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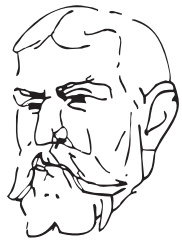

Memory of
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ORIGINAL ARTICLE

CLINICAL AND EPIDEMIOLOGICAL FEATURES OF MENINGOCOCCAL INFECTION AND ITS EARLY DIAGNOSIS IN RESIDENTS OF THE TRANSCARPATHIAN REGION

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ABSTRACT

The aim: To identify clinical and epidemiological features of meningococcal infection on the initial day of a patient's medical consultation, as well as the efficacy of laboratory examinations.

Materials and methods: A retrospective analysis of 76 patients' histories diagnosed with meningococcal disease was carried out.

Results: Children were more susceptible to meningococcal disease ($p < 0.001$). The majority of children were of preschool age, with the minority being adolescents and children under the age of one year. Among children disease incidence did not depend on gender. Among adults, the majority were women ($p=0.002$). All patients had a family history of a disease, close relatives tested positive for meningococcal diseases ($p=0.039$). The main symptom discovered during the primary examination on the day of admission to the hospital was a hemorrhagic rash ($p<0.001$). Most cases were of moderate severity ($p<0.001$) and cases of children having meningococcemia ($p<0.001$). A typical rash was found in 40% of patients with generalized meningococcal disease. A complete blood count showed leukocytosis in 47.8% of all cases. The most effective method of confirming the diagnosis was a thick blood smear and microscopic examination of cerebrospinal fluid ($p<0.001$).

Conclusions: Patients in the Transcarpathian region mainly develop an atypical form of meningococcal disease. Only half of all patients diagnosed with meningococcemia had a classical hemorrhagic rash. Generalized forms of meningococcal disease may proceed with normal or subfebrile temperature and without severe leukocytosis. We doubt the use of bacteriological methods of laboratory diagnosis due to their low effectiveness. The most sensitive method of laboratory diagnosis is a microscopic examination of blood smear, and cerebrospinal fluid.

KEY WORDS: meningococcal disease, epidemiology, thick blood smear

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INTRODUCTION

Meningococcal disease (MD) is an anthroponotic infection that is transmitted via droplets and has a wide spectrum of symptoms (from asymptomatic nasopharyngeal carriage to generalized forms with high mortality) [1]. The causative agent of MD is *Neisseria meningitidis*. Clinical forms of MS may wary from asymptomatic course to a fulminant form that leads to multiple organ failure and death within hours or days [2]. The overall mortality rate of generalized meningococcal infection (GMI) can be as high as 10%, and in some cases - 40-80% [3]. Despite low incidence rates in economically developed countries over the past decade, MD has consistently been the leading infectious cause of death in young children [4].

According to the International Health Regulations 2005, MD is included in the list of infectious diseases regulated by these regulations that constitute an exceptional national or regional problem [5]. Ukraine and the Transcarpathian region are not an exception. In Ukraine, 896 cases were registered in 2018-2022, of which 706 (78.8%) were children, with an intensive incidence rate ranging from 0.218 to 3.26 per 100,000 population for all patients and from 0.91 to 3.02 for children. In the Transcarpathian region, 205 patients were detected during this period, including 160 (78.0%) children, which is almost a quarter of all patients in our country. The intensive incidence rate per 100,000 population was 4-11 times higher than the national rate, ranging from 0.96 to 6.69, and for children it was 3-9 times higher, ranging from 3.1 to 22.3.

Meningococcal disease is the leading cause of bacterial meningitis and septicemia worldwide and

is associated with high mortality and serious lifelong complications in survivors [6]. Treatment requires antibiotics. The sooner treatment is started, the better it is likely to be. If MD is suspected, treatment should begin in at the pre-hospital phase [7].

THE AIM

The aim of the study is to identify the clinical and epidemiological particularities of meningococcal disease that may be found during primary medical examination, in order to suspect the diagnosis and begin an early antibiotic therapy.

MATERIALS AND METHODS

To determine the clinical, epidemiological and laboratory characteristics of the course of MD in the Transcarpathian region, 76 patients' histories were analyzed. All patients were admitted to the Regional Clinical Infectious Diseases Hospital in 2018-2020 years with a diagnosis of MD, including: 21 adults aged 19 to 43 years and 55 children aged from 3 months to 18 years. There were 34 males and 42 females. Family history of meningococcal disease, contact with a patient with meningococcal disease, main complaints, clinical manifestations and laboratory tests on the first day of admission were recorded. The diagnosis of MD was confirmed following the discovery of gram-negative diplococci in blood and cerebrospinal fluid smears, or the identification of the causative agent *N. meningitidis* based on bacteriological investigations of nasopharyngeal swabs, blood, and cerebrospinal fluid, as well as their combination. The survey was conducted at the permission of the Bioethics Commission of the Faculty of Medicine of the Uzhhorod National University (Minutes No. 4 dated February 2, 2022).

Statistical processing was performed in Jamovi 2.2.5. The Kruskal-Wallis test was employed to calculate the significance of individual variables in diagnosing and measuring the severity of the condition, and then a pairwise comparison of variables using the Dwass-Steel-Critchlow-Fligner test. The normality of the distribution of quantitative data was assessed using the Shapiro-Wilk test. The results were represented as M±SD and Me (Q1; Q3). A critical level of reliability of α=0.05 was employed.

RESULTS

Among patients diagnosed with MD, children were the dominant group with 55 cases (74.4%) compared to other age groups, with a p-value of <0.001. This includes: Nine individuals were under one year of age (16.4%), with slightly more patients aged between 1 and 3 years - a total of 13 individuals (23.9%). A majority of the patients were preschool children - 17 individuals (30.9%), which is significantly higher than the group comprised of individuals under one year and primary school age, with a total of 11 individuals (20.0%). The smallest percentage of patients were adolescents - 5 individuals (9.1%), which is significantly lower than all groups except for children under one year. There were no variations in gender composition, with 28 boys (50.9%) and 27 girls (49.1%).

The mean age of adult patients diagnosed with MD was (29.9±6.6) years, with a significant preponderance of female cases (14 individuals (66.7% (p=0.002)).

It is noteworthy that a total of 60.5% of individuals diagnosed with MD were found to be part of family foci (p<0.001), particularly among adults at 71.4% (p<0.001) and to a slightly lesser extent among children at 56.4% (p=0.039). Meanwhile, patients diagnosed with MD were likely less frequently identified in organized groups, with a decrease of 44.7% (p=0.042), particularly among adults, with a reduction of 23.8% (p<0.001). Such association was not observed during childhood (52.7% and 47.3%).

The primary motive for conducting patient examinations for the detection of MD was typically the appearance of a rash, either on its own or along with other symptoms of the disease (51.3% (p=0.039)), the presence of contact with a patient who has MD or with other related symptoms is reported at a rate of 26.3%. In other cases, 22.4% of patients underwent disease detection examinations for reasons unrelated to their disease. In children (61.8%, p<0.001), a rash was frequently the primary reason for examination, either alone or accompanied by other clinical manifestations. Conversely, in adults, contact with an infected individual was the main reason for examination, either alone or with other manifestations(47.6%, p=0.015).

The diagnoses of MD for which patients received treatment at the Regional Clinical Infectious Diseases Hospital can be found in Table I.

The table displayed above indicates that adults were primarily affected by meningococcal nasopharyngitis and meningococcemia. It is not likely that there was a discernible variation in the rate of detection between the generalized and localized forms of the disease. In childhood, there was a significantly higher frequency of meningococcemia diagnosis than adulthood (p<0.001). The prevalence of generalized meningococcal infections was nearly nine times higher than that of localized meningococcal infections, with statistical significance (p<0.001). In general, the prevalence of generalized

Table I. Forms of meningococcal disease in the examined patients

	Forms of meningococcal disease Absolute number	Adults (n=21)		Children (n=55)		Total (n=76)	
		%	Absolute number	%	Absolute number	%	
Localised forms	Asymptomatic carrier of meningococcal disease	1	4.8	3	5.5	4	5.3
	Meningococcal nasopharyngitis	9	42.9[*, 1, 2]	3	5.5	12	15.8
	Total	10	47.6[3]	6	10.9	16	21.1
Generalised forms	Meningococcemia	8	38.1[*]	45	81.8[**, 4]	53	69.7[***]
	Mixed form of meningococcal disease	3	14.3	4	7.3	7	9.2
	Total	11	52.4 [5, 6]	49	89.1 [7]	60	79.8 [8]

Notes: [*] – probable difference from asymptomatic carrier of meningococcal disease in adults p<0.001;
[**] – probable difference from asymptomatic carrier of meningococcal disease and meningococcal nasopharyngitis in childhood p<0.001;
[***] – probable difference from asymptomatic carrier of meningococcal disease and meningococcal nasopharyngitis of generalised forms in all subjects p<0.001;
[1] – probable difference of meningococcal nasopharyngitis in adults from meningococcal nasopharyngitis in children p<0.001;
[2] – probable difference of meningococcal nasopharyngitis in adults from meningococcal nasopharyngitis of all examined p=0.008;
[3] – probable difference between localised forms of meningococcal disease in adults and localised forms of meningococcal disease in children p=0.004;
[4] – probable difference between localised forms of meningococcal disease in adults and localised forms of meningococcal disease of all examined p=0.015;
[5] – probable difference between generalised forms of meningococcal disease in adults and generalised forms of meningococcal disease in children p<0.001;
[6] – probable difference between generalised forms of meningococcal disease in adults and generalised forms of meningococcal disease of all examined p=0.015;
[7] – probable difference between localised forms of meningococcal disease and generalised forms of meningococcal disease in children p<0.001;
[8] – probable difference between localised forms of meningococcal disease and generalised forms of meningococcal infection of all examined p<0.001.

Table II. Severity of meningococcal disease in patients of the Regional Clinical Hospital

Degrees of severity of the disease	Adults (n 21)		Children (n 55)		Total (n 76)	
	Absolute number	%	Absolute number	%	Absolute number	%
Asymptomatic course	1	4.8	2	3.6	3	3.9
Mild course	7	33.3 [3, 5]	4	7,3	11	14.5 [8]
Moderate degree of severity	10	47.6 [1, 2]	43	78.2 [4, 6]	53	69.7 [7]
Severe course	3	14.3	6	10.9	9	11.8

Notes:
[1] – difference between the moderate severity and asymptomatic course in adults p=0.0016;
[2] – difference between moderate severity and severe severity in adults P=0.0218;
[3] – difference between moderate and asymptomatic course in adults p=0.018;
[4] – difference between moderate severity and asymptomatic course, mild severity and severe course in children p<0.001;
[5] – difference between the mild severity of the disease in adults and children p= 0.0041;
[6] – difference between the moderate severity of the disease in adults and children p=0.0094;
[7] – the difference between moderate severity and asymptomatic course, mild severity and severe course in all subjects p<0.001;
[8] – difference between mild severity and asymptomatic course in all subjects p=0.0238.

forms of the disease was nearly quadruple that of localized forms amongst patients at the Regional Clinical Infectious Diseases Hospital (p < 0.001).

The degree of MD in patients who received treatment at the Regional Clinical Infectious Diseases Hospital is displayed in Table II.

Patients with moderate severity were significantly more likely to be identified among those diagnosed with MD, particularly during childhood.

In each instance, localized forms of meningococcal infection were bacteriologically confirmed via the detection of N. meningitidis in nasopharyngeal swabs. Generalized forms of MD were confirmed through bacterioscopic detection of gram-negative diplococci in blood and cerebrospinal fluid, and bacteriological detection of N. meningitidis in blood, cerebrospinal fluid and nasopharyngeal swabs. The efficacy of bacterioscopic and bacteriological examination in individuals with generalized meningococcal infection is illustrated in Table III.

The microscopic blood examination is the most effective means of confirming a diagnosis of gener-

Table III. Efficacy of microscopic and bacteriological examination in generalised forms of meningococcal disease

Research method	Generalised forms of meningococcal infection					
	Meningococcemia (n=53)		Mixed form of meningococcal disease (n=7)		Total (n=60)	
	Absolute number	%	Absolute number	%	Absolute number	%
Bacterioscopic blood test	49	92.3[1,2]	6	85.7[4]	55	91.6[6,7]
Bacteriological blood test	3	5,7	1	14.3	4	6.8
Bacterioscopic test of CSF	0	0	4	57.1	4	6,6
Bacteriological test of CSF	0	0	5	71.4[5]	5	8,3
Bacteriological test of nasopharyngeal swabs	24	43.4[3]	4	57.1	28	46.7

Notes:

[1] – difference between bacterioscopic and bacteriological blood tests in patients with meningococcemia $p<0.001$;

[2] – difference between bacterioscopic test of blood and bacteriological test of nasopharyngeal swabs in patients with meningococcemia $p<0.001$;

[3] – difference between the bacteriological test of nasopharyngeal swabs and bacteriological test of blood in patients with meningococcemia $p<0.001$;

[4] – difference between bacterioscopic and bacteriological blood tests in patients with generalised forms of meningococcal infection $p=0.008$;

[5] – difference between bacteriological tests of blood and CSF in patients with generalised forms of meningococcal infection $p<0.031$;

[6] – difference between bacterioscopic and bacteriological blood tests in all subjects $p<0.001$;

[7] – the difference between bacterioscopic tests of blood and bacteriological tests of nasopharyngeal swabs in all subjects $p<0.001$.

Table IV. Complete blood count in patients with different forms of meningococcal disease on the day of admission

Laboratory indicator	Forms of meningococcal disease			
	Asymptomatic carrier of meningococcal disease	Meningococcal nasopharyngitis	Meningococcemia	Mixed form of meningococcal disease
WBC ($*10^9$/L) *	6,78±2,04	7,719(6,29;9,41)	8,15(6,99; 11,2)	20,3±6,32[1,2,3]
LYM ($*10^9$/L)	3,38±1,55	2,11±1,13	2,5(1,29; 3,46)	1,1 (0,825; 1,56)
MID ($*10^9$/L)	0,295±0,154	0,22(0,165; 0,27)	0,39(0,21; 0,63)	0,16 (0,075; 0,235)
GRA ($*10^9$/L) *	2,35±1,65	5,66 (3,85; 6,59)	5,12(3,84; 7,49)	18,8±6,8[1,2,3]
RBC ($*10^{12}$/L)	4,86±0,215	4,43±0,429	4,78(4,42; 5,09)	4,45±0,732
HGB (g/L)	134±15,8	135±16,1	129 (120; 134)	117±56,7
PLT ($*10^9$/L)	290±82,4	271±78,5	285(229; 393)	217±84,7
GRA/LYM (%) *	0,895±0,689	2,31(2,01;4,34)	1,95(1,18; 3,43)	19,6±14,9[1,2,3]
MID/GRA(%) *	0,111(0,0965;0,236)	0,0428±0,0387	0,0634(0,0406; 0,123)	0,00661 (0,00291; 0,0147)[3]
MID/LYM (%)	0,102±0,0703	0,225(0,0685;	0,155(0,103; 0,246)	0,174 (0,0509; 0,222)
PLT/LYM (%)	94,5±37,9	120(109;202)	166(85,8; 183)	203±129

Notes:

* Statistically significant indicators (Kruskal-Wallis) * P≤0,001

[1]- difference between WBC counts in patients with generalised forms of meningococcal disease and asymptomatic carrier of meningococcal disease $p=0.041$;

[2] – difference between WBC counts in patients with generalised forms of meningococcal disease and meningococcal nasopharyngitis $p=0.013$;

[3] – difference between the WBC counts in patients with generalised forms of meningococcal disease and meningococcemia $p=0.003$;

[4] – difference between the GRA counts in patients with generalised forms of meningococcal disease and asymptomatic carrier of meningococcal disease $p=0.041$;

[5] – difference between the GRA counts in patients with generalised forms of meningococcal disease and meningococcal nasopharyngitis $p=0.01$;

[6] – difference between the GRA counts in patients with generalised forms of meningococcal disease and meningococcemia $p<0.001$;

[7] – difference between the GRA/LYM ratio in patients with generalised forms of meningococcal disease and asymptomatic carrier of meningococcal disease $p=0.041$;

[8] – difference between the GRA/LYM ratio in patients with generalised forms of meningococcal disease and meningococcal nasopharyngitis $p=0.035$;

[9] – difference between the GRA/LYM ratio in patients with generalised forms of meningococcal disease and meningococcemia $p=0.001$;

[10] – difference between the MID/GRA ratio in patients with generalised forms of meningococcal disease and meningococcemia $p=0.01$.

alized meningococcal infection. In this examination, a specific diplococcus was found most frequently in individuals with MD and in over half of meningococcal disease cases. Bacteriological testing of nasopharyngeal swabs was positive in almost half of the patients. The bacteriological blood test was determined to have the

lowest efficacy, as it validated the disease diagnosis in only one out of 15-17 patients. Bacteriological examination of cerebrospinal fluid and nasopharyngeal swabs proved more efficient, yielding a confirmatory diagnosis in nearly fifty percent of the patients. Bacteriological analysis of cerebrospinal fluid and nasopharyngeal swabs has been demonstrated to be a superior method, verifying approximately half of the patients.

When analyzing reasons for referral for a specific diagnosis of MD upon admission, we categorized all patients into the subsequent groups: patients with complaints of rash, either alone or in combination with other symptoms of the disease; patients who have been in contact with a MD patient without clinical manifestations or complaints and with their presence; patients who were not in contact with MD patients, did not exhibit a rash, but rather presented with complaints and clinical manifestations of the disease. The study found that a rash alone or in combination with other complaints and clinical manifestations, contact with a patient with MD alone or in combination with other symptoms, was the reason for provisional diagnosis of MD and referral for specific diagnosis in 45 patients (59.2%, $p<0.001$). For 20 (26.3%) patients, the reason was contact with a patient with MD or with other clinical manifestations, and for 11 (14.5%) patients, it was other complaints and manifestations. It is noteworthy that 31.6% (24 patients) were found to have a hemorrhagic rash consistent with meningococcemia, while 27.6% (21 patients) had presented with an atypical rash. Rash was not present as a pathognomonic sign of the disease in 16 patients (30.9%) with generalized forms of MD. Meningeal symptoms with a positive indication were found in 7 (9,2%) patients. Amongst other complaints, 46 (60.5%) individuals experienced fever, 17 (22.3%) reported a runny nose, 15 (19.7%) complained of a sore throat, and 14 (18.4%) experienced vomiting.

Body temperature, as an indicators of intoxication, in patients with MD ranged widely upon admission - from 36.1 ^{0}C to 40.2 ^{0}C and was in asymptomatic carriage of MD the temperature was (36.6±0.05) ^{0}C and all patients had a normal temperature; at meningococcal nasopharyngitis 7 patients had normal temperature and 5 had subfebrile, with an average temperature reading of (36.9±0.42) ^{0}C; at meningococcemia - (37.6±1.04) ^{0}C, a normal temperature was recorded in 20 patients, subfebrile - 11, febrile - 15, high - 6, excessive - 1; at mixed forms of MD - (38.0±1.01) ^{0}C, a normal temperature - 1 person, subfebrile - 3, febrile - 1, excessive - 1.

Thus, out of the 72 patients diagnosed with meningococcal nasopharyngitis, meningococcemia, and mixed forms of meningococcal infection, 28 (38.9%) had a normal temperature, 19 (26.4%) had a subfebrile temperature, 16 (22.2%) had a febrile temperature, 7 (9.8%) had a high temperature, and 2 (2.7%) had an excessively high temperature. In nearly two-thirds of cases (65.3%), MD manifested in patients with a normal or subfebrile temperature.

A typical rash, indicative of generalized meningococcal infection, was observed in 24 patients (40.0%), while 19 (31.6%) had an atypical rash, and 17 (28.4%) did not have any rash.

The complete blood count (CBC) results are detailed in the following table IV.

The complete blood count analysis showed that solely the leukocyte and granulocyte counts, along with the granulocyte-linked ratios (GRA1/LYM1, MID1/GRA1), had statistical significance ($p\leq0.001$). In a pairwise comparison, significant differences were observed in only the indicators of patients with mixed forms of MD when compared to all other examined groups. An increase in the number of leukocytes in the analysis of the entire examined group was found in 37 people (48.7%), a normal number - in 34 people (44.7%) without a statistically significant difference, and in 5 people (6.6% ($p<0.001$) the number of leukocytes was reduced. An elevation of leukocytes was noted in 37 individuals (48.7%) of the analyzed group, while 34 people (44.7%) demonstrated typical leukocyte counts without any significant statistical variation. Conversely, leukocyte levels were lowered in 5 participants (6.6%) ($p<0.001$). The latter were diagnosed with moderate meningococcemia and all of them belonged to the childhood age group.

DISCUSSION

Antibiotics constitute the primary treatment for meningococcal infection. Early use is crucial for successful recovery and a positive disease outlook. [1] It is particularly important in severe forms [8]. Our study identified the clinical and epidemiological features of meningococcal infection in residents of the Transcarpathian region, which enable early suspicion of meningococcal infection and prescribe proper treatment on the initial day of treatment. The crucial epidemiological feature is age, with particular emphasis on infants up to one year old [1, 2]. The peculiarity of our region lies in the fact that the majority of ill children are of pre-school age. We did not find any elderly individuals [7]. Another significant epidemiological indicator we identified was interaction with an ill individual, primarily in the family.

The vast majority of patients were diagnosed with moderate meningococcemia. The primary clinical manifestation is a characteristic stellate hemorrhagic rash accompanied by a range of general intoxication

symptoms [3]. During the initial examination, a characteristic hemorrhagic rash was identified in only a third of the patients in our study, while a different type of rash was observed in a quarter of the patients. Thus, a rash, characteristic and uncharacteristic in combination with other manifestations of the disease, was detected in more than half of patients with meningococcemia. Almost a quarter of the patients had been in contact with a patient with meningococcal infection during the clarification of the epidemiological history. A combination of clinical signs, including the presence of a rash, and epidemiological data on contact with a patient suffering from meningococcal infection, were present in the vast majority of hospitalized patients with a confirmed diagnosis of generalized meningococcal infections. This confirms the significance of considering epidemiological data.

One manifestation of intoxication is changes in body temperature. Over a third of patients with clinical signs of meningococcal infection at the Regional Clinical Infectious Diseases Hospital had a normal temperature. Only one-third of patients presented with febrile temperature, indicating a level of intoxication. The identification of an elevated quantity of leukocytes and granulocytes on a complete blood count serves as a vital indication of generalized infectious disease. A satisfactory leukocyte and granulocyte count were found in over half of the patients with meningococcal infection. Only in mixed forms of meningococcal infection was a significant rise in the number of the latter observed.

The diagnosis of meningococcal infection can be confirmed with reliability when the presence of Neisseria meningitidis is detected in the blood, nasopharyngeal mucosa, or CSF [3]. Bacteriological examination of nasopharyngeal swabs proved most efficient in localized forms, though markedly less so in cases of meningococcemia and mixed meningococcal infection. Nonetheless, it enabled us to reliably confirm the etiology of the diagnosis in almost half of all the patients we examined. Bacteriological examination of the blood samples from patients with meningococcemia was unsuccessful in our research. Bacteriological examination of the cerebrospinal fluid was more effective in the identification of the causative agent. Our findings are consistent with the literature [7]. In cases of generalized forms of disease, the most efficient method was the microscopic examination of blood and CSF to identify the presence of gram-negative diplococci. This approach enabled us to identify the causative agent in almost all cases.

CONCLUSIONS

1. Meningococcal infection is prevalent in children, with 74.4% of all cases occurring in this age group, particularly among preschoolers. Adolescents and infants under one year of age may be less affected.
2. The incidence of meningococcal infection in childhood does not exhibit any significant dependence on gender. However, during adulthood, women are 66.7% more likely to be affected by the infection compared to men.
3. Meningococcal infection patients are predominantly found in family foci, 74.6% in adults and 56.4% in children.
4. The most common sign of meningococcal infection was a skin rash, either alone or accompanied by other symptoms of the disease, notably in children (61.8%).
5. In most patients diagnosed with meningococcal infection, clinical symptoms of rash were combined with epidemiological evidence of contact with a patient or carrier of meningococcal infection.
6. Generalised forms of meningococcal infection are dominant during childhood, with a prevalence rate of 89.1%.
7. The condition generally exhibits moderate severity (69.7%), with a higher prevalence in children (78.2%).
8. The most efficient methods for confirming the diagnosis of meningococcal infection are: for localised forms, bacteriological examination of nasopharyngeal swabs; and for generalised forms, microscopy of blood smears and cerebrospinal fluid (92.3%, 85.7%).
9. Bacteriological examination of blood and cerebrospinal fluid is not a reliable method to confirm the diagnosis of generalised meningococcal infection.
10. In the majority of cases, meningococcal infection presents itself in an atypical manner. This means that it occurs with either a normal temperature (28.9%) or subfebrile temperature (26.4%); less than half of patients (43.6%) exhibit the characteristic haemorrhagic rash associated with meningococcemia, and only 47.5% show an increase in leukocyte count.

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