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RESEARCH NOTE

Adults with spontaneous aerobic Gram-negative bacillary meningitis admitted to the intensive care unit

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ABSTRACT

The characteristics of spontaneous aerobic Gram-negative bacillary meningitis (AGNBM) were determined in 40 adults requiring admission to an intensive care unit (ICU) during a 16-year period in ten French ICUs. Eight infections were hospital-acquired and most patients had predisposing factors, mainly chronic alcoholism and an immunocompromised status. Three immunosuppressed patients had disseminated strongyloidiasis. Gram's stain, cerebrospinal fluid and blood cultures were positive for 85%, 98% and 80% of cases, respectively. *Escherichia coli* (57%) and *Klebsiella pneumoniae* (17%) were the most frequent pathogens. In-ICU mortality was 38%. Spontaneous AGNBM is a rare complication of bacteraemia in adults. The severity of predisposing underlying diseases might explain the poor prognosis despite appropriate antimicrobial therapy.

Keywords *Escherichia coli*, Gram-negative meningitis, intensive care unit, *Klebsiella pneumoniae*, meningitis, strongyloidiasis

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Spontaneous aerobic Gram-negative bacillary meningitis (AGNBM) in adults is uncommon in Western countries, having been reported in only 4% and 0.7% of patients with community-acquired bacterial meningitis in the USA and Europe, respectively [1–4]. In contrast, AGNBM, especially that caused by *Klebsiella pneumoniae*, is more frequent in some other areas, e.g., Taiwan [5]. Most studies dealing with AGNBM include patients with post-trauma or neurosurgical meningitis and spontaneous episodes, without delineating clearly among the specific characteristics of the latter [6–9]. The present study determined the clinical characteristics and outcome of spontaneous AGNBM in adults requiring admission to intensive care units (ICUs) in France. The charts of consecutive patients aged >16 years with AGNBM who were admitted to ten ICUs in France between January 1988 and July 2003 were analysed retrospectively. Patients were included if they had cerebrospinal fluid pleocytosis (> 10 cells/μL) with a predominance of polymor-

phonuclear cells, and positive cerebrospinal fluid or blood cultures containing Gram-negative bacilli. Episodes caused by *Haemophilus influenzae*, or those associated with recent (< 1 month) head trauma or neurosurgical procedures, were excluded. Predisposing factors were recorded and the severity of any underlying medical condition(s) was evaluated according to the criteria of McCabe and Jackson [10]. Meningitis was further classified as community- or hospital-acquired according to the 1988 guidelines from the CDC [11]. The retrospective design of the study meant that the primary site of infection was only presumptive for most patients.

Initial antibiotic therapy was considered appropriate when the pathogen was susceptible to the chosen antibiotic, provided that the regimen included a third-generation cephalosporin (cefotaxime or ceftriaxone for Enterobacteriaceae; ceftazidime or cefepime for *Pseudomonas aeruginosa*), a carbapenem or high-dose (≥ 1200 mg/day) ciprofloxacin. Categorical variables were expressed as percentages and continuous variables as medians (25th and 75th percentiles).

During the 16-year period, 40 patients diagnosed with spontaneous AGNBM, including 32 community- and eight hospital-acquired episodes, were admitted to the participating ICUs. These 40 patients represented 2% of the cases of bacterial meningitis diagnosed during the study period. Demographic characteristics and underlying diseases that might have predisposed patients to meningitis are summarised in Table 1. Seven patients from endemic areas had intestinal parasites, including strongyloidiasis in the case of five patients (three of whom were immunocompromised and had disseminated strongyloidiasis). Salient clinical features and cerebrospinal fluid characteristics are summarised in Tables 1 and 2, respectively. Blood cultures from 32 (80%) patients yielded Gram-negative bacilli.

The causative microorganisms of meningitis were identified as *Escherichia coli* (n = 23), *K. pneumoniae* (n = 7), *Klebsiella oxytoca* (n = 2), *Ps. aeruginosa* (n = 3), *Proteus mirabilis* (n = 2), *Pasteurella multocida*, *Salmonella D*, *Serratia marcescens* and *Acinetobacter haemolyticus* (all n = 1). One patient was co-infected with *K. pneumoniae* and *Prot. mirabilis.* Nosocomial cases were caused by *Ps. aeruginosa* (n = 3), *E. coli* (n = 2), *K. oxytoca* (n = 1), *S. marcescens* and *A. haemolyticus* (one

Table 1. Demographic characteristics, clinical features and predisposing factors upon hospital admission (patients may have one or more underlying diseases or predisposing factors)

Characteristics	Episodes of meningitis (n = 40)
Age, years, median (Q1; Q3)	56 (41; 76)
Males/females, n	20/20
African or Caribbean origin, n (%)	5 (12.5)
McCabe and Jackson classification, n (%)	
Non-fatal underlying disease	24 (60)
Ultimately fatal underlying disease	7 (17.5)
Rapidly fatal underlying disease	9 (22.5)
Underlying disease, n (%)	30 (75)
Chronic alcoholism	13 (33)
Cirrhosis	9 (23)
Immunosuppressive therapy	4 (10)
Infection with human immunodeficiency virus	3 (7.5)
Agammaglobulinaemia or hypogammaglobulinaemia	2 (5)
Asplenia	1 (2.5)
Malignancy	7 (18)
Diabetes mellitus	7 (18)
Remote head trauma	4 (10)
Previous episode of bacterial meningitis	3 (7.5)
Signs and symptoms upon presentation	
Body temperature, °C, median (Q1; Q3)	38.6 (37.8; 39.4)
Triad of fever, neck stiffness and change in mental status, n (%)	24 (60)
Altered consciousness, n (%)	36 (90)
Score on Glasgow Coma Scale[a], median (Q1; Q3)	12 (9; 14)
< 8 (indicating coma)	6 (15)
Focal neurological deficit, n (%)	12 (30)
Hemiparesis, n (%)	12 (30)
Cranial nerve palsy, n (%)	2[b] (5)
Generalised seizures, n (%)	12 (30)
SAPS II[c], median (Q1; Q3)	40 (30; 56)
Mechanical ventilation, n (%)	28 (70)
Inotropic support for septic shock, n (%)	16 (40)

[a]GCS: Glasgow coma scale [17].
[b]Two patients had both hemiparesis and cranial nerve palsy.
[c]SAPS II: simplified acute physiology score [18].
Q1, 25th percentile; Q3, 75th percentile.

Table 2. Initial cerebrospinal fluid results for 40 adults with spontaneous Gram-negative bacillary meningitis. Results concerning leukocyte counts and protein concentrations were available for only 39 patients, and results concerning glucose concentration were available for only 37 patients. All three determinations were obtained for 36 patients

Variable	Median (25th percentile; 75th percentile)	n (%)
Leukocytes/mm^3	3000 (325; 7555)	
5–99		3/39 (8)
100–999		10/39 (26)
1000–4999		10/39 (26)
5000–9999		8/39 (21)
≥ 10 000		8/39 (21)
Protein (g/L)	3.6 (1.8; 7)	
0–0.99		2/39 (5)
1–4.99		23/39 (59)
5–9.99		10/39 (26)
≥ 10		4/39 (10)
Glucose (mmol/L)	0.3 (0.1; 2)	
0–0.99		23/37 (62)
1–2.99		7/37 (19)
≥ 3		7/37 (19)
Gram's stain-positive		34/40 (85)
Culture-positive		39/40 (98)

patient each). All Enterobacteriaceae were susceptible to cefotaxime and to fluoroquinolones, but 40% of *E. coli* isolates were resistant to aminopenicillins.

Seven patients had intestinal parasitosis. For seven other patients, a gastrointestinal origin was suspected for the following reasons: previously diagnosed haemorrhagic rectocolitis ($n = 1$), abdominal pain and/or diarrhoea ($n = 4$), concomitant acute cholecystitis ($n = 1$), and *Salmonella* D bacteraemia ($n = 1$). Three of these latter seven patients underwent abdominal ultrasonography or computed tomography scan, which did not detect specific lesions. Other presumed portals of entry were the urinary tract ($n = 14$) and dental ($n = 1$) or otitic ($n = 1$) lesions, but the portal was unknown for ten patients. A computed tomography scan was performed for 35 patients and showed abnormalities in five cases: diffuse oedema ($n = 3$), and parietal or occipital area of low attenuation consistent with ischaemia ($n = 1$ each).

The most frequent initial therapeutic regimens were: a third-generation cephalosporin alone ($n = 7$) or in combination with an aminoglycoside ($n = 13$), a fluoroquinolone ($n = 3$) or an aminopenicillin ($n = 3$); an aminopenicillin alone ($n = 5$); or a fluoroquinolone combined with an aminoglycoside ($n = 3$). Initial antibiotic therapy was appropriate for 33 patients and, for the remaining seven patients, was switched to an appropriate agent after 24 h. Among the latter group, five patients received an aminopenicillin alone, although the causative microorganisms were resistant in four cases (i.e., *K. oxytoca*, *S. marcescens*, *E. coli* and *Ps. aeruginosa*), and two patients received inappropriate antimicrobial agents for resistant *Ps. aeruginosa*. Only four patients received adjunctive steroid therapy. The overall in-hospital mortality rate was 38% (15/40). Among the 25 survivors, five (20%) had neurological sequelae at hospital discharge.

To the best of our knowledge, this is the largest reported series of patients with severe spontaneous meningitis caused by Gram-negative bacilli. In agreement with earlier reports [5–9], most of these patients had one or more predisposing factors, e.g., immunocompromised status, diabetes or alcoholism. A relatively high number of patients had intestinal parasitosis, and three patients had disseminated strongyloidiasis upon admission to the ICU. All patients with intestinal parasitosis were seen in the same Parisian hospital, which caters to a large population of African and French individuals from overseas territories. Spontaneous AGNBM in association with strongyloidiasis hyper-infection has been documented previously [12]. Meningitis occurs secondary to seeding of the meninges during persistent or recurrent episodes of bacteraemia associated with the migration of infective larvae. The larvae may also carry enteric organisms on their surfaces, or within their own gastrointestinal tracts, as they invade the meninges [13]. However, with the exception of patients with strongyloidiasis hyperinfection, the relationship between intestinal parasitosis and AGNBM is unclear.

Third-generation cephalosporins are considered to be a major therapeutic advance in the treatment of AGNBM [5,14] and should be included in the first-line antibiotic regimen for patients with suspected AGNBM. Ceftazidime or cefepime, in combination with an aminoglycoside, should be prescribed when *Ps. aeruginosa* infection is suspected, especially for patients with hospital-acquired meningitis [15]. Despite the early use of a third-generation cephalosporin for most of these patients, there was a mortality rate of 38%, comparable to that usually reported for pneumococcal meningitis, which is far more common [16].

Spontaneous AGNBM in adults is a rare complication of bacteraemia, occurring mainly in debilitated patients. Among predisposing factors, strongyloidiasis should be suspected in patients who have lived previously in an endemic area. The poor outcome can be explained, at least in part, by the severity of the underlying condition(s) and/or predisposing factors.

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RESEARCH NOTE

Influence of hepatitis C and hepatitis G virus co-infection on viral and cellular dynamics in patients infected with human immunodeficiency virus following interruption of highly active anti-retroviral therapy

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ABSTRACT

This study describes the influence of hepatitis C virus (HCV) and hepatitis G virus (HGV) co-infection on CD4 cell count decline and plasma human immunodeficiency virus (HIV) viral load in HIV-infected patients during a 1-year period following interruption of highly active anti-retroviral therapy (HAART) guided by CD4 count. CD4 cell count decline and plasma HIV viral load did not differ between HIV mono-infected patients and those patients co-infected with HCV and HGV. HCV genotype 1 had no apparent influence on the cellular and viral dynamics in HIV-infected patients compared with other HCV genotypes, although the unbalanced groups make larger studies desirable.

Keywords CD4 counts, hepatitis C virus, hepatitis G virus, highly active anti-retroviral therapy, human immunodeficiency virus, viral load

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The influence of hepatitis C virus (HCV) co-infection on CD4 cell re-population in patients infected with human immunodeficiency virus

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