Enfermedades Infecciosas y Microbiología Clínica 42 (2024) 4–12

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Original article

Streptococcus bovis infection of the central nervous system in adults: Report of 4 cases and literature review

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ARTICLE INFO

Article history:
Received 20 April 2022
Accepted 22 June 2022
Available online 17 April 2023

Keywords:
Central nervous system infections
Meningitis
Cerebral abscess
S. bovis
Intestinal diseases

ABSTRACT

Objectives: To describe the clinical features, history and association with intestinal disease in central nervous system (CNS) *S. bovis* infections.
Methods: Four cases of *S. bovis* CNS infections from our institution are presented. Additionally a systematic literature review of articles published between 1975 and 2021 in PubMed/MEDLINE was conducted.
Results: 52 studies with 65 cases were found; five were excluded because of incomplete data. In total 64 cases were analyzed including our four cases: 55 with meningitis and 9 with intracranial focal infections. Both infections were frequently associated with underlying conditions (70.3%) such as immunosuppression (32.8%) or cancer (10.9%). In 23 cases a biotype was identified, with biotype II being the most frequent (69.6%) and *S. pasteurianus* the most common within this subgroup. Intestinal diseases were found in 60.9% of cases, most commonly neoplasms (41.0%) and *Strongyloides* infestation (30.8%). Overall mortality was 17.1%, with a higher rate in focal infection (44.4% *vs* 12.7%; $p = 0.001$).
Conclusions: CNS infections due to *S. bovis* are infrequent and the most common clinical form is meningitis. Compared with focal infections, meningitis had a more acute course, was less associated with endocarditis and had a lower mortality. Immunosuppression and intestinal disease were frequent in both infections.

Infección del sistema nervioso central por *Streptococcus bovis* en adultos: reporte de 4 casos y revisión de la literatura

Palabras clave:
Infecciones del sistema nervioso central
Meningitis
Absceso cerebral
S. bovis
Enfermedad intestinal

RESUMEN

Introducción: Streptococcus bovis, una causa bien conocida de endocarditis asociada a cáncer colorrectal, es también una causa poco frecuente de infecciones del sistema nervioso central (SNC), incluyendo meningitis, abscesos cerebrales o empiema subdural. El objetivo de este estudio es describir las características clínicas, los antecedentes médicos y la asociación con la enfermedad intestinal en las infecciones por *S. bovis* en el SNC.
Métodos: Describimos 4 infecciones por *S. bovis* en el SNC en nuestra Unidad y, a continuación, presentamos una revisión bibliográfica de los artículos publicados entre 1975-2021 en PubMed/MEDLINE.
Resultados: Se encontraron 52 estudios con 65 casos; 5 se excluyeron por datos incompletos. En total se analizaron 64 casos incluyendo nuestros 4: 55 con meningitis y 9 con infecciones focales intracraneales. Ambas infecciones se asociaron con frecuencia a condiciones subyacentes (70,3%) como la inmunosupresión (32,8%) o el cáncer (10,9%). En 23 casos se identificó un biotipo, siendo el más frecuente el biotipo II (69,6%), y dentro de ellos, *S. pasteurianus*. En el 60,9% de los casos se detectaron enfermedades intestinales, siendo las más frecuentes las neoplasias (41,0%) y la infestación por *Strongyloides* (30,8%). La mortalidad global fue del 17,1%, con una tasa mayor en la infección focal (44,4 frente a 12,7%; p = 0,001).

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https://doi.org/10.1016/j.eimce.2022.06.019

Conclusiones: Las infecciones del SNC debidas a *S. bovis* son poco frecuentes y la forma clínica más común es la meningitis. En comparación con las infecciones focales, la meningitis tiene un curso más agudo, está menos asociada a la endocarditis y tiene una menor mortalidad. La inmunosupresión y la enfermedad intestinal fueron frecuentes en ambas infecciones.

Introduction

Streptococcus bovis, currently named *Streptococcus bovis/equinus complex*,[1] is a gram-positive bacterium and a part of the intestinal microbiota of healthy humans. *Streptococcus bovis* is a frequent endocarditis cause, being associated with colorectal carcinoma in a high rate.[2] *Streptococcus bovis* is an infrequent but known cause of meningitis in children[3] and is rarer in adults. In a non-*S. pneumoniae* streptococcal meningitis series, *S. bovis* caused 5% of the cases.[4] Other types of central nervous system (CNS) infections, like intracranial focal infections are less common; a few cases of brain abscesses and subdural empyema have been reported.[5–11] These cases are occasionally associated with colorectal carcinoma.[5,7]

Due to its low incidence, the clinical manifestations and management of *S. bovis* CNS infections are not fully characterized, neither are their related conditions. For example, *S. bovis* infective endocarditis, mainly *S. gallolyticus* subsp. *gallolyticus*, is associated with colorectal cancer, but whether this cancer associates also with CNS infections remains unknown.

The objective of the present study is to describe the clinical features and natural history of CNS infections caused by *S. bovis* and their degree of association with intestinal disease.

Methods

Patients

326 *S. bovis* bacteremia episodes were identified between 1990 and 2021 in our hospital. In two cases a concurrent CNS infection was demonstrated: one case of meningitis and one case of brain abscess. During the same period 532 positive isolates for *S. bovis* other than blood cultures were identified; from which one case was a pus sample from a subdural empyema and one case was a cerebrospinal fluid (CSF) culture from a patient with meningitis. This four case-series patients was extended with a systematic literature research.

Microbiological methods

Species identification of both strains was performed using the API 20 STREP and VITEK 2 systems using the Gram-positive (GP) identification card (both from bioMérieux, Marcy l'Etoile, France). Additional confirmatory tests were performed by conventional[12] and molecular methods by analysis of the complete rRNA gene sequence,[13] as well as the polymorphism of manganese-dependent superoxide dismutase gene (*sodA*) according to the indications of Poyart et al.[14] The sequences obtained were compared with those of the corresponding genes available in GenBank by using Blast sequence software (http://www.ncbi.nlm.nih.gov/). The minimal inhibitory concentration (MIC) of penicillin and cefotaxime was determined by E-test (AB Biodisk, Solna, Sweden) on Mueller-Hinton agar plates supplemented with 5% sheep blood.

Literature review

To identify additional cases of *S. bovis* CNS infections in adults, we conducted a limited search in Pubmed/Medline in July 2021. Articles published since 1975 to 30 July 2021 were included. The search terms used were [*Streptococcus bovis* OR *gallolyticus OR pasteurianus OR infantarius*] AND [meningitis OR brain OR spinal OR subdural OR "epidural abscess"]. Secondarily, references in the retrieved articles were also reviewed. All articles were screened for the following information: age, sex, type of CNS infection and other concomitant infections, systemic and neurological symptoms, diagnostic methods, *S. bovis* biotypes or subspecies if available, type of intestinal lesion where present, comorbidities, treatment and outcome. The absence of this information except the biotype conduced to the exclusion the articles. Epidural abscesses were also excluded because they are almost invariably secondary to spondylodiscitis.[15] All the information was codified in a separate database.

Statistical analysis and report of the results

Quantitative variables were expressed in mean and standard deviation; categorical variables with counts and percentages. Chi squared test was used when testing categorical variables between groups.

Results

Case report

Case 1. Cerebral abscess

A 61-year-old male farmer who has contact with cattle and with no previous significant medical problems presented with a week history of malaise, headache, fever and progressive weakness of the left arm. The physical examination revealed an afebrile patient with normal vital signs. He was alert and exhibited normal mental activity. The patient had hypoesthesia and paresis in his left arm. Meningeal signs were negative. The rest of the physical findings were unremarkable.

The results of the laboratory studies performed at admission were unremarkable (leukocyte count of 8000/mm^3 and 65 mg/L C-reactive protein). A contrast-enhanced CT of the head revealed a loculated ring-enhancing lesion of 2 cm in the right parietal lobe. The blood cultures yielded *S. bovis.* The isolate was identified as *S. gallolyticus* subsp. *gallolyticus* (*S. bovis* biotype I). The MICs for penicillin and cefotaxime were 0.064 and 0.19 mg/L respectively. Therapy with ceftriaxone 2 g every 12 h was initiated. The patient improved during the first 24 h. An echocardiogram revealed mitral and aortic valve vegetations, without valvular regurgitations. A colonoscopy showed diverticula and a 1 cm tubular adenoma in the descending colon and 2 tubular microadenomas in the hepatic flexure. After a total of 8 weeks of antibiotic therapy, the patient fully recovered all neurological function. A total follow-up of five years was completed without signs of recurrence.

Case 2. Subdural empyema

A 72-year-old male farmer who has contact with cattle was admitted to our hospital with a two-day course of fever and delirium. The patient had a history of insulin-treated diabetes, chronic lymphocytic leukemia and an aortic valve prosthesis implanted 22 months before. One month before this hospitalization, the patient was admitted with a spontaneous chronic right occipital subdural hematoma, and trepanation was conducted. The patient fully recovered.

During the second hospitalization, the physical examination revealed bradypsychia, disorientation and fever (38.5 °C), with no neurological deficit. Amoxicillin-clavulanate 1 g every 8 h was initiated at the Emergency Department for a putative urinary tract infection, although no urinary symptoms were reported. The results of the laboratory studies and chest radiograph were normal. Blood cultures and urine cultures collected after 2 antibiotic doses were negative.

At the fifth day of hospitalization, the patient complained of headache, experienced epileptic seizures and developed left hemiparesis. A brain CT scan revealed enlargement of the previously known subdural hematoma with peripheral areas of rebleeding with edema and midline deviation. The patient underwent craniotomy, during which pus was observed, and an empyema evacuation was performed. *Streptococcus bovis* was isolated in the sample submitted to Microbiology. The isolate was identified as *S. infantarius* subsp. *coli* (*S. bovis* biotype II/1). The MICs for penicillin and cefotaxime were 0.032 mg/L and 0.064 mg/L, respectively.

The study was completed with a transesophageal echocardiogram (TEE), which revealed a vegetation on the prosthetic valve, without valvular insufficiency. Treatment was completed with ceftriaxone 2 g every 12 h for 6 weeks, with favorable clinical and radiological evolution and resolution of the condition, as well as resolution of the vegetation in the TEE. For this reason, no valvular surgery was needed. A colonoscopy performed 16 months earlier was normal. He continued to be alive and well during a three-year follow-up.

Case 3. Acute meningitis with endocarditis

An 80-year-old man with a history of diabetes mellitus and chronic lymphocytic leukemia in progression was awaiting for chemotherapy initiation. He consulted at the Emergency Department with fever (39 °C), chills and stupor. Physical examination reveal stupor and neck stiffness with no focal neurogical deficit. Blood test results were unremarkable. A head CT scan showed no anomalies and lumbar puncture was performed. CSF analysis showed glychorrhachia of 65 mg/dL (plasmatic 132 mg/dL), proteinorrhachia of 358 mg/dL and neutrophil predominant pleocytosis (732 cells per mm3, 98%). Therapy with meropenem 2 g every 8 h, linezolid 600 mg every 12 h and ampicillin 2 g every 4 h was initiated and he was admitted to the Intensive Care Unit. After antimicrobial were instated fever submitted and neurological status improved during the following 48 h, allowing for his discharge to a conventional ward. Blood and CSF culture yielded *S. bovis*, thus therapy was modified to ceftriaxone 2 g every 12 h. The isolate was identified as *S. gallolyticus* subsp. *pasteurianus* (*S. bovis* biotype II/2), MICs for penicillin was 0.064 and for cefotaxime were 0.125 mg/L. A TEE was performed showing severe mitral regurgitation with tendinous string break-up and a vegetation. After the patient was stabilized, he underwent a colonoscopy which showed diverticula with no other abnormalities. A total of 4-week ceftriaxone therapy was completed. Patient died 25 months after due to progression of his hematological disease.

Case 4. Acute meningitis with spondylodiscitis

An 86-year-old man with medical history of valvular cardiopathy secondary to severe mitral regurgitation, expecting surgery decision, and a chronic subdural hematoma 9 years before with symptomatic epileptic seizures. He had contact with cattle.

He consulted to Emergency Department with decreased consciousness level since 5 h before. He had fever of 38.9 C with no other vital sign affected. Physical examination revealed stupor, neck stiffness and no focal neurological deficit. A head CT scan was performed which was normal, and a lumbar puncture was made. CSF was turbid, with hypoglychorrhachia (47 mg/dL, plasmatic 139 mg/dL), hyperproteinorrhachia (435 mg/dL) and neutrophil predominant pleocytosis (5800 cells per mm^3, 87%). Ceftriaxone, ampicillin and vancomycin were initiated and the patient was admitted into hospitalization. He showed sensorium improvement but disorientation and neck pain remained, so a brain and spine MNR scan were performed. Meningeal contrast enhancement and cervical spondylodiscitis were found but no abscesses nor meningeal space invasion. *Streptococcus bovis* was isolated in blood cultures but not in CSF culture. The isolate was identified as *S. gallolyticus* subsp. *gallolyticus* (*S. bovis* biotype I), MICs for penicillin was 0.094 and for cefotaxime was 0.190 mg/L. Therapy was simplified to ceftriaxone 4 gr per day for 6 weeks. Two successive TEE performed ten days apart revealed no vegetation. Colonoscopy was undertaken showing diverticulosis. Over the following two weeks, the patients showed progressive recovery and was finally discharged without any sequels. Four months later he was admitted with community acquired pneumonia and died of complications.

Literature review

Search results

Fifty-two studies were found including a total of 65 cases. All studies were cases report. Five cases were excluded because of incomplete data. 60 cases were included,[5–11,16–56] in addition to our 4 patients. A total of 64 cases were analyzed, 55 of which were meningitis and 9 were intracranial focal infections.

Clinical findings

- *Intracranial focal infections:* 9 patients were included, 7 cases of brain abscesses and 2 subdural empyemas. Mean age was 57.8 ± 15.0 years and the male to female ratio was 3.5:1. Fever was present in 8 (88.8%), headache in 5 (55.5%), focal neurological deficit in 7 (77.7%) and stupor or coma in 3 (33.3%). Patients' characteristics are summarized in Table 1.
- *Meningitis*: 55 patients were included. Mean age was 60.6 ± 17.6 years and the sex ratio (men/women) was 1.9:1. In 15 of the 30 (50%) patients in which the symptom duration was recorded, symptoms lasted less than 24 h; eight patients (26.6%) had a symptoms duration of more than three days. In 48 cases in which the symptoms were collected, fever was present in 40 (83.3%), headache in 29 (60.4%), neck stiffness in 38 (79.1%), and 2 had shock. Focal neurological deficit was observed in 6 patients (12.5%), coma in 4 (8.3%) and seizures in 2. Nine patients had associated endocarditis (16.4%) and 3 spondylodiscitis (5.4%); one of these patients had both endocarditis and spondylodiscitis. Association with endocarditis was higher in intracranial focal infections than meningitis (55.5% *vs* 16.4%, $p = 0.019$). CSF abnormalities were typical of bacterial meningitis (Tables 2 and 3), and only 12 of 46 (26%) in which CSF results were reported had less than 1000 cells/mm^3. The features of our 2 cases of meningitis and the 53 previously reported cases of *S. bovis* CNS infection are summarized in Table 2.

Table 1
Central nervous system abscess caused by *Streptococcus bovis* in adults. Literature review and two report cases.

Case [reference]	Age/sex	Infection	Symptoms	Neurologic features	Culture (+)/biotype	Underlying disease	Bowel disease	Duration of treatment (days)	Death (days)
Montejo[5]	69/F	Brain, kidney and splenic abscess. Peritonitis Endocarditis	Fever	Coma Hemiparesis	BC and peritoneal fluid	Cirrhosis. Diabetes mellitus	Carcinoma	6	Yes (5)
Leibovitch[6]	28/M	Brain abscess	Fever Headache	Coma Hemiparesis	Pus abscess	Bronchiectasis	Normal colonoscopy	98	No
Emiliani[7]	57/M	Brain abscess	Fever Stiffness	Confused	Pus abscess	Alcoholism	Villous adenoma	42	Yes (30)
Maniglia[8]	41/M	Brain abscess	Headache	Hemiparesis	Pus abscess	HIV Alcoholism	Normal barium enema	56	No
Attias[9]	54/M	Brain abscess. Endocarditis	Fever	No	BC		Not studied	(?)	No
Bigorra[10]	70/F	Brain abscess Endocarditis	Fever	Stupor Disarthria	BC/*S. gallolyticus*	Splenectomy Azathioprine	Not studied	1	Yes (1)
Cohen[11]	70/M	Subdural empyema	Fever Headache	Seizure Facial paresis	BC, CSF and pus abscess/*S. bovis* II	Diabetes mellitus Chronic renal failure Alcoholism	Tubular adenoma	42	Yes (36)
Present report (Case 1)	61/M	Brain abscess. Endocarditis	Fever Headache	Arm paresis Seizures	BC/*S. gallolyticus*		Villous adenoma	56	No
Present report (Case 2)	72/M	Subdural empyema. Endocarditis	Fever Headache	Obnubilation Hemiparesis Seizures	Pus abscess/*S. lutetiensis*	Chronic lymphocytic leukemia Diabetes mellitus	Normal colonoscopy[a]	42	No

F: female; M: male; BC: blood culture; CSF: cerebrospinal fluid; HIV: Human Immunodeficiency Virus.
[a] 16 months ago. (?) Data not reported.

Underlying conditions

Forty-five of the 64 patients (70.3%) had one or more underlying disease or predisposing factor (Tables 1 and 2). The most frequent conditions were immunosuppression (32.8%) and cancer (10.9%). The main cancer type was colorectal carcinoma (7 cases) and lymphoma/leukemia (7 cases). HIV/HTLV (10 cases) and steroids use (8 cases) was the most frequent immunosuppression causes. Four patients had local predisposing factors: CSF leak, surgery or spinal manipulation. Twelve patients (21.8%) with meningitis had *Strongyloides* disease.

Microbiology

In patients with intracranial focal infections, pus culture yielded diagnosis in 6 cases (66.7%), blood culture in 7 cases (77.8%) and CSF culture in one case (11.1%). In patients with meningitis CSF culture was positive in 13 cases (23.6%), blood culture was positive in 12 cases (21.8%) while 30 patients had both cultures positive (54.5%). CSF Gram stain revealed bacteria in 18 cases (46.1%).

In 23 cases, biotype or species identification was performed: 16 were caused by *S. bovis* biotype II (*S. gallolyticus* subsp. *pasteurianus*: 7 cases, *S. infantarius* subsp. *coli:* 1 case and biotype II with no specified subspecies: 7 cases) and 8 by *S. gallolyticus* subsp. *gallolyticus*. All tested strains were penicillin sensitive (MICs: 0.06–0.09 mg/L). *S. bovis* was isolated in pure culture, except in 3 cases: one cerebral abscess (*Fusobacterium necrophorum, Peptostreptococcus* sp., and group G *Streptococcus* sp.) and two meningitis associated with infection by *S. stercoralis* (*E. faecalis,* and *Klebsiella pneumoniae*, respectively).

Treatment, outcomes and mortality

The antibiotic therapy consisted of beta-lactam (penicillin or ceftriaxone in most cases) in 56 of 59 cases where treatment was specified. In 10 cases, the beta lactam was used in combination with other antibiotics (aminoglycosides in most cases). Duration of therapy ranged from 6 to 14 weeks in intracranial pyogenic infections; in patients with meningitis and no other infectious focus treatment duration ranged from 10 to 14 days, while in those with meningitis and either endocarditis or spondylodiscitis treatment lasted 4 weeks except in a case in which it lasted 6 weeks. Steroids were employed in 19 cases (in 17 cases of meningitis). Surgery was performed in 5 cases (2 abscesses, 2 subdural empyema and 1 case of meningitis with ventriculitis).

The overall mortality was 17.1% (11/64), being higher in intracranial infections than in meningitis: 55.5% (5/9) *vs.*16.4% (9/55); $p = 0.001$. One patient had hearing loss as a sequel. No relapse was reported, with a follow-up duration of between 1–54 months (median 12 months).

Bowel pathology

Underlying bowel disease was found in 39 patients (60.9%): 16 had neoplasms, 12 had intestinal Strongyloidiasis, 2 had actinic bowel disease, 2 had ulcerative colitis and 8 had diverticulosis.

Strongyloidiosis diagnostic was performed by visualizing eggs in stool in 8 cases and by intestinal biopsy in 4 cases. All four of them had abdominal symptoms, and all corresponded to meningitis. A thorough bowel study by pancolonoscopy or authopsy was performed in 40 patients found carcinoma or advanced adenoma in 11 (27.5%); only one patient had symptoms (2.5%).

Discussion

Streptococcus bovis often causes endocarditis, bacteremia, urinary tract infections and septic arthritis.[57] *Streptococcus bovis* rarely causes CNS infections in adults. In a large series of bacterial meningitis, *S. bovis* was found to cause only 0.3% of 1561 meningitis episodes.[52] In our area, even when there is a high incidence of *S.*

Table 2
Meningitis caused by *Streptococcus bovis* in adults. Literature review and two report cases.

Case [reference]	Age/sex	CSF WBC (%N) Protein/glucose	Cultures (+)/gram/biotype	Underlying disease/predisposing factor	Bowel disease	Duration of treatment (days)	Death (days). (Infection associated)
Cohen[11]	53/M	140 (39) 297/6	CSF and BC Gram (+) *S. bovis* II	HIV Splenectomy	Normal colonoscopy	14	No
Molina[16]	78/F	300 (80) 170/90	CSF and BC Gram (+)	Diabetes mellitus	Rectal cancer with liver metastasis	42	No (spondilodiscitis)
Cedena[17]	81/M	3845 (91) 412/5	CSF Gram (+) *S. gallolyticus*	Diabetes mellitus	Colitis ulcerosa	(?)	No
Wardle[18]	49/F	7200 (79) 186/41	CSF and BC Gram (−) *S. pasteurianus*	Splenectomy	Not studied	14	No
Cadavil[19]	43/M	3450 (78) 319/90	CSF, BC and orine		Normal colonoscopy	(?)	No
Pukkila[20]	39/M	13,800 (90) 195/46	CSF/Gram (+) *S. pasteurianus*	Steroids	Strongyloides.	28	No (endocarditis)
Khan[21]	27/M	3400 (96) 500/52	CSF Gram (+)	Kidney transplantation Steroids	Strongyloides	14	No
Lin[22]	53/M	10,700 (97) 765/94	CSF and BC	Diabetes mellitus Chronic renal failure	Large adenoma	16	Yes (16)
Neves da Silva[23]	75/F	812 232/0	CSF Gram (+)		Diverticulosis	14	No
Shipway[24]	75/M	850 (70) 730/43	BC		Rectal carcinoma	9	Yes (9)
Smith[25]	61/F	1000 (100) 4000/50	CSF and BC Gram (+) *S. pasteurianus*		Hemorrhoids	10	No
Sturt[26]	75/M	112 (62) 282/38	CSF and BC Gram (−) *S. pasteurianus*	Prostate cancer	Radiation proctitis	10	No
Hager[27]	69/F	4180 (74) 706/23	CSF and BC Gram (−)		Strongyloides	14	No
da Costa[28]	44/M	Purulent	CSF	Scoliosis surgery	Not studied	21	No
de Silva[29]	23/F	1625 403/4	CSF and BC Gram (+)	HIV Kaposi sarcoma	Strongyloides	14	No
Namiduru[30]	70/M	2400 (90) 320/20	BC and pleural fluid Gram (−) *S. bovis* II		Normal colonoscopy	14	No
Barragán[31]	62/M	1200 800/9	CSF and BC Gram (+) *S. bovis* II		Adenomatous polyp	24	No
Carnero[32]	74/M	48 (97) 88/36	CSF and BC Gram (−)		Diverticulosis	28	No (endocarditis)
Vilarrasa[33]	45/M	8900 (70) 300/32	CSF and BC Gram (−) *S. bovis* II		Normal colonoscopy	10	No
Hyvernat[34]	62/–	9600 (949) 8100/5	CSF/Gram (−) *S. bovis* II	Steroids	Diverticulosis	(?)	No
Fresco[35]	89/F	2480 (95) 315/33	BC Gram (−)		Diverticulosis	14	No
Link[36]	64/M	–	CSF and BC *S. gallolyticus*	Steroids	Strongyloidiasis	28	No (endocarditis)
Salazar[37]	22/F	3400(95) 3000/50	CSF Gram (−)		Normal barium enema	(?)	No
Fung[38]	72/M	356 (90) 3000/93.6	BC	Diabetes mellitus	Caecum and sigmoid carcinoma	28	No (endocarditis)
Gelfand[39]	68/M	9440 (100) 768/93	CSF and BC Gram (+)	Methotrexate	Not studied	14	No
Jain[40]	37/F	1251 (81) 218/5	CSF and BC Gram (−)	HIV	Strongyloidiasis	(?)	Yes (27)
Coret[41]	61/M	9800 (90) 421/20	CSF and BC Gram (−) *S. pasteurianus*	Steroids	Hyperplastic polyp	14	No
Harley[42]	41/M	8650 (90) 890/18	CSF Gram (−)		Adenomatous polyp	14	No
Purdy[43]	32/F	494 (58) 290/11	CSF	CSF leak Mondini malformation	Not studied	14	No
Purdy[43]	79/M	3493 (97) 790/18	CSF and BC		Diverticulosis	14	No

Table 2 (*Continued*)

Case [reference]	Age/sex	CSF WBC (%N) Protein/glucose	Cultures (+)/gram/biotype	Underlying disease/predisposing factor	Bowel disease	Duration of treatment (days)	Death (days). (Infection associated)
Jacobson[44]	59/M	8600 (98) 610/110	CSF and BC Gram (−)	Steroids Diabetes mellitus Cirrhosis	Normal barium enema	14	No
Jadeja[45]	56/F	1000 (55) 137/35	CSF and BC Gram (−)	Lymphoma Chemotherapy	Radiation enterocolitis	14	No
Schlesinger[46]	38/–	12,400 (97) 224/29	CSF Gram (+)	Myelography	Not studied	(?)	No
Longfield[47]	55/M	1600 (96) 49/63	CSF/Gram (−) *S. gallolyticus*	Nerve block	Normal colonoscopy	14	No
Gavryck[48]	66/M	250 (22) 208/32	CSF and BC Gram (−)	Steroids	Normal colonoscopy	28	No (endocarditis)
Weitberg[49]	90/F	5600 (96) 700/55	CSF and BC Gram (−)		Colon transverse carcinoma	12	Yes (12)
Panwalker[50]	61/M	6440 (97) 390/46	BC Gram (+)		Angle hepatic carcinoma	28	No (endocarditis)
Gray[51]	78/F	Purulent	BC/Gram (−) *S. gallolyticus*		Tubulovillous adenoma	(?)	No
Van Sankar[52]	74/M	2880 216/[a]	BC	Leukemia Bladder cancer	Not studied	(?)	No
Van Sankar[52]	91/F	2896 850/[a]	BC *S. gallolyticus*		Not studied	(?)	Yes (1)
Van Sankar[52]	77/M	36,300 560/[a]	CSF and BC	Immunosupressants Chronic renal failure	Not studied	(?)	Yes (1)
Van Sankar[52]	50/M	6780 –/[a]	CSF and BC *S. pasteurianus*		Normal	(?)	No
Van Sankar[52]	84/F	2280 760/[a]	CSF and BC		Polyps	(?)	No
Lerner[53]	56/M	69 (80) 56/75	CSF and BC	Cirrhosis	Not studied	28	No (endocarditis)
Lerner[53]	49/F	6086 (100) 244/34	BC		Not studied	28	No (endocarditis)
Onuma[54]	74/M	9472 (98) 400/26	CSF and BC Gram (−)		Rectal carcinoma	14	No
Ben-Ami[55]	74/F	4200 (89) 453/73	BC *S. bovis* II	Splenectomy Leukemia C4 deficiency	Normal barium enema	18	No
Sasaki[56]	66/M	–	BC/Gram (+)	HTLV-1	Strongyloidiasis	(?)	No
Sasaki[56]	40/F	–	CSF and BC/Gram (+)	HTLV-1	Strongyloidiasis	(?)	No
Sasaki[56]	44/M	–	CSF and BC/Gram (−)	HTLV-1 T leukemia/lymphoma Resected rectal cancer	Strongyloidiasis	(?)	No
Sasaki[56]	66/M	–	CSF and BC/Gram (+)	HTLV-1	Strongyloidiasis Diverticulosis	(?)	No
Sasaki[56]	46/M	–	CSF and BC/Gram (+)	HTLV-1 T leukemia/lymphoma	Strongyloidiasis	(?)	Yes
Sasaki[56]	49/M	–	CSF Gram (+)	HTLV-1	Strongyloidiasis Adenoma	(?)	No
Present report (Case 3)	80/M	732 (98) 358/65	CSF and BC Gram (+) *S. pasteurianus*	Leukemia	Diverticulosis	28	No (endocarditis)
Present report (Case 4)	86/M	580 (87) 435/47	BC/Gram (−) *S. gallolyticus*	Bladder cancer	Diverticulosis	28	No (spondylodiscitis)

F: female; M: male; BC: blood culture; CSF: cerebrospinal fluid. WBC (% N): White-cell count (per mm^3) and % of neutrophils. Protein (mg/dl). Glucose (mg/dl). HIV: Human Immunodeficiency Virus; HTLV-1: Human T-Lymphotropic Virus type 1.

[a] CSF/glucosa ratio $\leq$ 0.40. (?) Data not reported.

bovis infections,[57] only 4 cases of CNS infection have been identified in 31 years. During the same period, however, we diagnosed 96 cases of CNS pneumococcal infections and 45 of CNS listeriosis.

Most CNS infections caused by *S. bovis* are meningitis, both in adults and children.[3,43,52,58] Meningitis progresses as an acute clinical condition, not as fulminating as pneumococcal meningitis, although somehow more acute than in *Listeria monocytogenes* meningitis.[59–62] Fever, headache and meningeal signs are present in most cases. CSF presents findings typical of purulent meningitis, similar to those of pneumococcal meningitis;[59,60] 75.5% of patients had low CSF glucose concentrations, similar to pneumococcal meningitis[59] but higher than in Listeria infections.[61,62] The diagnosis is usually easy, given the high diagnostic yield results from CSF and blood cultures. Gram stain of CSF is positive in less than half of the cases, an inferior yield to that observed in pneumococcal meningitis,[59,60] but higher than in *Listeria* infections.[61,62] The neurological and extraneurological complications are much less frequent than those caused by *S. pneumoniae* or *L.*

Table 3
Bacteriological, cytological and biochemical parameters of cerebrospinal fluid in the *S. bovis* meningitis.

Parameter	N° practiced test	N° of positive tests (%)
Cells/mm³	46	
<999		12 (26.0%)
1000–9999		30 (65.2%)
>10,000		4 (8.7%)
Protein (g/L)	45	
<0.99		3 (6.6%)
1–9.9		38 (84.4%)
>10		4 (8.8%)
Glucose	45	
Hypoglycorrhachia[a]		34 (75.5%)
CSF culture	55	43 (78.1%)
CSF Gram stain	39	18 (46.1%)

[a] Less than 40% of the serum glucose or <40 mg/dl.
CSF, cerebrospinal fluid.

monocytogenes. For these reasons, infection-related mortality, neurological sequelae, and relapse are also more infrequent.[59–62]

Compared with other CNS pathogens, such as meningococcus or pneumococcus, which rarely cause brain abscesses, 11% of the reported *S. bovis* CNS infections are brain abscesses, similar than in *Listeria*.[63] Abscesses in *S. bovis* are more frequently supratentorial and multiple and entail a higher mortality than those caused by *Listeria*.[5–10,63] Unlike meningitis, intracranial focal infections caused by *S. bovis* frequently have a subacute course and are more frequently associated with focal neurological deficits and a poor prognostic as well.[5–10] Likewise, intracranial focal infections are frequently associated with other types of infection such as endocarditis, an association that is less frequent in meningitis.

Patients were mostly male and in their sixth and seventh life decades. Although *S. bovis* CNS infection can occur in healthy patients,[33,37] they are usually associated with underlying conditions, mainly immunodepression like, HIV or HTLV-1 infection, immunosuppressive treatment or asplenia[8,11,18,21,29,41,45,56] or cancer.[45,52,55,56] The rate of cancer and immunosupression are similar to CNS infections caused by *L. monocytogenes*.[61–63]

Contact with animals and manure has been proposed as a risk factor for bowel colonization by *S. gallolyticus* subsp. *gallolytiticus*.[64] Three of our four patients with CNS infection had contact with cattle. The rate of bacteremia has been previously linked with cattle population density in our geographical area.[65]

Streptococcus bovis is a commensal bacterium of the bowel, and systemic infections are probably secondary to intestinal translocation during an alteration in the intestinal mucosa.[66] In an appreciable percentage of cases bowel lesions such as intestinal neoplasms, radiation colitis or *Strongyloides* colitis are detected.[5,16,20,21,26,40,56]

Twelve cases of *S. bovis* meningitis associated with *S. stercoralis* infestation have been included in this review.[20,21,27,29,36,40,56] All but one had associated immunosuppression (steroids, HIV or HTLV-1 infections), and a number of cases had had other episodes of meningitis or bacteraemia caused by other intestinal flora.[56] Gastrointestinal manifestations were observed in most cases in which symptoms were described, so hyperinfection should be assumed in most cases. Only one patient had cutaneous manifestation of strongyloidiosis,[20] one patient had pseudomembranous colitis with a massive lower bleeding,[40] and no cases of disseminated disease were reported. Stool examinations may be negative, so other studies especially duodenal aspiration or intestinal biopsy specimen yield the diagnosis in approximately 90% of cases.[20,21,29,36,40]

Colorectal neoplasms associated with *S. bovis* infection are usually asymptomatic in contrast to *S. bovis* related *Strongyloides* infestation.[67] It is an accepted practice that all patients with bacteremia or endocarditis due to *S. gallolyticus* subsp. *gallolyticus* undergo a thorough evaluation of the colon.[2,67–69] However, the experience with CNS infections due to *S. bovis* is less well established. In this review, carcinomas or advanced adenomas were detected in 27.5% of the patients whose colon was properly studied. These figures are clearly higher than those of the general population of this age.[2,67] It is uncertain if all neoplasms were associated with *S. gallolyticus* subsp. *gallolyticus* (former *S. bovis* biotype I) since species identification was not universally performed. Only two cases (16.6%) of non-advanced adenomas in were found related to twelve cases of *S. pasteurianus* o *S. bovis* biotype II in our study, similar to the general population.[2,70,71]

Considering the impact of missing a neoplasm, in addition to those with infection by *S. gallolyticus* subsp. *gallolyticus* diagnosis colonoscopy should be performed in patients with untyped *S. bovis* CNS infection. An additional advantage of this examination is the detection of other bowel diseases, such as *Strongyloides* colitis,[20,21,29,36,40] ulcerative colitis, *etc.*

Streptococcus bovis is usually highly penicillin-sensitive, with few exceptions;[72] beta-lactams are therefore the treatment of choice. Given the rarity of neurological complications, corticosteroids do not appear to play a role as they do in pneumococcal meningitis.[59] Additionally, in endemic areas of Strongyloidiasis, these drugs can promote its dissemination and new episodes of meningitis.[20]

In pediatric patients, mainly neonates, *S. gallolyticus* subsp. *pasteurianus* causes approximately 90% of all *S. bovis* menigitis.[73] In adults the percentage is lower; in our review one third were caused by *S. gallolyticus* subsp. *gallolytiticus* and the rest were caused by *S. bovis* biotype II. Of the *S. bovis* biotype II identified, 87.5% were *S. gallolyticus* subsp. *pauteurianus*. It should be noted that our hospital reports a case of *S. infantarius* subsp. *coli* CNS infection. In our knowledge it is the first reported.in the literature.

Our study has limitations. Like all case report studies not all data are available for every patient. In addition, a rutinary test for Strongyloidiasis, neither colonoscopy or echocardiogram was performed in all patients. The biotype and species of *S. bovis* were also not determined in all cases.

In summary, CNS infections caused by *S. bovis* are rare in adults, and most are associated with *S. gallolyticus* subsp. *pasteurianus*. Meningitis is the most common clinical form. The CSF findings are indistinguishable from those of pneumococcal meningitis, but the neurological complications are fewer and the prognosis is better. Unlike intracranial focal infections, meningitis caused by *S. bovis* is rarely associated with endocarditis. A high share of the cases is associated to underlying diseases, mainly immunosuppression and malignancy, similar than in *Listeria* CNS infections. In endemic areas, Strongyloidiasis should be ruled out for immunosuppressed patients with meningitis by *S. bovis*. The association with advanced colon neoplasms is stronger than expected. These patients' bowel should therefore always be examined; however more studies are needed with proper species identification to establish whether the association is mainly with *S. gallolyticus* subsp. *gallolyticus*, as occurs in bacteraemia and endocarditis.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data availability

Anonymized clinical data sets are available upon corresponding author contact.

Financial support

No funding from any public or private institution was received for the elaboration of this manuscript.

Conflict of interest

The authors declare that they have no competing interests.

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