Bacterial meningitis in adults: clinical characteristics, risk factors and adjunctive treatment

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Chapter 3

Community-acquired *Listeria monocytogenes* meningitis in adults

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Abstract

Listeria monocytogenes is the third most common cause of bacterial meningitis. We prospectively evaluated 30 episodes of community-acquired *L. monocytogenes* meningitis, confirmed by culture of cerebrospinal fluid specimens, in a nationwide study in The Netherlands. Outcome was graded using the Glasgow outcome score; an unfavorable outcome was defined as a score of 1-4. All patients were immunocompromised or >50 years old. In 19 (63%) of 30 patients, symptoms were present for >24 h; in 8 patients (27%), symptoms were present for ≥4 days. The classic triad of fever, neck stiffness, and change in mental status was present in 13 (43%) of 30 patients. An individual cerebrospinal fluid indicator of bacterial meningitis was present in 23 (77%) of 30 cases. Gram staining of cerebrospinal fluid samples revealed the causative organism in 7 (28%) of 25 cases. The initial antimicrobial therapy was amoxicillin based for 21 (70%) of 30 patients. The coverage of initial antimicrobial therapy was microbiologically inadequate for 9 (30%) of the patients. The mortality rate was 17% (5 of 30), and 8 (27%) of 30 patients experienced an unfavorable outcome. Inadequate initial antimicrobial therapy was not related to outcome. In contrast with previous reports, we found that patients with meningitis due to *L. monocytogenes* do not present with atypical clinical features; however, typical cerebrospinal fluid findings predictive for bacterial meningitis might be absent. A high proportion of patients received initial antimicrobial therapy that did not cover *L. monocytogenes*.

Introduction

Bacterial meningitis is a serious and life-threatening disease. The estimated incidence is 4-6 cases per 100,000 adults per year in developed countries and is up to 10 times higher in less developed countries.[1, 2] *Streptococcus pneumoniae* and *Neisseria meningitidis* are the leading causes of bacterial meningitis in adults and cause 85% of all cases.[2, 3] *Listeria monocytogenes* is the third most frequent cause of bacterial meningitis.[2-5] This gram-positive bacillus is principally spread by contaminated food, which was discovered after outbreaks of listeriosis in the 1980s.[1,6-9] In the literature, meningitis due to *L. monocytogenes* is described as a disease in immunocompromised patients and elderly individuals, with high case-fatality rates (24%-62%);[1, 5, 10-17] however, all previous data on *Listeria meningitis* in adults were retrospective. We performed the first prospective nationwide cohort study in adults with community-acquired bacterial meningitis.[2] In this report, we describe the clinical features, complications, treatment, and outcome in adults with bacterial meningitis due to *L. monocytogenes* in this prospective case series.

Methods

In the Dutch Meningitis Cohort Study, a nationwide observational cohort study in The Netherlands, 696 episodes of community-acquired acute bacterial meningitis were assessed prospectively. All causative organisms were identified by CSF culture, which yielded *S. pneumoniae* in 352 episodes (51%), *N. meningitidis* in 257 (37%), *L. monocytogenes* in 30 (4%), and other bacteria in 57 (8%). Inclusion and exclusion criteria have been described elsewhere.[2] In summary, eligible patients were >16 years old, had bacterial meningitis confirmed by culture of CSF, and were listed in the database of The Netherlands Reference Laboratory for Bacterial Meningitis from October 1998 to April 2002. This laboratory provided daily updates of the names of hospitals where patients with bacterial meningitis had been admitted 2-6 days previously. The start of the cohort study was announced in the journal of the Dutch Neurological Society, with periodic reminders. Before the study started, all neurologists received information by mail about the study, including a case record form. For each patient, the treating physician was contacted, and informed consent was obtained from all participating patients or their legally authorized representatives. The Dutch Meningitis Cohort Study was approved by the ethics committee of the Academic Medical Center, University of Amsterdam (Amsterdam, The Netherlands).

Data registration was started at the time of inclusion. The study was undertaken in accordance with Dutch privacy legislation, and information was obtained via a case-record form. Patients receiving immunosuppressive drugs and patients with diabetes mellitus, alcoholism, asplenia, liver cirrhosis, end-stage renal disease, or HIV infection were judged to be immunocompromised. Persisting fever was defined as a body temperature of >38° C for >10 days after the start of appropriate antimicrobial treatment. Recurrent fever was defined as fever reoccurring after at least 1 afebrile day. Hyponatremia was defined as a plasma

sodium concentration <135 mmol/L. Patients underwent a neurological examination at discharge, and outcome was graded with the Glasgow outcome scale. This measurement scale is well validated, with scores varying from 1 (death) to 5 (good recovery). A favorable outcome was defined as a score of 5, and an unfavorable outcome was defined as a score of 1-4. Focal neurological abnormalities were divided into focal cerebral deficits (aphasia, monoparesis, or hemiparesis) and cranial nerve palsies. Causes of death were independently classified by 2 investigators (M.C.B. and D.v.d.B.) in 2 categories on the basis of criteria described in previous studies.[18, 19] These 2 categories were: (1) systemic causes, including septic shock, respiratory failure, multiorgan dysfunction, and cardiac ischemia; and (2) neurological causes, including brain herniation, cerebrovascular complications, intractable seizures, and withdrawal of care because of poor neurological prognosis. There were no differences in classification between clinicians.

The Mann-Whitney U test was used to identify differences between groups with respect to continuous variables, and dichotomous variables were compared with use of the $\chi 2$ test. All statistical tests were 2-tailed, and a P value of <0.05 was regarded as significant. Analyses were undertaken with SPSS software, version 12.0.1 (SPSS).

Results

In a 3.5-year period, 30 episodes of community-acquired *L. monocytogenes* meningitis were identified in 30 patients (Table 1). The calculated annual incidence was 0.07 cases per 100,000 adults. There was no seasonal pattern of occurrence of *L. monocytogenes* meningitis, although 5 (50%) of 10 episodes in immunocompetent patients occurred during the summer. Predisposing conditions were present in 21 (70%) of 30 patients; 20 (67%) of 30 patients were considered to be immunocompromised, and 1 patient had sinusitis (3%). All patients who were characterized as immunocompetent were >50 years old (Table 2). A previous episode of meningitis had occurred in 1 patient (3%). In 19 (63%) of 30 patients, symptoms were present for >24 h; in 8 (27%), symptoms were present for ≥4 days.

Classic symptoms and signs were present in most of the patients. The classic triad of neck stiffness, fever, and altered mental status was found in 13 (43%) of 30 patients. At least 2 of 4 symptoms and signs (classic triad plus headache) were present in 29 (97%) of the patients. One patient had a rash that was characterized as ecchymosis.

CT of the brain was performed at admission for 23 (77%) of 30 patients; the results were normal for 18 patients. Abnormalities were recorded for 5 patients (27%). Cerebral edema was present in 2 patients (9%), evidence of recent infarction was present in 1 patient (5%), lesions possibly indicating an infarction at an earlier date were present in 1 patient (5%), and atrophy was present in 2 patients (9%). Cranial CT was performed before lumbar puncture for 16 (70%) of the 23 patients; therapy was started before CT for only 5 (31%) of the patients. MRI of the brain was performed for 1 patient and revealed no abnormalities.

Lumbar puncture was performed for all patients. Opening pressure was recorded with a water-manometer for 8 (27%) of 30 patients; median pressure was 275 mm of water (range,

Table 1. Clinical and laboratory characteristics at admission to the hospital for 30 adults with community-acquired *Listeria monocytogenes* meningitis.

Characteristic	Frequency (%)	Characteristic	Frequency (%)
Mean age (SD)	65 (18)	Laboratory examination[a]	
Male gender	1530 (50%)		
Predisposing factors		Indices of CSF inflammations[b]	
Immunocompromised state	20/30 (67%)	Opening pressure mm of water	275 (150-400)
Pneumonia	1/30 (3%)	White cell count per mm3	620 (24-16003)
Otitis or sinusitis	1/30 (3%)	<100/mm^3	4/28 (13%)
Pretreated with antimicrobial agents	5/30 (17%0	100-999/mm^3	13/28 (46%)
Duration of symptoms <24 hours	11/30 (37%)	>999/mm^3	11/28 (39%)
Seizures	2/30 (7%)	Protein g/L	2.52 (1.1-19.3)
Symptoms upon presentation		CSF/serum glucose ratio	0.30 (0.03-0.86)
Headache	22/25 (88%)		
Nausea	20/24 (83%)	CSF Gram's stain	
Neck stiffness	22/30 (73%)	Negative	16/25 (60%)
Temperature ≥38° C	27/30 (90%)	Gram-positive rod	7/25 (46%)
Glasgow Coma Scale score upon presentation		Other[c]	2/25 (8%)
Median (SD)	12 (3)	Blood culture	
<14 (indicating altered mental status)	21/30 (70%)	*L. monocytogenes*	12/26 (46%)
		Other[d]	2/26 (8%)
<8 (indicating coma)	3/30 (10%)		
Triad of fever, neck stiffness, and change in mental status	13/30 (43%)	Erythrocyte sedimentation rate, mm per h	39 (10-242)
Focal neurologic deficits		C-reactive protein	117 (4-467)
Any	11/30 (37%)	Thrombocyte count per ml	186 (4-653)
Aphasia	7/25 (28%)	Hyponatremia	22/30 (73%)
Hemiparesis	2/30 (7%)		
Cranial nerve palsies	2/30 (7%)		
Ataxie	2/30 (7%)		

[a] Continuous data are denoted as the median value (range) unless otherwise stated. [b] CSF pressure was measured in 8 patients, CSF WBC count in 28, CSF protein concentration in 29, CSF/blood glucose ratio in 28, erythrocyte sedimentation rate in 25, C-reactive protein level in 22, and the thrombocyte count in 30.[c] Gram-negative bacteria in 2 patients. [d] *Streptococcus* and *Staphylococcus* species.

Table 2. Demographic and clinical characteristics of immunocompetent patients with *Listeria monocytogenes* meningitis.

Patient	Age, years	Sex	Duration of symptoms <24 hours	Classic triad of symptoms	Outcome
1	87	F	Yes	Absent	Death
2	65	M	No	Absent	Good recovery
3	90	F	Yes	Present	Good recovery
4	72	F	Yes	Absent	Good recovery
5	79	F	Yes	Present	Good recovery
6	58	M	No	Present	Good recovery
7	77	F	Yes	Absent	Good recovery
8	56	M	Yes	Present	Death
9	69	F	Yes	Absent	Good recovery
10	73	F	Yes	Absent	Good recovery

150- 400 mm of water), and 5 patients had very high pressure (>250 mm of water). At least 1 individual CSF finding indicative of bacterial meningitis (glucose concentration, <1.9 mmol/L; ratio of CSF glucose to blood glucose, <0.23; protein concentration, >2.20 g/L; WBC count, >2000 cells/mL; or CSF neutrophil count, >1180 cells/mL)[20] was found for 23 (77%) of 30 patients. There was no relation between low CSF leukocyte count and age or immunocompetence. Gram staining of CSF samples was performed for 25 (83%) of 30 patients and revealed no microorganisms in 16 (64%), gram-positive rods in 7 (28%), and gram-negative bacteria in 2 (8%).

Initial antimicrobial treatment consisted of penicillin or amoxicillin for 9 (30%) of 30 patients, a third-generation cephalosporin for 5 (17%), and a combination of amoxicillin and a third-generation cephalosporin for 8 (27%); other regimens were used for 8 patients (27%). In 21 episodes (70%), the initial therapy included penicillin or amoxicillin; a combination with aminoglycosids was given in 7 (23%) of the episodes. Nine (30%) of 30 patients received inappropriate initial antimicrobial therapy. Among these patients, the median time from admission to the hospital to receipt of adequate therapy was 3 days (range, 1-5 days). Adjunctive steroids were given in 5 episodes (17%); however, 3 patients had already used prednisone before admission to the hospital, and 1 patient received dexamethasone as treatment for an exacerbation of chronic obstructive pulmonary disease. In 1 additional patient, dexamethasone therapy was started after the patient experienced clinical deterioration.

Complications developed in a high proportion of patients (Table 3). Persisting fever was present in 11 (37%) of 30 patients. Subsequent lumbar punctures were performed for 3 patients, which all showed a decrease in CSF pleocytosis; CSF cultures had negative results for all patients. The cause of persisting fever was unknown in most patients (63%); other causes were pneumonia in 2 (18%), drug-related fever in 1 (9%), and sepsis in 1 (9%). Mean time to defervescence was 4.9 days (range, 1-18 days). Recurrent fever occurred in 11 episodes (37%); causes were unknown in 6 (54%), pneumonia in 3 (27%), and drugrelated fever in 2 (18%). During hospitalization, cranial CT scanning was repeated for 5 patients; 1 of these CT scans had abnormal findings, showing a subarachnoid hemorrhage.

Hyponatremia was found at admission to the hospital for 22 (73%) of 30 patients; 8 patients had severe hyponatremia (plasma sodium level, <130 mmol/L), and 14 patients had mild hyponatremia (plasma sodium level, <135 mmol/L). An additional 3 patients developed hyponatremia during hospitalization. Five (20%) of 25 patients were treated for hyponatremia; in 1 patient, this treatment consisted of fluid restriction.

Five (17%) of 30 patients in this cohort died. All of these patients died within 3 days after admission to the hospital, and all patients who died were 1>55 years old. Two of these 5 patients died of systemic complications, and 3 patients died of neurological complications. One patient died following a subarachnoid hemorrhage 1 day after admission to the hospital. Neurological examination was performed at discharge from the hospital for all 25 surviving patients and revealed cranial nerve palsies in 2 (8%) and focal cerebral deficits in 2 (8%). No patients had hearing impairment. In a univariate analysis, predictors for an unfavorable outcome were a low score on the Glasgow coma scale at admission to the hospital (p=0.015)

Table 3. Complications during hospitalization and outcome for patients with Listeria monocytogenes meningitis.

Characteristic	Frequency (%)
Complication	
Seizures	6/30 (20)
Cardiorespiratory failure	10/30 (33)
Receipt of mechanical ventilation	7/30 (23)
Sepsis	5/30 (17)
Hyponatremia	25/30 (83)
Recurrent fever	11/28 (39)
Persisting fever	11/30 (37)
Impaired consciousness	12/30 (40)
Other complications[a]	7/30 (23)
Outcome	
Score on the Glasgow outcome scale	
1 (death)	5/30 (17)
2 (vegetative state)	0/30 (0)
3 (severe disability)	1/30 (3)
4 (moderate disability)	2/30 (7)
5 (mild or no disability)	22/30 (73)
Sequelae at discharge	
Hemiparesis	2/25 (8)
Cranial nerve palsy[b]	2/25 (8)

[a] Other complications included pneumonia in 3 (10%) patients, drug-related fever in 2 (7%), alcohol abstinence delirium in 1 (3%), and joint pain in 1 (3%). [b] Trochlear and facial nerve palsy each occurred in 1 patient.

and a low platelet count (p=0.024). Of the 9 patients who received microbiologically inadequate initial antimicrobial therapy, 2 (22%) of died; the other 7 patients had favourable outcomes.

Discussion

Our findings show that meningitis due to *L. monocytogenes* is a disease that occurs among immunocompromised patients and elderly individuals. This corresponds with previous reports, which describe *L. monocytogenes* infection in patients with impaired cellular immunity (e.g., attributable to immunosuppressive therapy, immunosenescence, diabetes, or malignancies).[23, 24] *L. monocytogenes* meningitis in young, previously healthy adults has been reported only in anecdotal observations.[11, 14] In a large literature review including all case series and case reports, this group constitutes only 6% of patients with *L. monocytogenes* CNS infection.[14] In our series, all patients were either immunocompromised or >50 years old.

Symptoms and signs of patients presenting with *L. monocytogenes* meningitis were not different from those found in the general population of patients with community-acquired bacterial meningitis. The prevalence of the classic triad of fever, neck stiffness, and altered mental status was 43%, and almost all patients presented with at least 2 of the 4 classic symptoms of headache, fever, neck stiffness, and altered mental status. Similar prevalences

have been reported in the general population of patients with bacterial meningitis.[2, 21] This is in contrast with previous reports, which stressed the importance of the atypical presentation of patients with *L. monocytogenes* meningitis.[14, 22] This difference may well be explained by the retrospective design of these previous studies. This is the first prospective study of *L. monocytogenes* meningitis to date. Concordant with previous reports was the subacute development of disease in most cases.[14, 22] In a large proportion of patients, symptoms were present for ≥4 days (27%).

A high proportion of adults with *L. monocytogenes* meningitis had atypical CSF findings; 23% of the patients had no individual CSF findings indicative of bacterial meningitis. In addition, Gram staining had a low yield. The causative microorganism was revealed by Gram staining in only 24% of patients. The atypical CSF findings and the low yield of Gram staining have been described previously in *L. monocytogenes* meningitis.[3, 14]

Guidelines for suspected bacterial meningitis recommend amoxicillin-based empirical antimicrobial therapy for patients aged >50 years old or with risk factors to cover *L. monocytogenes*, because this bacterium is resistant to cephalosporins.[25, 26] Most patients in our case series received empirical therapy, including amoxicillin (70%). However, a considerable proportion of patients received third-generation cephalosporin monotherapy (27%). The median delay before these patients received adequate antimicrobial therapy was 3 days. This delay, however, was not associated with an unfavorable outcome. Although speculative, the absence of a relation between delay of adequate therapy and outcome might be explained by the limited number of patients included in the study. Another explanation could be the subacute development of disease in patients with *L. monocytogenes* meningitis. If meningitis due to *L. monocytogenes* is proven, either by Gram stain or CSF culture, we advise that patients be treated with amoxicillin, administered at a dosage of 2 g every 4 h for at least 21 days.[22, 25, 27-29]

A clinical trial showed a beneficial effect of early dexamethasone treatment in adults with bacterial meningitis.[30] A recent meta-analysis confirmed these results.[31] Although 5 patients in our case series were eventually treated with steroids, none received adjunctive dexamethasone according to current guidelines.[25] Immunocompromised patients were excluded from the studies of adjunctive dexamethasone;[30, 31] therefore, these patients should not receive dexamethasone. Dexamethasone treatment is indicated for most patients with suspected bacterial meningitis; however, it remains unclear whether dexamethasone has beneficial effects in *L. monocytogenes* meningitis.

Our study has several important limitations. First, only patients who had a positive CSF culture result were included. Negative CSF culture results occur in 11-30% of patients with bacterial meningitis, and this rate may be even higher among patients with *L. monocytogenes* meningitis, although exact figures are unknown.[2, 3, 13, 22] However, the clinical presentation of patients with positive and negative CSF culture results was closely similar in several studies.[3, 5, 24] Furthermore, patients with space-occupying lesions visible on CT may not undergo lumbar puncture.[26] Brain abscesses are found in 5% of *L. monocytogenes* infections of the CNS.[14] In patients with coagulation disorders or severe septic shock, lumbar puncture

might be postponed, which can result in CSF cultures with negative results, as well.[25] Therefore, these patient groups were probably only partly represented in our study.

We describe, to our knowledge, the first patient with a subarachnoid hemorrhage as a complication in *L. monocytogenes* meningitis. Subarachnoid hemorrhage is known to be a rare complication of tuberculous meningitis, actinomycotic meningitis, and bacterial meningitis due to *S. pneumoniae*, but it has never been described in *L. monocytogenes* meningitis.[32-34] Another interesting observation in our study was the high rate of patients with hyponatremia (83%). Although high rates of hyponatremia are known from case series of tuberculous and group A streptococci meningitis, this has not been described in *L. monocytogenes* meningitis.[35, 36] Probable causes of hyponatremia are the syndrome of inappropriate antidiuretic hormone secretion and the cerebral salt wasting syndrome.[37, 38] The appropriate treatment for syndrome of inappropriate antidiuretic hormone secretion—fluid restriction—is opposite from the usual treatment of hyponatremia caused by cerebral salt wasting syndrome. Differentiation between the syndromes, however, is difficult. In children with bacterial meningitis and hyponatremia, fluid restriction does not improve either brain edema or outcome.[39] Current guidelines recommend that treatment of adults with bacterial meningitis should aim for a normovolemic state .[25]

In conclusion, our study showed that *L. monocytogenes* meningitis is found in immunosuppressed patients and elderly individuals. Patients presented with signs and symptoms that were similar to those of the general population with bacterial meningitis, albeit with a longer prodromal phase. Despite frequent complications during hospitalization, the associated mortality rate was relatively low.

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