2.0 g of meropenem every 8 hours and 80 mg of trimethoprim-sulfamethoxazole tablets every 8 hours.

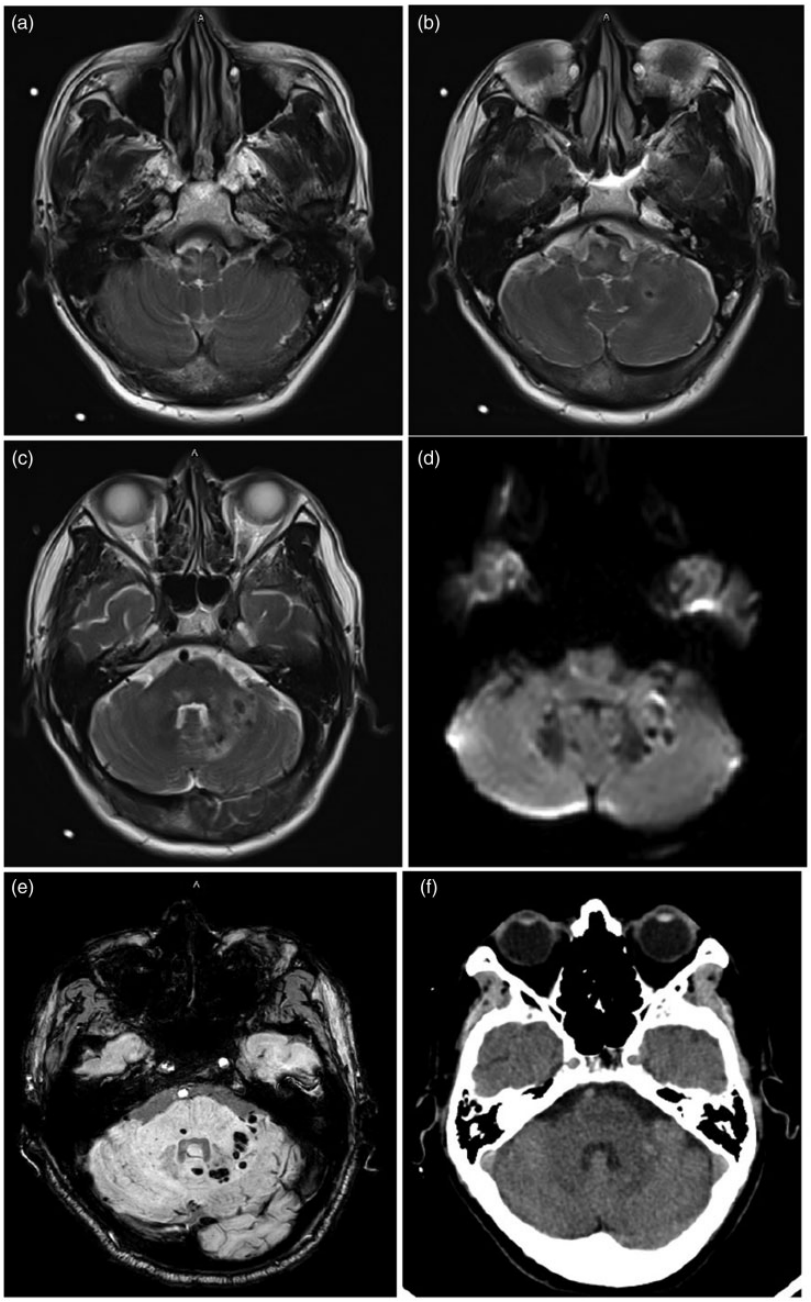

Figure 1. Brain imaging of a patient with *Listeria monocytogenes* rhombencephalitis. Different levels of T2-weighted imaging (T2WI), diffusion-weighted imaging, and susceptibility-weighted imaging in brain magnetic resonance imaging are shown (a–e). Multiple high signals mixed with low signals in the pons, medulla oblongata, and left cerebellar hemisphere appeared in T2WI (a–c) and diffusion-weighted imaging (d). Low signals in susceptibility-weighted imaging suggested that the lesions were a hemorrhagic manifestation (e). Brain CT imaging shows several speckle-like hypersignals (f). Similar levels of T2WI in brain magnetic resonance imaging as shown in panels a–c show that intracranial lesions are slightly reduced after treatment (g–i).

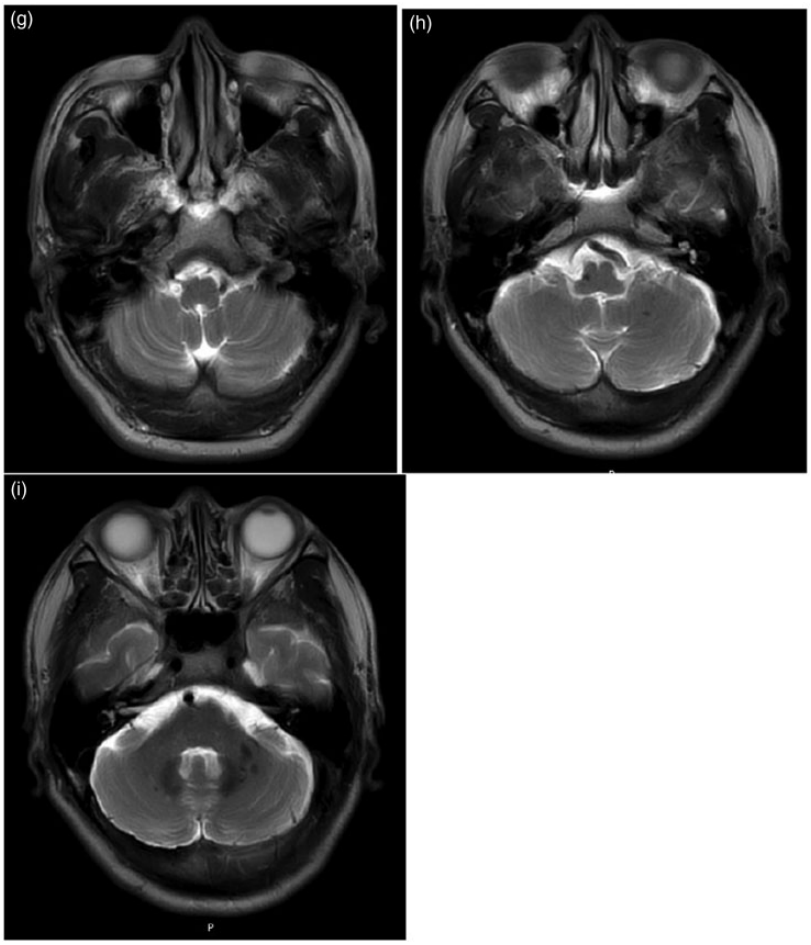

Figure 1. Continued.

We obtained consent for treatment from the patient and his relatives.

After 3 weeks of treatment, the patient dramatically recovered without any sequelae. CSF leukocyte counts and protein levels returned to normal, no *L. monocytogenes* was detected by next-generation sequencing or CSF culture. Additionally, intracranial lesions were slightly reduced on MRI (Figure 1g–h). At a 6-month follow-up, the patient complained of no discomfort and was satisfied with the treatment effect.

Discussion

There are 13 serotypes and 4 phylogenetic lineages of *L. monocytogenes*. Serotypes 1/2a (lineage II) and 1/2b (lineage I) show an increased virulence that is responsible for brain infections, including meningitis, meningoencephalitis, and rhombencephalitis. Serotype 4b can lead to brain and placental infection of *L. monocytogenes*. In multilocus sequence typing, sequence type 1 possesses neurotropism in ruminants.[6,7]

In our case, serum and CSF positivity for anti-*L.-monocytogenes* 1/2a antibody suggests that the disease severity was related to its virulence. *Listeria* is thought to invade the CNS in two ways as follows. First, *Listeria* could invade the CNS by a hematogenous route in which circulating *Listeria* in the blood breaks down the blood–brain barrier alone or in combination with leukocytes. Second, there may be a retrograde neural route in which *Listeria* is capable of retrograde intra-axonal migration along the cranial nerves to affect cranial nerves VII, V, IX, and X, as well as the medulla oblongata, cerebellum, and pons.[8] In contrast, *Listeria* infection of cranial nerves might be secondary to rhomboencephalitis, rather than retrograde infection from the cranial nerves to the rhombencephalon.[9] The molecular mechanism enabling *Listeria* to cross the blood–brain barrier may be associated with either or both of the *Listeria* surface proteins InlA and InlB. These proteins mediate species-specific interactions with their host receptor, E-cadherin, and by mesenchymal–epithelial transition across the microvascular endothelium and choroid plexus at the epithelial level. Additionally, expression of P- and E-selectin, intercellular adhesion molecule 1, vascular cell adhesion protein 1, and inflammatory factors, (i.e., interleukin-6 and interleukin-8 and monocyte chemoattractant protein-1) contribute to disruption of the blood–brain barrier.[10]

Listeria rhombencephalitis can occur in immunocompetent patients with nonspecific clinical manifestations, which causes difficulty in distinguishing this condition from other CNS diseases.[11] Our patient presented with a nonspecific prodrome of faintness, forehead tightness, and walking instability, followed by progressive cranial nerve palsies, limbs weakness, cerebellar signs, hyperpyrexia, and impaired consciousness. Our diagnostic differential was initially misguided by the patient's serum positivity for GQ1b IgM antibody, in conjunction with an unavailability of lumbar puncture up to that point. GQ1b is a type of ganglioside that is primarily distributed along the paraganglion myelin sheath and in neuromuscular junctions of the oculomotor nerve, trochlear nerve, abductor nerve, and limb muscle spindle. Recently, scholars categorized a group of GQ1b-IgG antibody-positive diseases with common autoimmune pathogeneses under the name "GQ1b antibody syndrome". These include Miller Fisher syndrome, Guillain–Barré syndrome, BBE, pharyngeal–cervical–brachial weakness, and multiple other overlapping syndromes.[12] Using this categorization, we diagnosed our patient with BBE. However, the patient's response to immunotherapy was unsatisfactory and his serum positivity for GQ1b-IgM antibody was inconsistent with IgG antibody-positive cases reported in the literature.[13] Fortunately, rapid next-generation sequencing results facilitated diagnosis of listeriosis, which was confirmed by subsequent CSF culture. GQ1b antibody syndrome is an infection-induced autoimmune disease. *Campylobacter jejuni*, cytomegalovirus, Epstein–Barr virus, and *Streptococcus pyogenes* are all reported antecedents of Miller Fisher syndrome.[14] However, to date, there is no evidence of *Listeria* triggering an autoimmune response and only one reported case of *Listeria* meningoencephalitis accompanied by GQ1b antibody syndrome.[15] Whether the current case of rhombencephalitis was the result of direct injury by *Listeria* accompanied by an autoimmune response remains unclear and requires further investigation.

The atypical imaging findings in this patient also complicated our diagnostic differential. Imaging has shown that *Listeria* manifests in the CNS as meningeal enhancement, brain abscess, hydrocephalus, and intracranial hemorrhage.[4,16] Recently, a 72-year-old man was reported to present with multiple rhombencephalic abscesses, and one of them was associated

with an atypical hemorrhagic lesion in brain MRI.[17] Our patient had multiple patchy hemorrhagic lesions on MRI and CT without enhancement. The underlying pathogenesis of his intracerebral hemorrhage remains unknown and may have been related to dysregulation of coagulation and fibrinolysis pathways. The pathogenesis of his intracerebral hemorrhage might also have been related to vascular swelling and endothelial cell activation, resulting in release of procoagulant factors and proinflammatory cytokines.[18]

Delays in diagnosis and treatment can lead to a higher mortality rate (51%) in patients with *Listeria* rhombencephalitis.[19] First-line antibiotic therapy for listeriosis of the CNS includes ampicillin or penicillin G plus aminoglycoside for at least 6 weeks. If penicillin and ampicillin are unavailable, meropenem or trimethoprim-sulfamethoxazole are the preferred alternative.[20] Our patient was positive for penicillin allergy in a skin test, and therefore, we chose a combination of meropenem and trimethoprim-sulfamethoxazole. Treatment for *Listeria* is difficult because of the intracellular nature of the infection and its high prevalence of single and multidrug antibiotic resistance.[21] Therefore, we treated our patient with a combination antibiotic therapy, which resulted in a positive response without any sequelae. The role of corticosteroids in managing CNS listeriosis is not well understood. Some recent reports have indicated that dexamethasone may contribute to rapid regression of neurological symptoms by reducing inflammation and controlling cerebral edema.[19,20] In our case, after corticosteroid therapy, the clinical symptoms partly improved. This indirectly suggests that our case of *Listeriosis* was accompanied by an autoimmune reaction. The effectiveness of corticosteroid therapy may have been related to suppression of the inflammatory response and reduced edema.

Conclusions

L. monocytogenes can infect immunocompetent adults and trigger rhombencephalitis. The clinical symptoms of this condition include fever, cranial nerve symptoms, brainstem and cerebellar signs, and in severe cases, altered consciousness may occur. This condition may be malignant and even life-threatening. Associated imaging of the CNS can show meningeal enhancement, brain abscess, hydrocephalus, and intracranial hemorrhage. Final diagnosis requires a pathogen examination because blood and CSF cultures are only positive in 61% and 11% to 41% of cases, respectively.[22] Next-generation sequencing can aid in rapid diagnosis of *Listeria* rhombencephalitis.[23] The combination of meropenem and trimethoprim-sulfamethoxazole therapy was effective in this case. This patient was positive for GQ1b antibody, but whether *Listeria* triggers an autoimmune response remains to be determined.

Ethics statement

The study protocol was approved by Capital Medical University Affiliated Beijing Friendship Hospital Bioethics Committee (Approval No. 2020-P2-015-01). The patient's daughter provided written consent for publication. We have de-identified the details of the patient.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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