

Successful treatment of refractory listeria meningitis and bacteremia with trimethoprim-sulfamethoxazole in an immunocompetent child

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Listeria monocytogenes is an important cause of life-threatening bacteremia and meningoencephalitis in neonates, pregnant women, the elderly, and immunocompromised individuals. However, it is an uncommon cause of illness in immunocompetent children beyond the neonatal period. Ampicillin with or without an aminoglycoside remains the best treatment for listeriosis. Here, we report a rare case of *Listeria meningitis* and bacteremia in a 7-month-old immunocompetent girl, which was refractory to ampicillin plus gentamicin treatment and successfully treated by the addition of TMP/SMX.

Key words: immunocompetent child, *Listeria meningitis*, trimethoprim-sulfamethoxazole.

The bacterium, *Listeria monocytogenes* (*L. monocytogenes*), is an important food-borne cause of life-threatening bacteremia and central nervous system (CNS) infection in certain high risk groups such as neonates, elderly people, pregnant women, and immunosuppressed patients. However, it is an uncommon cause of illness in immunocompetent children beyond the neonatal period¹⁻³.

L. monocytogenes is difficult to isolate and is not susceptible to third-generation cephalosporins commonly used for the empirical treatment of bacterial meningitis. Ampicillin alone or in combination with an aminoglycoside is the first line treatment for *L. monocytogenes* infections^{1,4}. However, treatment failures were previously reported with ampicillin plus aminoglycoside regimen.⁵ In patients who fail to respond to therapy, there is now increasing evidence to conclude that trimethoprim-sulfamethoxazole (TMP/SMX) may be the best alternative option⁵⁻⁷. We herein report a rare case of *L. monocytogenes* meningitis and bacteremia in a 7-month-old immunocompetent child, which was unresponsive to ampicillin plus gentamicin

treatment and improved dramatically after the substitution of gentamicin by TMP/SMX.

Case Report

A previously healthy, 7-month-old girl was admitted to our hospital due to persistent fever up to 40°C, vomiting and diarrhea lasting for 3 days followed by strabismus that was noticed by her mother 1 day prior to admission. There was a history of eating an undercooked meatballs 2 days before the onset of symptoms. The physical examination revealed fontanel bulging and bilateral abducens nerve palsy (Fig. 1a). Initial laboratory investigations showed elevated white blood cell (WBC) count of 19.3×10^9 cells/L (80% neutrophils, 15% monocytes, 5% lymphocytes), and C-reactive protein (CRP) level of 52 mg/dl. Cerebrospinal fluid (CSF) analysis revealed 1350 cells/mm³ (80% lymphocytes, 20% neutrophils), with a glucose and protein concentration of 42 and 132 mg/dl, respectively. Both computed tomography scan and magnetic resonance imaging of the brain were normal. Empiric treatment with

intravenous (IV) ceftriaxone (100 mg/kg per day) and vancomycin (60 mg/kg per day) was initiated with the aim of targeting the most common pathogens of bacterial meningitis. However, her fever persisted. On the 4th day of hospitalization, admission blood and CSF cultures grew diphtheroids subsequently identified as *L. monocytogenes*, fully susceptible in vitro to penicillin, ampicillin, gentamicin, TMP/SMX, and meropenem. Treatment was changed to IV ampicillin (300 mg/kg per day) plus gentamicin (7.5 mg/kg per day). On hospital day 9, after 5 days of ampicillin plus gentamicin treatment, the patient was still highly febrile with strabismus, fontanel bulging, vomiting, and markedly elevated CRP values. Follow-up blood cultures and a repeat CSF culture remained positive for *L. monocytogenes*. Echocardiographic examination for infective endocarditis was found to be normal. Because of the apparent lack of clinical and microbiological response to treatment, high-dose IV TMP/SMX (20 mg/kg per day of TMP) was substituted for gentamicin. Her clinical condition improved markedly within 2 days, and control blood and CSF cultures became negative 5 days after the initiation of TMP-SMX. Overall, the patient was treated with ampicillin for 26 days and TMP/SMX for 21 days. The patient was discharged in good condition on day 30. Her strabismus resolved completely two weeks after discharge (Fig. 1b). During follow-up, all immunological investigations were found to be normal, including peripheral blood lymphocyte subsets, in vitro lymphoproliferative response to mitogens, flow cytometric analysis of interleukin (IL)-12R β 1 cell surface expression on activated T cells, and IFN- γ cell surface

expression on monocytes. Serological testing for HIV was non-reactive.

Discussion

Listeria monocytogenes is a facultative, intracellular, gram-positive bacillus that is the agent of listeriosis, a serious infection usually caused by the ingestion of contaminated food. Meningitis and septicemia are the most commonly observed clinical presentations of listeriosis; however, they are rare in immunocompetent children^{1-3,8}. Herein we described a rare case of *L. monocytogenes* meningitis and bacteremia in an immunocompetent child that was probably infected through ingestion of undercooked meat.

In clinical specimens, the organisms can be gram-variable and can resemble diphtheroids, cocci, or diplococci. Laboratory misidentification as diphtheroids, streptococci, or enterococci is not uncommon, and the isolation of a "diphtheroid" from blood or CSF should always alert one to the possibility that the organism may be *L. monocytogenes*. *L. monocytogenes* is isolated from the blood in 40-75% of cases of meningitis due to the organism¹.

Listeria infections are associated with a high mortality rate, and thus effective antibiotic treatment is essential. Although Listerias are uniformly susceptible in vitro to most common antibiotics except cephalosporins, ampicillin alone or in combination with gentamicin remains the treatment of choice. However, some patients may require alternative therapies due to penicillin intolerance or unresponsiveness to initial treatment. In such cases, TMP/SMX can be used as alternative therapy^{1,4}.

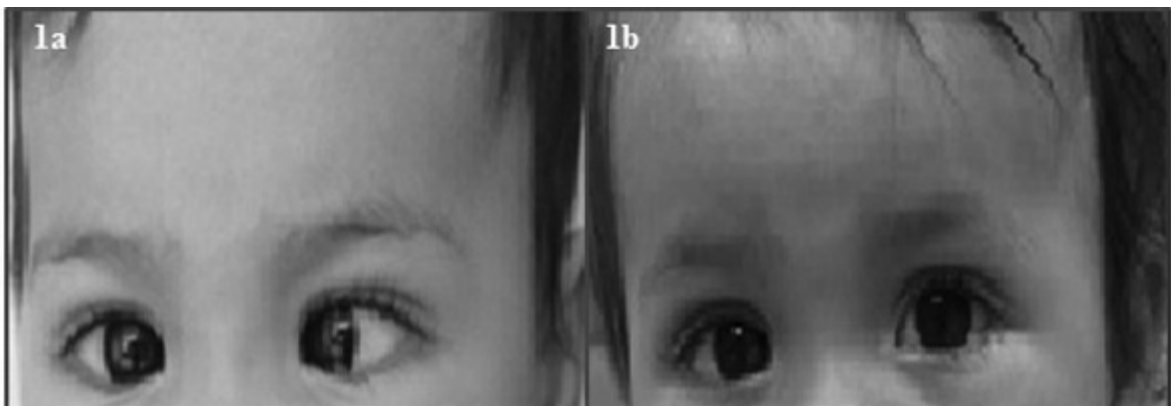


Fig. 1. Bilateral abducens nerve palsy at the time of admission (a), and complete improvement after treatment (b).

In this case, despite in vitro susceptibility result, we could not eradicate the microorganism in vivo. As in our case, treatment failures were previously reported with ampicillin plus aminoglycoside regimen in *Listeria meningoenzephalitis*^{5,9}. Ampicillin and gentamicin, although synergistic and bactericidal against *Listeria* in vitro, unfortunately have limited intracellular penetration and activity¹⁰. In contrast, TMP/SMX has bactericidal extracellular and intracellular activity against *Listeria* and penetrates well into CNS¹⁰. In a retrospective study, it was found that the combination of TMP/SMX and ampicillin was associated with a significantly lower failure rate and a lower mortality rate than the combination of ampicillin and aminoglycoside⁵. Additionally, *L. monocytogenes* is located mainly within macrophages and parenchymal cells of the spleen and liver, hardly accessible to certain drugs, such as ampicillin and gentamicin¹⁰, which may be a reason for the persistent bacteremia in our patient.

Although *L. monocytogenes* is a rare cause of meningitis and bacteremia in previously healthy children, it should be considered when treating a child with meningitis that is unresponsive to empiric antibiotic treatment with third-generation cephalosporins and when blood, CSF or other normally sterile specimen reported to have “diphtheroids” on Gram stain or culture. TMP/SMX can be effective for the treatment of CNS listeriosis refractory to conventional treatment.

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