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ARTICLE

The clinical features, diagnosis, treatment, and prognosis of neuroinvasive listeriosis: a multinational study

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Abstract The aim of this study was to determine the independent risk factors, morbidity, and mortality of central nervous system (CNS) infections caused by *Listeria monocytogenes*. We retrospectively evaluated 100 episodes of neuroinvasive listeriosis in a multinational study in 21 tertiary care hospitals of Turkey, France, and Italy from 1990 to 2014. The mean age of the patients was 57 years (range, 19–92 years), and 64% were males. The all-cause immunosuppression rate was 54 % (54/100). Forty-nine (49 %) patients were referred to a hospital because of the classical triad of symptoms (fever, nuchal rigidity, and altered level of consciousness). Rhombencephalitis was detected radiologically in 9 (9 %) cases. Twenty-seven (64 %) of the patients who had cranial magnetic resonance imaging (MRI) performed had findings of meningeal and parenchymal involvement. The mean delay in the initiation of specific treatment was 6.8±7 days. Empiric treatment was appropriate in 52 (52 %) patients. The mortality rate was 25 %, while neurologic sequelae occurred in 13 % of the patients. In the multivariate analysis, delay in treatment [odds ratio (OR), 1.07 [95 % confidence interval (CI), 1.01–1.16]] and seizures (OR, 3.41 [95 % CI, 1.05–11.09]) were significantly associated with mortality. Independent risk factors for neurologic sequelae were delay in treatment (OR, 1.07 [95 % CI, 1.006–1.367]) and presence of bacteremia (OR, 45.2 [95 % CI, 2.73–748.1]). Delay in the initiation of treatment of neuroinvasive listeriosis was a poor risk factor for unfavorable outcomes. Bacteremia was one of the independent risk factors for morbidity, while the presence of seizures predicted worse prognosis. Moreover, the addition of aminoglycosides to ampicillin monotherapy did not improve patients' prognosis.

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Introduction

*Listeria monocytogenes*is a Gram-positive, facultatively anaerobic, intracellular bacterium that causes invasive disease in humans and animals. An important foodborne pathogen, *L. monocytogenes* has a specific affinity for the central nervous system (CNS), especially in cell-mediated immunodeficient individuals [1]. This species' ability to penetrate the intestinal, blood–brain, and fetoplacental barriers is one of its most important virulence factors [2]. Although the exact mechanism is unknown, *L. monocytogenes* is thought to cause infection via the neural retrograde (in rhombencephalitis) and hematogenous (in meningitis and encephalitis) routes [2–4]. In one US study, *L. monocytogenes* was reportedly the cause of nearly 4 % of the cases of bacterial meningitis [5]; it also ranked as the fourth most common etiologic agent of encephalitis in a study from France [6]. Rhombencephalitis, a progressive dysfunction of the brain stem, can also be caused by *L. monocytogenes* and has been reported as a case series in the literature [7, 8].

Very few cases of neuroinvasive listeriosis have been reported [9–13]. To the best of our knowledge, this study evaluated the largest number of cases with neuroinvasive listeriosis to date. We analyzed the epidemiological, clinical, laboratory, radiological, and therapeutic characteristics of 100 cases with neuroinvasive listeriosis derived from 21 centers in three different countries and investigated their impact on neurologic sequelae and mortality. We also compared our results with those of cohort groups previously published in the medical literature.

Methods

This study was designed as a retrospective cohort study including 100 cases with neuroinvasive listeriosis derived from 21 centers in Turkey, Italy, and France. The study criteria included the following: (1) patients with any clinical forms of meningitis, meningoencephalitis, rhombencephalitis, and/or brain abscess; (2) patients whose cerebrospinal fluid (CSF)and/or blood cultures grew *L. monocytogenes*; and (3) patients who were followed up in the aforementioned three countries from 1990 to 2014. A standard data-recording form was prepared and sent to the collaborating centers by email. This form recorded demographic and clinical characteristics (symptoms on admission and their duration), laboratory findings (complete blood count, CSF microbiological and biochemical results, and blood culture results), radiological features [computed tomography (CT) and magnetic resonance imaging (MRI)], and therapeutic data (initial empiric treatment, specific treatment, and treatment duration). These parameters were evaluated to determine the independent risk factors predicting neurologic sequelae and mortality.

Definition of neuroinvasive listeriosis

Cases in which *L. monocytogenes* was isolated from the CSF and/or blood culture and included signs of meningeal irritation, pleocytosis [white blood cell (WBC) count >10/μL] in the CSF, hypoglycorrhachia (CSF glucose <40 mg/dL) or CSF glucose/blood glucose <60 %, or increased CSF protein level (>45 mg/dL). Encephalitis was defined as the presence of an altered level of consciousness, epileptic seizures, focal neurologic deficits, or radiographic parenchymal involvement. Rhombencephalitis was defined as the involvement of the mesencephalon, pons and/or cerebellum based on cranial MRI, cranial nerve involvement or cerebellar signs (ataxia, tremor), or the development of hemiparesis [14].

Definition of immunosuppression

The presence of hematologic malignancy, solid organ transplantation, diabetes mellitus, chronic renal failure, alcoholism, cirrhosis, human immunodeficiency virus (HIV) infection, history of corticosteroid use, chemotherapy, or monoclonal antibody use.

Definition of neurological signs

The classical triad of fever, nuchal rigidity, and altered level of consciousness. The presence of focal neurologic signs was defined as cranial nerve involvement (diplopia, anisocoria,

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ptosis, dysphagia, or facial hypoesthesia), hemiparesis, and cerebellar involvement (dysarthria, ataxia, or ataxic gait).

Hyponatremia

Serum sodium (Na) level <135 mmol/L.

Epileptic seizures

Convulsions on admission and during patient follow-up.

Radiological signs

The presence of only hydrocephalus on CT scan or the presence of both hydrocephalus and parenchymal involvement on MRI.

Delay in treatment

The period of time from the beginning of symptoms until the day on which treatment with an appropriate antibacterial agent at the proper dose was initiated.

Appropriate empiric treatment

The use of any of the following agents: ampicillin, penicillin, meropenem, or ampicillin–sulbactam plus an aminoglycoside.

Adjuvant corticosteroid therapy

A dose of >5 mg/day of prednisolone or an equivalent dose of another corticosteroid used for the underlying disease.

Unfavorable clinical outcomes

Neurological sequelae were defined as signs detected in the first outpatient visit after discharge from the hospital. Mortality was defined as death within 2 months after the first admission. The neurological sequelae and mortality risk factors are summarized in Table 1.

Statistical analysis

For the evaluation of the predictors of neurologic sequelae or mortality, the Chi-square test was used for categorical variables, whereas Fisher's exact test, Student's *t*-test, and the Mann–Whitney *U*-test were used for categorical, normally distributed, and non-normally distributed variables, respectively. Multivariate logistic regression analysis was performed to identify independent predictors of neurological sequelae and mortality in patients with neuroinvasive listeriosis. The Hosmer–Lemeshow test was used to determine the overall fit of the model. All statistical tests were two-tailed. Conditions in which the type 1 error rate was <5 % were considered statistically significant. Analyses were performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL).

Results

Patients

A total of 100 cases with *Listeria* meningitis derived from 21 centers in Turkey, Italy, and France were involved in our study. The mean age of the patients was 57 years (range, 19–92 years), and 64 % of the patients were male. The all-cause immunosuppression rate was 54 %. We detected the following underlying immunosuppressive conditions (in order of frequency): 43 % (23/54) were prescribed corticosteroids, 16 % (9/54) had alcoholism or cirrhosis, 13 % (7/54) had an underlying hematologic malignancy, 9 % (5/54) had uncontrolled diabetes mellitus, 9 % (5/54) had undergone chemotherapy due to a solid organ tumor, 5 % (3/54) had undergone renal transplantation, 1 % (1) had active HIV infection, and 1 % (1) had chronic renal failure.

Clinical findings

The mean duration of symptoms of the patients before admission to the hospital was 5.1 days (range, 1–30 days). Thirty-seven (37 %) patents were admitted to the hospital within the

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Table 1 Univariate analysis of the risk factors for mortality or severe neurological sequelae due to neurolisteriosis

	Death*			Neurological sequelae		
Variable	No	Yes	*p*-Value	No	Yes	*p*-Value
No. of patients	75	25		62	13	
Age (years)	51±17	54±14.5	0.73	60 (23–89)	57 (19–79)	0.15
Gender (male)	49 (65 %)	15 (60 %)	0.63	44 (71 %)	5 (39 %)	**0.05**
Predisposing factors	32 (42.7 %)	18 (72 %)	0.01	24 (38.7 %)	8 (62 %)	0.21
Immunocompromised conditions*						
Delay in proper initial treatment (days)	5 (2–26)	8 (4–32)	0.03	4 (1–25)	6 (2–26)	**0.014**
Symptoms on admission						
Classical triad	31 (41 %)	18 (72 %)	0.008	26 (42 %)	5 (39 %)	0.81
Fever	71 (94.7 %)	25 (100 %)	0.56	60 (97 %)	11 (85 %)	0.13
Altered sensorium	47 (62 %)	23 (92 %)	0.06	37 (60 %)	10 (77 %)	0.34
Nuchal rigidity	56 (74.7 %)	19 (74 %)	0.89	49 (79 %)	7 (54 %)	0.08
Headache	73 (97.3 %)	24 (96 %	1.00	61 (98 %)	12 (92 %)	0.31
Focal neurologic findings	19 (25.3 %)	12 (48 %)	0.03	7 (11 %)	12 (92 %)	**0.00**
Seizures	17 (24.6 %)	14 (58 %)	0.03	10 (18 %)	7 (54 %)	**0.012**
CSF findings						
WBC count	535 (80–4,000)	285 (50–1,000)	0.51	833±1042	730±867	0.22
Pleocytosis (neutrophilic)	35 (76 %)	16 (84.2)	0.74	29 (81 %)	6 (60 %)	0.22
Protein level (g/L)	188±98.2	229±100	0.32	196±110	211±136	0.09
Glucose	44.6±24	54.8±29	0.60	35 (1.7–126)	45 (0–100)	0.25
Gram stain (Gram-positive rods)	14 (27 %)	3 (14 %)	0.36	10 (25 %)	4 (33 %)	0.71
Positive culture	68 (76 %)	88 (58 %)	0.55	59 (97 %)	9 (69 %)	**0.007**
Blood parameters						
WBC count (/mm^3)	14,250±7,763	14,762±5,642	0.53	13,377±7,280	11,282±5,800	0.37
Hemoglobin (g/dl)	12.7±1.6	12.1±2.7	0.85	12.8±1.7	11.9±1.8	0.18
Platelet count (/mm^3)	182,520±76,452	249,800±100,154	0.21	179,580±74,230	181,270±50,829	0.94
C-reactive protein (mg/L)	111±85	115±82	0.87	102±85	144±80	0.13
Hyponatremia (Na <135 meq/L)	14 (30 %)	13 (68 %)	0.04	7 (18 %)	7 (78 %)	**0.001**
Positive culture	26 (34 %)	9 (36 %)	0.90	14 (22 %)	12 (92 %)	**0.001**
Focal neurological findings						
Cranial nerve palsies	14 (19 %)	5 (20 %)	0.08	4 (7 %)	10 (77 %)	**0.001**
Hemiparesis	9 (12 %)	5 (20 %)	0.33	2 (3 %)	7 (54 %)	**0.001**
Cerebellar dysfunction	11 (12 %)	5 (20 %)	0.53	3 (5 %)	8 (62 %)	**0.001**
CT and/or MRI parameters						
Parenchymal involvement (MRI)	21 (64 %)	7 (78 %)	0.44	11 (50 %)	10 (91 %)	**0.04**
Hydrocephalus	5 (14 %)	5 (31 %)	0.14	2 (7 %)	3 (38 %)	**0.06**
Rhombencephalitis	7 (19 %)	16 (20 %)	0.22	1 (2 %)	4 (80 %)	**0.03**
Treatment						
Ampicillin/penicillin monotherapy	38 (51.4 %)	13 (56.5 %)	0.66	37 (61 %)	1 (8 %)	–
Ampicillin+gentamicin therapy	36 (47 %)	10 (43 %)	0.41	24 (39 %)	12 (92 %)	
Concomitant steroid therapy	34 (45 %)	9 (36 %)		28 (45 %)	6 (46 %)	0.94

CSF cerebrospinal fluid, *CT* computed tomography, *MRI* magnetic resonance imaging, *WBC* white blood cell

*All of the deaths occurred within 1 month except in two patients (times to death were days 47 and 56, respectively)

first 2 days of showing symptoms, 50 (50 %) patients in the first 2–7 days, and 13 (13 %) patients in the first 7 or more days. Forty-nine (49 %) patients presented with the classical triad of symptoms on admission to the hospital. Neck stiffness was present in 75 (75 %) of the cases. Thirty-one (31 %) cases presented with focal neurologic signs. Additional findings included coma at the time of presentation in 7 (7 %) cases, pneumonia in 3 (3 %) cases, diarrhea in 3 (3 %) cases,

diverticulitis in 2 (2 %) cases, and maculopapular rash in 1 (1 %) case. Nineteen (19 %) patients had at least one cranial nerve paralysis, and 5 (5 %) cases had multiple cranial nerve paralysis. Involvement of the sixth and seventh cranial nerves was the most common, appearing in 9 (9 %) patients each. Other nerves involved included the third, ninth, and tenth cranial nerves. Additionally, patients presented with focal neurological symptoms, including hemiparesis in 13 (13 %) patients, aphasia and dysarthria in 12 (12 %) patients, and ataxia in 6 (6 %) patients. Thirty-one (31 %) patients presented with epileptic seizures. Twenty-nine (29 %) cases required mechanical ventilation during clinical follow-up, 19 (66 %) of whom died. Nine (9 %) cases had rhombencephalitis, 8 (89 %) of whom were≤60 years of age (p=0.020) and 4 (45 %) of whom had neurological sequelae (p=0.003). Nearly 80 % (7/9) of the cases had no underlying disease.

Laboratory findings

Lumbar puncture was performed in 97 % of the cases. The mean leukocyte count was 1,051 cells/mL, and 79 % (51/65) of the cases had neutrophilic pleocytosis. The mean CSF glucose was 39 mg/dL (range, 0–130 mg/dL) and the mean CSF protein count was 234 mg/dL (range, 30–2,196 mg/dL). Gram staining revealed microorganisms in 23 % (17/73) of the cases in which Gram stain results were recorded. The mean WBC count was 13,100 cells/mm^3 (range, 1,690–36,900 cells/mm^3), the mean hemoglobin level was 12.6 mg/dL (range, 7.9–16 mg/dL), the mean platelet count was 188,000 cells/mm^3 (range, 29,000–455,000 cells/mm^3), the erythrocyte sedimentation rate (ESR) was 60 mm/h (range, 6–136 mm/h), and the C-reactive protein (CRP) count was 112 mg/L (range, 5–330 mg/L). Although CSF cultures grew *L. monocytogenes* in 90 % of the cases, only 35 cases had bacteremia. Hyponatremia (serum Na <135 mmol/L) was present in 41 % (27/66) of the cases in which serum sodium levels were recorded.

Cranial CT and MRI were performed in 63 (63 %) and 43 (43 %) cases, respectively. Whereas no involvement was detected by CT imaging in 44 (70 %) of the patients who had CT imaging performed, 9 (14 %) had parenchymal involvement, 6 (10 %) had hydrocephalus, 3 (5 %) had vascular phenomena (acute/subacute infarct and hemorrhage), and only 1 (2 %) had meningeal contrast enhancement. Twenty-seven (63 %) patients who underwent cranial MRI had findings of meningeal and parenchymal involvement. Hydrocephalus was present in 19 % of the cases in whom both types of cranial imaging were performed (CT and MRI).

Treatment

The mean delay in the initiation of specific treatment was 6.8± 7 days. Empiric treatment was appropriate in 52 (52 %) patients. Ampicillin monotherapy and ampicillin–gentamicin combination therapy were preferred for definitive therapy in 51 (51 %) and 46 (46 %) patients, respectively. Three (3 %) patients received meropenem for treatment. Adjuvant corticosteroid therapy was given in 43 (43 %) cases. The median duration of treatment was 21 days (range, 1–90 days). Combination therapy was preferred in 87.5 % (7) of the cases with rhombencephalitis (p=0.025). There was no significant difference in treatment modalities (monotherapy or combination therapy) in patients with mental status changes or a requirement for mechanical ventilation (p=0.92 and p=0.063, respectively).

Predictors of mortality and neurologic sequelae

A number of risk factors were statistically significant for both mortality and the development of neurologic sequelae in the univariate analysis (Table 1). In the multivariate analysis, delay in treatment [odds ratio (OR), 1.07 [95 % confidence interval (CI), 1.01–1.16]] and epileptic attack (OR, 3.41 [95 % CI, 1.05–11.09]) were significantly associated with mortality (Table 2). Delay in treatment (OR, 1.07 [95 % CI, 1.006–

Table 2 Binomial logistic regression analysis of independent risk factors for mortality or severe neurological sequelae in patients with neurolisteriosis

	Death (n=25)		Neurological sequelae (n=13)	
Variable	OR (95 % CI)	p-Value	OR (95 % CI)	p-Value
Age (years)	1.01 (0.97–1.04)	0.44	0.93 (0.86–1.01)	0.12
Gender (male)	1.286 (0.43–3.80)	0.65	0.60 (0.07–5.23)	0.64
Classical triad	3.22 (0.93–11.07)	0.06	–	
Immunocompromised conditions	3.43 (0.92–12.7)	0.06	0.07 (0.004–1.56)	0.09
Delayed initiation of treatment	1.07 (1.01–1.16)	**0.04**	1.07 (1.006–1.367)	**0.042**
Focal neurological findings	1.57 (0.47–5.18)	0.45	–	
CSF culture positivity	–		0.80 (0.08–7.60)	0.85
Bacteremia	–		45.2 (2.73–748.1)	**0.008**
Seizures	3.41 (1.05–11.09)	**0.04**	–	
Treatment (combination)	–		5.35 (0.38–74.7)	0.21

CI confidence interval, *CSF* cerebrospinal fluid, *OR* odds ratio

1.367]) and the presence of bacteremia (OR, 45.2 [95 % CI, 2.73–748.1]) were independent risk factors for neurologic sequelae. A delay in treatment of 7 or more days significantly increased the risk of mortality (p=0.011) and the risk of development of neurologic sequelae (p=0.042).

Discussion

The finding that the clinical picture of neuroinvasive listeriosis may differ from that of community-acquired purulent meningitis is controversial [13, 15]. Studies have emphasized that neck stiffness occurs less commonly, whereas focal neurologic deficits and epileptic seizures develop more frequently, in patients with neuroinvasive listeriosis compared to those with community-acquired purulent meningitis [10]. In our study, headache (97 %), fever (96 %), and neck stiffness (75 %) were detected in most cases, and the classical triad was present in nearly half of the cases. Focal neurological deficits and epileptic seizures occurred in 31 % of cases. In a German prospective cohort study evaluating 696 cases of bacterial meningitis, the classical triad was reported in 44 % of the cases [16]. Additionally, the presence of focal neurological signs was reported in 33 % of cases, which was similar to the rate in our study. The frequency of the complete classical triad was also similar in immunosuppressed cases and patients older than 50 years of age. These data demonstrate that the possibility of atypical presentation in neuroinvasive listeriosis (with the exception of rhombencephalitis) was no different from that in other bacterial meningitis cases.

Epileptic seizures developing within the first 24 h were found to be an independent risk factor for mortality in another study involving 493 cases of acute bacterial meningitis, in which 10 % were due to *L. monocytogenes* [17]. The presence of epileptic seizures was an independent predictor for mortality in two other studies; other risk factors included hydrocephalus, advanced age, inappropriate antibiotic therapy, and combination therapy with aminoglycosides [10–12, 18].

Despite the high yield (67–90 %) of CSF Gram staining performed under suitable conditions in bacterial meningitis, the rates are significantly lower (nearly 30 %) in cases of neuroinvasive listeriosis [19, 20]. In our study, Gram staining revealed the causative agent in ~25 % (17/73) of the cases. In a case series of neuroinvasive listeriosis, the rate of hyponatremia ranged between 44 and 73 %. Although the presence of hyponatremia (41 %; 27/66) was found to be a risk factor for both mortality and neurologic sequelae in the univariate analysis, we did not include hyponatremia in our multivariate analysis because serum sodium levels were not recorded in the majority of cases. In another series examining neuroinvasive listeriosis, cranial CT was performed in 7–91 % of the cases, but very few patients were reported to have cranial involvement on MRI [10, 11, 13]. Two possible reasons for this finding may be the inclusion of old cases when MRI was not widely used or that cranial CT was considered sufficient for the diagnosis. In those series, abnormal findings from cranial CT were present in 23–27 % of the cases, particularly focal involvement or hydrocephalus. Newly developed infarcts and hemorrhage were specifically reported in very few cases. In our study, no involvement was detected in the cranial CT imaging of 44 patients (70 % of those who had CT imaging). However, it was remarkable that significant radiologic involvement was detected in 64 % of patients who underwent cranial MRI. Moreover, eight patients whose cranial CT imaging was reported to be normal had significant radiologic involvement on cranial MRI. Therefore, we propose that cranial MRI is superior to cranial CT scanning in patients with neuroinvasive listeriosis.

Antimicrobial therapy in community-acquired meningitis is recommended empirically according to the age and immunosuppression status of the patient. Ampicillin is recommended if the patient is <1 month or >50 years of age, and particularly if the patient is immunosuppressed [21]. Inappropriate initial empiric treatment was reported in 30 % of cases in a prospective series of 30 cases with neuroinvasive listeriosis [13]. Interestingly, in another prospective study investigating 43 cases of neuroinvasive listeriosis (out of 278 patients with community-acquired acute bacterial meningitis), inappropriate initial empiric treatment was only prescribed in 3 % of the listeriosis cases [11]. In contrast, in the present study, the rate of inappropriate initial treatment was nearly 50 %. Despite the retrospective nature of our study, we believe that these findings better describe real-life data. The increased inappropriate antibiotic usage was related to the failure of the physicians to consider neuroinvasive listeriosis in the differential diagnosis. For this reason, adults >50 years of age should receive an antimicrobial agent with activity against *L. monocytogenes* as part of the empiric regimen, regardless of their immunocompromised status.

The optimal therapeutic regimen and its optimal duration for the treatment of CNS infections caused by *L. monocytogenes* have not been definitively defined. *L. monocytogenes* is very sensitive to penicillin G and ampicillin in vitro. Additionally, increased bactericidal activity in susceptibility tests with streptomycin or gentamicin combinations have encouraged physicians to prefer combination treatment [22, 23]. Case reports have been published of patients treated with trimethoprim–sulfamethoxazole, meropenem, or linezolid [24, 25]. For example, combination regimens (ampicillin plus an aminoglycoside versus ampicillin/amoxicillin plus cotrimoxazole) for treatment were compared in a study that included 22 cases of meningitis caused by *L. monocytogenes* who were admitted to the intensive care unit. Combination regimens including cotrimoxazole have been reported to be more effective [26]. In another retrospective study investigating 102 listeriosis cases, the mortality rate

was reported to be increased in the gentamicin group compared to the monotherapy group [27]. In our study, combination therapy had no remarkable effect on morbidity and mortality rates. Thus, tailoring neuroinvasive listeriosis treatment to the individual and his or her evolving clinical condition is necessary. The duration of uncomplicated meningitis treatment should not be less than 3 weeks, and brain abscesses, encephalitis, or rhombencephalitis should be treated for at least 6 weeks with careful radiological monitoring [10, 23, 28]. In our study, the median duration of treatment was 21 days (range, 1–90 days) in surviving patients. Seven (78 %) rhombencephalitis patients were treated for longer than 6 weeks. Early transition to oral therapy is another controversial issue due to the high morbidity and mortality of the infection [29]. In our study, cotrimoxazole and linezolid therapy was used as subsequent oral therapy in two patients, who were treated for 70 and 90 days, respectively.

Adjuvant steroid therapy has been shown to be beneficial in treating pneumococcal meningitis, suggesting its potential use for treating other forms of bacterial meningitis [30]. However, in our study, corticosteroid treatment for other underlying diseases made a definitive conclusion difficult in neuroinvasive listeriosis cases. Koopmans et al. reported that adjuvant steroid use for the treatment of neuroinvasive listeriosis had no favorable effect on mortality and morbidity. However, it must be noted that the authors of this study evaluated two cohorts followed for different time periods and that the number of patients in the adjuvant steroid therapy group was lower (n=5) than the number of patients in the other group (n=44). In our study, adjuvant steroid therapy had no remarkable effect on morbidity and mortality rates (p=0.41).

Rhombencephalitis is characterized by the progressive dysfunction of the brain stem [7, 8, 14]. Apart from bacterial agents such as *Brucella* spp. and *Mycobacterium tuberculosis* causing chronic meningitis, only *L. monocytogenes* causes this clinical picture. Initial symptoms, including headache, fever, nausea, and vomiting, may progress to respiratory insufficiency, convulsions, hemiparesis, and, occasionally, cerebellar involvement. Although CSF examination does not aid in the diagnosis, contrast-enhanced MRI may reveal brain stem involvement. Rhombencephalitis is usually a disease of young patients without any predisposing factors. Only two of our patients had a history of corticosteroid use for the underlying diseases of interstitial pneumonia and rheumatoid arthritis. Focal neurologic deficits were previously shown to develop more commonly in this patient group [7, 10, 14]. Our results are in agreement with this finding (p=0.004).

In this study, mortality occurred in 25 % of cases and neurologic sequelae occurred in 13 %. Nosocomial infection-related deaths were not reported for our patients. In this study, we present a detailed evaluation of the prognosis (as mortality and neurologic sequelae) of neuroinvasive listeriosis. In large-scale studies conducted to date, immunosuppression and

Table 3 Demographics, clinical information, treatment characteristics, and mortality predictors of central nervous system (CNS) listeriosis: case series from the literature

Reference literature	Mylonakis et al. [10] (1964–1997) (44 patients)	Brouwer et al. [13] (1998–2002) (30 patients)	Amaya-Villar et al. [11] (39 months) (46 patients)	Dzupova et al. [9] (1997–2012) (31 patients)	Pelegrín et al. [12] 1977–2009 (59 patients)	Our series (1990–2014) (100 patients)
Immunocompromised (%)	48	67	67	61	39	54
Median or mean age in years (median or mean±SD; range in parentheses)	49 (16–85)	65 (25–90)	69±30	63 (26–80)	64 (24–94)	57 (19–92)
Lack of meningeal signs (%)	42	8	30	29	22	25
Monotherapy/combination (%)*	38/19	70/23	39	3/77	25/66	51/46
Neurologic deficit (%)	4/31 (13 %)	8	16	29	18	17
Mortality (%)	24	17	29	13	24	25
Mortality predictors	Seizure, age >65 years	–	Combination therapy	–	Hydrocephalus, inappropriate empirical antibiotic therapy	Seizure, delayed proper empirical treatment
Country	USA	Netherlands	Spain	Czech Republic	Spain	Turkey, France, Italy

advanced age have been emphasized as important predisposing factors for neuroinvasive listeriosis. In addition to those predisposing factors, we found multiple therapeutic issues (i.e., choice of empiric treatment, addition of aminoglycosides, and adjuvant steroid therapy) that were independent risk factors predicting unfavorable outcomes. Importantly, these risk factors also differed from those described in the previously published case series. Whereas in one large-scale retrospective literature review half of the patients were immunosuppressed, in another prospective study, all of the cases were reported to be immunosuppressed [10, 13]. In both studies, the mean age of the immunocompetent patients was higher than that of the patients in the immunosuppressed group, and the morbidity and mortality rates ranged between 27 and 35 % [9–13]. In the present study, the rate of immunosuppression in patients older than 50 years of age was 68 %, which is different from that in previous reports. Fourteen (14 %) cases younger than 50 years of age had no form of immunosuppression. The evaluation of those cases with rhombencephalitis was statistically significant (p=0.002). The main characteristics of all of the aforementioned studies and the present study are summarized in Table 3.

In conclusion, the occurrence of epileptic seizures and delay in treatment were independent risk factors for mortality due to CNS infections caused by *L. monocytogenes*. The presence of bacteremia, delay in the initiation of treatment, and parenchymal involvement on cranial MRI were independent risk factors for rhombencephalitis. Finally, ampicillin plus aminoglycoside combination therapy was not superior to ampicillin monotherapy for treatment.

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Conflict of interest The authors declare that they have no conflict of interest.

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