Streptococcus gallolyticus meningitis in adults: report of five cases and review of the literature

A. van Samkar[1], M. C. Brouwer[1], Y. Pannekoek[2], A. van der Ende[2,3] and D. van de Beek[1]

1) *Department of Neurology,* 2) *Department of Medical Microbiology, Academic Medical Centre, Centre of Infection and Immunity Amsterdam (CINIMA) and* 3) *Netherlands Reference Laboratory for Bacterial Meningitis, Academic Medical Centre, Amsterdam, The Netherlands*

Abstract

We describe the incidence and patient characteristics of *Streptococcus gallolyticus* meningitis. We identified *S. gallolyticus* meningitis in a nationwide cohort of patients with community-acquired bacterial meningitis, and performed a systematic review and meta-analysis of all reported adult cases in the literature. Five cases were identified (0.3%) in a cohort of 1561 episodes of bacterial meningitis. In one patient, bowel disease (colon polyps) was identified as a predisposing condition for *S. gallolyticus* infection, whereas no patients were diagnosed with endocarditis. In a combined analysis of our patients and 37 reported in the literature, we found that the median age was 59 years. Predisposing factors were present in 21 of 42 patients (50%), and mainly consisted of immunosuppressive therapy (seven patients), cancer (four patients), and alcoholism (four patients). Colon disease was identified in 15 of 24 patients (63%) and endocarditis in five of 27 patients (18%). Co-infection with *Strongyloides stercoralis* was identified in 14 of 34 patients (41%), ten of whom were infected with human immunodeficiency virus or human T-lymphotropic virus. Outcomes were described for 37 patients; eight died (22%) and one (3%) had neurological sequelae. *S. gallolyticus* is an uncommon cause of bacterial meningitis, with specific predisposing conditions. When it is identified, consultation with a cardiologist and gastroenterologist is warranted to rule out underlying endocarditis or colon disease. Stool examinations for *Strongyloides stercoralis* should be performed in patients who have travelled to or originate from endemic areas.

Keywords: Bacterial meningitis, *Streptococcus bovis*, *Streptococcus gallolyticus*, *Streptococcus gallolyticus* ssp. *pasteurianus*, *Strongyloides stercoralis*
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Corresponding author: D. van de Beek, Department of Neurology, Academic Medical Centre, University of Amsterdam, PO Box 22660, 1100DD, Amsterdam, The Netherlands
E-mail: d.vandebeek@amc.uva.nl

Introduction

Bacterial meningitis is usually caused by *Streptococcus pneumoniae* and *Neisseria meningitidis* [1]. These bacteria form part of the normal human nasopharyngeal flora, and can cause meningitis in both immunocompromised and healthy individuals. Other bacteria causing meningitis are commonly associated with specific risk factors, such as *Listeria monocytogenes* and *Staphylococcus aureus* [2].

Streptococcus gallolyticus, formerly known as a member of the *Streptococcus bovis* group, is a bacterium that has been reported to cause meningitis and endocarditis [3,4]. Three subspecies of *S. gallolyticus* are known: *gallolyticus*, *macedonicus*, and *pasteurianus* [5]. The bacteria were first discovered in cattle, and have been reported to be colonic commensals in 10–15% of healthy humans [6]. Among patients with *S. gallolyticus* bacteraemia, 50–70% have been reported to have colon carcinoma or benign colon abnormalities, such as diverticulosis and colon adenomas [5,7]. *S. gallolyticus* infection is also associated with strongyloidiasis, for which different hypotheses have been suggested: (a) *Strongyloides stercoralis* makes the bowel wall more permeable to bacteria such as *S. gallolyticus*, which can invade the body and cause sepsis and/or meningitis; and (b) the migrating *Strongyloides* larvae penetrate the gut mucosa and

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enter the portal circulation, carrying with them *S. gallolyticus* [8,9]. The incidence and patient characteristics of *S. gallolyticus* meningitis are unknown.

We describe five cases of bacterial meningitis caused by *S. gallolyticus* identified in a prospective nationwide cohort study on community-acquired bacterial meningitis, and the results of a systematic review of the literature. In this review, we describe the epidemiology, clinical characteristics, risk factors and outcomes of *S. gallolyticus* meningitis.

Patients and methods

Case series

In a prospective observational cohort study in The Netherlands, we included episodes of community-acquired bacterial meningitis in adults confirmed by cerebrospinal fluid (CSF) culture. The methods have been described previously [10]. In summary, all patients were aged ≥16 years, and were listed in the database of the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) from January 2006 to December 2014. This laboratory receives CSF isolates from approximately 90% of all patients with bacterial meningitis in The Netherlands. The NRLBM provided daily updates of the names of the hospitals to which patients with bacterial meningitis had been admitted in the preceding 2–6 days and the names of physicians. Physicians were contacted, and informed consent was obtained from all participating patients or their legally authorized representatives. Physicians could also contact the investigators without a report by the NRLBM for inclusion of patients.

Episodes with negative CSF cultures could also be included if the following criteria were present: (a) blood cultures showed *S. gallolyticus*; (b) CSF analysis showed at least one individual predictor of bacterial meningitis, defined as a glucose level of <34 mg/dL (1.9 mmol/L), a CSF glucose/blood glucose ratio of <0.23, a protein level of >220 mg/dL, or a leukocyte count of >2000/mL [1]; and (c) the clinical presentation was compatible with bacterial meningitis.

All patients with *S. gallolyticus* meningitis were selected from this cohort. *S. gallolyticus* subspecies were identified with VITEK 2 (BioMérieux, Marcy-l'Etoile, France). *S. gallolyticus* subspecies of cases 2 and 4 were identified with an in-house-developed molecular biological technique sequencing a part of the gene encoding ribosomal protein S2 (*rpsB*). The primers targeting *rpsB* were Str_F4 (3′-ATGGCAGTAATTTCAATG-5′) and Str_R2 (3′-GAATTTTTCAAGACG-5′). Sequences of the amplicon were clustered with reference sequences obtained from GenBank by use of the neighbour-joining algorithm in MEGA 6.06 with 1000 bootstraps.

Patients with hospital-associated meningitis, with a neurosurgical device or who had undergone a neurosurgical operation within 1 month before bacterial meningitis onset were excluded. Patients using immunosuppressive drugs, with asplenia, with diabetes mellitus, with alcoholism or with infection with human immunodeficiency virus (HIV) were considered to be immunocompromised [10]. Additional clinical data on specific risk factors, i.e. colon disease and endocarditis, were retrospectively collected from the discharge letters. At discharge, all patients underwent a neurological examination performed by a neurologist. The study was approved by the ethics committee of the Academic Medical Centre, Amsterdam, The Netherlands.

Review of the literature

We performed a literature search in PubMed with the terms '*Streptococcus bovis* AND meningitis', '*Streptococcus gallolyticus* AND meningitis', and '*Streptococcus caprinus* AND meningitis'. *S. gallolyticus* meningitis was defined as described in 'Case series'. Articles reporting on children or animals, duplicate articles and articles in which no specific data were given for *S. gallolyticus* meningitis patients (e.g. articles in which there was only an analysis of the whole group, and no subanalysis for *S. gallolyticus*) were excluded. Articles with neither an abstract nor access to the full text were excluded. Studies written in English, German, French, Dutch, Spanish, Italian and Portuguese were included. In a meta-analysis of clinical data, we systematically scored baseline and presenting characteristics (including predisposing conditions), clinical course, and outcome.

Results

We identified five cases of *S. gallolyticus* meningitis among 1561 episodes (0.32%) included in our cohort study (Table 1, Fig. S1). The median age of the patients was 77 years (range, 50–91 years). Three patients were immunocompromised (Table 1). All patients presented with fever and neck stiffness, and headache was reported in three. Blood cultures were positive in all patients, and CSF cultures were positive in three patients. None of the patients was diagnosed with endocarditis, although two died quickly before this had been investigated, and echocardiography results were not known for one other patient. Colonoscopy was reported in two patients, and showed colon polyps in one. Two patients died from the meningitis, and three patients recovered without sequelae.

Case 1

A 74-year-old man presented with fever and confusion after a holiday in Thailand. His medical history revealed chronic

TABLE 1. Clinical characteristics, aetiology, laboratory findings, treatment and clinical outcome for five adults with *Streptococcus gallolyticus* meningitis

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	74	91	77	50	84
Gender	Male	Female	Male	Male	Female
Predisposing factor(s)	Leukaemia	None	Immunosuppressants, renal failure	None	Diabetes
Clinical presentation					
Temperature (°C)	40.0	38.5	40.4	39.2	39.7
Neck stiffness	Yes	Yes	Yes	Yes	Yes
Headache	Unknown	Yes	Unknown	Yes	Yes
Score on Glasgow Coma Scale	14	9	3	15	14
Neurological deficits	Disorientation	Aphasia	Right-sided hemiparesis	None	Disorientation
CSF findings					
Leukocyte count/mm^3	2880	2896	36 300	6780	2280
Protein level (g/L)	2.16	8.5	5.6	Unknown	7.6
CSF/blood glucose ratio	0.40	0.23	0.30	0.32	0.36
Cranial CT	Normal	Normal	Infarction in left cerebral hemisphere	Normal	Normal
Cultures					
Blood culture	Positive	Positive	Positive	Positive	Positive
CSF culture	Negative	Negative	Positive	Positive	Positive
S. gallolyticus-associated disease					
Endocarditis	Unknown	Unknown	Unknown	No	No
Bowel abnormalities	Unknown	Unknown	Unknown	Normal	Colon polyps
Empirical treatment					
Antibiotics	Amoxycillin, ceftriaxone	Amoxycillin, cefotaxime	Penicillin	Ceftriaxone	Penicillin
Dexamethasone	Yes	Yes	Yes	Yes	Yes
Outcome	Recovery	Death	Death	Recovery	Recovery

CSF, cerebrospinal fluid; CT, computed tomography.

lymphocytic leukaemia and transitional cell carcinoma of the bladder. Physical examination showed fever, disorientation, and neck stiffness. CSF examination was consistent with bacterial meningitis (Table 1). Blood cultures were positive for *S. gallolyticus*; CSF cultures were negative. Amoxycillin 2 g six times daily, ceftriaxone 2 g twice daily and dexamethasone 10 mg four times daily were started. The patient was discharged after 11 days. Investigations for endocarditis, colon disease and strongyloidiasis were not performed.

Case 2

A 91-year-old woman presented with headache, vomiting, and aphasia. Her medical history revealed hypertension, anaemia, and atrial fibrillation, for which she used antihypertensives and acenocoumarol. Physical examination showed fever, neck stiffness, and aphasia. After correction of the coagulation status, lumbar puncture was performed, and showed CSF abnormalities consistent with meningitis (Table 1). The patient was treated with amoxycillin 2 g six times daily, cefotaxime 2 g six times daily, and dexamethasone 10 mg four times daily. She died 1 day after admission. Blood cultures became positive for *S. gallolyticus* ssp. *gallolyticus* (Fig. S1); CSF cultures were negative.

Case 3

A 77-year-old man with a medical history including haemodialysis for renal failure presented with fever. Physical examination showed neck stiffness and a right-sided hemiparesis. Cranial computed tomography showed a hypodensity consistent with left-hemisphere cerebral infarction. CSF examination was consistent with bacterial meningitis (Table 1). The patient was treated with penicillin 6 MU six times daily and dexamethasone 10 g four times daily. He developed respiratory failure and died on the same day. Blood and CSF cultures were positive for *S. gallolyticus*.

Case 4

A 50-year-old man complained of fever and progressive headache lasting for 3 days. His medical history showed no abnormalities. Physical examination showed fever and neck stiffness. CSF examination was consistent with bacterial meningitis (Table 1). Treatment with ceftriaxone 2 g twice daily and dexamethasone 10 mg four times daily was started. *S. gallolyticus* ssp. *pasteurianus* (Fig. S1) was cultured from CSF and blood. Transthoracic ultrasound and colonoscopy did not show endocarditis or colon abnormalities. The patient was discharged after 11 days in good clinical condition.

Case 5

An 84-year-old woman presented with headache and confusion. Her medical history showed atrial fibrillation, diabetes, and heart failure. Physical examination showed disorientation and no neck stiffness. CSF examination was consistent with bacterial meningitis (Table 1). Empirical treatment was started with amoxycillin 2 g six times daily, ceftriaxone 2 g daily, and dexamethasone 10 mg four times daily. *S. gallolyticus* was cultured from blood and CSF, and antibiotic treatment was switched to penicillin 2 MU six times daily. Transthoracic

ultrasound did not show endocarditis; colonoscopy showed colon polyps. The patient was discharged after 19 days in good clinical condition.

Review of the literature

In total, 86 studies were identified, of which 28 met the inclusion criteria, describing 37 patients (Fig. 1). The identified studies were performed between 1975 and 2015 (Table S1, Supplementary reference list).

Combining these data with those of our patients (Table 2), we found that the median age was 59 years, and that 27 of 41 patients (66%) were male. Predisposing factors were described for 18 of 42 patients (43%), and mainly consisted of immunosuppressive therapy (seven patients), cancer (four patients), and alcoholism (four patients) (Table 2). Three patients had an anatomical defect (CSF leak, ventriculostomy, and postoperative cystic cavity communicating with the intradural space). Fourteen patients suffered from strongyloidiasis, and in 13 the strongyloidiasis infection was associated with an underlying disease (human T-lymphotropic virus (HTLV)-1 infection in eight, HIV infection in two, and immunosuppressive medication in three).

Presenting symptoms were reported for 31 patients (Table 2). Colon abnormalities were identified in 15 of 24 patients (63%): diverticulosis (five patients), colon adenoma (five patients), colon carcinoma (two patients), and ulcers, radiation enterocolitis, and radiation proctitis (each in one patient). Endocarditis was diagnosed in five of 28 patients (18%). One patient had both colonic diverticulosis and endocarditis.

CSF cultures were positive in 36 of 41 patients (88%), and blood cultures were positive in 33 of 38 patients (87%) (Table 1). For nine patients, the subspecies of *S. gallolyticus* was reported; eight were *S. gallolyticus* ssp. *pasteurianus* [11–17].

Fourteen of 42 patients (33%) received adjuvant treatment with dexamethasone. Complications of *S. gallolyticus* meningitis were reported in eight of 36 patients (22%), and consisted of atrial fibrillation, respiratory insufficiency, pneumonia, hearing loss, transient facial nerve paralysis, seizures, hyponatraemia, and progression despite treatment, occurring in one patient each.

Eight of 37 patients died (22%) and three survivors (10%) had sequelae, consisting of hearing loss in one patient and persisting

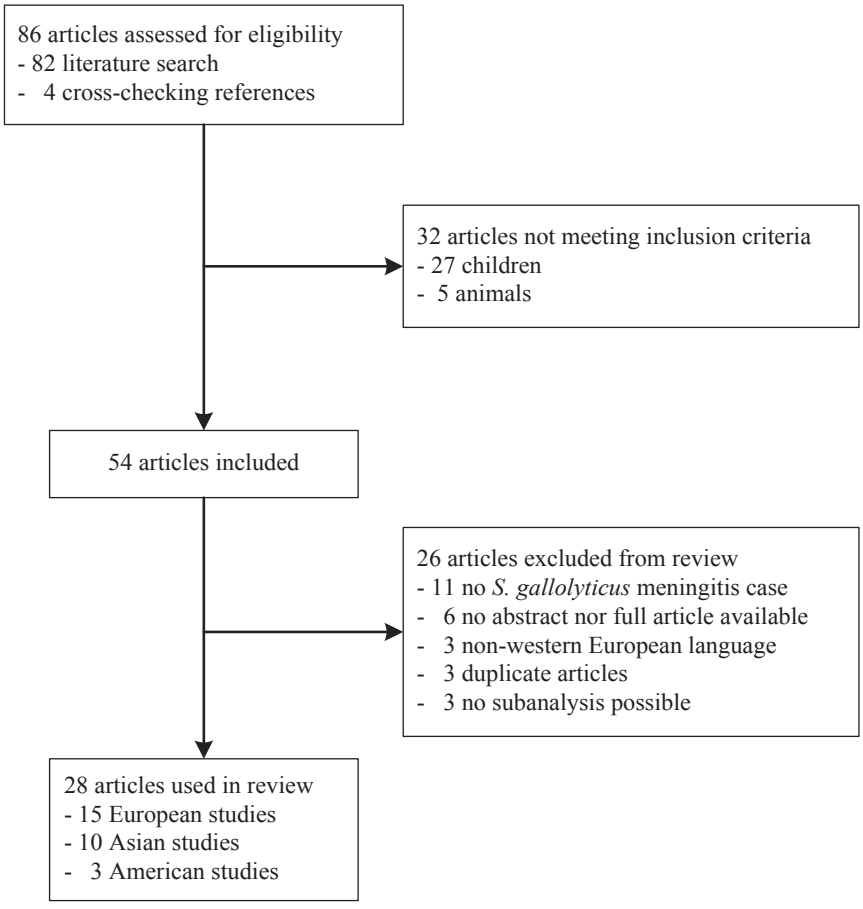

FIG. 1. Flow chart of review of articles on *Streptococcus gallolyticus* meningitis.

TABLE 2. Clinical characteristics, aetiology and clinical outcome for adults with *Streptococcus gallolyticus* meningitis; combination of our patients and patients described in the literature

Characteristics	Value
Median age (years), range	59 (23–91)
Male, *n*/*N* (%)	27/41 (66)
Predisposing factor(s), *n*/*N* (%)	18/42 (43)
Immunosuppressants, *n* (%)	7 (17)
Cancer, *n* (%)	4 (10)
Alcoholism, *n* (%)	4 (10)
HIV infection, *n* (%)	3 (7)
Diabetes mellitus, *n* (%)	3 (7)
Renal failure, *n* (%)	2 (7)
Splenectomy, *n* (%)	1 (2)
Clinical presentation, *n*/*N* (%)	
Headache	21/31 (68)
Fever	26/31 (84)
Neck stiffness	20/31 (65)
Altered consciousness	13/31 (42)
Nausea	6/31 (19)
Photophobia	6/31 (19)
S. gallolyticus-associated disease, *n*/*N* (%)	
Strongyloidiasis	14/34 (41)
Endocarditis	5/28 (18)
Colon abnormalities	15/24 (63)
Positive cultures, *n*/*N* (%)	
Blood	33/38 (87)
Cerebrospinal fluid	36/41 (88)
Both	27/37 (43)
Complications, *n*/*N* (%)	8/36 (22)
Outcome, *n*/*N* (%)	
Death	8/37 (22)
Sequelae	3/29 (10)
Full recovery	26/29 (90)

HIV, human immunodeficiency virus.

nausea in two patients; both patients appeared to have strongyloidiasis, and the nausea disappeared after treatment.

Discussion

S. gallolyticus is a rare cause of community-acquired bacterial meningitis. Only five of 1561 patients in our cohort (0.3%) were infected with *S. gallolyticus*. In the literature, cases of *S. gallolyticus* meningitis have been described in cohorts of patients with specific risk factors. In a cohort of patients with bacterial meningitis and liver cirrhosis, one of 12 patients had *S. gallolyticus* meningitis, and in a case series of patients with bacterial meningitis and coexisting strongyloidiasis, one of six patients had *S. gallolyticus* meningitis [18,19]. In two cohorts of patients with streptococcal meningitis, the relative incidence rates of *S. gallolyticus* meningitis were one in 26 cases and one in 29 cases [20,21].

Risk factors for *S. gallolyticus* meningitis are endocarditis [3] and colon disease [5,7]. *S. gallolyticus* infection is the cause of 2–10% of cases of bacterial endocarditis, and is associated with advanced age as compared with bacterial endocarditis caused by other pathogens [22]. Endocarditis has been reported to be caused by *S. gallolyticus* ssp. *gallolyticus* more frequently than by *S. gallolyticus* ssp. *pasteurianus*—reported rates vary between 43% and 100%, as compared with rates of 8–29% [23,24]. In our study, one patient was infected with *S. gallolyticus* ssp. *pasteurianus*, and none of the patients was diagnosed with endocarditis. The rate of endocarditis could have been under-reported, because only two patients underwent echocardiography. In our meta-analysis, five of 28 patients were diagnosed with endocarditis, and colonoscopy findings were abnormal in 15 of 24 patients. When *S. gallolyticus* is identified in patients with bacterial meningitis, consultation with a gastroenterologist and cardiologist is warranted to identify whether a colonic disease or endocarditis is present as a risk factor for *S. gallolyticus* meningitis, in most cases by colonoscopy and echocardiography [25].

Strongyloidiasis has been described as a risk factor for *S. gallolyticus* meningitis [18,26]. This is due to increased permeability of the bowel wall, through which *S. gallolyticus* can invade the bloodstream and thus cause sepsis and meningitis. In endemic areas such as Brazil and Thailand, *Strongyloides stercoralis* infection has an estimated prevalence of 10–40% [27]. One of our patients had visited Thailand prior to developing *S. gallolyticus* meningitis, where he could have been infected with *Strongyloides stercoralis*. Strongyloidiasis has been described as a disease imported by travellers to endemic areas even 60 years after travel [27]. In our patient, no stool examination was performed to detect *Strongyloides stercoralis*. So far, all patients with *S. gallolyticus* meningitis due to *Strongyloides stercoralis* infection reported in the literature have lived in an endemic area, and imported cases have not been described. Strongyloidiasis may cause mild gastrointestinal symptoms such as diarrhoea, pulmonary symptoms, or no symptoms at all, and may therefore go unnoticed. High-risk groups for *Strongyloides stercoralis* infection are alcoholics, HIV-infected and HTLV-1-infected persons, cancer patients, and other patients who are immunocompromised. All but one of the patients with strongyloidiasis in our meta-analysis were immunocompromised. It has previously been reported that immunocompromised patients with strongyloidiasis are prone to meningitis or sepsis with enteric organisms [28]. Testing for *Strongyloides stercoralis* and (if positive) HIV testing should be performed in patients with *S. gallolyticus* meningitis who have travelled to or originate from areas endemic for strongyloidiasis.

Our study has several limitations. As this is an observational cohort study, patients did not undergo diagnostic procedures or testing according to a prespecified protocol. Therefore, the patients were not routinely tested for HIV, HTLV-1, and strongyloidiasis, and colonoscopy and echocardiography were not performed in all patients; risk factors for *S. gallolyticus* meningitis could therefore have been missed. Furthermore, not all patients with suspected bacterial meningitis may undergo a lumbar puncture, e.g. patients with coagulopathy due to sepsis or those with space-occupying lesions on cranial imaging. These patients were not included in our cohort, which may have led

to a possible underestimation of the incidence of *S. gallolyticus* meningitis. In our meta-analysis, it was often the case that not all characteristics of interest were reported in the retrieved case reports. Therefore, we have presented the total number of patients for whom the specific characteristic was reported. Furthermore, there are inherent difficulties in identifying *S. gallolyticus* accurately to the subspecies level, in particular because of the use of multiple methods for identification, changing nomenclature, and the wide variations in time and geographical regions analysed.

We conclude that *S. gallolyticus* is a rare cause of bacterial meningitis. When it is identified, consultation with a gastroenterologist and cardiologist is warranted, to identify whether a concomitant colon disease or endocarditis is present. Stool examinations for *Strongyloides stercoralis* should be performed in patients who have travelled to or originate from endemic areas.

Transparency declaration

The authors report no conflicts of interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2015.08.003.

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