

CLINICAL ALERT

Listerial brainstem encephalitis – treatable, but easily missed

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Listerial brainstem encephalitis (LBE) is an uncommon form of listerial central nervous system infection that progresses rapidly and is invariably fatal unless detected and treated early. We report on six adult patients with LBE, of whom five were managed or co-managed by our unit during the period January - June 2012. All presented with a short prodromal illness followed by a combination of brainstem signs, including multiple cranial nerve palsies with emphasis on the lower cranial nerves, ataxia, motor and sensory long-tract signs, a depressed level of consciousness and apnoea. In two cases the diagnosis was delayed with adverse outcomes. LBE may be difficult to diagnose: clinicians may not be aware of this condition, the brainstem location may not be recognised readily, general markers of inflammation such as the erythrocyte sedimentation rate, C-reactive protein level or white cell count may be normal, and the cerebrospinal fluid is typically normal or there are only mild and nonspecific findings. Serological tests are unreliable, and diagnosis is achieved through blood cultures, magnetic resonance imaging and clinical recognition.

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Listeria monocytogenes is a very common intracellular Gram-positive coccobacillus occurring in the soil, and humans may be affected via the oral route from contaminated food. The organism has a remarkable resistance to eradication during food processing, has unique virulence factors,^[1,2] and is an important cause of food-borne epidemic disease with high associated mortality.^[3] Following ingestion, infection occurs across the intestinal epithelium and spreads to the liver, where it becomes established within the cytosol of macrophages. Macrophages may then traffic infection via the bloodstream to the meninges and fetoplacental unit.^[1] The disease usually presents as a febrile diarrhoeal illness, but may also cause septicaemia, meningitis and chorioamnionitis. Listerial meningitis may be the third most common cause of acute community-acquired bacterial meningitis.^[2]

Listerial brainstem meningitis (LBE), however, is an uncommon, sporadically occurring form of listerial infection that progresses rapidly and is invariably fatal unless treated early.^[3-5] Cases are often undetected.^[5] It is characterised by a prodromal febrile illness followed within 4 - 10 days by the abrupt onset of cranial nerve deficits associated with encephalopathy, hemiparesis, hemisensory loss and/or cerebellar signs.^[3-5] Unlike the other forms of central nervous system (CNS) listeriosis, LBE is striking in respect of the stepwise development of brainstem signs in the absence of meningism. This presentation is probably accounted for by a novel route of infection that exploits retrograde axonal transport to the brainstem along the cranial nerves that supply the oropharynx.^[2,6]

Methods

We report on six patients with LBE, of whom five were managed or co-managed by the neurology unit at Tygerberg Hospital, Western Cape, South Africa, during the period January - June 2012. Definite cases were defined as cases with a compatible clinical syndrome

(prodrome followed by stepwise neurological deficits due to brainstem disease) and microbiological demonstration of *L. monocytogenes* in blood, cerebrospinal fluid (CSF) or brain tissue. Probable cases were defined as cases with a compatible clinical syndrome with ancillary tests (brain imaging and CSF analysis) supporting the diagnosis and evidence of improvement after commencement of antilisterial therapy.

The Stellenbosch University Human Research Ethics Committee approved the reporting of clinical material (S13/10/223).

Case report

The index case (patient 1) was a 59-year-old woman who presented with a 1-week flu-like illness followed by ataxia and sensory loss involving the face. Thereafter she developed a deteriorating level of consciousness and died within 3 weeks.

At onset she complained of fever, dizziness and unremitting frontal headache, and she was treated with telithromycin followed by moxifloxacin for suspected sinusitis. One week later, she developed hoarseness, numbness of the left cheek and ataxia of the left arm. A chest radiograph was normal. Magnetic resonance imaging (MRI) of the brain showed signal abnormalities in the pons and left middle cerebellar peduncle on fluid-attenuated inversion recovery (FLAIR) sequences, with subtle contrast enhancement on T1-weighted images. Intravenous (IV) methylprednisolone was given for 3 days for a presumptive diagnosis of acute disseminated encephalomyelitis (ADEM), during which her condition remained stable and she was afebrile. However, a day later, she developed a fever and became comatose, and was found to have bilateral papilloedema. CSF protein and glucose levels were normal, and there were 4 polymorphonuclear cells per high-power field on microscopy. A CSF Gram stain was negative, and neither the CSF nor initial blood cultures yielded growth after 5 days of incubation. Repeat MRI of the brain showed extension of signal abnormalities into both cerebellar peduncles, the cerebellum

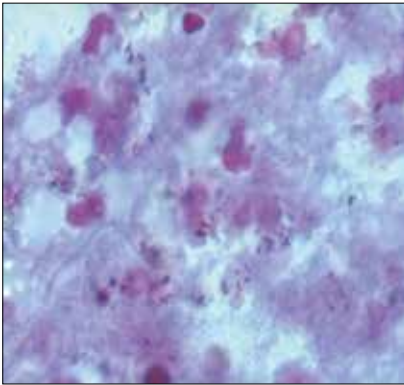


Fig. 1. Oil-immersion photomicrograph at × 1 000 magnification shows Gram-positive short intracellular rods.

and rostrally into the basal ganglia. There was no clinical response to treatment with IV corticosteroids and acyclovir. Subsequent MRI brain imaging revealed progression of disease to involve the upper cervical cord, brainstem, cerebellum, bilateral basal ganglia and rostral left cerebral hemisphere. A repeat CSF sample was acellular with normal chemistry and microscopy. The patient died after 17 days of illness. Blood cultures taken on day 15 as well as CSF cultures taken on day 17 cultured *L. monocytogenes*, and at autopsy *L. monocytogenes* microabscesses were confirmed (Fig. 1).

Discussion

We report two definite (patients 1 and 4) and four probable cases of LBE. The clinical data and ancillary tests are summarised in Tables 1 and 2, respectively. LBE typically begins with a prodrome of up to 16 days (median 4 days),^[3,4] with isolated cases reported to have prodromes of more than a month.^[3] In our series, the median time before the onset of neurological signs was 5.5 days. Headache (73%), fever (85%) and nausea or vomiting (64%) are the most commonly reported early features,^[3,4] but these were absent in a third of our patients. Mental state at admission is often preserved (59%).^[3] The prodrome is followed by the onset of focal signs of lower brainstem and cerebellar involvement. Patients frequently present with asymmetrical cranial nerve dysfunction (VII, VI, IX, X and V, in order of descending frequency).^[3-5] Untreated patients deteriorate over days with new cranial nerve deficits and the emergence of ‘crossed’ or bilateral long-tract signs (hemiparesis more often than hemisensory loss), cerebellar signs and/or encephalopathy. At maximal evolution, most patients have combined cranial nerve deficits and long-tract signs (81%), and more than half have cerebellar signs.^[3-5] Cranial

Table 1. Clinical presentation, course and outcomes

	Patient					
	1	2	3	4	5	6
Geographical location	PE, E Cape	Caledon, W Cape	Paarl, W Cape	Kleinmond, W Cape	Villiersdorp, W Cape	Atlantis, W Cape
Age (years)	59	37	51	36	25	32
Gender	F	M	M	F	M	F
Comorbid disease	Recent sinusitis	Hpt, DM	HIV*, ethanol abuse	RA on immunosuppressants	None	None
Length of prodrome (days)	6	3	5	1	7	7
Symptoms (in order of onset)	HA, dizziness, facial numbness, hoarseness	Fever, dizziness, ataxia	Unilat HA; N&V, gait ataxia, dysphonia (d5); L facial numbness, D/V (d6)	fever, dysarthria, dysphagia, numb L arm	HA, dizziness; R facial palsy, N&V (d7)	HA; dizziness, gait ataxia (d7); L facial numbness, R facial palsy (d15); D/V, N&V
Signs (in order of onset)	Fever, L CN V2 (S), CN X; L arm dysmetria, coma	Fever, nystag, L dysmetria, gait ataxia (d3), drowsiness, apnoea (d6); bilat CN IV, L CN VII (LMN), nystag, CN X, mild quadriparesis (d8)	R Horner's, bilat CN VI, nystag, L CN V (S), L CN X, worsening L dysmetria, gait ataxia (d11)	Fever, coma, bilat ptosis, bilat gaze palsies, skew deviation, R CN VII (LMN), quadriparesis, hyperreflexia (d11)	Fever, meningism, R CN VII (LMN) (d7); drowsiness, vertigo, hiccups, L gaze palsy, R hemisensory (d17)	R CN VI, R CN VII, L CN X, L hemisensory, bilat leg dysmetria (d15), R hemiplegia (d35)
Antibiotics prior to cultures	TEL, MXF	AMP (d2), CRO (d3)	RHZE (d5)			
Treatment	MP (d11)	AMP (d8); ACV (d5); RHZE (d8 - d22)	AMP (d11)	ACV, CRO, DXM (d11); AMP (d12); GEN (d14)	CRO (d14); DXM (d17); AMP (d20)	MP (d15); CRO, TMP/SXT, MTZ, AMP (d35)
Nadir		d10	d13		d20	d35
Outcome	Death (d17)	Alive, no focal signs (d41)	Alive, residual facial numbness, mild gait ataxia (d33)	Death (d18)	Alive, residual mild R facial palsy, L gaze palsy (d60)	Alive, no focal signs (d72)

PE = Port Elizabeth; E Cape = Eastern Cape Province, South Africa; W Cape = Western Cape Province; F = female; M = male; Hpt = hypertension; DM = diabetes mellitus; RA = rheumatoid arthritis; CN = cranial nerve; L = left; R = right; bilat = bilateral; unilat = unilateral; LMN = lower motor neuron; nystag = nystagmus; HA = headache; N&V = nausea and vomiting; D/V = double vision; d = days since illness onset; TEL = telithromycin; MXF = moxifloxacin; AMP = amoxicillin; CRO = ceftriaxone; RHZE = rifampicin, isoniazid, pyrazinamide, ethambutol; MP = methylprednisolone; AMP = ampicillin; ACV = acyclovir; DXM = dexamethasone; GEN = gentamycin; TMP/SXT = trimethoprim/sulfamethoxazole; MTZ = metronidazole.
*Not on combination antiretroviral therapy.

Table 2. Laboratory, pathology and radiological investigations

	Patient					
	1	2	3	4	5	6
Inflammatory markers						
WCC	13	13.07	6.52	12.17	15.31	9.57
CRP	ND	97	86	85	ND	ND
CSF						
Cells (PMN, Ly, E)	4, 0, 0	11, 484, 5	66, 21, 6	12, 68, 9	4, 375, 0	0, 60, 0
Protein (g/L)	0.3	0.8	0.69	0.5	0.59	0.63
Glucose (mmol/L)	6.3	6	3.2	2.8	3.3	3.3
<i>L. monocytogenes</i> culture						
Blood	Pos (d15)	Neg (× 2)	Neg (× 2)	Pos (× 2)	Neg (× 2)	Neg (× 2)
CSF	Pos (d17)	Neg	Neg	ND	Neg	Neg
Brain biopsy	Pos	ND	ND	ND	ND	ND
CT	ND	N	Well-defined ring lesions dorsal Po, L MCP	Poorly defined lesions R Po, R MCP; incomplete ring enhancement	N	N
MRI						
Distribution of high signal on T2WI & FLAIR sequences	L Po, MCP, and Cb	L cerebral ped, L MCP, L Cb	ND	R cerebral ped, R MCP, Me, upper cord	R cerebral ped, R MCP, dorsal Po, Me, upper cord	Mb, dorsal Po, Cb vermis, Me; after 9 d interval: new lesions L thalamic, L parietal
Enhancement pattern on T1WI pre-/post gadolinium	Subtle, incomplete ring dorsal Po	Complete ring	ND	Incomplete ring	Patchy, nodular	Patchy, nodular; complete ring
CN enhancement present	N	Y	Y	Y	N	N
Radiological differential reported	Demyelination (BS/ADEM), glioma	Abscess	Tuberculoma, listerial abscess	Demyelination (ADEM)	Demyelination (ADEM)	Abscess, demyelination

WCC = white cell count; CRP = C-reactive protein; CSF = cerebrospinal fluid; PMN = polymorphonuclear cell; Ly = lymphocyte; E = erythrocyte; CT = computed tomography; MRI = magnetic resonance imaging; T2WI = T2-weighted imaging; FLAIR = fluid attenuated inversion recovery; Pos = positive; Neg = negative; d = days since symptom onset; ND = not done; N = normal; L = left; R = right; Mb = midbrain; Po = pons; MCP = middle cerebellar peduncle; Cb = cerebellum; Me = medulla; ped = peduncle; CN = cranial nerve; N = no; Y = yes; BS = Bickerstaff encephalitis; ADEM = acute disseminated encephalomyelitis.

nerve involvement is seen in all patients at the nadir of the illness. Frequently, non-contiguous cranial nerve nuclei will be affected during the course of the illness; for instance, patient 6 had left trigeminal sensory involvement, right abducens palsy and lower motor neuron facial weakness, as well as a left palatal palsy (cranial nerve X), indicating multifocal brainstem involvement. Respiratory failure due to involvement of the medulla may occur early and necessitate ventilatory support.^[3,5] A reduced level of consciousness was present in four of the six patients.

The differential diagnosis of brainstem encephalitis varies depending on population

and geographical region.^[7] Broadly, this presentation may be due to demyelination (e.g. multiple sclerosis, ADEM) or autoimmune/inflammatory (e.g. Behçet's disease, paraneoplastic), infectious and very rarely neoplastic diseases (e.g. lymphoma).^[7,8] Infectious causes in adults include viruses, such as entero- and herpesviruses. Surprisingly, however, a bacterial infection such as listeria is one of the most common infectious causes of brainstem encephalitis. In an SA setting, tuberculosis and progressive multifocal leucoencephalopathy due to JC virus infection are also important considerations in the setting of progressive brainstem disease.

With CNS invasion, listeriosis may target the meninges resulting in the typical clinical picture of acute/subacute bacterial meningitis,^[2] but unlike other bacteria may also target the brain parenchyma and specifically the rhombencephalon (pons, medulla, cerebellum). In humans, brainstem infection occurs in up to 11 - 24% of patients with CNS listeriosis.^[3,5] In LBE, it appears that food-borne bacteria invade the brainstem by retrograde axonal migration along the oropharyngeal cranial nerves.^[2] A postmortem study of nine human cases of LBE revealed brainstem microabscesses that were prominently distributed within the nuclei, tracts and intraparenchymal

portions of the cranial nerves innervating the oropharynx (V, VII, IX, X and XII).^[9] Injection of listerial bacteria into the facial nerves of mice was followed 5 - 10 days later by ipsilateral CNS deficits that were prevented by section of the nerve proximal to the inoculation site.^[10] Similarly, injection of listerial bacteria into the sciatic nerves of mice resulted in a flaccid paraparesis that was prevented by sectioning the sciatic nerve proximal to the inoculation site.^[10] Actin-dependent locomotion of *L. monocytogenes* along microtubules has been demonstrated in other eukaryote cells and remains the most plausible explanation for bacterial propagation along axons.^[11]

Factors predisposing to LBE in humans have not been identified. Unlike listerial meningitis, where two-thirds of patients are immunosuppressed by medication, advanced age or comorbid disease, LBE has been reported to occur mainly in immunocompetent adults.^[3] Of our patients, three had comorbid conditions such as immunosuppressant therapy, diabetes, alcoholism and HIV infection.

Of importance, CSF abnormalities in LBE are not typical of bacterial infections of the CNS, and one in five patients may have normal CSF on initial sampling.^[3] A relatively normal CSF glucose level, moderate lymphocytic pleocytosis and a moderately increased CSF protein level may mistakenly be attributed to viral or mycobacterial infection, or, as in one of our patients, to inflammatory demyelination.^[3-5] The CSF was normal in one of our patients, and patient 3 had a neutrophil-predominant mild pleocytosis.

In a review of patients with LBE by Armstrong and Fung,^[3] CSF Gram stains were positive in only 10% of cases, with CSF cultures positive in 33 - 41% and blood cultures in 61%. Positive cultures were

obtained in two of our six patients (two on blood, one on CSF).

MRI is the radiological investigation of choice in the diagnosis of brainstem disease. In our series, findings on MRI were abnormal in all patients studied (five scanned, see example in Fig. 2), and showed T2 signal change in the brainstem, cerebellar peduncles and cerebellum associated with variable enhancement on contrasted T1-weighted images. Computed tomography (CT) is less sensitive than MRI in LBE;^[3-5] two of five patients in this study had abnormal findings. Striking cranial nerve enhancement may be seen on MRI,^[12] or, less often, on CT, and was present in three of our six patients (two MRI, one CT). Radiological appearances are nonspecific, however, and in a region of high tuberculosis prevalence listerial brainstem abscesses may be radiologically indistinguishable from tuberculomas. In the absence of microbiological or histopathological confirmation, empiric treatment for both *L. monocytogenes* and *Mycobacterium tuberculosis* may have to be considered. Rapid radiological and clinical improvement would favour listeriosis over tuberculosis as the likely cause.

Supratentorial abscess formation may occur in conjunction with LBE and was present in patients 1 and 6 in our series.^[3,13] Following the prodrome and initial neurological deficit, patient 6 received high-dose corticosteroids for a presumed diagnosis of ADEM, after which disease progression appeared stable until abrupt deterioration on day 35. MRI showed left thalamic and parietal lobe abscess formation. A biopsy specimen of brain tissue for culture, obtained 5 days after starting intravenous ampicillin, was negative. The patient made a remarkable recovery.

High-dose ampicillin is the drug of choice. The recommended treatment is ampicillin 2 g IV 4-hourly for 21 days,^[14] although some authors suggest longer treatment periods and the addition of an aminoglycoside.^[15] Gentamicin acts synergistically with ampicillin and may be added in patients with immune impairment.^[3] Co-trimoxazole is an acceptable alternative in penicillin-allergic patients.^[14] It is important to note that third-generation cephalosporins, commonly recommended as first-line therapy for bacterial meningitis of unknown cause, have no activity against *Listeria* species.

Untreated patients invariably die,^[3-5] usually within 5 - 18 days after symptom onset.^[3] Treated survival rates of 49 - 64% have been reported.^[3,4] Early treatment with ampicillin is associated with improved survival (76%)

compared with delayed treatment or initial treatment with inappropriate antibiotics such as cephalosporins.^[3] Neurological dysfunction improves within 2 - 7 days of drug initiation.^[4] In our series, no patient suffered disabling sequelae.

Small epidemics of listeriosis from contaminated food sources are frequently reported in countries where the infection is notifiable, and the source of the contaminated food has often been identified. Given the high fatality rate of listeriosis, contaminated food is an important public health hazard. In SA, however, the disease is not notifiable at present. It is of interest that, as three patients in this series presented within 6 months of each other and came from geographically closely related areas, the infection may have been caused by a common contaminated food source.

References

- Freitag NE, Port GC, Miner MD. *Listeria monocytogenes* - from saprophyte to intracellular pathogen. *Nat Rev Microbiol* 2009;7(9):623-628. [http://dx.doi.org/10.1038/nrmicro2171]
- Disson O, Lecuit M. Targeting of the central nervous system by *Listeria monocytogenes*. *Virulence* 2012;3(2):213-221. [http://dx.doi.org/10.4161/viru.19586]
- Armstrong RW, Fung PC. Brainstem encephalitis (rhombencephalitis) due to *Listeria monocytogenes*: Case report and review. *Clin Infect Dis* 1993;16(5):689-702. [http://dx.doi.org/10.1093/cid/16.5.689]
- Uldry PA, Kuntzer T, Bogousslavsky J, et al. Early symptoms and outcome of *Listeria monocytogenes* rhombencephalitis: 14 adult cases. *J Neurol* 1993;240(4):235-242. [http://dx.doi.org/10.1007/BF00818711]
- Antal E-A, Dietrichs E, Löberg E-M, Melby KK, Maehlen J. Brain stem encephalitis in listeriosis. *Scand J Infect Dis* 2005;37(3):190-194. [http://dx.doi.org/10.1080/00365540410020938]
- Madarame H, Seuberlich T, Abril C, Zurbriggen A, Vandeveld M, Oevermann A. The distribution of E-cadherin expression in listeric rhombencephalitis of ruminants indicates its involvement in *Listeria monocytogenes* neuroinvasion. *Neuropathol Appl Neurobiol* 2011;37(7):753-767. [http://dx.doi.org/10.1111/j.1365-2990.2011.01183.x]
- Jubelt B, Mihai C, Li TM, Veerapaneni P. Rhombencephalitis/brainstem encephalitis. *Curr Neurol Neurosci Rep* 2011;11(6):543-552. [http://dx.doi.org/10.1007/s11910-011-0228-5]
- Moragas M, Martínez-Yélamos S, Majós C, Fernández-Viladrich P, Rubio F, Arbizu T. Rhombencephalitis: A series of 97 patients. *Medicine (Baltimore)* 2011;90(4):256-261. [http://dx.doi.org/10.1097/MD.0b013e318224b5af]
- Antal E-A, Löberg E-M, Dietrichs E, Maehlen J. Neuropathological findings in 9 cases of *Listeria monocytogenes* brain stem encephalitis. *Brain Pathol* 2005;15(3):187-191. [http://dx.doi.org/10.1111/j.1750-3639.2005.tb00519.x]
- Antal E-A, Löberg E-M, Bracht P, Melby KK, Maehlen J. Evidence for intraaxonal spread of *Listeria monocytogenes* from the periphery to the central nervous system. *Brain Pathol* 2001;11(4):432-438. [http://dx.doi.org/10.1111/j.1750-3639.2001.tb00411.x]
- Dons L, Jin Y, Kristensson K, Rottenberg ME. Axonal transport of *Listeria monocytogenes* and nerve-cell-induced bacterial killing. *J Neurosci Res* 2007;85(12):2529-2537. [http://dx.doi.org/10.1002/jnr.21256]
- Moro A, Albino PHDC, Bresciani AP, et al. Rhombencephalitis caused by *Listeria monocytogenes* with striking involvement of trigeminal nerve on MR imaging. *Arq Neuropsiquiatr* 2011;69(3):568-569. [http://dx.doi.org/10.1590/S0004-282X2011000400033]
- Soares-Fernandes JR, Bezele P, Cerqueira JJ, et al. Simultaneous supratentorial and brainstem abscesses due to *Listeria monocytogenes*. *J Neuroradiol* 2008;35(3):173-176. [http://dx.doi.org/10.1016/j.neurad.2007.07.009]
- Van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Advances in treatment of bacterial meningitis. *Lancet* 2012;380(9854):1693-1702. [http://dx.doi.org/10.1016/S0140-6736(12)61186-6]
- Mylonakis E, Hohmann EL, Calderwood SB. Central nervous system infection with *Listeria monocytogenes*: 33 years' experience at a general hospital and review of 776 episodes from the literature. *Medicine (Baltimore)* 1998;77(5):313-336. [http://dx.doi.org/10.1097/00005792-199809000-00002]

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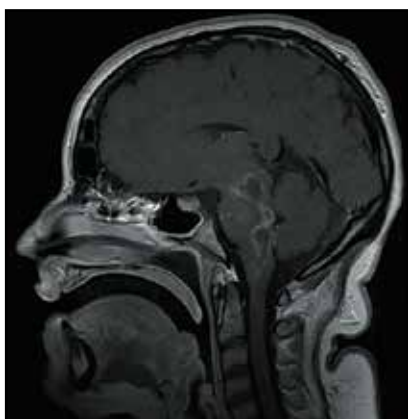


Fig. 2. Sagittal MRI brain scan (T1WI post gadolinium) of patient 4 showing rim-enhancing lesions in the brainstem. (MRI = magnetic resonance imaging.)