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ORIGINAL ARTICLE

Community-acquired meningitis caused by beta-haemolytic streptococci in adults: a nationwide population-based cohort study

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Abstract

The objective of this study was to examine the clinical presentation of community-acquired beta-haemolytic streptococcal (BHS) meningitis in adults. This is a nationwide population-based cohort study of adults (≥ 16 years) with BHS meningitis verified by culture or polymerase chain reaction of the cerebrospinal fluid (CSF) from 1993 to 2005. We retrospectively evaluated clinical and laboratory features and assessed outcome by Glasgow Outcome Scale (GOS). We identified 54 adults (58% female) with a median age of 65 years (IQR 55–73). Mean incidence rate was 0.7 cases per 1,000,000 person-years. Alcohol abuse was noted among 11 (20%) patients. Group A streptococci (GAS) were found in 17 (32%) patients, group B (GBS) in 18 (34%), group C (GCS) in four (8%) and group G (GGS) in 14 (26%). Patients with GAS meningitis often had concomitant otitis media (47%) and mastoiditis (30%). Among patients with GBS, GCS or GGS meningitis, the most frequent concomitant focal infections were bone and soft tissue infections (19%) and endocarditis (16%). In-hospital mortality was 31% (95% CI 19–45), and 63% (95% CI 49–76) had an unfavourable outcome at discharge (GOS < 5). BHS meningitis in adults is primarily observed among the elderly and has a poor prognosis. GAS meningitis is primarily associated with concomitant ear-nose-throat infection.

Keywords Bacterial meningitis · Beta-haemolytic streptococci · *Streptococcus pyogenes* · *Streptococcus agalactiae* · *Streptococcus dysgalactiae* · Epidemiology · Prognosis · Outcome

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Introduction

Bacterial meningitis remains a serious infection with a case fatality rate of 15–17% and severe neurologic sequelae in up to 38% of survivors [1–3]. As a result of vaccination, bacterial meningitis caused by *Haemophilus influenzae* type b, *Neisseria meningitidis* and *Streptococcus pneumoniae* has declined [1, 2, 4]. Accordingly, other pathogens are now responsible for a relatively higher proportion of bacterial meningitis including beta-haemolytic streptococci (BHS). Invasive BHS disease is often associated with severe disease and a predilection for heart, bone and soft tissues. Yet, BHS were recently shown to be the third most common cause of community-acquired bacterial meningitis in adults in Denmark accounting for 7% of cases [3]. Case fatality rates of BHS meningitis have ranged from 19 to 34% [5–8]. However, most reports were limited to single-centre studies of both children and adults [8–10] or consisted of general accounts of bacterial meningitis without specific descriptions of BHS meningitis.

In this study, we aimed to examine the clinical features and outcome of community-acquired BHS meningitis in adults in a nationwide population-based retrospective cohort study.

Methods

Setting and study population

First, we identified all patients ≥ 16 years of age with cerebrospinal fluid (CSF) positive for BHS by either culture or polymerase chain reaction (PCR) at all departments of clinical microbiology in Denmark. Dates of inclusion spanned from the implementation of local electronic laboratory information systems in clinical microbiology (varying from 1993 to 2005) until December 31, 2018 (Supplementary Table A). During the study period, invasive isolates of BHS have also been referred to Statens Serum Institut (Copenhagen) for national surveillance ensuring a standardized identification of isolates [11]. Next, we only included such patients if they also had a clinical presentation suggestive of bacterial meningitis assessed by chart review. Patients with nosocomial infections as defined by the Centers for Disease Control and Prevention [12], previous neurosurgery and primary brain abscess were excluded.

Patient data

Clinical and laboratory characteristics at admission were obtained by chart review. We documented concomitant infectious foci, microbiological reports either on paper or electronic, radiological examinations, antibiotic treatment and use of adjunctive dexamethasone (adopted in treatment guidelines in 2003 [13]). Fever was defined as a temperature above 38.0 °C. Outcome was assessed by the Glasgow Outcome Scale (GOS) score at discharge: 1, death; 2, a vegetative state; 3, severe sequelae and dependency upon others in daily life; 4, moderate sequelae but retainment of the capability of independent living; and 5, minor or no sequelae [14]. A score of 5 was categorised as favourable and 1–4 as unfavourable.

Data management and statistics

Study data were collected and managed using REDCap electronic data capture tools hosted at North Denmark Region [15]. Categorical variables are reported as *n*/*N* (%) with 95% confidence intervals (95% CI) for key variables in analyses of outcome, i.e. unfavourable outcome and death during admission. Continuous variables are presented as median with interquartile range (IQR). When appropriate, categorical variables were compared by Fisher's exact test or chi-squared test using a p value of 0.05 for statistical significance. Statistical analyses were performed using Stata/MP® version 15 (StataCorp LLC, College Station, TX, USA).

Ethical considerations

Before data collection, the project was approved by the Danish Data Protection Agency (record no. 2008-58-0028, local ID-number 2017-218) and the Danish Board of Health (record no. 3-3013-2365/1). Acceptance from a research ethics committee is not required for this type of study in Denmark.

Results

We included 54 patients with community-acquired BHS meningitis (Fig. 1) with a median age of 65 years (IQR 55–73) of which 57% were female (Table 1). Mean incidence rate was 0.7 cases per 1,000,000 person-years (Supplementary Table B). Group A streptococci (GAS) were the causative pathogen in 17 (31%) patients, group B streptococci (GBS) in 18 (33%), group C streptococci (GCS) in five (9%) and group G streptococci (GGS) in 14 (26%). Comorbidity was present in 24 of 54 (44%) with a predominance of alcoholism ($n = 11$, 20%) and liver disease ($n = 5$, 9%). There were no substantial differences in the distributions of age or sex according to the bacterial aetiology.

Duration of illness before admission was below 24 h in 15 of 47 (32%) patients. Symptoms and signs of meningitis at the time of admission included headache in 20 of 31 (65%), nausea or vomiting in 13 of 30 (43%), neck stiffness in 22 of 45 (49%) and altered mental status in 38 of 54 (70%) patients. The meningitis triad (altered mental status, neck stiffness and fever) was present in 11 of 41 (27%) patients.

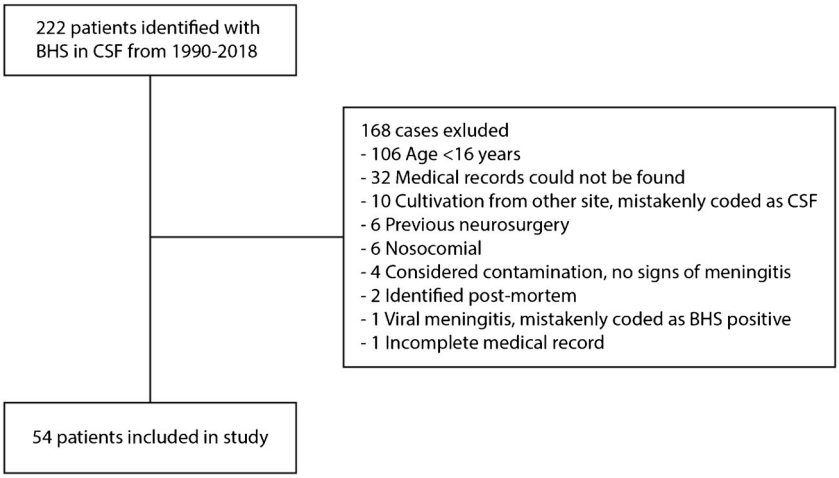

Fig. 1 Flowchart of inclusion. Study inclusion period varied (Supplementary Table A)

Biochemical analysis of blood showed a median C-reactive protein (CRP) of 214 mg/L (IQR 130–335) and leukocytes of 13.5×10^9/L (IQR 7.2–19). In the CSF, the median leukocyte cell count was 791×10^6/L (IQR 144–1809) with a predominance of neutrophils (89%, IQR 76%–95%), a median level of protein of 2.0 g/L (IQR

Table 1 Baseline and clinical characteristics of adults with community-acquired meningitis caused by beta-haemolytic streptococci according to specific pathogen

Characteristic	GAS‡ *N* = 17	GBS‡ *N* = 18	GCS‡ *N* = 5	GGS‡ *N* = 14	Total‡ *N* = 54
Age (years)	65 (58–73)	61 (55–72)	70 (70–81)	62 (57–73)	65 (55–73)
Female	13/17 (76)	12/18 (67)	1/5 (20)	5/14 (36)	31/54 (57)
Comorbidity[a]	4/17 (24)	10/18 (56)	2/5 (40)	8/14 (57)	24/54 (44)
Alcoholism	3/17 (18)	6/18 (33)	0/5 (0)	2/14 (14)	11/54 (20)
Duration of symptoms < 24 h	5/16 (32)	3/15 (20)	1/4 (25)	4/12 (33)	15/47 (32)
Headache	6/9 (67)	7/11 (64)	1/2 (50)	6/9 (67)	20/31 (65)
Nausea/vomiting	2/7 (29)	6/12 (50)	2/2 (100)	3/9 (33)	13/30 (43)
Neck stiffness	7/13 (54)	6/14 (43)	2/4 (50)	7/14 (50)	22/45 (49)
Neurological deficits	2/17 (12)	5/13 (28)	1/5 (20)	5/14 (36)	13/54 (24)
Temperature > 38 °C	12/15 (80)	7/15 (47)	4/5 (80)	11/14 (79)	34/49 (69)
Glasgow coma score	12 (8–13), *n* = 10	8 (4–13), *n* = 11	12 (11–12), *n* = 2	12 (6–13), *n* = 11	11 (7–13), *n* = 34
Altered mental status[b]	11/17 (65)	14/18 (78)	4/5 (80)	9/14 (64)	38/54 (70)
Meningitis triad[c]	3/11 (27)	3/9 (25)	2/4 (50)	3/14 (21)	11/41 (27)
Laboratory tests					
CRP (mg/L)	259 (200–372), *n* = 16	136 (52–288), *n* = 15	276 (117–332), *n* = 4	199 (157–360), *n* = 11	214 (130–335), *n* = 46
> 80 mg/L	15/16 (94)	10/15 (67)	3/4 (75)	10/11 (91)	38/46 (83)
Blood culture positive	15/17 (88)	7/12 (58)	2/3 (67)	12/13 (92)	36/45 (80)
CSF					
Leucocytes (10^6/L)	1410 (943–3700), *n* = 13	981 (143–2000), *n* = 15	805 (136–1586), n = 4	246 (47–436), *n* = 12	791 (144–1809), *n* = 44
Protein (g/L)	2.9 (2–6), *n* = 10	2.9 (1.7–6), *n* = 10	1.9 (1.2–3.6), *n* = 4	0.8 (0.5–2.3), *n* = 10	2 (0.8–5.2), *n* = 34
≥ 1 Spanos criterium fulfilled[d]	11/13 (85)	11/15 (73)	3/4 (75)	4/13 (31)	29/45 (64)
Abnormal neuroimaging[e]	3/14 (21)	2/14 (14)	1/5 (20)	3/12 (24)	9/45 (20)

‡ Values expressed as *n*/*N* (%) or median (IQR), *n*

[a] Other comorbidities than specified include (for total cohort) liver disease (5), diabetes mellitus (4), atrial fibrillation (4), other heart disease (2), solid cancer (2), haematological cancer (1), COPD (1) and chronic kidney failure (1). Some patients had more than one comorbidity

[b] Glasgow coma score < 14. No Glasgow coma score was specified in admission records for 20 patients, but was estimated based on description of clinical status

[c] Defined as altered mental status, neck stiffness and temperature > 38 °C

[d] Defined as CSF leucocytes > 2000×10^6 /L, CSF neutrophils > 1180×10^6 /L, CSF protein > 2.2 g/L, CSF glucose < 1.9 mmol/L or CSF to plasma glucose ratio < 0.23 [16]

[e] Includes (for total cohort) brain infarction (5), generalized oedema (4), hydrocephalus (1), haemorrhage (1) and secondary brain abscess (1). Some patients had more than one abnormal find on imaging

0.8–5.2) and a median CSF to plasma glucose ratio of 0.21 (IQR 0.02–0.58).

A computed tomography (CT) scan of the brain was performed in 45 patients, of which nine (20%) had abnormal findings. These included infarction (five patients), generalised oedema (four patients), hydrocephalus (one patient) and intracerebral haemorrhage (one patient). Another patient developed brain abscess during treatment for meningitis.

The majority of patients were treated in the intensive care unit during admission (34 of 54, 63%). We observed an overall in-hospital mortality of 31% (95% CI 19–45%) and an unfavourable outcome at discharge in 63% (95% CI 49–76%). Dexamethasone was administered to 27 of 54 (50%) patients and was not associated with increased survival compared with patients not treated with dexamethasone (19 of 26, 73% vs. 17 of 26, 65%; $p = 0.6$).

In 17 patients with GAS meningitis, 15 (88%) had documented bacteraemia, and 12 (71%) had concomitant focal infections including otitis media in eight patients, mastoiditis in five patients and sinusitis in three patients (Table 2). At discharge, 10 patients had an unfavourable outcome (GOS ≤4) (59%) including five (29%) in-hospital fatalities (Table 3).

Among 18 patients with GBS meningitis, six (33%) had alcohol abuse and five (28%) had liver disease (Table 1). The median Glasgow coma score at admission was eight (IQR 4–13), and an extra-neurological focus of infection was found in 12 (67%) including epidural abscess and spondylodiscitis in three patients (17%) (Table 2). We observed an unfavourable outcome at discharge in 11 (65%) patients with GBS meningitis, and four (24%) had a fatal outcome.

In the GCS group, a concomitant skin infection was present in one of five patients (Table 2). Four patients had an unfavourable outcome, and two died during admission (Table 3).

Among 14 patients with GGS meningitis, blood cultures were positive in 11 of 12 patients who had blood cultures drawn during admission (92%) (Table 1). Concomitant infections were present in six of 14 patients (43%) of which four (29%) had endocarditis (Table 2). Neurological complications during admission occurred in eight patients (57%) and included a decrease in consciousness in six and seizures in another four. Unfavourable outcome at discharge was observed in eight of 13 (62%) patients, and five (38%) died during admission (Table 3).

Discussion

We observed that community-acquired BHS meningitis in adults is a rare and often fatal disease that occurs almost exclusively in elderly and comorbid patients. In our cohort, ear-nose-throat infections were common among patients with GAS meningitis, while concomitant bone and soft tissue infections as well as endocarditis were only occasionally observed among patients with GBS, GCS or GGS meningitis.

Alcohol abuse was present in 20% of our cases with BHS meningitis compared with 6% in a large Dutch cohort of 1412 adults with bacterial meningitis predominantly of pneumococcal aetiology [1, 17]. Although pneumonia often occurs in people with alcohol abuse and is an independent risk factor

Table 2 Concomitant focal infections according to pathogen in adults with community-acquired beta-haemolytic streptococcal meningitis in Denmark

Infection	*n*/*N* (%)	Infection	*n*/*N* (%)
GAS[a]	12/17 (71)		
Otitis	8/17 (47)	Dental infection	2/17 (12)
Mastoiditis	5/17 (30)	Endocarditis	1/17 (6)
Sinusitis	3/17 (18)	Urinary tract infection	1/17 (6)
Pneumonia	2/17 (12)	Epidural abscess/spondylodiscitis	1/17 (6)
GBS[a]	12/18 (67)		
Epidural abscess/spondylodiscitis	3/18 (17)	Infected ulcer	1/18 (6)
Urinary tract infection	2/18 (11)	Endophthalmitis	1/18 (6)
Pneumonia	2/18 (11)	Arthritis	1/18 (6)
Endocarditis	2/18 (11)	Erysipelas	1/18 (6)
Sinusitis	1/18 (6)		
GCS[a]	1/5 (20)		
Infected ulcer	1/5 (20)		
GGS[a]	6/14 (43)		
Endocarditis	4/14 (29)	Endophthalmitis	1/14 (7)
Urinary tract infection	1/14 (7)	Arthritis	1/14 (7)
Dental infection	1/14 (7)		

[a] Some patients had more than one concomitant focus of infection

Table 3 Course of disease and outcome of adults with community-acquired beta-haemolytic streptococcal meningitis in Denmark

Treatment, course of admission and outcome	GAS‡ *N* = 17	GBS‡ *N* = 18	GCS‡ *N* = 5	GGS‡ *N* = 14	Total‡ *N* = 54
Adjunctive dexamethasone	8/17 (47)	10/18 (56)	4/5 (80)	5/14 (36)	27/54 (50)
Neurological complications during admission[a]	7/17 (41)	8/18 (44)	3/5 (60)	8/14 (57)	26/54 (48)
Seizures	2/17 (12)	2/18 (11)	1/5 (20)	4/14 (29)	9/54 (17)
Decrease in consciousness	6/17 (35)	7/18 (39)	3/5 (60)	6/14 (43)	22/54 (41)
Progressive or new neurological deficits	3/17 (18)	3/18 (17)	3/5 (60)	3/11 (21)	12/54 (22)
ICU admission	9/17 (53)	13/18 (72)	4/5 (80)	8/14 (57)	34/54 (63)
Need for mechanical ventilation	7/17 (41)	10/18 (56)	3/5 (60)	6/14 (43)	26/54 (48)
Glasgow Outcome Score (GOS) at discharge					
1 (death)	5/17 (29)	4/17 (24)	2/5 (40)	5/13 (38)	16/52 (31)
2 (vegetative state)	0/17 (0)	0/17 (0)	0/5 (0)	0/13 (0)	0/52 (0)
3 (severe disability)	3/17 (18)	1/17 (6)	1/5 (20)	1/13 (8)	6/52 (12)
4 (moderate disability)	2/17 (12)	6/17 (35)	1/5 (20)	2/13 (15)	11/52 (21)
5 (mild or no disability)	7/17 (41)	6/17 (35)	1/5 (20)	5/13 (38)	19/52 (37)

‡ Values expressed as *n*/*N* (%)

[a] Some patients had more than one neurological complication

for bacterial meningitis [18], it was infrequently diagnosed among our patients and did not seem to explain the observed relation between alcohol abuse and BHS meningitis. On the other hand, alcohol has a direct toxic effect on the host immune response that along with immuno-senescence may be important predisposing factors for BHS meningitis [19]. Based on our findings, it remains important for clinicians to have a low threshold of performing lumbar punctures in severely ill patients with an altered mental status including patients with an alcohol abuse.

Concomitant foci of infection were common and noticeably different among groups of BHS. An otogenic focus of infection was present in 76% of patients with GAS meningitis in our study compared with 81% in a similar recent Dutch prospective cohort study [5]. In addition, 88% of patients with GAS meningitis in our study were also bacteraemic. These observations are concordant with the predilection of GAS to cause pharyngitis, tonsillitis and otitis media in addition to soft tissue and skin infections, bacteraemia or pneumonia [20, 21]. However, they preclude any firm conclusion on whether GAS meningitis mainly occurs secondary to bacteraemia or by direct invasion from an otogenic focus. Nonetheless, all patients with GAS meningitis should undergo evaluation for an infectious focus in the upper respiratory airways by an oto-rhinolaryngologist similar to meningitis caused by *S. pneumoniae* and *H. influenzae.*

Other concomitant infections in GBS meningitis patients in our cohort consisted of bone and soft tissue infections (17%) and endocarditis (11%). Similarly, a recent Dutch study on community-acquired GBS meningitis found spondylodiscitis and endocarditis in 7% and 13% of their patients [6]. Endocarditis was diagnosed in nearly a third of all GGS meningitis patients in our study. Therefore, relevant investigations should be undertaken to rule out these conditions in patients with GBS or GGS meningitis.

Common for all groups of BHS meningitis were a severe course of disease and high risks of unfavourable outcome and in-hospital mortality, which is in line with previous accounts of BHS meningitis [5, 6, 8]. In addition to the severity of the disease, the high risks of poor outcome may be attributed to advanced age of patients, presence of comorbidities and concomitant infections.

Our study has some limitations. Incompleteness of data is inevitable due to the retrospective design including unavailability of more unusual exposures (e.g. horses for cases with GCS meningitis [8]). Moreover, missing records of deceased patients were especially pronounced in the greater Copenhagen area after implementation of a new electronic patient record system in 2016. As a consequence, the observed mortality may be underestimated. Moreover, we consistently presented the total number of patients in whom the specific characteristic was reported in order to account for incompleteness of data and differences in the diagnostic workup and treatment of patients. Strengths of our study include the nationwide population-based design that decreased risk of selection bias. In addition, our data represent the largest series of community-acquired BHS meningitis in adults to date and thereby provides clinically relevant data for physicians treating such patients.

In conclusion, community-acquired BHS meningitis among adults occurs primarily in patients with advanced age and carries a high risk of fatality or unfavourable outcome at discharge.

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Compliance with ethical standards

Before data collection, the project was approved by the Danish Data Protection Agency (record no. 2008-58-0028, local ID-number 2017-218) and the Danish Board of Health (record no. 3-3013-2365/1). Acceptance from a research ethics committee is not required for this type of study in Denmark.

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

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