Meningococcal infection: a brief review and personal observations of the generalized form of the disease in three-month-old twins

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Meningococcal infection in the form of sporadic cases or minor group outbreaks, mostly among children, is registered in all countries of the world. The disease has a wide range of clinical manifestations – from an asymptomatic bacterial carriage and acute nasopharyngitis to the rapid development of meningococcemia, acute meningococcal sepsis and meningitis. The article highlights and summarizes literature data related to the incidence of meningococcal infection, ways of infection, features of the clinical course of the disease in the newborn period, and modern views on the problem. A rare clinical case of the development of severe generalized forms of meningococcal infection in 3-month-old twins with a fatal outcome in one child is described. The decisive role in the development of the disease of twins is determined by the way and duration of children’s contact with their father, who has a bacteriologically confirmed (Neisseria meningitidis, biovar C) meningococcal nasopharyngitis. Early diagnosis and treatment of all forms of meningococcal infections are important to prevent the development of GMI. The key method of MI prevention is vaccination.

Keywords: N. meningitidis, infants, meningococcemia in twins, morbidity.
Introduction

In the structure of infection-related morbidity, meningococcal infection (MI) is one of the most life-threatening and unpredictable in terms of disease course. MI has a wide range of clinical manifestations – from an asymptomatic bacterial carriage and acute nasopharyngitis to the rapid development of meningococcemia, which can be fatal even on the first day of the disease. Despite the significant advances in modern infectology, generalized forms of meningococcal infection are of concern today: especially meningococcemia – severe meningococcal sepsis and meningitis.

MI in the form of sporadic cases or minor group outbreaks, mostly among children, are registered in all countries worldwide. According to the CDC (Centers for Disease Control and Prevention), the highest incidence rates are observed in Africa, in the so-called African meningitis belt, which stretches along sub-Saharan Africa. In this region, large outbreaks of MI occur every 5-12 years, with an incidence of 1,000 per 100,000 population [1]. In other regions of the world, there is a lower overall incidence rate. Thus, in the United States, Europe, Australia and South America, the incidence rates range from 0.12 to 3 cases per 100,000 population a year [2]. The highest incidence of generalized meningococcal infection (GMI) is observed in infants under the age of 1 year. The mortality rate ranges from 10 to 14% for patients receiving treatment and up to 50% for patients not receiving treatment [3]. Mortality is associated almost exclusively with a fulminant form of meningococcemia complicated by infectious toxic shock, DIC syndrome.

In recent years, reports of the development of GMI in children in the first months of life have become more frequent [4,5,6], however, there is very little data on the disease in twins at this age. Taking into account this fact, we consider it appropriate to share the data of our observations.

Case presentation

Three-month-old infants (twins) were admitted to the intensive care unit of Lviv Regional Infectious Disease Clinical Hospital from a district hospital in an extremely serious condition. The anamnesis of life shows that children were born healthy from the first full-term pregnancy as a result of uncomplicated childbirth. They had been growing and developing according to their age.

Disease symptoms in both children started developing acutely with an interval of 16 hours. At about 10 p.m., the first child’s body temperature spiked to 38 °C, and then rhinitis, coughing, and subsequently, vomiting appeared. The mother of the children requested medical help after 12 hours, at 10 a.m. the next morning. In the central district hospital, the examination resulted in the diagnosis of SARS. Antipyretics and detoxification therapy were prescribed. The general condition of the child remained serious. Manifestations of general intoxication increased, and fever remained within 38 °C – 38.5 °C. During re-examination at 7 p.m., elements of hemorrhagic rash were noted on the patient's skin, with predominant localization on the buttocks and legs. Manifestations of septic shock were rapidly increasing. The diagnosis of SARS was changed to MI, meningococcemia. Treatment was introduced immediately according to the changed diagnosis. Meanwhile, another child was considered healthy. However, due to living in a remote mountainous area, she was hospitalized while breastfeeding with her mother and a sick sister at the central district hospital. In the hospital, her body temperature rose to 37.8 °C, she developed a runny nose, signs of intoxication, and a moderate protrusion of a large tendon. She was diagnosed with MI, meningitis. Both children were immediately transferred by ambulance for further treatment to Lviv Regional Infectious Disease Clinical Hospital. During transportation, the first child received dopamine support intravenously.

In the hospital, children were hospitalized in the intensive care unit. Diagnosis of the first patient on admission: MI, Meningococcemia, Toxic shock syndrome, Cerebral edema. Clinically: unconsciousness, pallor and marble pattern of the skin, characteristic elements of hemorrhagic rash 0.3-0.7 cm all over the body, including the face. Tachycardia (Ps – 160/min), RR – 60/min, BP – 70/40 mmHg, body temperature – 36.3 °C, oliguria.

In the general analysis of blood anemia, the expressed shift of a leukocyte formula to the left to myelocytes, thrombocytopenia and high ESR. Hemogram: HB – 68 g/l, erythrocytes –2.33 × 10^{12}/l, leukocytes – 12.9 × 10^{9}/l, myelocytes – 1%, immature neutrophils – 2%, band neutrophils – 18%, segmented neutrophils – 46%, lymphocytes – 25%, monocytes – 8%, ESR – 44 mm/h, platelets – 73 × 10^{12}/l. The patient was punctured due to the severity of the condition. She received ceftriaxone, dexamethasone, Lasix, and detoxification therapy. Despite the treatment, the patient's condition deteriorated progressively. The child died 57 hours after the occurrence of the first clinical symptoms of the disease. The diagnosis of GMI was confirmed as a result of the pathoanatomical
examination. The immediate cause of death is multiple organ failure. It should be noted that hemorrhage into the adrenal cortex was not detected during the pathoanatomical examination.

Manifestations of meningitis dominated in the other child – protrusion of a large tendon, skin hyperesthesia, Lesage’s symptom, and 2-3 barely noticeable petechiae were found in the area of the legs. Anemia left shift of the leukocyte formula. Hemogram: Hb – 72 g/l, erythrocytes – 2.25 × 10^{12}/l, leukocytes – 6.1 × 10^{9}/l, immature neutrophils – 1%, band neutrophils – 9%, segmented neutrophils – 22%, lymphocytes – 62%, monocytes – 6%. ESR – 18 mm/h. Cerebrospinal fluid: gray, turbid, Pandy’s reaction +++, protein – 2.64 g/l, neutrophilic pleocytosis – 14,507 in mm³, glucose – 2.3 mmol/l. Bacterioscopy of cerebrospinal fluid and blood revealed gram-negative diplococci. The child received antibacterial (ceftriaxone), dehydration (mannitol), detoxification therapy, and glucocorticosteroids (dexamethasone). The cerebrospinal fluid was sanitized on the 8th day of illness. The child recovered.

*Neisseria meningitidis*, biovar C, was received from the nasopharyngeal mucus during the examination of the child’s father. It is known from the medical history that he had a respiratory tract infection (RTI) for three days and complained of a sore throat and low-grade body temperature. He had not sought medical help.

**Search strategy**

Methods included a literature review of scientific articles that studied the issue of meningococcal infection. According to the results of the analysis of articles obtained in the PubMed, SCOPUS, Web of Science, and MedScape databases, using the combination of the terms “meningococcal infection”, “incidence of meningococcal infection”, “meningococcal disease in twins”, “meningococcal infection in young children”, only 3 reports about GMI in twins were found [7, 8, 9]. Cases described by Hummell DS et al. and Levy DI et al. date to 1987 and 1988. Literary data related to the incidence, patterns of development of an unfavorable epidemic situation, features of the clinical course and treatment of MI in young children were studied and summarized. Data analysis of the inpatient card and results of the pathoanatomical examination protocol of the child who died from GMI as a result of multiple organ failure were analyzed.

**Discussion**

*Neisseria meningitidis* (*N. meningitidis*) was first discovered in 1887 by Weichselbaum based on the cerebrospinal fluid of a patient with meningitis. *N. meningitidis* is a gram-negative diplococcus, a human obligate pathogen that usually colonizes the upper respiratory tract. Colonization of the nasopharyngeal mucosa is mostly asymptomatic. Meanwhile, asymptomatic carriage of meningococcus can last from 3 (serogroup A) to 9 (serogroup B) months, which increases the risk of new cases of infection [10]. Although the contagiousness index in MI usually does not exceed 15%, when examining relatives of patients with MI, 20-40% of contacts were found to be carriers of *N. meningitidis* [11].

Infection and development of different clinical forms of the disease according to their severity is largely determined by the functionality of local defense mechanisms at the level of the mucous membrane in the upper respiratory tract, and the state of the patient’s immune system. Under conditions of impaired systemic immune response, life-threatening generalized forms of MI are possible: meningitis and/or septicemia [4], pneumonia [12], septic arthritis [13,14], and pericarditis in children and adolescents [15].

It is known that the main transmission mechanism of the pathogen is airborne. However, today the antenatal and intranatal transmission of the infection deserve special attention, the realization of which is possible under the conditions of meningococcal contamination of the pregnant woman’s genital tract [16,17,18]. In recent years, there have been increasing reports of female genitalia meningococcal infection [19] and male meningococcal urethritis in different countries worldwide [20,21]. In fact, these cases require caution in terms of possible generalization of the infection. The development of GMI with manifestations of shock and meningitis that developed 2 weeks after the clinical manifestations of colpitis in women is described by Offman R et al. According to the authors, the extraction of *N. meningitidis* from the vagina, which is not a typical site of the pathogen, led to a delay in proper antibacterial treatment and caused the generalization of the process with severe disease course [22].

Asymptomatic bacterial carriage of the causative agent in the vagina may be the cause of infection of the child during birth through the natural birth canal. Scientists from Tijuana (Mexico) report a case of neonatal meningococcal conjunctivitis and sepsis in a 3-day-old baby. Clinical manifestations of meningococcal conjunctivitis were abundant purulent drainage from the conjunctiva. *N. meningitidis* of serogroup Y was isolated from the conjunctival exudate and blood of a newborn. During the examination of parents, a culture of *N.
*meningitidis* of serogroup Y was isolated from the nasopharynx and the mother’s vagina [18]. Timothy Gilbey et al. provide convincing data on prenatal meningococcal infection with the subsequent development of early neonatal sepsis in a full-term child. Histopathological examination of the placenta revealed acute funisitis and chorioamnionitis associated with ascending infection. Bacteriologically, *N. meningitidis* of serogroup W was isolated from the placenta [17]. The development of GMI in the neonatal period [16, 23] is characterized by high mortality and the development of severe neurological complications [5, 24]. The disease develops violently: a sharp deterioration of the general condition against the background of an increase in temperature with the development of shock and multiple organ failure within a few hours. Mortality is 40% among patients in whom the disease develops during the first week of life [23].

It should be noted that the transmission of *N. meningitidis* from mother to fetus is extremely rare [17, 25]. Indicative in this regard is the description of the case of a premature baby born at 31 weeks, confirmed by the release of *N meningitidis* from amniotic fluid, ear, stomach, throat and nose of the newborn [16].

Infection and course of MI depend on many factors, primarily age, meningococcal serogroups, available antibodies, geographical location and living conditions. However, these factors make up a small share of the total population. The innate immune response plays a key role in preventing the development of GMI after colonization of the nasopharynx with meningococcus [26].

Concerning this case, we believe that the crucial role in the development of the twins’ disease is determined by the nature and duration of the child’s contact with the father suffering from meningococcal nasopharyngitis. The possible presence of *N. meningitidis*, as an etiological factor, in the clinical manifestation of RTI in the father was not considered at all. Catarrhal manifestations were regarded as a viral infection, antibacterial treatment was not carried out. However, it is known that early detection and isolation of patients with meningococcal nasopharyngitis and sanitation of bacterial carriers are the main preventive measures for the spread of MI. The relative insufficiency of humoral and cellular immunity, characteristic for this age, obviously contributed to the development of severe GMI in 3-month-old twins.

Today, various scientific studies are being carried out, related to the study of both the genetic predisposition of people to the development of GMI [27, 28] and the genetic variants of the meningococcal genome in terms of their influence on the severity of development and the course of the disease. According to Philip Kremer et al., the influence of genetic variants of the meningococcal genome on the severity of the disease is limited [29]. In another study, Joram N, et al. demonstrated that TLR4 gene polymorphism is a risk factor for the development of severe meningococcalemia in young children. At the same time, it was found that under the conditions of the development of an infectious disease in one of the twins, the probability of disease development in the second child is significantly higher in monozygotic than in dizygotic twins [30]. Regarding our case, unfortunately, we were not able to conduct molecular genetic studies of the affected twins to find out possible genetic features.

It should be noted that the key method of MI prevention is vaccination. Today, effective vaccines are available worldwide against all major meningococcal serogroups that cause GMI. The effectiveness of preventive vaccinations in children and numerous campaigns of vaccination of the adult population, as defining components of a complex of anti-epidemic measures, is illustrated by the steady decline in MI incidence rates over the past two decades in most countries of the world [31,32,33]. There is no doubt that in our case, timely vaccination of children and adults against MI could drastically affect the course and consequences of the disease. Unfortunately, today in Ukraine, vaccination against MI is included only in the list of recommended vaccines.

This case demonstrates the development of severe generalized forms of meningococcal infection in 3-month-old twins. The risk of infection is related to the nature and duration of contact with the undiagnosed meningococcal nasopharyngitis carrier, their parent. Early diagnosis and treatment of all forms of meningococcal infections are important to prevent the development of GMI. We see the solution to the problem in the inclusion in the calendar of preventive vaccinations of mandatory vaccination of infants from the age of 2 months, as well as prophylactic antibiotic administration for contact persons, regardless of vaccination status.
References

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