Rhomboencephalitis caused by *Listeria monocytogenes*

STEPHEN WORKMAN MD FRCP, MICHAEL THEAL

S WORKMAN, M THEAL. Rhomboencephalitis caused by *Listeria monocytogenes*. *Can J Infect Dis* 1997;8(2):xx-xx. Listerial rhomboencephalitis is a rare, devastating treatable disease. A previously well 72-year-old man presented with a one-week history of fever and headache. Four days before admission he developed right facial numbness and ataxia. Diagnosis and treatment are described, including the relevant clinical, laboratory and radiological findings.

Key Words: Abscess(es), Brain stem, *Listeria monocytogenes*, Magnetic resonance imaging, Rhomboencephalitis

Rhomboencéphalite causée par *Listeria monocytogenes*

RISUMI : La rhomboencéphalite causée par *Listeria monocytogenes* est une maladie rare et dévastatrice mais curable. Un homme de 72 ans, auparavant bien-portant, se présente pour fièvre et céphalées d'une durée d'une semaine. Quatre jours avant l'admission, il a présenté un engourdissement du visage et de l'ataxie. Cet article en explique le diagnostic et le traitement, y compris les signes cliniques et radiologiques et les résultats d'analyses de laboratoire pertinents.

Rhomboencephalitis, also known as pontomedullary or brain stem encephalitis, has a variety of causes including viral agents, autoimmune diseases and granulomatous infections of the central nervous system (CNS). *Listeria monocytogenes*, a Gram-positive motile bacterium that exhibits CNS tropism, is a rare cause of rhomboencephalitis in humans. CNS infections in humans include meningitis (1) and supratentorial abscess (2), commonly in immunocompromised individuals, and rhomboencephalitis in immunocompetent patients (3). In ruminants, where the organism is found in the intestinal flora, listerial infection of the brain stem produces 'circling disease' in which the animals develop a circling unsteady gait, torticollis, strabismus and difficulty swallowing (4,5). Documented outbreaks of meningitis and neonatal sepsis have occurred via the consumption of contaminated food (6), presumably as a result of hematogenous spread. However, the mechanism by which *L. monocytogenes* gains access to the

brain stem is not known. Animal models have shown that conjunctival or buccal inoculation can result in rhomboencephalitis (7). We describe a case that illustrates the relevant clinical, laboratory and radiological findings.

CASE PRESENTATION

A 72-year-old man was admitted to hospital complaining of a right-sided headache, fever and malaise that had been present for one week. Four days before admission he had developed right facial numbness, diplopia and vertigo, and he had fallen three times on the day of admission.

The patient had no past medical problems and was taking no medications. He was Mantoux negative in 1992. He had travelled to Germany two months before admission. During that time he had been in close contact with farm animals and horses. After his return home he had consumed unpasteurized milk.

Division of General Internal Medicine, Victoria General Hospital; and Faculty of Medicine, University of Dalhousie, Halifax, Nova Scotia
Correspondence: Dr S Workman, Joint Centre for Bioethics, 88 College Street, Toronto, Ontario M5G 1L4. Telephone 416-964-1858, fax 416-978-1911, e-mail stephen.workman@utoronto.ca

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TABLE 1
Cerebral spinal fluid findings

Test	Results			
	Day 1	Day 4	Day 8	Day 26*
WBC	204	137	191	N/A
Neutrophils (%)	26	18	0	
Monocytes (%)	74	82	100 [†]	
Glucose (mmol/L)	3.80	4.00	4.80	1.7
Protein (mg/L)	688	856	890	483
Culture	Negative	Negative	Negative	Positive

*Results obtained via ventriculostomy five days after open biopsy; [†]Note progress of monocytosis. N/A Not available; WBC White blood cell count

Physical examination at the time of admission revealed an alert and oriented man. His oral temperature was 38.8°C. Mild meningismus was present. Fundoscopic examination was normal. Examination of the cranial nerves revealed a right sixth nerve palsy, decreased sensation in the V1 distribution of the right trigeminal nerve and weakness in the right temporalis and masseter muscles. Cerebellar function was impaired with nystagmus in all directions of gaze, difficulty with rapid alternating movement of the right hand, right upper limb ataxia on finger-nose testing and an ataxic gait. Heel-shin testing was normal bilaterally. The remainder of the neurological examination was normal.

Peripheral white blood cell (WBC) count was 9.8×10^9 cells/L, and serum sodium was 131 mmol/L. An unenhanced computer assisted tomography (CAT) scan of the head was normal. Cerebrospinal fluid (CSF) was clear with no red blood cells; CSF findings were nonspecific (Table 1).

The patient was admitted with a provisional diagnosis of viral meningoencephalitis. His headache improved but neck stiffness persisted. WBC count remained within the normal range and serum sodium was between 130 and 134 mmol/L. Admission blood and CSF cultures were negative. Results of repeat CSF analysis are presented in Table 1. On day 7 he became confused and had difficulty speaking and swallowing. He had developed right and left sixth nerve palsies, decreased sensation in the distribution of the right trigeminal nerve and a decreased gag reflex. There was nystagmus in all directions of gaze, increased ataxia and bilateral upper extremity dysdiadokinesis.

On day 8 the patient developed acute respiratory failure and required emergency intubation and ventilation. Magnetic resonance imaging (MRI) was performed. T1-weighted gadolinium-enhanced images revealed five ring-enhancing lesions in the brain stem and one in the cerebellum. The largest lesion was at the pontomedullary junction (Figure 1). There were no supratentorial lesions. Bilateral medullary lesions were thought to have caused central hypoventilation (Figure 2).

Empiric therapy with ceftriaxone (2 g intravenous every 12 h), cloxacillin (2 g intravenous every 6 h), and dexamethasone was started. On day 15 metronidazole (500 mg intrave-

Figure 1) Ring enhancing lesion (6 mm) at the level of the pons in magnetic resonance image performed on day 8

nous every 12 h) was added. Ampicillin 1 g intravenous every 6 h was begun, but was given for only two doses.

Blood cultures repeated on days 6 and 7 were negative. Repeat CSF examination on day 8 revealed monocytosis. Stains for bacteria, fungi and acid-fast bacilli were negative. CSF cytology showed atypical inflammatory cells and raised the possibility of carcinomatous meningitis.

Intermittent apneic periods necessitated continued intubation and ventilation; however, the patient became alert and oriented 12 h after resuscitation and extubated himself on day 13. Repeat neurological examination demonstrated improvement. The patient was able to speak and swallow without difficulty. His right sixth nerve palsy had resolved, and sensation in the area of the right trigeminal nerve returned. Cerebellar function was also improved.

MRI on day 17 revealed a new large nonring-enhancing lesion in the cerebellum (Figure 3). Headache and a fever recurred, and over the next two days he became increasingly confused and disoriented. Peripheral WBC count increased from 12.3×10^9 cells/L on day 16 to 18.5×10^9 cells/L on day 19. On day 20 he suffered a second respiratory arrest. CAT scan of the head revealed obstructive hydrocephalus. Emergency ventriculostomy was followed by craniotomy and open cerebellar biopsy.

Blood cultures from day 17 were reported on day 21 to be growing Gram-positive organisms identified as *L monocytogenes*. Gram stain of biopsy tissue demonstrated a large number of Gram-positive organisms, and cultures of biopsy tissue grew *L monocytogenes*. On day 21 ampicillin (4 g intravenous every 6 h) and gentamicin (1.5 mg/kg intravenous every 8 h) were started. Dexamethasone was continued. CSF was collected daily from the ventriculostomy, and viable organisms were recovered on day 26. On day 27 rifampin 300 mg intravenous twice a day was added. CSF was sterile. One month of intravenous therapy with ampicillin, gentamicin and rifampin was given.

Brain tissue obtained at biopsy demonstrated areas of necrosis with acute inflammatory cell infiltrates, focal areas of hemorrhage, fibrinoid necrosis of vessels and widespread dissemination of Gram-positive rods.

Figure 2) Ring enhancing lesion in the medulla with bilateral medullary lesions in magnetic resonance image performed on day 8

The patient was discharged home on no medications after seven weeks in hospital. At discharge he had problems with intermittent confusion but was ambulatory without cranial nerve or cerebellar deficits.

DISCUSSION

Infection in humans caused by *L. monocytogenes*, listeriosis, is rare and is most common in pregnant women, infants, the elderly and patients who are immunocompromised (8).

Transplacental fetal infection (granulomatous infantisep-ticum) is usually fatal to the fetus. Maternal infection may be an asymptomatic or a mild febrile illness. In the neonate infection may develop shortly after delivery causing bactere-mia with or without sepsis. Late onset listeriosis occurs sev-eral days to weeks after birth, and meningitis is the most common clinical manifestation.

In adult patients meningitis is the most common manifes-tation of listeriosis (8). *L. monocytogenes* is the fourth leading cause of meningitis in adults. The majority of patients who develop meningitis are immunocompromised or elderly (8). Other less common CNS infections include rhombencephali-tis, cerebritis and abscesses in the brain, brain stem and spinal cord. Other focal infections such as endocarditis, arthritis, adenitis and osteomyelitis occur rarely.

Rhombencephalitis caused by *L. monocytogenes* is a very rare disease. A recent comprehensive review article surveyed the world literature and described 62 confirmed cases (3). A typical presentation was of a prodromal illness of less than two weeks' duration characterized by fever, headache and malaise. At presentation patients were usually febrile, and neck stiffness was noted in half of the cases reported. This prodromal phase ended with the development of progressive neurological signs. Cranial nerve dysfunction with or without long tract signs or cerebellar dysfunction was seen in 90% of the cases; 10% had only long tract signs as the initial neurologic abnormality. The majority of patients had involve-ment of multiple areas of the brain stem. Occasionally, pa-tients presented with an abbreviated prodromal illness and had significant neurological deficits at or shortly after disease

Figure 3) Repeat magnetic resonance imaging (MRI) performed 10 days after the first MRI. The pontine lesion shows less intense enhance-ment. A new nonring enhancing lesion can be seen in the left cerebellar hemisphere

onset. Diagnosis was often difficult, and the majority of survi-vors had persistent neurological deficits.

Most patients who develop rhombencephalitis are immu-nocompetent (3). This contrasts with other CNS infections caused by *L. monocytogenes*, which are found principally in immunocompromised patients (8). If the brain stem is indeed 'fertile soil' and is infected via hematogenous dissemination, it is difficult to understand why it is not preferentially infected in both immunocompromised and immunocompetent patients. This discrepancy raises the possibility that the organism may gain access to the brain stem directly, possibly via the fifth cranial nerve (7), thereby avoiding normal immune defences.

Our patient presented with rhombencephalitis. MRI sug-gested multiple brain stem abscesses could be causative. A recent review article on brain stem abscesses did not include listeria in a list of causative organisms (9). *L. monocytogenes* is a treatable cause of rhombencephalitis and must be con-sidered in the differential diagnosis of brain stem abscesses.

Listerial rhombencephalitis is difficult to diagnose. CSF parameters may be normal or consistent with bacterial or viral meningitis (10) or parameningeal inflammation, as in this case. Positive CSF cultures have been present in only 41% of reported cases (3). Consequently, CSF analysis and culture cannot be used to exclude or diagnose listerial rhombo-encephalitis. CSF differential counts may demonstrate increas-ing monocytosis (Table 1). Blood cultures, which have been positive in 61% of reported cases (3), are often negative initially and do not allow an early diagnosis. Multiple blood and CSF cultures were taken, but all were negative until day 21.

Of nine reported cases of listerial rhombencephalitis in which MRI scanning of the head was performed, only one was normal (3). In our case the initial CAT scan was normal. Patients with a clinical diagnosis of rhombencephalitis should have an MRI scan performed, if CAT scanning is not helpful. Demonstration of focal lesions in the brain stem, cerebellum or cervical spinal cord (11) strongly suggests the possibility of listeria.

Empiric therapy with dexamethasone resulted in some transient improvement. A temporary response to dexametha-

sone was noted in three other cases (3,11), suggesting that edema plays an important role in the development of symptoms. In this case there is evidence of bacterial dissemination after the introduction of dexamethasone. Dissemination is suggested by the positive blood culture results obtained after therapy with dexamethasone began and by the second MRI that showed a new diffuse cerebellar lesion. Corticosteroid usage has been associated with the development of listeriosis (8), and it is not surprising that this patient ultimately worsened after a corticosteroid was introduced.

Empiric therapy with ceftriaxone, cloxacillin and metronidazole was ineffective. Blood cultures collected one week after instituting empiric therapy were positive, and viable organisms were easily recovered from tissue obtained at biopsy.

Respiratory failure has occurred in 41% of cases of listerial brain stem infections (3). This case suggests two mechanisms by which respiratory failure occurs. The patient suffered two respiratory arrests. The first was caused by abscesses impinging on medullary respiratory centres; the second occurred as a result of obstructive hydrocephalus. Another case report has documented ventricular dilation on CAT scan (12); repeat lumbar puncture should be pursued with caution because of the risk of precipitating brain stem herniation. If recognized and treated promptly, obstructive hydrocephalus is a survivable complication of this disease.

In our patient, CSF cultures remained positive for five days

after beginning therapy with gentamicin and ampicillin. Rifampin was added on the day that CSF became sterile. A previous case report has suggested that rifampin has good in vivo activity against listeria and is effective in rhomboencephalitis (13). It may be prudent to include this drug initially in order to sterilize CSF more rapidly.

CONCLUSIONS

L. monocytogenes infection of the brain stem is a rare but clinically recognizable disease of immunocompetent patients. For patients with a clinical diagnosis of rhomboencephalitis or brain stem abscess(es) recognition of the symptom complex caused by listerial brain stem infection is of foremost importance in allowing an early diagnosis and ensuring an optimal outcome. MRI scanning is the radiological investigation of choice. Empiric antibiotic therapy in patients with rhomboencephalitis must include agents effective against *L. monocytogenes*. Rifampin may be a useful adjunct medication. In the absence of appropriate antibiotic coverage decadron will transiently improve neurological function but may increase the severity of infection. Continuous monitoring in an observation unit is required to prevent fatal respiratory arrest. Obstructive hydrocephalus may occur; repeat neuroimaging should be obtained if there is any worsening in neurological status, and lumbar puncture should be performed only after significant CSF outflow obstruction has been excluded.

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REFERENCES

1. Lavetter A, Leedom JM, Mathies AW Jr, et al. Meningitis due to *Listeria monocytogenes*: A review of 25 cases. *N Engl J Med* 1971;285:598-603.
 2. Dee RR, Lorber B. Brain abscess due to *Listeria monocytogenes*: Case report and literature review. *Rev Infect Dis* 1986;8:968-77.
 3. Armstrong RW, Fung PC. Brainstem encephalitis (rhomboencephalitis) due to *Listeria monocytogenes*: Case report and review. *Clin Infect Dis* 1993;16:689-702.
 4. Gill D. Circling disease: A meningoencephalitis of sheep in New Zealand. *Vet J* 1933;89:258-70.
 5. Bosjen O, Moller J. Human listeriosis: Diagnostic epidemiological and clinical studies. *Acta Pathol Microbiol Scan* 1972;229(Suppl B):1-155.
 6. Schlech WF, Lavigne PM, Bortolussi RA, et al. Epidemic listeriosis – Evidence for transmission by food. *N Engl J Med* 1993;308:203-6.
 7. Asahi O, Hosoda T, Akiyama Y. Studies on the mechanism of infections of the brain with *Listeria monocytogenes*. *Am J Vet Res* 1957;18:147-57.
 8. Gellin BG, Broome Claire V. Listeriosis. *JAMA* 1989;261:1313-20.
 9. Carpenter JL. Brain stem abscesses: Cure with medical therapy, case report, and review. *Clin Infect Dis* 1994;18:219-26.
 10. Weinstein AJ, William AS, Anthony JF. Listeria rhomboencephalitis. *Arch Neurol* 1982;39:514-6.
 11. King SJ, Jeffree MA. MRI of an abscess of the cervical spinal cord in a case of listeria meningoencephalomyelitis. *Neuroradiology* 1993;35:495-6.
 12. Christian JB, Gialluly E, Gerhardt R, et al. Fatal nonmeningitic listeria rhomboencephalitis. *Arch Intern Med* 1985;145:1982-5.
 13. Bach MC, Kent DM. Listeria rhomboencephalitis mimicking tuberculous meningitis. *Rev Infect Dis* 1987;1:130-3.
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