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ORIGINAL ARTICLE

Cerebral Infarction in Adults with Bacterial Meningitis

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Abstract
Background To evaluate clinical features and prognostic factors of cerebral infarctions in adults with community-acquired bacterial meningitis.
Method An observational cross-sectional study, including 696 patients of whom 174 had cerebral infarction, from a prospective nationwide cohort of community-acquired bacterial meningitis (period, 1998–2002), confirmed by culture of cerebral spinal fluid (CSF) in patients aged over 16 years. Two investigators independently determined the presence of infarction.
Result Cerebral infarction occurred in 174 episodes (25%), with a high inter-rater agreement for determining the presence of cerebral infarction (kappa 0.95). Cerebral infarctions occurred in 128 of 352 patients (36%) with pneumococcal meningitis, in 22 of 257 (9%) with meningococcal meningitis and in 24 of 87 patients (28%) with meningitis caused by other bacteria. Patients with infarctions were older ($P < 0.001$) and often presented with predisposing conditions, such as otitis and/or sinusitis ($P = 0.001$) or an immunocompromised state ($P = 0.003$) compared to those without infarction. Patients with infarctions presented with lower scores on the Glasgow Coma Scale ($P < 0.001$), lower CSF white cell counts ($P = 0.001$), and higher serum erythrocyte sedimentation rate (ESR) ($P < 0.001$). Unfavorable outcome occurred in 108 (62%) patients with infarctions. In a multivariate analysis, infarction was related with unfavorable outcome (odds ratio 3.37; 95% confidence interval 2.19–5.21; $P < 0.001$). We identified lower CSF white cell counts and high ESR to be independent risk factors for cerebral infarction.
Conclusion Cerebral infarction is a common and severe complication in adults with community-acquired bacterial meningitis. Preventing cerebral infarctions will be important in reducing the high morbidity and mortality rate in adults with community-acquired bacterial meningitis.

Keywords Meningitis · Cerebral infarction · Neurological infections

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Introduction

Bacterial meningitis is a serious and life-threatening disease. *Streptococcus pneumoniae* and *Neisseria meningitidis* are the predominant causative pathogens in adults, causing 80–85% of all cases, with mortality rates up to 30% for the pneumococcal meningitis and 10% for meningococcal

meningitis [1–4]. Cerebrovascular complications are particularly common in pneumococcal meningitis, with reported rates of 10–29% [2, 5, 6]. Few cohort studies on cerebral infarctions in bacterial meningitis have been published [5, 7, 8]. We performed a nationwide prospective cohort study on clinical features and prognostic factors of 696 episodes of community-acquired bacterial meningitis in adults [3]. Here we report the features and prognostic factors of cerebral infarction in bacterial meningitis identified in this cohort.

Methods

The Dutch Meningitis Cohort Study, a prospective nationwide observational cohort study in the Netherlands, included 696 episodes of community-acquired bacterial meningitis, confirmed by culture of cerebrospinal fluid (CSF) in adults. Inclusion and exclusion criteria are described more extensively elsewhere [3]. In summary, all patients were aged over 16 years and were listed in the database of the Netherlands Reference Laboratory for Bacterial Meningitis from October 1998 to April 2002. This laboratory receives CSF isolates from approximately 90% of all patients with bacterial meningitis. Informed consent was obtained from all participating patients or their legally authorized representatives. Patients using immunosuppressive drugs, with asplenia, diabetes mellitus, alcoholism, or infection with human immunodeficiency virus (HIV) were considered immunocompromised.

This study is an observational case–control study on cerebral infarction. Clinical data, including specific queries about cerebral infarction, had been prospectively collected by means of a case record form. Two clinicians independently reviewed all case record forms and classified patients as having no cerebral infarction, probable cerebral infarction or definite cerebral infarction (ES, MDV). Inter-rater agreement was assessed by calculation of the kappa coefficient. Differences in classification were resolved by discussion. Definite cerebral infarction was defined as focal neurologic signs on admission or during the course of the disease, diagnosed by a neurologist, with a lesion consistent with recent infarction visualized on cranial computed tomography (CT). Probable cerebral infarction was defined as mono- or hemiparesis, central facial weakness, ataxia, or aphasia on admission or during clinical course, which could not be explained by epileptic seizures or other neurological complications, without confirmation by cranial CT. In these patients CT scanning was either not performed, or was performed but did not show lesions that could explain the patient's clinical condition.

On admission and at discharge, all patients underwent a neurologic examination performed by a neurologist, and outcome was graded according to the Glasgow outcome scale. This is a well-validated measurement scale with scores varying from 1 (indicating death) to 5 (good recovery). A favorable outcome was defined as a score of 5, and an unfavorable outcome as a score of 1–4. We categorized the cause of death in patients who died within 14 days after admission, since death within this period is likely to be caused by direct consequences of the meningitis [3, 9]. Two clinicians independently classified the cause of death into systemic causes (e.g., septic shock, respiratory failure, multiple-organ dysfunction, and cardiac ischemia) or neurologic causes (e.g., brain herniation, cerebrovascular complications, intractable seizures, and withdrawal of care because of poor neurologic prognosis). Inter-rater agreement was assessed by calculation of the kappa coefficient [6]. Differences were resolved by discussion.

Population description was done with medians and interquartile ranges. The Mann–Whitney U test was used to identify differences between episodes with and without cerebral infarction with respect to continuous variables, and the χ^2 test was used to compare categorical variables. The analyses were performed for definite cerebral infarctions (confirmed by cranial CT) and all cerebral infarctions. We used logistic regression to examine the association between potential predictors and cerebral infarction. Odds ratios (OR) and 95% confidence intervals (CI) were used to quantify the strength of these associations. Based on previous research and pathophysiologic interest nine potentially relevant predictors were chosen. We evaluated whether the prognostic value of these risk factors could be attributed to the causative pathogen, by adjusting the analysis with the inclusion of this variable into the prognostic model. Statistical analyses were performed using PASW software, version 18 (SPSS Institute) and P values <0.05 were considered significant.

Results

From 1998 to 2002, 696 episodes of community-acquired bacterial meningitis were included in 671 patients. CSF culture yielded *S. pneumoniae* in 352 episodes (51%), *N. meningitidis* in 257 episodes (37%), and other bacteria in 87 episodes (13%). In 174 of 696 episodes (25%) patients were classified as having cerebral infarctions. The kappa for inter-rater agreement on determining cerebral infarction was high (0.95). Infarctions were classified as definite in 60 of 696 episodes (9%) and probable in 114 of 696 episodes (16%).

Of 174 patients with cerebral infarctions 80 patients (46%) presented with focal neurologic signs on admission, consisting of monoparesis in 15 episodes (9%), hemiparesis in 42 episodes (25%), quadriparesis in seven episodes

(4%), aphasia in 59 episodes (48%), and ataxia in ten episodes (9%). In the other 94 patients, symptoms of infarction developed during clinical course.

Patients with cerebral infarctions were older than patients without cerebral infarctions (median age, 61 years [IQR 47–72] vs. 48 [IQR 28–64], $P < 0.001$; Table 1). The proportion of females among patients with cerebral infarctions was higher than among patients without cerebral infarctions (59 vs. 48%, $P = 0.013$). Patients with infarctions presented more often with predisposing conditions, such as otitis and/or sinusitis (35 vs. 22%, $P = 0.001$) or an immunocompromised state (24 vs. 14%, $P = 0.003$). They presented with lower levels of consciousness (median score on the Glasgow Coma Scale, 10 [IQR 8–13] vs. 12 [IQR 9–15]; $P < 0.001$), and were therefore more likely to present with the classic triad of symptoms, consisting of fever, neck stiffness, and a change in mental status (52 vs. 41%; $P = 0.015$). Patients with infarctions had higher median systolic blood pressures (150 [IQR 130–170] vs. 135 [IQR 120–157]; $P < 0.001$) and presented less often with skin rash (9 vs. 31%; $P < 0.001$).

Cranial imaging was performed in 124 of 174 patients with infarctions (71%); all 124 patients underwent CT. Cerebral infarctions were diagnosed by cranial CT in 60 of 174 patients. On admission, CT confirmed clinical suspicion of infarction in only 23 of 80 patients (29%) with infarctions presenting with focal neurologic signs. Sixty-four of 114 patients with probable cerebral infarctions had normal CT (56%). Other abnormalities on cranial imaging were: sinusitis/otitis (62 episodes, 9%), cerebral edema (48 episodes, 7%), hydrocephalus (14 episodes, 2%), and cerebritis/empyema which by themselves could not fully account for the clinical focal deficits (25 episodes, 4%). These abnormalities were either seen in combination with cerebral infarction on CT or could not explain the focal neurologic signs.

Lumbar puncture was performed in all episodes and showed lower median CSF white blood cell (WBC) counts in patients with infarctions as compared with patients without cerebral infarctions (1877 per mm^3 [IQR 356–6031] vs. 339 [IQR 947–9122]; $P = 0.001$). Patients with infarctions also had lower median CSF: blood glucose ratio (0.05 [IQR 0.01–0.20] vs. 0.08 [IQR 0.01–0.31]; $P = 0.023$), higher C-reactive protein levels (234 mg/l [IQR 125–357] vs. 206 [IQR 128–293]; $P = 0.05$) and erythrocyte sedimentation rates (51 mm/h [51 {IQR 30–77] vs. 36 [IQR 128–293]; $P < 0.001$). CSF culture yielded *S. pneumoniae* in 74% of episodes complicated by cerebral infarction and in 43% of episodes without cerebral infarction ($P < 0.001$).

Patients with cerebral infarction had higher proportions of systemic and neurologic complications (Table 2): cardiorespiratory failure in 43%, impairment of consciousness in 58%, and seizures in 28%. There was a higher rate of unfavorable outcome in patients with cerebral infarctions: 108 of 174 (62%) patients with cerebral infarctions compared to 129 of 522 (25%) patients without cerebral infarctions ($P < 0.001$). Overall, 55 of 174 (32%) patients with cerebral infarctions died, compared to 88 of 522 (17%) patients without cerebral infarction ($P < 0.001$). The majority (55%) of patients with cerebral infarctions died due to a neurologic cause, whereas death was due to a systemic cause in most patients without infarctions (61%; $P = 0.06$). The kappa for the classification of cause of death was 0.60. Death occurred in 45% of patients with definite cerebral infarction and in 25% of patients with probable cerebral infarction.

In the multivariate analysis, advanced age, a low score on Glasgow Coma Scale on admission, a high erythrocyte sedimentation rate and a CSF leukocyte count below 1000 cells/mm^3 were identified as risk factors for cerebral infarction (Table 3). After correction for bacterial cause, advanced age and high erythrocyte sedimentation rate remained independent risk factors for cerebral infarctions. Cerebral infarction was independently related with unfavorable outcome (OR 3.37; 95% CI 2.19–5.21; $P < 0.001$; Table 4).

Discussion

Our study shows that cerebral infarction is a common and severe complication, occurring in 25% of adults with bacterial meningitis, resulting in a high mortality rate (32%). Cerebral infarction was independently related with unfavorable outcome. This high incidence of cerebrovascular complications is in agreement with results reported by others [2, 4, 8].

In a multivariate analysis we identified advanced age, a decreased level of consciousness, parameters of systemic inflammation, and infection with *S. pneumoniae* as factors predicting the development of cerebral infarction. First, advanced age is a well-known general risk factor for cerebral infarction [10]. The higher incidence of atherosclerosis in the elderly may predispose for cerebral infarction during bacterial meningitis. Second, a decreased level of consciousness has previously been described as a major marker for severity of cerebral inflammation in bacterial meningitis [11]. Apparently, the severity of inflammation is directly related to the risk of cerebral infarction. Third, a low CSF WBC and a high ESR on admission have both been described as markers of the inflammatory response in the systemic compartment and sepsis [12]. Our results are in line with those of a retrospective study in 68 meningitis patients describing a decreased level of consciousness and low CSF white blood cell count to be risk factors for cerebral infarctions in a

Table 1 Clinical and laboratory characteristics and outcome in patients with and without cerebral infarctions complicating bacterial meningitis

Characteristic	Cerebral infarctions ($n = 174$)	No cerebral infarction ($n = 522$)	P value
Age (Median, IQR)	61 (47–72)	48 (28–64)	<0.001
Female	102/174 (59%)	249/522 (48%)	0.01
Predisposing conditions			
Otitis/sinusitis	60/174 (35%)	116/522 (22%)	0.001
Immunocompromised state[a]	41/174 (24%)	73/522 (14%)	0.003
Diabetes mellitus	18/171 (11%)	28/519 (5%)	0.02
Pneumoniae	25/174 (14%)	58/522 (11%)	0.25
Symptoms on presentation			
Headache	122/150 (81%)	422/476 (89%)	0.02
Nausea	104/143 (73%)	345/467 (74%)	0.785
Rash	16/171 (9%)	160/512 (31%)	<0.001
Triad of fever, neck stiffness, and change in mental status	90/174 (52%)	215/522 (41%)	0.02
Systolic blood pressure (mmHg)[b]	150 (130–170)	135 (120–157)	<0.001
Heart rate (beats/min)[c]	100 (84–120)	98 (80–110)	0.070
Focal neurologic signs on admission			
Monoparesis	15/165 (9%)	1/512 (0.2%)	<0.001
Hemiparesis	42/168 (25%)	7/514 (1.4%)	<0.001
Quadriparesis	7/171 (4%)	6/514 (1%)	0.015
Ataxia	10/115 (9%)	8/434 (2%)	<0.001
Score on Glasgow Coma Scale			
Median	10 (8–13)	12 (9–15)	<0.001
<14 (indicating change in mental status)	145/172 (84%)	332/522 (63%)	<0.001
<8 (indicating coma)	39/172 (23%)	57/522 (11%)	<0.001
Blood chemistry tests[d]			
Leukocyte count (cells/mm^3)	17 (13–22)	19 (13–23)	0.111
ESR (mm/h)	51 (30–77)	36 (16–66)	<0.001
Thrombocyte count (platelets/mm^3)	181 (132–233)	185 (142–241)	0.20
C-reactive proteine (mg/liter)	234 (125–357)	206 (128–293)	0.05
Indexes of inflammation in the CSF[e]			
CSF opening pressure (cm H_2O)	40 (27–50)	36 (24–50)	0.336
Leukocyte count			
Median (cells/mm^3)	1877 (356–6031)	3339 (947–9122)	0.001
<1000/mm^3	62/165 (38%)	122/480 (25%)	0.003
Protein (g/l)	4.8 (3.0–6.7)	4.0 (2.1–6.9)	0.40
CSF: blood glucose ratio (mg/dl)	0.05 (0.01–0.20)	0.08 (0.01–0.31)	0.023
CSF culture			
Streptococcus pneumoniae	128/174 (74%)	224/522 (43%)	<0.001
Neisseria meningitidis	22/174 (13%)	235/522 (45%)	<0.001
Other	24/174 (14%)	63/522 (12%)	0.551

Data are number/number evaluated (%) or median (interquartile range)

[a] Immunocompromised state is defined as the use of immunosuppressive drugs, presence of asplenia, diabetes mellitus, alcoholism, or infection with HIV

[b] Blood pressure was determined in 670 patients

[c] Heart rate was determined in 652 patients

[d] Blood leukocyte counts were determined in 690 patients, erythrocyte sedimentation rate (ESR) in 549 patients, thrombocyte count in 653 patients, C-reactive protein levels in 392 patients

[e] CSF opening pressure was determined in 216 patients, CSF leukocyte count in 645 patients, CSF protein level in 634 patients and CSF: blood to glucose ratio in 617 patients

Table 2 Complications and outcome in patients with and without cerebral infarctions complicating bacterial meningitis

Characteristic	Cerebral infarctions ($n = 174$)	No cerebral infarction ($n = 522$)	P value
Systemic complications			
Cardiorespiratory failure	75/174 (43%)	126/522 (24%)	<0.001
Hyponatremia[a]	52/161 (32%)	134/499 (27%)	0.182
Fever during admission	154/168 (92%)	451/503 (90%)	0.450
Persistent fever[b]	30/158 (19%)	54/460 (12%)	0.043
Recurrent fever[c]	52/154 (34%)	109/449 (24%)	0.016
Neurologic complications			
Impairment of consciousness	101/174 (58%)	175/522 (34%)	<0.001
Hearing impairment	50/174 (29%)	94/522 (18%)	0.002
Seizures	49/173 (28%)	58/514 (11%)	<0.001
Glasgow outcome scale score			
1 (death)	55/174 (32%)	88/522 (17%)	<0.001
2 (vegetative state)	2/174 (1%)	1/522 (0.2%)	0.095
3 (severe disability)	16/174 (9%)	8/522 (2%)	<0.001
4 (moderate disability)	35/174 (20%)	32/522 (6%)	<0.001
5 (mild or no disability)	66/174 (38%)	393/522 (75%)	<0.001
Cause of death[d]			
Systemic	25/55 (45%)	54/88 (61%)	0.06
Neurologic	30/55 (55%)	34/88 (39%)	0.06

[a] Hyponatremia was defined as a serum sodium level <135 mmol/l

[b] Persistent fever is defined as fever that continued longer than 10 days after initiation of appropriate antibiotic therapy

[c] Recurrent fever is defined as a (rectal) temperature of 38°C or higher occurring after at least one afebrile day during the course of hospitalization

[d] Evaluated in patients who died within 2 weeks after admission

Table 3 Multivariate analysis of factors associated with cerebral infarction

Characteristic	All patients Odds ratio (95% CI)	P value	Adjusted for bacterial cause Odds ratio (95% CI)	P value
Age (yr)	1.02 (1.01–1.03)	0.001	1.02 (1.00–1.03)	0.012
Predisposing conditions				
Otitis/sinusitis	1.58 (0.98–2.54)	0.061	1.13 (0.67–1.91)	0.638
Immunocompromised state[a]	1.52 (0.89–2.58)	0.124	1.42 (0.83–2.44)	0.197
Pneumoniae	1.08 (0.57–2.06)	0.806	1.23 (0.64–2.36)	0.540
Clinical characteristics on admission				
Score on Glasgow Coma Scale	0.92 (0.86–0.99)	0.029	0.94 (0.87–1.01)	0.097
Heart rate	1.00 (0.99–1.01)	0.852	1.00 (0.99–1.01)	0.837
Laboratory features				
ESR (mm/h)	1.13 (1.01–1.26)	0.033	1.14 (1.02–1.27)	0.025
CSF white cell count <1000/mm^3	1.67 (1.04–2.67)	0.035	1.56 (0.97–2.53)	0.069
CSF culture				
Streptococcus pneumoniae			2.25 (1.34–3.77)	0.002

ORs are calculated for 1 year increments for age, per 20 mm per hour for erythrocyte sedimentation rate (ESR), per 100.000 per mm^3 and per one-point decrease on the Glasgow Coma Scale

[a] Immunocompromised state is defined as the use of immunosuppressive drugs, presence of asplenia, diabetes mellitus, alcoholism, or infection with HIV

univariate analysis [7]. However, only six patients in this previous study had cerebral infarctions, limiting the power of the study to correct for possible confounders.

Cerebral infarctions in bacterial meningitis have previously been attributed to cerebral vasculitis, after autopsy studies in the 1950s and 1960s described inflammatory

Table 4 Factors associated with unfavorable outcome in multivariate analysis

Characteristic	Odds ratio (95% CI)	*P* value
Age	1.02 (1.01–1.03)	0.001
Score on Glasgow Coma Scale	0.86 (0.80–0.92)	<0.001
CSF leukocyte count <1000/mm^3	4.55 (2.95–7.04)	<0.001
Streptococcus pneumoniae	2.63 (1.71–4.04)	<0.001
Cerebral infarction	3.37 (2.19–5.21)	<0.001

ORs are calculated in 1 year increments for age and per one-point decrease on the Glasgow Coma Scale

infiltrations of cerebral arteries and veins [13–15]. Clinical studies have described segmental arterial narrowing on cerebral angiography in patients with ischemic stroke complicating bacterial meningitis [2, 16]. However, cerebral infarctions have also been described in patients with a normal cerebral angiography and abnormal angiographies have been described in patients with no clinical signs of vasculitis [8]. Vasospasm has also been implicated in the pathogenesis of ischemic stroke in bacterial meningitis. A transcranial Doppler ultrasonography study in 22 bacterial meningitis patients showed increased cerebral blood flow velocities in 18 patients, of which two had definite cerebral infarctions [17]. This increased cerebral blood flow was attributed to vasospasm, although arterial narrowing due to other causes (e.g., vasculitis, arterial thrombosis) will cause a similar increase in cerebral blood flow. In recent years accumulating data shows that severe infections result in activation of the coagulation pathway [6, 18]. Activation of the coagulation cascade and inhibition of the fibrinolysis pathway were also shown in patients with bacterial meningitis, especially in patients who have cerebral infarctions as a complication [5, 19]. A recent autopsy study showed that fibrin thrombi and cerebral infarctions were mostly present in the absence of inflammatory vessel wall infiltrates suggesting that diffuse cerebral intravascular coagulation might be an additional mechanism causing ischemic stroke in pneumococcal meningitis [5, 20].

Several therapies have been evaluated to decrease the rate of cerebral infarctions in bacterial meningitis patients. A small trial performed in 1976–1977 evaluated heparin therapy in 15 bacterial meningitis patients and showed increased mortality in the seven patients treated with heparin [21]. Activated protein C (APC) is an endogenous protein that promotes fibrinolysis and inhibits thrombosis and inflammation, that has shown to benefit patients with severe sepsis [22]. However, the 128 patients with bacterial meningitis included in a retrospective analysis of 4,096 patients included in APC trials had a high rate of intracranial hemorrhage [23]. Therefore, heparin and APC are contra-indicated in bacterial meningitis patients. Antiplatelet agents to prevent stroke have only been studied in tuberculous meningitis [24]. In this trial 118 patients with tuberculous meningitis were randomised to aspirin or placebo treatment. Aspirin resulted in an absolute risk reduction of stroke of 19.1% and a significant reduction in mortality compared to placebo (22 vs. 43%). Potential targets for new therapies may be identified by genetic association studies. Recently, a meta-analysis showed a strong association of genetic variation in the plasminogen activator inhibitor 1 gene with vascular complications and mortality in meningococcal disease (including meningitis and sepsis cases) [2]. Targeting adjunctive treatment to patients with a genetically increased risk for vascular complications may provide benefits while limiting the risks in the whole population of bacterial meningitis patients [25].

The study was performed nationwide and was descriptive by nature. As a result patients did not receive cranial imaging according to a pre-specified protocol, and cerebral infarctions were diagnosed clinically and/or by the absence of abnormalities on cranial imaging, which is common in the acute phase of cerebral infarctions. Since stroke was more common in individuals with sinusitis or otitis, the possibility that many of the "probable" strokes actually had cerebritis from contiguous spread of infection cannot be excluded. Although infarctions were considered arterial in most cases, our data do not allow a clear distinction between venous and arterial infarctions, since no vascular imaging studies were performed and results of post-mortem examinations, if performed, were not available. The use of diffusion-weighted MRI could result in a higher proportion of neuro-imaging confirmed cerebral infarctions in adults with bacterial meningitis. A further limitation of our study was that only patients with positive CSF cultures were included. Negative CSF cultures are estimated to occur in 11–30% of patients with bacterial meningitis [3, 4, 25, 26]. However, no significant differences in clinical presentation have been reported between patients with culture-positive bacterial meningitis and patients with culture-negative bacterial meningitis [4, 26, 27]. In addition, the successful implementation of dexamethasone in the Netherlands has led to a significant reduction of mortality and unfavorable outcome in patients with pneumococcal meningitis [28, 29]. Most patients in our current study did not receive steroid therapy and therefore the rate of cerebral infarction may be higher than in patients treated with dexamethasone [28, 30]. Finally, the epidemiology of bacterial meningitis has changed as a result of the widespread use of conjugate vaccines [1]. The rates of bacterial meningitis have decreased since 1998, but the disease still often results in death [31]. *S. pneumoniae* is now the most common etiological agent of bacterial meningitis in the United States and Europe, accounting for approximately two-thirds of adult cases in the United States and the Netherlands

[29, 31]. Our study showed that this group in particular is at risk for cerebral infarction.

In conclusion, we found that cerebral infarction is a common and severe complication in adults with community-acquired bacterial meningitis. Preventing cerebral infarctions will be important in reducing the high morbidity and mortality rate in adults with community-acquired bacterial meningitis.

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Conflict of interest None.

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