Pediatr Pol 2023; 98 (1): 74-78
DOI: https://doi.org/10.5114/polp.2023.125063
Submitted: 21.05.2022, Accepted: 10.08.2022, Published: 02.03.2023

PEDIATRIA Polska
Polish Journal of PAEDIATRICS

CASE REPORT

Fatal Waterhouse-Friderichsen syndrome due to *Neisseria meningitidis* group B in a paediatric patient during the phone consultation era

Marta Serafin[1], Ewa Czerwińska[2], Marian Koźbiał[1], Mariusz Leszczyński[1], Leszek Szenborn[2]

[1]Department of Paediatrics with Children's Intensive Care Unit, Regional Public Hospital, Świdnica, Poland
[2]Clinical Department of Paediatrics and Infectious Diseases, Wroclaw Medical University, Wroclaw, Poland

ABSTRACT

Owing to uncharacteristic initial symptoms and rapid progression, invasive meningococcal disease is still a challenge to diagnose and treat, even in high-income countries. Waterhouse-Friderichsen syndrome is a potentially fatal complication of invasive meningococcal disease, presenting as acute adrenal insufficiency due to haemorrhagic necrosis of the adrenal glands. We report a case of 5.5-year-old boy who presented to the hospital with fever, impaired consciousness, vomiting, and upper respiratory tract infection symptoms. Despite prompt diagnosis of invasive disease and adequate treatment, the patient died. We underline the need to increase parents' knowledge and better access to vaccines against meningococci for Polish paediatric patients. Paediatricians and primary care physicians must remain alert and be ready to suspect invasive meningococcal disease in their patients.

KEY WORDS:

bacterial meningitis, preventive vaccinations, invasive meningococcal disease, Waterhouse-Friderichsen syndrome.

INTRODUCTION

Although uncommon, invasive meningococcal disease remains one of the most important causes of bacterial meningitis and sepsis worldwide. It is caused by a Gram-negative bacterium *Neisseria meningitidis* (*N. meningitidis*). The majority of cases can be attributed to organisms from the A, B, C, X, Y, or W-135 serogroups [1]. *N. meningitidis*, an obligate human pathogen, is a part of nasopharynx flora of 4.5–23.7% of the population. It is spread through saliva and respiratory secretions of patients or asymptomatic carriers. The highest incidence rate of invasive meningococcal disease is observed among children, adolescents, and young adults. The disease progresses rapidly, has severe outcomes, and can be life-threatening [2]. Waterhouse-Friderichsen syndrome, associated with adrenal insufficiency resulting from bilateral adrenal haemorrhage, is a rare and severe complication observed in patients with meningococcal sepsis [3]. The treatment of invasive meningococcal disease is focused on shock management, antibacterial therapy, and supportive care [4].

Due to ongoing COVID-19 pandemics, many countries have introduced restrictions in everyday life to control the spread of the SARS-CoV-2 virus. As a result of the pandemic lockdown, the frequency of many infectious conditions has decreased [5]. Despite this fact, invasive meningococcal disease is still a threat.

Here we present a case report of a young Polish child who died because of meningococcal sepsis despite prompt and adequate treatment implementation.

ADDRESS FOR CORRESPONDENCE:

Ewa Czerwińska, Clinical Department of Paediatrics and Infectious Diseases, Wroclaw Medical University, Wroclaw, Poland, e-mail: czerwinska.ed@gmail.com

CASE REPORT

A 5.5-year-old boy presented to the Emergency Department of the Regional Public Hospital in Świdnica, Poland due to impaired consciousness and fever. During the night before hospital admission, he had been vomiting and then had a fever. Even though he had appointed an online consultation with a paediatrician later that day, due to the boy's deteriorating condition, his mother decided to go to the hospital.

The patient, the first child of healthy parents, was born on time with an Apgar score 10 and a birth weight of 3650 g. His medical and family history were unremarkable. The boy did not have any siblings. Because he had already been coughing for about a week before admission to the hospital, during that time he did not attend kindergarten nor had any contact with other children or potentially infected people. He was vaccinated according to the obligatory Polish vaccination schedule, but he did not receive any recommended vaccinations, including meningococcal vaccines.

On admission to the Emergency Department the general condition of the patient was described as severe. He was sleepy, confused, and responsive only to pain stimuli. His vital signs were as follows: body temperature – 39.9°C, blood pressure – 90/70, heart rate – 150/min, and capillary blood saturation – 97%. Capillary refill time was prolonged > 3 s. On physical examination, warm, pale skin, dry oral mucosa, coated tongue, caries, and harsh vesicular breath sound with transmitted rhonchi were noticed. He was lying in the foetal position. The patient did not present meningeal signs. A rapid antigen SARS-CoV-2 test was negative. Intravenous antipyretic drugs and fluids were administered. Laboratory tests revealed elevated glucose level – 274 mg/dl, slightly elevated CRP level – 29.38 mg/l, and electrolyte imbalance (hyponatraemia, hypokalaemia). Peripheral blood gas tests revealed low oxygen partial pressure (pO_2), high lactate (8.7 mmol/l), and low base excess. Creatinine and aminotransferases levels as well as complete blood count were within normal ranges (white blood count 5.4 K/µl, neutrophils 3.9 K/µl). The details are presented in Table 1.

TABLE 1. Summary of consecutive laboratory tests

Parameters	Emergency Department 1 p.m.	Department of Paediatrics with Children's Intensive Care Unit		
		2–3 p.m.	8 p.m.	2 a.m.
Blood gas test	pH – 7.4 pCO_2 – 20.8 mm Hg pO_2 – 62.9 mm Hg Lactate – 8.7 mmol/l Base excess –11.9 mmol/l HCO_3 – 16.7 mmol/l		pH – 7.314 pCO_2 – 28.1 mm Hg pO_2 – 47.4 mm Hg Lactate – 8.9 mmol/l Base excess –11.9 mmol/l HCO_3 – 14.3 mmol/l	pH – 7.361 pCO_2 – 22.4 mm Hg pO_2 – 55.2 mm Hg Lactate – 7.3 mmol/l Base excess –12.7 mmol/l HCO_3 – 12.7 mmol/l
Complete blood count	WBC – 5.4 K/µl (5.0–15.5) Neutrophils – 3.9 K/µl (1.9–8.0) Lymphocytes – 0.89 K/µl (0.6–4.1) PLT – 143 K/µl (140–440)	Blood clot	Lymphocytes – 0.33 K/µl (0.6–4.1) PLT – 35 K/µl (140–440)	WBC – 24.2 K/µl (5.0–15.5) Neutrophils – 17.46 K/µl (1.9–8.0) Lymphocytes – 5.25 K/µl (0.6–4.1) PLT – 86 K/µl (140–440)
Inflammatory markers	CRP – 29.38 mg/l	CRP – 49.4 mg/l Procalcitonin > 100 ng/ml	CRP – 104.28 mg/l Procalcitonin > 100 ng/ml	
Blood ionogram	Sodium – 131 mmol/l (135–143) Potassium – 2.94 mmol/l (3.4–5.4)		Sodium – 135 mmol/l (135–143) Potassium – 3.89 mmol/l (3.4–5.4)	
Glucose concentration	274 mg/dl		90 mg/dl	
Coagulation tests		APTT – 73.2 s (27.5–41.3) PT% – 43.6% (80–120) INR – 1.84 (0.8–1.3) D-dimers > 10000 ng/ml (0–500)	APTT – 203 s (27.5–41.3) PT% – 32.7% (80–120) INR – 2.37 (0.8–1.3) Fibrinogen – 71.5 mg/dl (170–400)	APTT – 164.2 s (27.5–41.3) PT% – 27.5% (80–120) INR – 2.78 (0.8–1.3) Fibrinogen – 157 mg/dl (170–400)
Other	No other relevant abnormalities; creatinine and aminotransferase levels – within normal ranges		Urea – 48 mg/dl (17–43) Creatinine – 1.27 mg/dl (0.24–0.73) eGFR – 32.4 ml/min/1.73 m^2 Albumin – 3.1 g/dl (3.5–5.2) Total protein – 5.05 g/dl (5.60–7.70)	

FIGURE 1. Skin lesions (petechiae) on the head and upper limbs

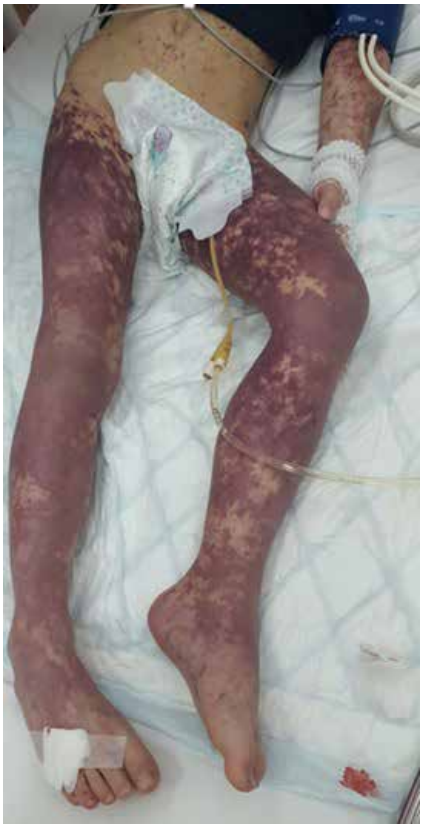

FIGURE 2. Skin lesions (petechiae) on the lower limbs

During the second physical examination, conducted about an hour after the first one, non-blanching dark red macules with 1–3 mm diameter on the right thigh were found. Due to the patient's serious condition, he was transferred to the Department of Paediatrics with Children's Intensive Care Unit in the same hospital. Two intravenous accesses were immediately obtained, a urinary catheter was inserted, and blood and urine samples were taken for basic laboratory tests and microbiologic analysis. The boy's blood type was determined. The patient's vital signs were monitored continuously, and supplementation with oxygen and fluid resuscitation were provided. Lumbar puncture was performed – the cerebrospinal fluid in the initial visual assessment was clear. Blood and cerebrospinal fluid samples were sent to the National Reference Centre for Bacterial Meningitis (Krajowy Ośrodek Referencyjny ds. Diagnostyki Bakteryjnych Zakażeń Ośrodkowego Układu Nerwowego). Immediately after the lumbar puncture, the boy received the first dose of dexamethasone, cefotaxime, vancomycin, and penicillin G. Laboratory tests performed on admission to the intensive care unit revealed numerous abnormalities: hyperglycaemia, elevated inflammatory markers, and signs of coagulopathy (prolonged APTT, high INR, and elevated D-dimers). Bedside chest radiography revealed bilateral peribronchiolar parenchymal opacities of inflammatory aetiology. Additional control laboratory tests were performed a few hours later. They disclosed partially compensated metabolic acidosis, high inflammatory markers, low albumin and protein levels, signs of kidney injury, and exacerbation of coagulopathy. Cerebrospinal fluid was clear. Its evaluation revealed cytosis (3 cells/μl), proteins (17 mg/dl) and chloride (121 mmol/l) levels within normal ranges, and elevated glucose concentration (137 mg/dl). A rapid cerebrospinal fluid test result was positive for *N. meningitidis*.

Despite intensive treatment, the boy's condition was worsening. The physical examination revealed central cyanosis and exacerbation of skin lesions, which were present on the whole body, particularly on the lower limbs (Figure 1, 2). The patient was passing many fetid stools. He required implementation of intravenous heparin, as well as transfusions of plasma and platelets. On the 16th hour of hospitalization there was a decrease in oxygen blood saturation (80%) with consequent cardiac arrest in the mechanism of asystole. Cardiopulmonary resuscitation was ineffective; after 30 minutes the boy was confirmed dead.

Three days later, the results of blood and cerebrospinal fluid laboratory tests were obtained from the National Reference Centre for Bacterial Meningitis, and the presence of genetic material specific for *N. meningitidis* B was confirmed. Cerebrospinal fluid and blood cultures were performed in the hospital laboratory. Cerebrospinal fluid culture was negative, while blood culture detected the presence of *N. meningitidis*. A specific prophylaxis in the form of one dose of ciprofloxacin was implemented in the patient's parents and medical personnel.

The boy's autopsy demonstrated massive, bilateral renal and adrenal haemorrhages (Waterhouse-Friderichsen syndrome), purulent effusion in the lateral ventricle of the brain, oedema of cerebellum and spinal cord, haemorrhages and lymphocytic infiltration of alveolar membranes of the lungs, thrombi in pulmonary artery branches, and petechiae on the pericardium. A diagnosis

of multiorgan failure due to meningococcal sepsis was established.

DISCUSSION

Despite our detailed knowledge about *N. meningitidis* and better access to adequate antibiotic treatment, the fatality rate of invasive meningococcal disease is still oscillating around 10% depending on the serogroup and patient's age [2, 6]. Initial symptoms are uncharacteristic (fever, nausea/vomiting, irritability, fatigue, headache, upper respiratory tract symptoms) and can be mistaken for other conditions. Classic symptoms, like petechial rash, neck stiffness, confusion, or photophobia occur late in the course of the disease [7, 8].

Waterhouse-Friderichsen syndrome is a rare disorder connected with adrenal failure attributable to acute adrenal haemorrhage and necrosis. It can result from infectious causes, with *N. meningitidis* being the most common, or have non-infectious origin, such as anticoagulant treatment, antiphospholipid syndrome, trauma, and surgery. It very rarely occurs spontaneously. Its exact pathophysiology is unclear. The symptoms probably result from massive coagulation, fibrinolysis, and pro-inflammatory cytokine gene activation due to bacteria endotoxins. Intravascular changes (disseminated intravascular coagulation) of the adrenal vessels cause adrenal insufficiency, which can lead to shock and death [9, 10].

Serogroup B meningococci are the main cause of invasive meningococcal disease among Polish patients in all age groups, accounting for 67% cases in the year 2021 [11]. Available data indicate that vaccination against serogroup B meningococci is effective in preventing invasive meningococcal disease among children who received at least 2 doses of the vaccine [12, 13]. What is more, one of the studies demonstrated no deaths or serious complications in children who developed invasive meningococcal disease despite vaccination. In comparison, among unvaccinated children, the number of complications and deaths was significant (18% and 8%, respectively) [12]. Unfortunately, vaccination against group B meningococci is not included in the mandatory vaccination schedule in Poland [14]. Many parents are not familiar with the possibility of buying recommended vaccines, and their cost may be beyond the family budget.

Epidemiological data indicate a lower incidence of invasive meningococcal disease in Poland during the calendar years 2020 and 2021 compared with previous years [11, 15, 16]. According to data published by the National Institute of Public Health – National Institute of Hygiene (Narodowy Instytut Zdrowia Publicznego – Państwowy Zakład Higieny), there were 105 and 106 cases of invasive meningococcal disease in the years 2021 and 2020, respectively, while there were 193 and 200 cases reported in the preceding years [15–17]. This may be due to the everyday restrictions (hand washing/disinfection, social distancing, and wearing face masks) implemented by the government to control the ongoing COVID-19 pandemic. Unfortunately, the pandemic lockdown resulted not only in a decrease in the incidence of many infectious diseases, but also in the decline of vaccination coverage [18]. Because of the interruption or timely suspension of routine childhood vaccination practices, the population of patients susceptible to infectious diseases is rising. With pandemic restrictions easing, we will probably observe higher incidence rates of infectious diseases that were previously controlled by means of vaccination. Thus, particularly in the pandemic situation, comprehensive interview, face-to-face examination, and readiness to diagnose invasive meningococcal disease can save the patient's life.

CONCLUSIONS

Invasive meningococcal disease is still a challenge to diagnose and treat. It can be fatal despite rapid and adequate treatment. This case indicates the importance of vaccinations against meningococci and broad education about vaccination availability among the Polish population.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Jafri RZ, Ali A, Messonnier NE, et al. Global epidemiology of invasive meningococcal disease. Popul Health Metr 2013; 11: 1-9.
2. Olbrich KJ, Müller D, Schumacher S, Beck E, Meszaros K, Koerber F. Systematic review of invasive meningococcal disease: sequelae and quality of life impact on patients and their caregivers. Infect Dis Ther 2018; 7: 421-438.
3. Tattoli L, Marzullo A, Di Vella G, Solarino B. Postmortem detection of Neisseria meningitidis in a case of Waterhouse-Friderichsen syndrome from fulminant meningococcal disease in an adult patient. Rom J Leg Med 2015; 23: 29-32.
4. Albrecht P, Hryniewicz W, Kuch A, Przyjałkowski W, Skoczyńska A, Szenborn L. Rekomendacje postępowania w zakażeniach bakteryjnych ośrodkowego układu nerwowego. Rekomendacje diagnostyczno-terapeutyczno-profilaktyczne 2011.
5. Czerwińska E, Szenborn L. The COVID-19 pandemic lockdown causes a decrease in the number of cases of other infectious diseases in Poland. Pediatr Pol 2020; 95: 73-79.
6. Wang B, Santoreneos R, Giles L, Haji Ali Afzali H, Marshall H. Case fatality rates of invasive meningococcal disease by serogroup and age: a systematic review and meta-analysis. Vaccine 2019; 37: 2768-82.
7. Hovmand N, Christensen HC, Lundbo LF, et al. Nonspecific symptoms dominate at first contact to emergency healthcare services among cases with invasive meningococcal disease. BMC Fam Pract 2021; 22: 1-8.
8. Haj-Hassan TA, Thompson MJ, Mayon-White RT, et al. Which early "red flag" symptoms identify children with meningococcal disease in primary care? Br J Gen Pract 2011; 61: 97-104.
9. Heitz AFN, Hofstee HMA, Gelinck LBS, Puylaert JB. A rare case of Waterhouse-Friderichsen syndrome during primary Varicella zoster infection. Neth J Med 2017; 75: 351-353.

10. Spagnolo EV, Mondello C, Roccuzzo S, et al. A unique fatal case of Waterhouse-Friderichsen syndrome caused by Proteus mirabilis in an immunocompetent subject case report and literature analysis. Medicine (Baltimore) 2019; 98: 1-5.
11. Skoczyńska A, Gołębiewska A, Wróbel-Pawelczyk I, et al. Inwazyjna choroba meningokokowa (IChM) w Polsce w 2021 roku (dane KOROUN) 2022.
12. Rodrigues FMP, Marlow R, Simões MJ, Danon L, Ladhani S, Finn A. Association of use of a meningococcus group B vaccine with group B invasive Meningococcal disease among children in Portugal. J Am Med Assoc 2020; 324: 2187-194.
13. Ladhani SN, Andrews N, Parikh SR, et al. Vaccination of infants with Meningococcal group B vaccine (4CMenB) in England. N Engl J Med 2020; 382: 309-317.
14. Komunikat Głównego Inspektora Sanitarnego z dnia 28 października 2021 r. w sprawie Programu Szczepień Ochronnych na rok 2022, 2021.
15. Zakład Epidemiologii NIZP-PZH. Zachorowania na wybrane choroby zakaźne w Polsce od 1 stycznia do 31 grudnia 2020 r. oraz w porównywalnym okresie 2019 r., 2021.
16. Zakład Epidemiologii NIZP-PZH. Zachorowania na wybrane choroby zakaźne w Polsce od 1 stycznia do 31 grudnia 2021 r. oraz w porównywalnym okresie 2020 r., 2022.
17. Zakład Epidemiologii NIZP-PZH. Zachorowania na wybrane choroby zakaźne w Polsce od 1 stycznia do 31 grudnia 2019 r. oraz w porównywalnym okresie 2018 r., 2020.
18. Oostrom TG, Cullen P, Peters SA. The indirect health impacts of the COVID-19 pandemic on children and adolescents: a review. J Child Heal Care 2022: 136749352110599.