Original Investigation / *Özgün Araştırma*

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Evaluation of Clinical, Laboratory Findings and Prognoses of Meningococcal Infections in Children: A Single Center Experience

Çocuklarda Meningokok Enfeksiyonlarının Klinik, Laboratuvar Bulguları ve Prognozlarının Değerlendirilmesi: Tek Merkez Deneyimi

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Abstract

Objective: Invasive meningococcal infection caused by *Neisseria meningitidis* leads to meningitis and sepsis with high mortality and morbidity and is a serious public health problem all over the world. In our country, it is one of the most common causes of community-acquired meningitis in children. Rapid diagnosis and therapy are life-saving. In our study, it was aimed to evaluate the clinical features, risk factors, laboratory findings and prognosis of pediatric patients we followed up in our clinic for invasive meningococcal disease (IMD).

Material and Methods: In this retrospective study, records of 26 children with IMD who were followed in the Pediatric Infectious Diseases Clinic of Selçuk University Faculty of Medicine between January 2013 and December 2022 were evaluated. The patients were divided into two groups as ≤5 years and >5 years, and their laboratory and clinical findings were compared. Microbiological examinations of the patients, serotypes, mortality and morbidities were evaluated.

Results: Median age of the patients was 45.5 (min-max= 1-203) months and 61.5% (n= 16) were males. Fever was present in all patients. Nausea-vomiting (84.6%), restlessness (80.8%), rash (53.8%), tachypnea and nuchal rigidity (46.2%), tachycardia (n= 42.3%) were the most common clinical findings. While *N. meningitidis* was shown in microbiological examinations in 88.4% of the patients, clinical diagnosis was made in 11.5% of the patients. Isolated meningitis was 57.7% (n= 15), sepsis and men-

Öz

Giriş: *Neisseria meningitidis*'in neden olduğu invaziv meningokok enfeksiyonu, menenjit ve sepsis kliniği ile seyreden yüksek mortalite ve morbiditeye neden olan tüm dünyada ciddi bir halk sağlığı sorunudur. Ülkemizde, çocuklarda toplumsal kaynaklı menenjitin en sık etkenlerindendir. Meningokok hastalığın erken tanı ve tedavisi hayat kurtarıcıdır. Çalışmamızda, invaziv meningokok hastalığı (İMH) nedeniyle takip ettiğimiz çocuk hastaların klinik özellikleri, risk faktörleri, laboratuvar bulguları ve prognozlarını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Retrospektif çalışmada, İMH nedeniyle Ocak 2013-Aralık 2022 tarihleri arasında Selçuk Üniversitesi Tıp Fakültesi Çocuk Enfeksiyon Hastalıkları Kliniğinde takip edilen 26 çocuk hastanın dosyaları değerlendirildi. Hastalar ≤5 yaş ve >5 yaş olmak üzere iki gruba ayrılarak laboratuvar ve klinik bulguları karşılaştırıldı. Hastaların mikrobiyolojik tetkikleri, saptanan serotipler, mortalite ve morbiditeler değerlendirildi.

Bulgular: Hastaların ortanca yaşı 45.5 (min-maks= 1-203) ay ve %61.5 (n= 16)'i erkekti. Ateş şikayeti tüm hastalarda vardı. Bulantı-kusma (%84.6), huzursuzluk (%80.8), döküntü (%53.8), takipne ve ense sertliği (%46.2), taşikardi (n= %42.3) en sık saptanan klinik bulgulardı. Hastaların %88.4'ünde *N. meningitidis* mikrobiyolojik tetkiklerde gösterilmişken, %11.5'inde klinik olarak tanı konuldu. Hastaların %57.7'sinde (n= 15) izole menenjit, %38.5 (n= 10)'inde sepsis ve menenjit kliniği saptan-

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ingitis were in 38.5% (n= 10) of the patients. Patients with concomitant arthritis, bronchiolitis, and myocarditis findings were also detected. Isolated pericarditis and pleuritis findings were found in 3.8% (n= 1) of the patients. Cerebrospinal fluid polymerase chain reaction positivity was detected in 69.2% of the patients (n= 18), although there was no growth in the culture. While isolated meningitis was at a higher rate in the age group >5 years (p= 0.005), coexistence of sepsis-meningitis was found at a higher rate ≤5 years (p= 0.014). Fifty percent of the patients were followed up in the intensive care unit. Mortality rate was 7.6% (n= 2), and morbidity rate was 19.2% (n= 5, hearing loss, skin-extremity necrosis, neurologic deficit).

Conclusion: There is no routine meningococcal vaccination in our country, so children with fever and poor general condition should be evaluated in detail for meningococcemia. Clinical findings of meningococcemia may develop within hours, therefore children with fever and poor general condition should be closely monitored in the hospital. It should be kept in mind that patients may present with rare clinical findings.

Keywords: Child, meningitis, meningococcemia, mortality

dı. Artrit, bronşiyolit ve miyokardit eş zamanlı gözlenen bulgulardandı. Hastaların %3.8 (n= 1)'inde izole perikardit, plevrit bulguları saptandı. Hastaların %69.2 (n= 18)'sinde kültürde üreme olmayıp beyin omurilik sıvısı polimeraz zincir reaksiyonu pozitifliği saptandı. İzole menenjit >5 yaş grubunda daha yüksek orandayken (p= 0.005), sepsis-menenjit birlikteliği ≤5 yaş daha yüksek oranda (p= 0.014) saptandı. Hastaların %50'si yoğun bakımda takip edildi. Mortalite %7.6 (n= 2), morbidite %19.2 (n= 5; işitme kaybı, cilt-ekstremite nekrozu, nörolojik defisit) oranında saptandı.

Sonuç: Rutin meningokok aşılamasının yapılmadığı ülkemizde ateş, genel durum bozukluğu olan çocuklar meningokoksemi için ayrıntılı değerlendirilmelidir. Meningokoksemi klinik bulguları saatler içinde gelişebileceği için ateş ve genel durum bozukluğu olan çocuklar hastanede gözlem altında takip edilmelidir. Hastaların nadir klinik bulgularla başvurabilecekleri de akılda bulundurulmalıdır.

Anahtar Kelimeler: Çocuk, menenjit, meningokoksemi, mortalite

Introduction

Neisseria meningitidis is a gram-negative, encapsulated diplococcus bacterium. It is classified into 13 serogroups according to the polysaccharide composition of the capsule. The most common serotypes causing invasive meningococcal disease (IMD) are serogroups A, B, C, W, X and Y (1). Although rare, IMD is the leading cause of childhood infectious mortality and is responsible for 8% of childhood mortality (2). In Türkiye, the <18 age group is mostly affected by IMH; the incidence of IMH in 1985-2006 was 1.01-5.5/100.000, and Türkiye is considered a moderately endemic region (3). In subsequent surveillance studies, the incidence was 0.6-1.9/100.000 in 2006-2012 and 0.3-0.9/100.000 in 2013-2014. Of the IMRs, 75% are in children aged <5 years, with a second small peak in incidence in adolescents and young adults (4).

Naso-oropharyngeal mucosa colonization of *N. meningitidis*, which infects only humans, causes asymptomatic carriage (10%). Most carriage is spontaneously eradicated. In some cases, the pathogen may enter the bloodstream through the naso-oropharyngeal mucosa and cause IMH. The incubation period is 1-14 days (5). The formation of invasive disease from colonization is thought to depend on host susceptibility, environmental factors and bacterial virulence (6).

In our study, demographic characteristics, symptoms at hospital presentation, underlying risk factors, clinical and laboratory findings, treatments and prognoses of the patients who were followed up due to IMH were evaluated.

Materials and Methods

In our study, we retrospectively evaluated the file records of 26 patients who were followed up for IMH in the Pediatric Infection Clinic of Selçuk University Faculty of Medicine between January 2013 and December 2022. Patients in whom *N. meningitidis* was detected in the cerebrospinal fluid (CSF) gram, culture/polymerase chain reaction (PCR) or blood culture or clinically suspected meningococcemia were included in the study.

Patients were divided into two groups according to age: group 1 (≤5 years) and group 2 (>5 years). Hospitalization symptoms, underlying risk factors, clinical findings (isolated meningitis, isolated sepsis, association of meningitis and sepsis) were evaluated. Patients with rare clinical findings and specific findings in the anamnesis were recorded. Hemogram, sedimentation, C-reactive protein (CRP), procalcitonin, coagulation parameters (INR, PT, PTT), fibrinogen, D-dimer, CSF tests (gram, PCR, culture), blood culture, antibiogram, *N. meningitidis* serotypes, brain imaging, treatments administered, intensive care needs, duration of hospitalization, mortality and morbidity (hearing loss, skin necrosis, amputation, neurological deficit) were recorded.

CSF pleocytosis >4 leukocytes/mm^3, elevated protein >45 mg/dL, and low glucose <40 mg/dL were evaluated. Multiplex PCR for the investigation of meningitis agents was performed using Fast Track Diagnostics (FTD) bacterial and viral meningitis kits (Fast Track Diagnostics, Junglinster, Luxembourg) on Rotor Gene QIAGEN (Netherlands), a real-time PCR device. Blood culture samples obtained from the patients were monitored in BacT/ALERT 3D (bioMérieux, France) or BACTEC 9240 (Becton Dickinson, USA) automated blood culture devices. The bottles showing growth signal were passaged onto 5% sheep blood Columbia agar (bioMérieux, France), chocolate agar (bioMérieux, France) and eosin methylene blue agar (Oxoid, UK). CSF cultures were inoculated on 5% sheep blood Columbia agar (bioMérieux, France), chocolate agar (bioMérieux, France) and eosin methylene blue agar (Oxoid, UK). The media were evaluated after 18-24 hours of incubation at 35 °C in an aerobic environment with 5% CO_2. The grown bacteria were identified using conventional methods and VITEK

2 (bioMérieux, France) automated system. CSF samples stored at -80 °C of patients with positive PCR results or clinical suspicion of *N. meningitidis* were sent to Hacettepe University Pediatric Infectious Diseases Laboratory. In PCR positive samples (GeneAmp PCR system model 9700; Applied Biosystems, Foster City, CA, USA), *N. meningitidis* serogroup determination was performed by the detection of oligosaccharides in the ctrA X gene for serogroup X, in the siaD gene for B, C, W, Y and in the orf-2 gene for serogroup A. All amplicons were analyzed by electrophoresis on standard 3% agarose gels and visualized using UV fluorescence.

Approval for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of Selçuk University Faculty of Medicine Hospital (Decision no: 2023/189).

Statistical Analysis

Data obtained in the study were statistically analyzed with SPSS version 22.0 for Windows. Quantitative variables were expressed as median (minimum-maximum) and categorical variables as number (n) and percentage (%). In statistical evaluations, Mann-Whitney U test was used to analyze quantitative data, and Fisher's exact chi-square test was used to analyze qualitative data. Statistical significance was determined as $p< 0.05$.

Results

Demographic Characteristics and Risk Factors

Of the 26 patients followed up for IMH, 57.7% were ≤5 years of age. Median age of the patients was 45.5 (min-max= 1-203) months and 61.5% (n= 16) were males. There was no statistically significant difference between the sexes of patients with IMH (p= 0.428). Of the patients, 30.7% (n= 8) presented in spring, 26.9% (n= 7) in winter, 23% (n= 6) in fall, and 19.2% (n= 5) in summer. There was no history of congenital or acquired immunodeficiency, functional or anatomical asplenism, immunosuppressive therapy (eculizumab, etc.), or meningococcal vaccination. Patients' conditions that may be at risk for IMH are summarized in Table 1.

History of contact with individuals who traveled to Umrah was present in patients 1, 10, 13, and 26. Although his father received meningococcal vaccine before Umrah, IMH developed in patient one on the fifth day of his father's return from Umrah. Isolated meningitis was found in two adolescents (patients two and 13) who had a history of staying in a student dormitory. Patient three, who had a history of hydrocephalus and premature birth, was followed and treated for sepsis and meningitis, but had a mortal course. Isolated meningococcal meningitis was found in the 5th patient who had a history of trauma to the head with a hard object twenty days before admission to the hospital. The 7th patient, whose twin brother was found dead in bed at home in the morning and whose postmortem examination findings were compatible with IMH, presented with fever and rash the same morning and was diagnosed with meningococcal meningitis. Two of the patients (patients 16 and 17) had a history of premature birth and developed IMH in the infant period. One week before the diagnosis of IMH, influenza positivity was detected in the respiratory panel of patient 26 at an external center.

Clinical Characteristics of the Patients

Mean interval between the onset of symptoms and hospital admission was 42.9 (12-168) hours. While fever was present in all patients, nausea-vomiting was found in 22 (84.6%), restlessness in 21 (80.8%), rash in 14 (53.8%), tachypnea and nuchal rigidity in 12 (46.2%), tachycardia in 11 (42.3%), headache, kutis marmaratus and fontanelle bulging in 10 (38.5%), loss of consciousness and leg pain in 9 (34.6%), hypotension and increased intracranial pressure in six (23.1%), purpura fulminans in four (15.4%), and photophobia in one (3.8%). Restlessness, tachypnea, tachycardia and cutis marmaratus were statistically higher in group 1 while nuchal rigidity and headache were higher in group 2.

N. meningitidis was demonstrated by culture (blood/CSF) or CSF PCR in 88.4% (n= 23) of the patients while 11.5% (n= 3) were clinically diagnosed.

Isolated meningitis was detected in 57.7% (n= 15) of the patients, and sepsis and meningitis clinic was detected in 38.5% (n= 10). Purpura fulminans developed in four patients. While there was no patient with isolated sepsis, pleural and pericardial effusion was found in a seven-month-old patient (23rd). The patient who presented with fever and restlessness had two-three petechial lesions on the lower extremities, no cells were observed in the CSF examined with suspicion of meningococcemia, blood culture was taken and the patient was followed up with cefotaxime treatment. The patient's rashes disappeared in 24 hours and bronchiolitis developed. While there was no growth in blood and CSF cultures, tachypnea and tachycardia developed on the fourth day of hospitalization. Four cm pleural effusion was found on chest X-ray and one cm pericardial effusion was found on echocardiography. *N. meningitis* PCR was positive in pleural fluid. The 12th patient who was followed up due to sepsis and meningitis had bronchiolitis findings at presentation. The 15th patient who had sepsis-meningitis and purpura fulminans developed arthritis findings in the knee joint on the eighth day of follow-up. A two-month-old patient (17th) with a history of premature birth had tachycardia and tachypnea at presentation, a moderately elevated troponin value of 38.5 (0-14) ng/L, and normal echocardiography.

Isolated meningitis was statistically more common in group 2 (p= 0.005), and sepsis-meningitis association was more common in group 1 (p= 0.014). Clinical characteristics of the patients are summarized in Table 2.

Table 1. Risk factors, clinical and microbiologic findings of children with invasive meningococcal disease

Patient	Age (month)	Risk factor	Clinical finding	Diagnostic method	Serotype
1.	81	Umrah visit by the father	Sepsis + meningitis	CSF (Gram + PCR + culture)	Not tested
2.	174	Staying in a dormitory	Isolated meningitis	CSF PCR	Not tested
3.	49	Prematurity-hydrocephaly	Sepsis + meningitis	CSF PCR	Not tested
4.	69	-	Isolated meningitis	CSF PCR	Could not be typed
5.	3	History of head trauma	Isolated meningitis	CSF PCR	Could not be typed
6.	18	-	Isolated meningitis	CSF (Gram + PCR)	Not tested
7.	33	Twin brother dies of meningococcemia	Isolated meningitis	CSF (Gram + PCR)	MenB
8.	1	-	Isolated meningitis	CSF PCR	Could not be typed
9.	25	-	Sepsis + meningitis	CSF PCR	MenB
10.	7	Umrah visit by the grandmother	Sepsis + meningitis + PF	CSF PCR + blood culture	Not tested
11.	95	-	Isolated meningitis	CSF PCR	Could not be typed
12.	4		Sepsis + meningitis + bronchiolitis	CSF PCR	MenW
13.	198	Contact with umrah visitor, staying in a dormitory	Isolated meningitis	CSF PCR	Not tested
14.	123	-	Isolated meningitis	CSF PCR	MenB
15.	46	-	Sepsis + meningitis + arthritis + PF	Clinical diagnosis	Not checked
16.	6	Prematurity	Isolated meningitis	CSF PCR	Could not be typed
17.	2	Prematurity	Sepsis + meningitis + myocarditis	CSF PCR	MenA
18.	20	-	Sepsis + meningitis + PF	Clinical diagnosis	Not tested
19.	61	-	Isolated meningitis	Clinical diagnosis	Not tested
20.	45	-	Sepsis + meningitis	CSF (PCR + culture)	MenB
21.	3	-	Sepsis + meningitis + PF	CSF Gram + PCR + culture + blood	MenB
22.	104	-	Isolated meningitis	CSF PCR	Not tested
23.	7	-	Sepsis + bronchiolitis + pericarditis + pleuritis	Pleura PCR	Could not be typed
24.	75	-	Isolated meningitis	CSF PCR	MenB
25.	203	-	Isolated meningitis	CSF PCR	MenB
26.	167	Umrah visit by the grandfather, influenzae PCR+	Isolated meningitis	CSF Gram + PCR	MenY

CSF: Cerebrospinal fluid, PCR: Polymerase chain reaction, PF: Purpura fulminans.

Table 2. Clinical findings and prognosis of children followed for invasive meningococcal disease according to age groups

	Total patient, n= 26 (100%)	**≤5 years (group 1), n= 15 (57.7%)**	**>5 years (group 2), n= 11 (42.3%)**	**p**
Age (month)	45.5 (1-203)	7 (1-49)	104 (61-203)	-
Sex (F/M)	10/16 (38.5/61.5)	7/8 (46.7-53.3)	3/8 (27.3-72.7)	0.428
Clinical findings				
Fever	26 (100%)	15 (100%)	11 (100%)	-
Nausea-Vomiting	22 (84.6%)	11 (73.3%)	11 (100%)	0.113
Restlessness	21 (80.8%)	15 (100%)	6 (54.5%)	**0.007**
Rash	14 (53.8%)	7 (46.7%)	7 (63.6%)	0.646
Tachypnea	12 (46.2%)	10 (66.7%)	2 (18.2%)	**0.040**
Neck stiffness	12 (46.2%)	3 (20.0%)	9 (81.8%)	**0.06**
Tachycardia	11 (42.3%)	10 (66.7%)	1 (9.1%)	**0.005**
Headache	10 (38.5%)	1 (6.7%)	9 (81.8%)	**<0.05**
Cutis marmoratus	10 (38.5%)	10 (66.7%)	-	**0.001**
Fontanel bulge	10 (%38.5)	10 (66.7%)	-	
Loss of consciousness	9 (34.6%)	6 (40.0%)	3 (27.3%)	0.683
Leg pain	9 (34.6%)	3(20.0%)	6 (54.5%)	0.103
Hypotension	6 (23.1%)	5 (33.3%)	1 (9.1%)	0.197
Increased intracranial pressure	6 (23.1%)	4 (26.7%)	2 (18.2%)	1
Purpura fulminans	4 (15.4%)	4 (26.7%)	-	0.113
Photophobia	1 (3.8%)	-	1 (9.1%)	0.423
Diagnosis				
Isolated meningitis	15 (57.7%)	5 (33.3%)	10 (90.9%)	**0.005**
Isolated sepsis	-	-	-	-
Sepsis + meningitis	10 (38.5%)	9 (60.0%)	1 (9.1%)	**0.014**
Pleuritis-pericarditis	1 (3.8%)	1 (6.7%)	-	-
Treatment				
Plasmapheresis	1 (3.8%)	-	1 (9.1%)	0.423
Inotropic supportive therapy	5 (19.2%)	2 (13.3%)	3 (27.3%)	0.620
Intensive care hospitalization	13 (50.0%)	10 (66.7%)	3 (27.3%)	**0.044**
Prognosis				
Mortality	2 (7.7%)	2 (13.3%)	-	0.492
Morbidity	5 (19.2%)	3 (20.0%)	2 (18.2%)	1
Hearing loss	1 (3.8%)	1 (6.7%)	-	1
Skin necrosis	3 (11.5%)	3 (20.0%)	-	0.238
Focal neurologic deficit	3 (11.5%)	1 (6.7%)	2 (18.2%)	0.556
Limb necrosis	1 (3.8%)	1 (6.7%)	-	1

*Fisher's exact chi-square test.

Table 3. Laboratory findings according to age groups of children followed for invasive meningococcal disease

	Total patient, (n= 26, %100)	<5 years (n= 15, %57.7), group 1	>5 years (n= 11, %42.3), group 2	p
Laboratory findings				
Leukocytes (K/µL)	17.9 (3.950-35.85)	16.2 (3.95-35.85)	20.9 (5.1-35.16)	0.164#
Leukocytosis	17 (65.4%)	8(53.3%)	9 (81.8%)	0.217*
Neutrophils (K/µL)	14.36(1.88-33.01)	7.3 (1.88-19.98)	18.2 (2.16-33.010)	**0.009#**
Neutrophilia	17 (65.4%)	8 (53.3%)	9 (81.8%)	0.217*
Lymphocytes (K/µL)	1.455 (0.43-14.2)	1.8 (0.81-14.2)	1.070 (0.430-2.210)	**0.013#**
Lymphopenia	5 (19.2%)	1 (6.7%)	4 (36.4%)	0.128*
Hemoglobin (g/dL)	11.8 (8.6-14.3)	10.9 (8.6-13.1)	12.7 (10.4-14.3)	**0.004#**
Anemia	10 (38.5%)	7 (46.7%)	3 (27.3%)	0.428*
Platelets (K/µL)	242 (87-964)	235 (87-964)	264 (171-456)	0.574#
Thrombocytopenia	3 (11.5%)	3 (20.0%)	-	0.238*
Thrombocytosis	3 (11.5%)	2 (13.3%)	1 (9.1%)	1*
Sedimentation (mm/h)	9 (2-52)	3.5 (2-51)	22 (2-52)	0.349#
C-reactive protein (mg/L)	196 (45-326)	125 (45-265)	253 (109-326)	**0.051#**
Procalcitonin (µg/L)	74 (15-469)	247 (74-469)	20 (15-74)	0.100#
Coagulopathy	7 (28%)-469)	6 (%40)	1 (10%)	0.179*
Growth in blood culture	2 (7.7%)	2 (13.3%)	0	0.492*
CSF findings				
CSF pleocytosis	25 (96.2%)	14 (93.3%)	11 (100%)	1*
CSF bacteria	5 (19.2%)	3 (20%)	2 (18.2%)	1*
CSF glucose (mg/dl)	57 (11-106)	60 (11-106)	54 (19-82)	0.721#
CSF protein	64.2 (8.5-1972)	66 (8.5-937)	62.5 (18.5-1972)	0.760#
CSF PCR positivity	22 (88%)	12 (85.7%)	10 (90.9%)	1*
Low CSF glucose	6 (23.1%)	4 (26.7%)	2 (18.2%)	1*
CSF protein elevation	15 (57.7%)	8 (53.3%)	7 (63.3%)	0.701*
Growth in CSF culture	3 (11.5%)	2 (13.3%)	1 (9.1%)	1*

*Fisher's exact chi-square test
#Mann-Whitney U test.
CSF: Cerebrospinal fluid, PCR: Polymerase chain reaction.

Laboratory, Radiologic and Microbiologic Examination Findings

Median values of the patients' laboratory data at hospital admission were as follows: leukocytes 17.9 (3.950-35.85) K/µL, neutrophils 14.36 (1.88-33.01) K/µL, lymphocytes 1.455 (0.43-14.2) K/µL, hemoglobin 11.8 (8.6-14.3) g/dL, platelets 24 (87-964) (K/µL), sedimentation 9 (2-52) mm/h, CRP 196 (45-326) mg/L, procalcitonin 74 (15-469) (µg/L). Neutrophil count and CRP values were statistically higher (p= 0.009, p= 0.051) and lymphocyte count was lower (p= 0.013) in group 2. Hemoglobin values were statistically lower in group 1 (p= 0.004).

Neutrophilia was found in 65.4% (n= 17), anemia in 38.5% (n= 10), coagulopathy in 28% (n= 7), lymphopenia in 19.2% (n= 5), thrombocytopenia in 11.5% (n= 3), thrombocytosis in 11.5% (n= 3), and no statistically significant difference was found between the age groups. Laboratory findings of the patients are summarized in Table 3.

No papillary edema was detected in 18 patients who underwent fundus examination before lumbar puncture (LP), and tortuosity of bilateral retinal vessels was detected only in the 21st patient. Among the patients who underwent LP brain CT (n= 6), revealed diffuse ischemia in the 10th patient while the others were normal. Six of the nine patients who underwent brain MR imaging were normal while diffusion restriction in the parietooccipital region was found in the 9th patient, increased meningeal contrast enhancement at the level of basal cisternae and brainstem was found in the 21st patient, and pansinusitis was found in the 14th patient.

LP was performed in all patients at admission or follow-up, and CSF pressure >20 cm H_2O was found in six patients. When CSF tests were evaluated, CSF pleocytosis was found in 25 (96.2%) patients, bacteria in CSF Gram staining in five (19.2%), CSF PCR positivity in 22 (88%), low CSF glucose in six (23.1%), elevated CSF protein in 15 (57.7%), and growth in CSF culture in three (11.5%) patients. Median value of CSF glucose was 57 (11-106) mg/dL, and median value of CSF protein was 64.2 (8.5-1972) mg/dL. No statistically significant difference was found between the age groups. CSF and/or blood cultures grew in 15.3% (n= 4) of the patients. In 69.2% (n= 18) of the patients, there was no growth in the cultures and only CSF PCR positivity was detected. CSF findings of the patients are summarized in Tables 1 and 3.

Antibiograms could not be performed in the 1st patient with growth in CSF culture and the 10th patient with growth in blood culture. In the 20th patient with growth in CSF culture, MIC values in E test were cefotaxime (0.004 mcg/mL, sensitive), meropenem (0.004 mcg/mL, sensitive). Penicillin susceptibility could not be studied. In the 21st patient with growth in blood and CSF cultures, E test MIC values were penicillin (0.24 mcg/mL, moderately sensitive), cefotaxime (0.015 mcg/mL, sensitive), meropenem (0.015 mcg/mL, sensitive). *N. meningitidis* serotype determination was performed in 16 patients. Serotype distributions of patients was serotype A 0.06% (n= 1), serotype B 43.7% (n= 7), serotype Y 0.06% (n= 1), serotype W 0.06% (n= 1), non-group 37.5% (n= 6). Serotype C was not detected.

Evaluation of Treatment and Prognosis

Of the patients, 11.5% (n= 3) received oral antibiotics before admission, and 19.2% (n= 5) were treated with ceftriaxone before LP. The 1st patient with growth in CSF culture had no antibiotic use while the 20th patient had ceftriaxone administration before LP. The 10th patient with blood culture growth had a history of oral amoxicillin-clavunate use while the 21st patient with blood and CSF culture growth had no history of antibiotic use.

All patients (n= 26, 100%) received ceftriaxone (100 mg/kg/day) or cefotaxime (200-300 mg/kg/day) at the meningitis dose for a mean of 8.5 ± 2.9 days. Vancomycin was added to 34.6% of the patients with poor general condition and discontinued when *N. meningitidis* positivity was detected. The 10th patient who developed nosocomial infection during follow-up was treated with piperacillin sulbactam for 46 days after ceftriaxone treatment. The 13th patient, an adolescent with isolated meningitis, received dexamethasone treatment (four days). 50% (n= 13) of the patients were followed up in the intensive care unit. Of the patients with coagulopathy, 15.3% (n= 7) received fresh frozen plasma (TDP) and 21.7% (n= 5) patients received inotropic treatment. Plasmapheresis was performed in the 18th patient (n= 2). Of the patients, 7.6% were followed up on mechanical ventilator. Mortality (7.6%) occurred in the 3rd and 21st patients with sepsis, and meningitis and morbidity was 19.2% (n= 5). Patients were followed up in the hospital for a mean of eight (min-max= 5-51) days.

Discussion

In our study, we aimed to raise awareness among pediatricians about IMH and to emphasize once again the importance of vaccination in this disease with high mortality and morbidity. IMH due to *N. meningitidis* is one of the vaccine-preventable infectious diseases with high mortality despite early diagnosis and appropriate treatment. Demographic findings, risk factors, clinical and laboratory features and prognosis of children who were followed up for IMH in our tertiary care university hospital during a 10-year period were evaluated. Clinical and laboratory findings of IMH were similar to those in the literature.

Although meningococcal disease can be observed throughout the year, it is more common in late winter and early spring (7). In our study, the majority of the patients (57.6%) were diagnosed in the winter-spring period in accordance with the literature, and no significant difference was found between genders. In a study by Thompson et al. (2006), sepsis was found in 66%, meningitis in 22%, and sepsis and meningitis in 12% of 448 pediatric patients with IMH in England, and it was reported that meningitis clinic was more frequent and the disease had a better prognosis in the adolescent age group (8). In the 2006 multicenter study of Kaplan et al. (2006), it was reported that 70% of 159 children with IMH between 2001 and 2005 had meningitis and 27% had bacteremia without meningitis (9). In Brazil, it was reported that the age range of meningococcal meningitis cases was between 2-4 years in the period before meningococcal vaccination between 2000-2010 (10). While 96.1% of our patients had meningitis findings, the rate of sepsis was higher in children aged <5 years and isolated meningitis was higher in patients aged >5 years.

Transmission in IMH is by droplet route. Previous viral infection, crowded family, active or passive smoking, deficiency of late components of the complement system (C5-9) and properdinin, functional or anatomical asplenism, eculizumab use and HIV infection are important risk factors for IMH (7). In a case-controlled study conducted in France (2012-2017) evaluating the risk factors associated with IMH, it was found that congenital and acquired immunodeficiency, asplenism/hyposplenism were the most important risk factors and autoimmune diseases, chronic respiratory tract infections, hemophilia and low economic income were the other risk factors. Prematurity has also been reported to be an independent risk factor (11,12). Among the risk factors defined in our patients, prematurity was found in three patients. In our

study, four patients had a history of contact with individuals going to Umrah. In a multicenter study conducted by Tekin et al. in Türkiye (2017), 6.3% were found to be positive in meningococcal nasopharyngeal screening by PCR in 1518 healthy individuals aged 10-24 years, and MenW was found most frequently, while MenC was not detected (13).

N. meningitidis is the most common cause of bacterial meningitis in the childhood and adolescence, usually after hematogenous spread. Meningitis accounts for 80-85% of all cases of IMH, with 15-20% of cases having a sepsis-only clinic. Patients with meningitis have sudden-onset fever, headache, nuchal rigidity, confusion, myalgia, and vomiting; patients with meningococcemia have petechiae or purpura, weakness, and hypotension (14). It has been reported that leg pain, skin color change, coldness in the hands and feet are among the clinical findings of IMH in the first 12 hours, and it is thought to be related to peripheral circulatory disorder in the early period of sepsis. While most children have only non-specific symptoms in the first 4-6 hours, it may result in death in 24 hours (8). Although the clinical findings of IMH have a wide spectrum and the initial findings are similar to viral infection, follow-up of early sepsis symptoms is important in the differential diagnosis of IMH. In the study by Strelow et al., fever has been found in 96%, headache in 99%, nuchal rigidity in 94%, and petechiae in 89% of patients with IMH (n= 316). In our study, fever was found to be 100%, headache 38.5%, nuchal rigidity 46.2%, and petechiae 53.8% (15).

In 2-20% of the patients presenting with fever and petechial rash, the etiology is related to meningococcemia (2,15). Purpura fulminans is a serious complication of meningococcal disease and is observed in approximately 15-25% of patients with meningococcemia. It is characterized with acute onset cutaneous hemorrhage and vascular necrosis due to thrombosis and diffuse intravascular coagulopathy (16). In our patients, rash was found in 53.8% in accordance with the literature. Mortality (n= 1), extremity necrosis (n= 1), and skin necrosis (n= 3) were found in four patients who developed purpura fulminans. It may rarely cause focal infections including septic arthritis, pericarditis, conjunctivitis, urethritis, epiglottitis, otitis media, gastroenteritis and invasive pneumonia (14). Although pneumonia is observed with a rate of 5-15% in IMH, the diagnosis is difficult and it cannot be distinguished whether bacterial isolation is due to carriage or invasion (2,15). Acute gastroenteritis (MenW), primary pneumonia (MenY), septic arthritis (MenC and MenW) have been reported in different serotypes presenting with atypical clinic (4).

Although meningococcal pneumonia is rare, it has been associated with previous viral respiratory tract infection (especially influenza). In the study by Young et al. in an outbreak of meningococcal infection in adults, most patients had positive serologic tests for recent influenza (17). One week before the diagnosis of IMH, influenza positivity was found in the respiratory tract panel of the 26th patient at an external center, but no finding of pneumonia was found.

Ladhani et al. reported that the majority of clinical findings in 129 cases of IMH were septic arthritis and severe respiratory tract infection in a study conducted in England between 2010 and 2013 (18). Primary purulent septic arthritis in IMH is rare compared to immune complex arthritis. Similarly, purulent pericarditis is rare, and pericarditis due to immunologic causes has been reported with a rate of 19% in the recovery period under treatment (19). In five cases of IMH presented by Faye et al., it was reported that pericardial effusion developed in two pediatric patients on the 5th and 7th days of treatment and was evaluated as reactive extrameningeal involvement. In IMH, 15.3% of serogroup-independent immunocomplex-related diseases (arthritis, vasculitis, pleurisy) have been reported in children. These complications are usually observed in the subacute period of the disease after the 4th-10th day of antibiotic treatment (20). Treatment is usually symptomatic, antipyretic and non-steroidal anti-inflammatory drugs are used. In our study, arthritis in the 15th patient during treatment follow-up was evaluated as reactive and extrameningeal involvement. The 23rd patient with positive *N. meningitidis* PCR in pleura was followed up due to purulent pericarditis. Troponin value of the 17th patient, who was two months old at hospital admission, was moderately elevated and echocardiography findings were normal. In postmortem cases, it has been reported that myocarditis is detected in more than 50% of patients with IMH (21). In a study by Akyıldız et al. (2000-2005), myocarditis was found in 4.6% of 86 pediatric patients (4).

Meningococcal patients were the patient group in which cytokines such as interleukin-1, interleukin-6, tumor necrosis factor etc. were detected in the blood for the first time, and it has been reported that cytokine levels affect the prognosis of the disease. In IMH, microthrombi and necrotic purpura occur due to endothelial damage (22). It is known that CRP, procalcitonin, elevated sedimentation, neutrophilia, neutropenia and thrombocytosis occur in different systemic infections due to cytokine response (23). Leukocytosis and neutrophilia were found in 65.4% (n= 17), lymphopenia in 19.2% (n= 5), anemia in 38.5% (n= 10), and thrombocytosis in 11.5% (n= 3) of our patients at hospital admission. Coagulopathy developed in 26.9% (n= 7) and thrombocytopenia in 11.5% (n= 3) patients.

Brain CT scan before LP is performed to rule out an intracranial mass. Therefore, brain CT scan is not recommended for every patient before LP. Pre-LP imaging is recommended for patients with immunodeficiency, history of central nervous system disease, history of seizures, impaired consciousness and focal neurologic findings. In the stduy by Hasbun et al., CT was found to be normal in 93 of 96 patients without risk factors for

intracranial mass (24). In our study, no contraindication for LP was found in brain MR or tomography imaging.

In most cases of meningococcal meningitis, there is increased CSF pressure, pleocytosis, elevated protein and low glucose. The association of CSF pleocytosis, elevated CSF protein and low glucose was found in 24% (n= 6) of our patients, whereas it was found in 79% in the study by Strelow et al. Although Gram staining is a cheap and easy method, the rate of detection of microorganisms in Gram staining varies according to clinical experience. While gram-negative diplococci were found in 20% (n= 5) of our patients, this rate varies between 30-89% in the literature (15).

PCR test is frequently used in the diagnosis of meningococcal meningitis, serotype determination, especially in CSF gram staining and when it cannot be isolated in culture (25).

In a retrospective study by Strelow et al. consisting of 316 patients who were followed up due to meningococcal meningitis, positivity rates of 90% in gram staining, 91% in PCR and 32% in culture were reported (15). In our study, while growth in CSF culture was found at a low rate of 11.5% (n= 3) and growth in blood culture at a low rate of 7.6% (n= 2), CSF PCR positivity was found at a rate of 84.6% (n= 22).

In the IMH surveillance study in our country, MenW (42.7%) and MenB (31.1%) were the most common serogroup in 2005-2006, MenA (36.6%), MenW (55.6%), MenB (7.3%) in 2009-2010, and MenW (56.5%), MenB (6.5%), MenA (6.5%) in 2011-2012 (26-27). In 2013-2014, the incidence of MenB increased to 32.9% and MenW was observed at a rate of 42.4%. In 2015, MenB incidence decreased (15.8%) and MenW was found to be 42.1% (28). In the surveillance study conducted by Ceyhan et al. in 2015-2018, 71% of 994 CSF samples were positive for *N. meningitidis*, and the most common serotype was MenB (29). In our study, *N. meningitidis* serotype determination could be performed in 16 patients; the most common serotypes were serotype B 43.7% (n= 7) and untyped 37.5% (n= 6), while serotypes A, Y and W were shown in only one patient each. Serotype C was not detected in any patient.

Immediate initiation of antibiotic treatment when IMH is clinically suspected reduces complications. Two parameters that determine prognosis in patients are shock and increased intracranial pressure. Despite being sensitive to penicillin and other antibiotics, mortality in meningococcal meningitis is 10-15% (30). It is known that mortality is due to cerebral edema caused by bacterial toxins such as lipo-oligosaccharide (31). Antibiotic treatment rapidly decreases the antitoxin level in plasma (32). The increase in penicillin resistance in *N. meningitidis* strains is a worrisome situation worldwide. In meningococcal sepsis and meningitis, ceftriaxone or cefotaxime should be started until susceptibility results are available. In the USA, between 2013 and 2020, penicillin resistance and susceptibility to 3rd generation cefolosporins were detected in 372 *N. meningitidis* serogroups with a rate of approximately 9%. In a study conducted in the USA between 2012 and 2016 in which 695 isolates were evaluated, it was found that all strains were susceptible to cefotaxime, ceftriaxone, meropenem and rifampicin and 25% were moderately susceptible to penicillin or ampicillin (33,34). Antibiograms could be performed in two of the patients with growth in CSF culture. Cefotaxime and meropenem susceptibility was found in both patients. Moderate susceptibility (MIC= 0.24 mcg/mL) was found in one patient in whom penicillin E test was performed.

Adequate response to treatment is evaluated with a decrease in fever, normalization of blood pressure, consciousness and hematologic parameters and treatment is recommended for an average of 5-7 days in children (35). All of our patients were treated with ceftriaxone/cefotaxime. Although data on the use of dexamethasone in meningococcal meningitis are limited, it has been reported to decrease the days of hospitalization and is not recommended in cases of sepsis (36).

In a meta-analysis study on IMH in Eastern Mediterranean and North African countries, it was reported that the duration of hospitalization of children was 9.8-21.9 days, 30% needed intensive care and the length of hospitalization was 5-7.8 days (4). Our patients were hospitalized for a median of eight (min-max= 5-51) days and 50% needed intensive care. Patients with rash (p= 0.47), cutis marmaratus (p= 0.041), coagulopathy (p= 0.07) and age <5 years (p= 0.047) had higher rates of intensive care hospitalization, while patients with isolated meningitis (p= 0.015) had lower intensive care requirements.

Morbidity rate varies between 10-30%; hearing loss, mental retardation, hydrocephalus, seizures, behavioral disorders, skin necrosis and limb ischemia requiring orthopedic intervention may be observed (2). When compared with other purulent meningitis, focal neurologic deficit has been reported more rarely in meningococcal meningitis (31). Although focal neurologic deficits have been reported with a rate of 5-11% in different studies, we found 4th and 6th cranial nerve paralysis in two patients with meningitis. Disturbance of consciousness, which was reported with a rate of 50-55% in different studies, was found in 36% of our patients with meningitis (15).

Although mortality rate varies according to age and region, it is known to be 5-25%, higher in infants and in patients aged >65 years (4). While the diagnosis of sepsis cases without focal infection in IMH is difficult and the prognosis is poor, both the diagnosis is easy and the prognosis is good in isolated meningitis cases. Mortality is (1-5%) in meningococcal meningitis and 40% in non-meningitis IMH (37). We think that

the low mortality rate in our patients may be related to the fact that almost all of them also had meningitis.

Conclusion

IMH is a serious and life-threatening vaccine-preventable infectious disease with high mortality and morbidity despite effective treatment. Since conjugated meningococcal vaccines are not included in the routine vaccination schedule in our country, every pediatric patient with fever and general condition disorder should be evaluated in detail for meningococcemia. It should also be kept in mind that findings may be nonspecific in the early period of the disease and patients may present with different clinical findings. Increasing the confidence of clinicians and patients in vaccination and keeping vaccination rates high will play an important role in preventing the disease.

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