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BRIEF REPORT

Chronic meningococcemia: a report of 26 cases and literature review

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Abstract

Chronic meningococcemia is defined by blood culture(s) positive for *Neisseria meningitidis*, symptoms duration > 7 days, and neither meningitis nor shock on admission. This series of 26 consecutive cases illustrates that this is a rare disease (< 5% of meningococcemia, < 0.05 cases per 100,000 inhabitants per year), mostly affecting young adults, males, with no predisposing condition. Major symptoms include fever, rash, and arthralgia. Median time between symptoms onset, and diagnosis is 28 days. Most patients fully recover with a 1-week course of parenteral betalactams.

Keywords *Neisseria meningitidis* · Meningococcemia · Chronic · Virulence · Immunity

Purpose

Neisseria meningitidis, an encapsulated Gram-negative diplococcus, is a common commensal of human nasopharynx, found in 8–25% of healthy individuals [1, 2]. A minority of pharyngeal isolates will develop invasive meningococcal infection, mostly rapidly progressing meningitis, or shock, with an incidence of invasive meningococcal infection estimated at 1 case per 100,000 population per year in developed countries. Chronic meningococcemia is a rare form of invasive meningococcal infection, first described in 1902, defined as meningococcal sepsis of at least 1 week duration, with blood culture(s) positive for *N. meningitidis*, and no meningeal symptoms [3, 4]. Chronic meningococcemia, characterized by prolonged clinical course, intermittent fever, rash, and migratory arthralgia, remains largely unknown by clinicians, and is usually detected as an unexpected result from blood culture [5]. We aimed to better characterize this rare entity, and its incidence, from a multicenter retrospective cohort study in Western France.

Methods

Le Groupe d'Epidémiologie et Recherche en Infectiologie Clinique du Centre et de l'Ouest (GERICCO) is a network of physicians and biologists with specific interest in infectious diseases, working in public and private hospitals in Western France, established in 1986 for educational and clinical research purposes (association #07433). Members of the GERICCO study group were invited to participate in this retrospective cohort study if they were able to identify all patients with blood culture(s) positive for *N. meningitidis* during the study period (1994–2016), either through blood

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cultures registry from the laboratory, and/or from computerized database allowing identification of patients with invasive meningococcal infection. Of note, notification of invasive meningococcal infection to the national health authority was mandatory in France throughout the study period. One of us (BL) screened all medical charts to select patients who fulfilled the criteria for chronic meningococcemia, as previously described: (1) blood culture(s) positive for *N. meningitidis*; (2) symptoms duration > 7 days; (3) without meningeal symptom or shock on admission. Data were collected on a standardized questionnaire, and included age, sex, comorbidities, clinical characteristics, treatment, in-hospital mortality, hemogram, routine biochemical tests, C-reactive protein (CRP), number of positive blood culture(s), serogroup of *Neisseria meningitidis*, and drug susceptibility testing. Results of immunological investigations were collected, when performed.

Continuous variables were reported as median with interquartile range [IQR]. Qualitative variables were expressed as number and proportion. To estimate the incidence of chronic meningococcemia during the study period, we multiplied the mean incidence of invasive meningococcal infection with blood culture(s) positive for *N. meningitidis* in Western France in 1995–2016 from the national surveillance system (http://invs.santepubliquefrance.fr/surveillance/iim/web_meni.htm), by the proportion of chronic meningococcemia among patients with blood culture positive for *N. meningitidis* in our study. Literature review: two independent researchers (BL and PT) searched Medline for articles in English or French published anytime before July 2018, using the following keywords: "meningococcemia", and "chronic". In addition, we systematically searched for additional articles in the reference lists of all articles reviewed. This study has been approved by the CER-MIT Ethics committee.

Results

Within the 36 hospitals who agreed to participate, 550 patients had at least one blood culture positive for *N. meningitidis*. Of these, 26 (4.7%) fulfilled criteria for chronic meningococcemia: 9 females, and 17 males, with a median age of 24.5 years [19–46]. Five patients (19%) were previously identified as immunocompromised, for the following reasons: prolonged corticosteroids ($n = 2$), multiple myeloma, HIV infection, and kidney transplant (one patient each). Most common symptoms were fever ($n = 26$), rash ($n = 18$), and arthralgia ($n = 14$), with a median duration of 28 days [11–49] before admission. Focal meningococcal infections included arthritis ($n = 7$), uveitis ($n = 3$), and pneumonia ($n = 2$). Biological tests on admission were as follows: median white blood cells count, 14 G/L [9–17]; neutrophils, 11 G/L [7–14]; lymphocytes, 1.5 G/L [0.7–2]; platelets, 292 G/L [208–343]. All patients had elevated CRP (> 5 mg/L), with a median of 89 mg/L [61–150]. Eleven patients (42%) underwent lumbar puncture, despite the absence of any neurological symptoms. Specific tests for immunodeficiency included complement fractions ($n = 15$), plasma proteins electrophoresis with quantification of gammaglobulins ($n = 16$), and HIV tests ($n = 16$): no patient with immunodepression was identified in addition to the 5 previously known as immunocompromised.

The median number of blood culture sets sampled before antibiotics was 3 [2–4], of which 2 [1–2] yielded *N. meningitidis*. All isolates were susceptible to third-generation cephalosporins, and 81% were susceptible to amoxicillin/ampicillin. Minimum inhibitory concentrations (MIC) were available for 16 isolates: all had third-generation cephalosporins MIC ≤ 0.125 mg/L, and 14 (87.5%), had amoxicillin/ampicillin ≤ 0.125 mg/L. *N. meningitidis* serogroups were B ($n = 18$), C ($n = 5$), or not specified ($n = 3$). Antibacterial treatment included intravenous ceftriaxone ($n = 19$), amoxicillin ($n = 8$), and cefotaxime ($n = 5$), initiated with a median time from admission to first administration of 1.5 days [0–4], and a median duration of 7 days [7–10]. The median duration of hospital stay was 8.5 days [6–11]. No patient developed meningitis, or hypotension. One patient died (3.8%), immunocompromised (multiple myeloma with various immunosuppressive treatments): he was admitted to the intensive care unit for severe community-acquired pneumonia. *N. meningitidis* was isolated from bronchoalveolar lavage and blood cultures. He died of acute respiratory distress syndrome. Of the 25 patients who survived, 24 (96%) had no sequel, and one had persistent peripheral neuropathy.

During the study period, the incidence of invasive meningococcal infection in Western France was calculated at 1.1 per 100,000 inhabitants per year through the mandatory notification system [6], with a proportion of patients with positive blood culture(s) estimated at 60%, and a completeness estimated at 92.0% [IC 95%=89.6–93.3] by the capture–recapture method (unpublished data, available at http://opac.invs.sante.fr/doc_num.php?explnum_id=119). As we found that 4.7% of 550 consecutive patients with blood culture(s) positive for *N. meningitidis* fulfilled criteria for chronic meningococcemia, the incidence of chronic meningococcemia may be estimated at 1.1 per 100,000 inhabitants per year (incidence of invasive meningococcal infection)/0.92 (completeness) × 0.6 (proportion of patients with invasive meningococcal infection who have positive blood cultures), and × 0.047 (proportion of patients with blood cultures positive for *N. meningitidis* who fulfill criteria for chronic meningococcemia), = 0.033 cases per 100,000 inhabitants per year (95% confidence interval, 0.020–0.044). The literature review identified 252 cases of chronic meningococcemia published since 1902 (for references, see electronic supplementary material). The main characteristics of

our case series, and the literature review, are presented in Table 1.

Discussion

This case series of 26 consecutive cases of chronic meningococcemia is in line with most previous reports on this unusual presentation of invasive meningococcal infections [3, 4, 7]: (1) chronic meningococcemia is a rare disease, representing less than 5% of all cases of meningococcemia, with an incidence < 0.05 cases per 100,000 inhabitants per year in developed countries; (2) it mostly affects young adults, predominantly males, with no predisposing condition; (3) fever, rash, and arthralgia are by far the most common signs; (4) the median duration of symptoms before diagnosis is much longer than would be expected for a bloodstream infection caused by a notoriously virulent pathogen; (5) despite the time elapsed between symptoms onset, and diagnosis, most patients recover with no sequel with a 1-week course of parenteral betalactam agent (i.e., third-generation cephalosporin, or ampicillin/amoxicillin).

The pathophysiology of chronic meningococcemia remains largely unknown: this protracted presentation of a usually fulminant infectious disease could be related to specific characteristics of the host (i.e., strong immunity), and/or the bacteria (i.e., low virulence). The predominance of adults (25/26 in our series, and 231/252 in the literature), and the male-to-female ratio (respectively, 17/9 in our series, and 179/73 in the literature), differ from the characteristics of the overall population of patients with invasive meningococcal infection: indeed, children represent approximately 50% of cases in most surveillance studies (including France), and females are usually as affected as males. Of note, most cases of chronic meningococcemia have been reported in patients with no predisposing condition (21/26 in our series, and 234/252 in the literature). When immunological investigations are performed in these patients, the yield is usually low (0/16 in our series, when testing for complement fractions, HIV serology, and plasma protein electrophoresis were performed). Although chronic meningococcemia has been reported in patients with terminal complement deficiency, properdin deficiency, low IgG or IgM levels, IgA deficiency, and HIV [8], > 90% of cases reported to date occurred in patients with no apparent immunodeficiency. The serogroups of meningococcal strains isolated in patients with chronic meningococcemia in our series are similar to those of strains isolated in the overall population with invasive meningococcal infection in France, with a predominance of B serogroup, followed by C [6]. However, serogroup

Table 1 Characteristics of chronic meningococcemia in our case series, and in the literature

	GERICCO (this study) $n = 26$ (1995–2016)	Literature review $n = 252$ (1902–2018)
Age, years	24.5 [19–46]	21 [15–34]
Male/female (ratio)	17/9 (1.9)	179/73 (2.5)
Immunocompromised, *n* (%)	5 (19.2%)	18 (7.1%)
Symptoms		
Time from symptoms onset to admission, days	28 [11–49]	35 [19–39]
Fever	26 (100%)	251 (99.6%)
Rash	15 (57.7%)	223 (88.5%)
Arthralgia	14 (53.8%)	173 (68.7%)
Meningococcal serogroup		
B	18 (69.2%)	45 (17.9%)
C	5 (19.2%)	17 (6.7%)
Others (A, Y, W135)	0	8 (3.2%)
Not specified	3 (11.5%)	187 (74.2%)
Outcome[a]		
Meningitis	0	34 (13.5%)
Sequels	1 (3.9%)	2 (0.8%)
Death	1 (3.9%)	17 (6.7%)

Continuous variables are reported as median with interquartile range [IQR]. Qualitative variables are reported as number and proportion

[a]A substantial proportion of cases reported in the literature occurred before the advent of antimicrobial therapy. Cases who developed meningitis, or who died, typically presented with a long course of chronic meningococcemia, sometimes with periods of spontaneous improvement, before relapses, and finally evolved into more classical invasive meningococcal infections (i.e., meningitis, or purpura fulminans)

merely reflects structural differences in capsular polysaccharide. Other important players in the virulence of meningococcal strains include lipo-oligosaccharide (endotoxin), and outer membrane proteins [1, 2]. Interestingly, in vitro studies suggested that endotoxin release and cytokine production are decreased with clinical isolates responsible for chronic meningococcemia, as compared to isolates responsible for rapidly progressing meningococcal disease [9]. More recently, a study on 15 strains isolated from patients with chronic meningococcemia identified a mutation in the *lpx*L1 gene, resulting in underacylated lipopolysaccharide [10].

Our study has limitations. Firstly, its retrospective, multicenter, observational design, over 22 years, implies a large heterogeneity in patients management, and data collection (including the outcome), with many potential biases. Secondly, we had no access to clinical isolates, and no specific study on potential virulence factors could be performed. Thirdly, our estimate of chronic meningococcemia incidence suffers from potential biases, both on the numerator (e.g., undiagnosed cases, or cases not notified, were missed), and the denominator (population catchment area). However, this is the largest contemporary case series on chronic meningococcemia, which adds a brick in the wall for better characterization, and awareness, of this rare, and potentially fatal invasive meningococcal infection.

In conclusion, chronic meningococcemia is a rare manifestation of invasive meningococcal infection, characterized by the triad of fever, rash, and arthralgia, mostly encountered in young adults. The diagnosis, obtained with a median delay of 28 days after symptoms onset, is often an unexpected result of blood cultures. One-week course of third-generation cephalosporin, or ampicillin/amoxicillin, will cure > 95% of cases.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval This study has been approved by the CER-MIT Ethics committee.

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