Treatment difficulties of a listerial rhombencephalitis in an adult patient allergic to penicillins

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Rhombencephalitis is not a rare presentation of listerial central nervous system infections in healthy adults. This report describes a case with several management difficulties linked to antibiotic related adverse events, pointing to alternative solutions to aminopenicillins. In addition, the role of dexamethasone in the management of inflammation and neurological symptoms is discussed.

The microorganism Listeria monocytogenes is a common cause of central nervous system (CNS) infections associated with an unfavourable prognosis; series published in the past decade indicate a lethality of 12–43%.

Overall, acute meningitis is the most frequently encountered form of listerial CNS infection, but healthy adults more frequently develop rhombencephalitis (RE). Optimal treatment for RE is not yet defined because bacterial resistance and the blood–brain barrier limit the efficiency of antimicrobials. Many consider a combination of ampicillin and gentamicin as the “gold standard”, although some reports have found that aminopenicillin combination with trimethoprim-sulfamethoxazole (TMP/STX) is at least as good.

Corticosteroids, usually avoided, are now being reconsidered because anecdotal case reports have shown that listeria induced neurological lesions have a good response to dexamethasone.

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We report a case of listerial RE that required several antimicrobial treatment changes because of drug related adverse events and in which dexamethasone was required to improve the neurological manifestations.

CASE REPORT

A 38 year old man was admitted to the intensive care unit of the Regional Hospital of Orleans, France as a result of photophobia, confusion, fever (temperature, 40°C), and severe headache, which had developed two days earlier, and which had not responded to symptomatic treatment.

The physical examination on admission revealed meningeal irritation. Laboratory evaluation tests showed inflammation (C reactive protein, 257 mg/litre), high white blood cell count (WBC; 13 × 10^9/litre), and myelosis (creatine kinase, 653 U/litre). Computed tomography (CT) of the brain was unremarkable. Cerebrospinal fluid (CSF) analysis revealed a WBC count of 0.83 × 10^9/litre (58% lymphocytes and 42% neutrophils), a protein concentration of 135 mg/litre, lactates of 3.3 mmol/litre, and a glucose concentration of 2.8 mmol/litre. Again, no microorganisms were detected on Gram staining of the CSF.

Initial treatment comprised ceftriaxone (2 g daily), amoxicillin (2 g every four hours), gentamicin (120 mg every 12 hours), and acyclovir (1 g every eight hours). After a two day course, ceftriaxone and acyclovir were discontinued, when CSF cultures yielded Listeria monocytogenes serovar 4b (confirmatory identification was done by the French National Reference Centre for Listeriosis—Pasteur Institute, France), and a diagnosis of listerial RE was thus confirmed. The strain was susceptible to amoxicillin, rifampicin, chloramphenicol, and TMP/STX; moderately susceptible to quinolones and trimethoprim; and resistant to sulphonamides.

On the fourth day of hospitalisation, the patient was transferred to the infectious diseases unit, where he remained febrile, confused, and developed ataxic gait and bilateral oculomotor nerve paralysis. On day 6, the inflammation diminished (C reactive protein, 55 mg/litre), but a generalised rash and pruritus appeared, indicating a probable hypersensitivity to β lactams. The antimicrobial regimen was switched to thiamphenicol and rifampicin.

On day 8, the rash disappeared completely.

With antibiotic treatment, the patient’s neurological status slowly improved, and his temperature remained at 38°C. On day 9, analysis of the CSF revealed a WBC count of 0.13 × 10^9/litre (62% lymphocytes and 38% neutrophils), a protein concentration of 124 mg/litre, lactates of 3.3 mmol/litre, and a glucose concentration of 2.8 mmol/litre. Again, no microorganisms were detected on Gram staining of the CSF and cultures remained sterile. A CT scan of the brain performed the next day showed no other lesions, in particular, no microabscesses. At this point, intravenous dexamethasone was added to the treatment regimen and helped to induce apyrexia after 24 hours, and completely reversed the neurological signs 72 hours later. Gait retraining necessitated seven days of physical treatment.

On day 15, our patient developed hepatitis, as indicated by high alanine aminotransferase and aspartate aminotransferase concentrations of 788 U/litre (19 × normal) and 250 U/litre (5 × normal), respectively. Rifampicin was replaced by TMP/STX. On day 28, the alanine aminotransferase and aspartate aminotransferase values had returned to normal and no concomitant viral infection was discovered. In addition, the liver imaging exploration (echography and CT scan) was negative.

The antibiotics and dexamethasone were stopped on day 28, when C reactive protein reached a concentration of 5 mg/litre. After a three month follow up, no signs of relapse have been noted. A later evaluation established no immunodeficiency conditions.

Epidemiological investigations uncovered no specific food vehicle for L monocytogenes.

Abbreviations: CNS, central nervous system; CT, computed tomography; CSF, cerebrospinal fluid; RE, rhombencephalitis; TMP/STX, trimethoprim-sulfamethoxazole; WBC, white blood cell count.
Take home messages

- We report a case of rhombencephalitis resulting from infection with Listeria monocytogenes in which the gold standard treatment with an amoxicillin based regimen was stopped because of probable hypersensitivity to β-lactams.
- Subsequent treatment with thiamphenicol and rifampicin was active against the isolated strain but had to be stopped because of hepatitis, probably related to treatment with rifampicin.
- The third regimen, trimethoprim-sulfamethoxazole combined with thiamphenicol proved successful, and after three months relapse has not occurred.
- In addition, dexamethasone helped reduce inflammation and improve the neurological symptoms.

DISCUSSION

Listerial RE usually occurs in healthy adults. Its typical clinical picture is a biphasic illness, with neurological signs appearing four to five days after the onset of fever. Mortality exceeds 26% and serious sequela are common in survivors. The diagnosis can be delayed if no meningeal signs are present in the early stages of the disease; fortunately, this was not the case with our patient. Although the age and immunocompetent status of our patient argued against listerial meningitis, the CSF analysis pointed to this aetiology.

The initial regimen for RE with meningitis includes aminopenicillin, which is active against L. monocytogenes; however, in our patient we had to discontinue amoxicillin because of the occurrence of a rash. Rapid resolution of the erythema after the discontinuation of amoxicillin argued in favour of hypersensitivity to β-lactams.

Although TMP/STX is thought to be the second best treatment for listerial CNS infection, the weak in vitro efficacy of trimethoprim and sulfonamides on the isolated strain prompted us to replace the amoxicillin based regimen with thiamphenicol and rifampicin. Reports on thiamphenicol and rifampicin in the literature are less favourable: phenicols are less potent than TMP/STX against listeria, and clinical experience with rifampicin is insufficient. However, both of these drugs resulted in excellent CSF and cerebral tissue measurements and were active against the isolated strain. We used thiamphenicol instead of chloramphenicol because it is the only phenicol available in France and CSF diffusion is at least equivalent to chloramphenicol. Furthermore, because of its intracellular activity, rifampicin is strongly recommended for listeria infections.

“In our patient, the occurrence of hepatitis was probably rifampicin related because the hepatic cytolysis resolved quickly after discontinuation of the drug.”

Our third regimen was TMP/STX in combination with thiamphenicol; we abandoned our initial reservations regarding TMP/STX because there were no other therapeutic alternatives. In fact, clinical data on the efficiency of TMP/STX in CNS listeriosis are highly favourable, with some authors considering TMP/STX to be better than the “gold standard” combination of ampicillin and aminoglycoside.5,7,8 The absence of relapse indicated that TMP/STX was still active in our patient.

There are a few case reports of hepatic involvement in adult listeriosis.4,10 However, in our patient, the occurrence of hepatitis was probably rifampicin related because the hepatic cytolysis resolved quickly after discontinuation of the drug. A two week delay between liver and CNS manifestations is another argument against listerial hepatitis.

The optimal duration of antimicrobial treatment in CNS listeriosis is from three to six weeks,1,2 with longer durations reserved for cerebral abscesses. The good clinical response and the absence of localised CNS lesions in our patient allowed for a length of therapy of only 28 days; the decision to stop treatment at four weeks was supported by the absence of a relapse of illness during the following three months.

Dexamethasone seems to be an important agent in treating most CNS infection because of its potent anti-inflammatory activity and its role in controlling cerebral oedema.5,11,12 Classically, dexamethasone is not widely used in adults with listerial infections because of the frequent association of these infections with immunodeficiency. Nonetheless, if necessary, corticosteroids can be administered in immunocompromised patients (for example, patients with AIDS and severe pneumocystis pneumonia). Moreover, some recent anecdotal reports have indicated that dexamethasone might be useful in listerial RE.5 For our patient, the slow improvement of neurological manifestations after the administration of dexamethasone proved beneficial.

Further studies are needed to evaluate alternatives to the gold standard antimicrobial treatment and the role of dexamethasone in the management of CNS listeriosis.

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