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ENVIRONMENTAL AND CLINICAL CONTEXT IN MENINGOCOCCEMIA: BIOCHEMICAL MODIFICATION OF STIEHM-DAMROSCH/NIKLASSON SEVERITY SCORE – PROGNOSTIC FACTOR

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Abstract

The study considers meningococcemia which is one of the most severe form of meningococcal disease and represents a significant worldwide health problem. The occurrence of meningococcemia was investigated based on a case study developed in a Romanian hospital using data taken from the medical records of patients with the diagnosis of meningococcemia. The pathogen can produce a fulminant form of the disease that can lead to death within a few hours of onset. The signs and symptoms of meningococcemia can include an early upper respiratory tract infection with coryza, pharyngitis, tonsillitis, and/or laryngitis which can rapidly be followed by a collapse of the immune system and can ultimately cause multisystem organ failure. We considered the Stiehm-Damrosch/ Niklasson severity score a useful instrument which includes biochemical and clinical factors. Regarding the biochemical factors of the score, the absence of leukocytes in cerebrospinal fluid together with the low level of glucose can be considered important predictors of a severe prognosis.

Key words: environmental factors, Neisseria meningitidis, pediatric pathology, seasonal occurrence, severity score

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1. Introduction

Historically, infectious diseases are among the most significant causes of death in humans. It is estimated that by the beginning of the twentieth century, more than half of the people who ever lived had died of smallpox caused by a virus, or malaria caused by a protozoa. Bacteria have also been the cause of some of the most deadly diseases and widespread epidemics of human civilization such as tuberculosis, typhus, plague, diphtheria, typhoid fever, cholera, dysentery and pneumonia, lyme disease, which had a huge effect on humanity (Beigelman et al., 2014; Caslariu et al., 2018; Hall-Stoodley et al., 2004; Manciuc et al., 2019; Vata et al., 2018; Vouga and Greub, 2016).

The increasing prevalence of diseases caused by microorganisms with high pathogenic potential and high contagiousness in recent decades has been considered to be related to lifestyle, environmental quality and bacterial exposure. This hypothesis of a cleaner environment was proposed more than 25 years ago, when multiple epidemiological studies supported this theory.

Meningococcemia represents a significant worldwide health problem and one of the biggest emergencies being a life-threatening infectious disease during childhood. Despite the progress in

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patient management it remains a severe disease, associated with significant mortality.

Neisseria meningitidis, often called meningococcus, is a species of Gram-negative bacterium of the genus *Neisseria*, being the etiological agent of meningococcemia. The microorganism is a highly contagious pathogen, which greatly affects human health, and can cause epidemics and endemic disease. The bacterium can be carried by the host (which can manifest asymptomatically), as a result of inhalation of large air droplets, generated by sneezing or coughing by carriers. The disease can also occur after direct contact with respiratory secretions and saliva contaminated with the pathogen. In addition, it has been shown that the pathogenic microorganism and meningococcal disease can be transmitted depending on the characteristics of the environment: the presence of moisture, particulate pollutants, smoke (including that from smokers) (Rouphael and Stephens, 2012; Sultan et al., 2005; Tseng et al., 2014).

Numerous scientists investigate the linkage between environmental conditions and meningitis disease occurrence. For example, Sultan et al. (2005) highlighted that each year, countries in the Sahelo-Sudanese group in West Africa are affected by major outbreaks of meningococcal meningitis, which can affect a large number of individuals (25,000 and 200,000 disease cases per year, with about 10% of them resulting in death, especially young children). Studies have shown that the epidemic begins in February and ends in late May, while the spatial distribution of cases of disease indicates a close link between the life cycle of the pathogen and climate variability, but further studies are still needed to elucidate the mechanisms responsible for observed patterns.

Recently, serogroup types as W-135 and X (predominantly in Africa) and group Y (in the United States and European countries) have occurred as significant disease-causing isolates (Stephens et al., 2007). The current trend in European countries is represented by the decline of meningococcemia caused by serogroup C meningococcus, due to implementation of seroprevalence by vaccination against this serotype. The reduction of the healthy carriers and the incidence of meningococcal disease (MD) with the increase of collective immunity lead to a lower susceptibility and a lower implication of serotype C in MD. In contrast with that, serotype B is the one that is in a continuous rising (Guidance, 2019). The distribution of serogroups in Europe is illustrated in Table 1.

Other studies investigated the associations between monthly weather patterns and the incidence of meningococcal disease. Kinlin et al. (2009) developed such research in some areas of the US, both long-term using Poisson multivariate regression models that control seasonal oscillation, and short-term, respectively, applying a case-crossover approach. In addition, it has been found that extended periods of high humidity and acute changes in ambient B ultraviolet radiation forecast meningococcal disease in Philadelphia. The latter effect may be due to decreased survival of the pathogen or virulence and may explain the meningococcemia occurrence winter season in temperate regions of North America. In this context, the paper investigates the occurrence of meningococcal disease based on a case study developed in a Romanian hospital using data taken from the medical records of patients with the diagnosis of meningococcemia.

Table 1. Serogroup distribution of confirmed cases of invasive meningococcal disease, EU/EEA, 2016 (ECDC, 2016)

Serogroup	***Cases***	***%***
B	1647	54
C	485	16
W	464	15
Y	344	11
Other	91	3
Total	3031	100

2. Environmental and clinical context of meningococcemia in Europe and Romania

Neisseria meningitidis can produce a variety of clinical manifestations, from transient fever and bacteremia to a fulminant form that leads to death within a few hours of onset. Even with optimal treatment, mortality is high (one in 10 patients will die) and one in 5 survivors remains long-term with severe sequel, such as physical or neurological disabilities. A number of 3 280 confirmed cases of invasive meningococcal disease (IMD), including 304 deaths, were reported in 30 EU/EEA Member States in 2016 (ECDC, 2016).

The features regarding the seasonality followed, in 2016, a similar model with the previous years in the sense that IMD appeared mainly in the winter months. The lowest number of cases was recorded during the summer (Fig. 1). The dynamics over time showed that the number of reported confirmed cases decreased in mid-2014 to 2012 and subsequently increased, showing an overall decrease of 7% from 2012 to 2016. (Fig. 2) (ECDC, 2016).

In Romania, 69% of the total number of confirmed cases of meningococcal meningitis in the last 4 years were caused by serogroup B. In 2018 alone, 73 cases were confirmed, the highest incidence being in children aged 0-1 year and 1-5 years (https://raportuldegarda.ro/articol/vaccin-meningita-meningococ-grup-b-disponibil-romania-persoane-peste-2-luni/). A study conducted in Romania during 1971-1992 investigated 1496 *Neisseria* strains isolated from patients and carriers from 24 counties of Romania. The study identified 84.5% of serogroup A in 1987, while in pre- and post-epidemic periods, serogroups B and C reached values from 0 to 66.6% in 1975 for B and 38.8% in 1974 for C strains (Leveneţ et al., 1993).

The disease spectrum caused by *Nisseria meningitidis* ranges from asymptomatic carrier to death due to fulminant meningococcemia. Due to endotoxemia caused by *N. meningitidis*, in meningococcemia, the defense mechanisms of are blocked and as a consequence septic shock where inadequate perfusion of tissues occurs is the path to an unfavorable outcome (Goldacre et al., 2003; Stephens et al., 2007).

The signs and symptoms of meningococcemia include an early upper respiratory tract infection with coryza, pharyngitis, tonsillitis, and laryngitis, which can produce asymptomatic pharyngeal colonization as the initial step of infection. Typically, patients with meningococcemia have a fever and hemorrhagic rash, followed by signs of severe circulatory collapse with purpura and shock that develop within hours which represents a mark of Waterhouse–Friderichsen syndrome. Diffuse mottling to extensive purpuric lesions is the skin manifestations. Petechiae or purpura are seen in 50% to 60% of patients (Branco and Tasker, 2010; Sabatini et al., 2012). The severity score of a disease represents one of the most useful instruments used in the infectious diseases pathology. Stiehm-Damrosch/Niklasson severity score includes biochemical and clinical factors (Table 2) (Stiehm and Damrosch, 1966). The severity score of meningococcemia implies 7 factors. For every factor present the patient receives 1 point. The prognostic can be classified as: i) good - if there is an association of 0-2 factors; ii) reserved - when 3 factors are associated; iii) severe - when more than 3 factors can be found.

3. Case study

3.1. Material and methods

We conducted an observational retrospective study to patients admitted in “Sf. Parascheva” Infectious Diseases Hospital for a period of 24 months (January 2018 - December 2019).

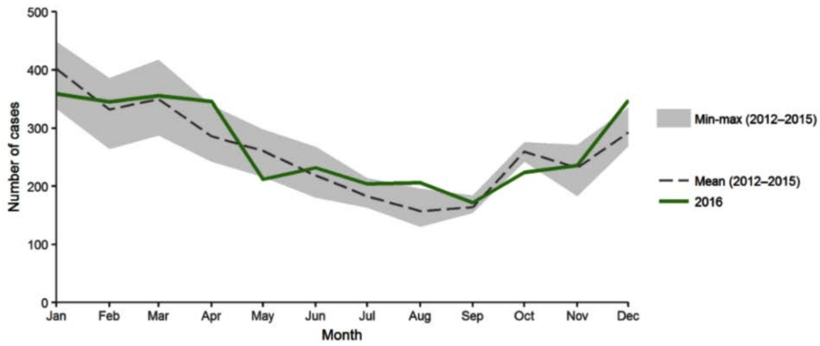

Fig. 1. Seasonal distribution of reported confirmed cases of invasive meningococcal disease, EU/EEA, 2016 compared with 2012 to 2015 (ECDC, 2018)

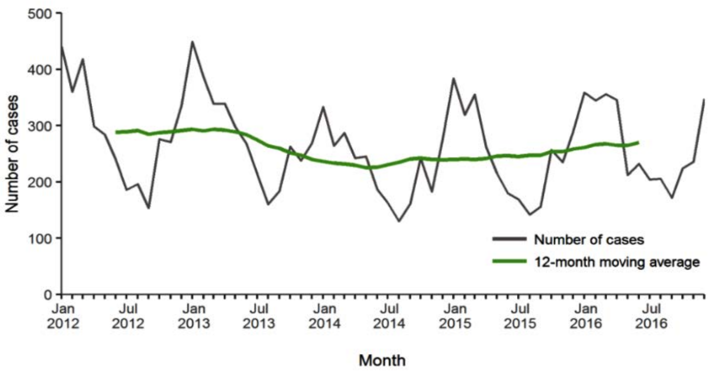

Fig. 2. Trend and number of confirmed cases of invasive meningococcal disease, EU/EEA, 2012 to 2016 (ECDC, 2018)

Table 2. Stiehm-Damrosch/ Niklasson severity score (5)

Level	*Symptom*
Clinical	The appearance of petechiae for less than 12 h pre-admission
	Marked hyperpyrexia (rectal temperature >40C)
	Presence of shock (systolic blood pressure < 70mmHg)
Biochemical	Normal blood leucocyte count (10000 WBC/mm^3)
	Low or normal ESR (< 10mm/h)
	Thrombocytopenia (< 100000 /mm^3)
	Absence of the elements in CSF (< 20 elements in CSF)

CSF - Cerebrospinal Fluid; ESR - Erythrocyte Sedimentation Rate; WBC – White Blood Cells

Collection of data was done from the medical records of patients with the diagnosis of meningococcemia and we included in our study 10 patients that were admitted in our hospital with the diagnosis of meningococcemia. To assess the severity of meningococcemia we used Stiehm-Damrosch/ Niklasson severity score. We followed: the prognostic score with the clinical and biochemical modification, hours/days of hospitalization, if the patient died or was discharged after treatment, laboratory data.

3.2. Results

Ten patients were admitted to Sf. Parascheva Infectious Diseases Hospital in the studied period, with an average incidence (according to the Public Health Department) of 0.81/100000 inhabitants. We calculated the prognostic score for each patient. It can be observed that in the first three cases and the last one the score was above 2, which can be correlated to the severe outcome of the patients. The patients had a fulminant evolution of the infection and survived only a few hours in our hospital. Most patients were smaller than 1 year old (60%) with a range of 3 months to 15 years with a median of age 3.3 years old. A total of 4 deaths were recorded representing an overall mortality of 40%. None of the patients had received meningococcal vaccination. The appearance of petechial and ecchymotic elements <12 hours was found in 7 cases, 57.4 % (4 cases) of whom with fatal outcome (Table 3). The odds ratio for the time of petechial presentation <12 hours in comparison to the time of petechial presentation >12 hours was OR = 1.55.

A normal value of white blood cells (WBC) count was found in 70% of the patients (7 cases), with a rate of fatality over 50%. Thrombocytopenia was present in 4 cases and the fatal outcome occurred in all cases in the first 72 hours. Also, in the same 4 cases the erythrocyte sedimentation rate (ESR) was normal. The absence of meningitis was identified in the first and the last case, which had the fastest progression to exitus in the first 12 hours. The Latex agglutination, which has a low sensitivity to the B strain of meningococcus, only showed if there were capsular antigens for either A, C, Y or W135 strains (Table 4). The detection of the gram stain showed (except in cases 4 and 9 that received antibiotic before the tests) the presence of a gram-negative diplococcus.

As the literature states, antibiotic reduces the detection of the bacteria up to 75%. Blood culture revealed *Neisseria spp*. in all the cases, except those that received antibiotic prior to the blood tests, and in 3 cases serotype B was incriminated as the causative agent. The biochemical analysis of the CSF showed in half of the cases a high level of protein and chlorine and in 90% of the cases a low level of glucose (Table 4).

3.3. Discussion

Studies have showed that the mortality rate in meningococcemia can range from 20 to 80%. In our study, the mortality rate was 40% (Pollard and Finn, 2012). In every case, the Stiehm-Damrosch/ Niklasson severity score was over 2, which predicted a reserved prognostic.

Table 3. Stiehm-Damrosch/ Niklasson severity score in every patient in evolution

Criteria	***Case 1***	***Case 2***	***Case 3***			***Case 4***	***Case 5***	***Case 6***	***Case 7***	***Case 8***	***Case 9***	***Case 10***
			Day 1	***Day 2***	***Day 3***							
Onset of petechiae for less than 24 h pre-admission	1	1	1	1	1	0	0	1	1	1	0	1
Presence of shock (systolic blood pressure < 70 mmHg	1	1	0	0	1	0	0	0	0	0	0	0
Absence of meningitis (<20 elements in CSF)	1	0	0	0	0	0	0	0	0	0	0	1
Blood leucocyte count normal or low (10000 WBC/mm^3)	1	0	1	0	0	1	1	0	0	1	1	1
ESR normal or low (< 10mm.h)	1	1	0	0	1	0	0	0	0	0	0	1
Presence of marked hyperpyrexia (rectal temperature >40^{O}C)	0	0	1	1	1	1	1	1	1	1	1	1
Presence of thrombocytopenia (<100000/mm^3)	1	1	1	1	1	0	0	0	0	1	0	0
Total	**6**	**4**	**4**	**3**	**5**	**2**	**2**	**2**	**2**	**4**	**2**	**5**
Hours/days of hospitalization	7 hours	16 hours	-	-	70 hours	11 days	37 days	11 days	9 days	17 days	9 days	10 hours

Table 4. Laboratory results of the patients

Criteria	*Case 1*	*Case 2*	*Case 3*	*Case 4*	*Case 5*	*Case 6*	*Case 7*	*Case 8*	*Case 9*	*Case 10*
Latex agglutination	Negative	Negative	Positive for capsular antigens A, C, Y, W135	Negative	Positive for capsular antigens A, C, Y, W135	Negative	Negative	Negative	Negative	Negative
Detection of Gram strain	Gram negative Diplococcus	Gram negative Diplococcus	Gram negative Diplococcus	Negative	Gram negative Diplococcus	Gram negative Diplococcus	Gram negative Diplococcus	Gram negative Diplococcus	Negative	Negative
Blood culture	Serotype B	Serotype B	Neisseria spp.	Negative	Neisseria spp.	Serotype B	Negative	Neisseria spp.	Negative	Neisseria spp.
CSF albumin	Normal	Normal	High	Normal	Normal	High	High	Normal	High	High
CSF glucose	Low	Low	Low	Low	Low	Low	Low	Normal	Low	Low
CSF chlorine	Normal	Normal	Low	Normal	Low	Low	Low	High	Normal	Low
Family throat swab	Negative	Negative	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Negative

Because of the innate immaturity of the defense mechanisms in children, the infection is capable to block the activity of the cells responsible with protection (neutrophils and macrophages) (Mogensen, 2009). The most affected by this invasive disease was the pediatric age group, half of the children being under one year old, with an average age of 3.3 years old.

Factoring the age of the patients in our study, because the rate of fatality was equal on the patients under 12 months with those with the age over 12 months, we can\`t draw any clear conclusions, but we can presume that because of the immaturity of the innate immunologic systems the evolution of the disease was exponential faster on the newborns on which the death produced on a median of 13 hours.

The level of CSF glucose seems to have the closest prediction of fatal prognostic, compared to the other CSF biochemical values (CSF protein/ chlorine) (Table 3). In our study, all the patients that died had a low level of CSF glucose compared with the level of CSF proteins/ chlorine which can\`t be associated with any particular information. We can speculate that the CSF level of Protein/ Chlorine didn\`t offered any special information because of the rapid progression of the disease (hours) with the blockage of the defense mechanisms and the impossibility of the defense interleukins to act as suppose.

A multidisciplinary staff that integrates also a psychologist that can help with the emotional burden of the disease is a thing to strive for (Manciuc et al., 2014, 2016). As a line of research, it could be interesting to see the role NADPH- oxidases that was originally identified as a component of innate host defense and is involved in many key biological functions (Filip-Ciubotaru et al., 2016). Even there have been progresses, mortality rate still remains very high, which is why vaccines are an important form of prevention. Because of the low level of education and the and low socio-economic status of the families of the patients, the vaccines against of different serotypes of meningococcal wasn't performed (Manciuc et al., 2018). Given that from our results, none of the patients had a history of meningococcal vaccination, we believe that identifying the unfavorable prognostic factors help to decrease the mortality rate, but the best way is preventing infection through meningococcal vaccination.

4. Conclusions

Meningococcemia represents one of the biggest medical emergencies in the pediatric pathology and continues to make an impact in the medical community. Recognition of this disease from the first medical practitioner that sees it represents an important step on lowering the infaust prognostic of the patient.

Stiehm-Damrosch / Niklasson severity score continues to have an important value for every infectious disease and every pediatric specialist, with the possibility of being updated in every moment. This fact was also confirmed by our statistic, even though it has been made on a small number of cases

Thrombocytopenia and a normal/low ESR were significant findings, predicting mortality in these patients. Also, the absence of the meningitis and a normal WBC count are important predictors even though it was found in just 2 cases, because those had the most rapid evolution.

Even though this study was performed on a small number of cases due to the lack of the cases of this rare pediatric pathology, we can conclude that of all biochemical constants of the CSF, when the glucose level is low from the beginning, the prognostic of the patient is reserved.

Populational hygiene measures in the cold season and also the vaccination, by families request, with the meningococcal vaccine, can create a protective net of antibodies. In time, the continuous vaccination would decrease the susceptible population, while also would minimizing the circulation of strains.

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