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Risk Factors and Clinical Parameters Associated with the Severity of the Clinical Picture of Enteroviral Meningitis in Neonates Treated in the Tertiary Neonatal Unit in Slovenia

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Abstract

Objective – To describe the clinical course of enteroviral meningitis in neonates in a tertiary neonatal unit. **Materials and Methods** – We analysed maternal and perinatal history, clinical and laboratory data, therapy and short-term outcomes in neonates who had enterovirus detected in the cerebrospinal fluid (CSF) and compared the group of neonates with early-onset (≤7 day of life (DOL)) meningitis to the group of neonates with late-onset (>7 DOL) meningitis. **Results** – A total of 30 term neonates were included (63% male). Majority (73%) presented during the summer and autumn months, 57% were in contact with siblings who had signs of viral disease, 10% of mothers had signs of viral disease at delivery or shortly after. Neonates presented with irritability (97%), fever (83%), feeding intolerance (66%), diarrhoea (56%), nonspecific rash (23%), seizures (10%). Both the C-reactive protein (CRP) and pro-calcitonin (PCT) were elevated in 23% of patients; only CRP was elevated in 57%, only PCT in 37%. Twelve (40%) had elevated leukocyte count in the CSF. Antibiotics were initiated in 80% (median treatment 1.5 days). Majority of the neonates with early-onset meningitis had jaundice, higher urea and creatinine serum concentration, and lower thrombocyte numbers. **Conclusion** – Enteroviruses are an important cause of meningitis in neonates during summer and autumn months. Neonates in close contact with ill family members or carers are particularly at risk. Neonates present with fever, irritability, feeding intolerance, diarrhoea, normal or mildly elevated CRP and/or PCT values. Neonates with early-onset meningitis had a similar grade of infection and outcome as did the neonates with late-onset disease. Our findings confirm that enteroviral meningitis carries a good prognosis in the majority of neonates.

Key Words: Enterovirus ▪ Meningitis ▪ Infant ▪ Neonate.

Introduction

Infections caused by enteroviruses (EV) are common in the neonatal period (1-3). EVs are small, non – enveloped ribonucleic acid (RNA) viruses belonging to the *Picornaviridae* family. EVs that cause infections in humans were reclassified into four groups (A, B, C, and D) according to their genetic similarities (4). EVs are transmitted by direct or indirect contact with infected saliva or faeces (transmission occurs by close contact with ill person or indirectly through contact with contaminated surfaces). The incubation period for enteroviral infection is 3 – 10 days. Following adsorption of virions to cell surface receptors (e.g. integrins or immunoglobulin – like receptors), viral replication is rapid (5-10 hours). The primary sites of replication are the epithelial cells of the oropharyngeal and intestinal mucosa. After crossing the epithelial cells, the virus reaches the tonsils, deep cervical nodes, Peyer's patches in the lamina propria and mesenteric lymph nodes where significant viral

replication occurs. Major viremia that follows may lead to viral replication and tissue damage in secondary sites like the central nervous system, myocardium, liver, pancreas, respiratory tract, skin, and mucous membranes. Multiplication of viruses in secondary sites coincides with the onset of clinical signs. When antibodies appear, viremia ceases and viral concentration in secondary infection sites begins to diminish (usually around the seventh day). However, viruses can still be detected in faeces and the respiratory tract for several weeks (5, 6). Due to different serotypes of EV, there are marked differences in tropism, virulence, and clinical manifestations. The most common presentation of enteroviral infection is a nonspecific febrile illness, but the infection can also cause a sepsis – like illness, myocarditis, hepatitis with coagulopathy, aseptic meningitis and encephalitis (4, 5, 7). Neonates with enteroviral meningitis often present with nonspecific febrile illness or sepsis – like illness (5).

Neonates can acquire EV vertically from an infected mother (in utero, during birth or shortly after). Additionally, viruses can also be transmitted postpartum from community sources (7). Transplacental transmission is rare but potentially devastating. An infection caused by EVs in a mother just before labour was associated with a fatal course of meningoencephalitis in the neonate (8). Ascending infection and contact infection during birth is possible. Infections of neonate occurring 2 – 7 days after birth could have been acquired during passage through the birth canal (5). Transmission through breastmilk has also been described (9), as well as outbreaks in nurseries (10-13).

In our study, we described clinical courses and short – term outcomes of neonates with confirmed enteroviral meningitis in a tertiary neonatal unit from 2006 to 2019. To better elucidate the immune reaction to infection we have compared some of the clinical and laboratory characteristics of neonates who got sick in the first 7 days of life (DOL) (early-onset group) to those who got sick after the 7th DOL (late-onset group).

Patients and Methods

We performed a retrospective cohort study of neonates with enteroviral meningitis by retrospectively reviewing medical records of all neonates treated for enteroviral meningitis at The Department of Neonatology, Division of Paediatrics, University Medical Centre Ljubljana, during the period from 2006 to 2019. We collected data on maternal and neonatal risk factors, clinical characteristics, diagnostic and laboratory parameters, and treatment. The aim of the study was to analyse the risk factors and natural history of the disease.

Case definition

Enteroviral meningitis in neonates was diagnosed with a positive result of reverse transcriptase polymerase chain reaction test (RT – PCR) for EV in CSF. We used AusDiagnostic W.17 test and in-house real-time PCR test (before 2018). We also performed PCR for EV in stool samples and nasopharyngeal swab, but not in all patients (in 4 and 17 patients, respectively).

Risk Factors, Clinical Characteristics, Diagnostic and Laboratory Parameters, and Treatment

We reviewed maternal risk factors: the prolonged rupture of membranes (time between the rupture of amniotic sac and time of delivery is longer than 18 hours), chorioamnionitis, fever, diarrhoea or signs of viral illness, or if the mother was treated with antibiotics. Neonatal risk factors that we reviewed were preterm birth (less than 37 weeks of gestational age), low birth weight (birth weight of less than 3rd percentile for the gestational age), low Apgar score (≤ 6 five minutes after birth), meconium – stained amniotic fluid, if they had siblings or if siblings had signs of viral disease.

We defined positive clinical signs as: increased (≥38 °C) or decreased axillary temperature (<36 °C), raised heart rate (>160 beats/minute) and respiratory rate (>60 breaths/minute), prolonged capillary refill time (>3 seconds), feeding difficulties, jaun-

dice (bilirubin level >95 percentile for gestational and chronological age), diarrhoea, rash, signs of acute upper respiratory infection, apnoea, cyanosis.

We evaluated abnormal neurological signs regarding the state of consciousness, behaviour and clinical and/or neurophysiological seizures. We analysed the inflammatory parameters (C-reactive protein (CRP), procalcitonin (PCT)), liver function tests, urea and creatinine and prescribed antibiotics or antivirals. Haematological tests that we analysed were white blood cell count (WBC) with neutrophil and thrombocyte count. Leukopenia was diagnosed if WBC was $<5 \times 10^9$/L, and neutropenia if the absolute neutrophil count was $<1.5 \times 10^9$/L. We also analysed liver enzymes levels - aspartate transaminase (AST), alanine transaminase (ALT) and gamma-glutamyl transferase (gamma-GT). We used definition of systemic inflammatory response syndrome (SIRS) for neonates according to Goldstein et al. (14). We analysed leucocyte count and differential, protein, and glucose concentration in the CSF. Pleocytosis was marked if the number of leucocyte count in the CSF was more than 20/mm^3, elevated protein above 1.2 mg/L and decreased glucose under 2 mmol/L.

We reviewed imaging diagnostics and electroencephalograms (EEG). A neonatologist examined all patients upon admission and before discharge. The follow-up of patients was achieved by reviewing electronic medical records in our hospital. Patients without any sequelae were followed by their primary care providers, who were instructed to refer patients if needed. We compared the characteristics of two groups of neonates: those who got sick in the first 7 DOL (early-onset group) to those who got sick after the 7th DOL (late-onset group).

Ethics Statement

The study was approved by the National Medical Ethics Committee (0120-647/2017/16).

Statistical Analysis

Categorical variables are described with frequencies and percentages, normally distributed continuous variables with means and standard deviations and non-normally distributed variables with medians and ranges. Normality of data distribution was tested by Shapiro-Wilk test. Association between the time of onset of meningitis and clinical characteristics or laboratory values of neonates was examined by univariate logistic regression. Likelihood ratio test was used when cells with zero count were present in contingency table. The association was considered statistically significant if $P < 0.05$. Statistical analysis was performed using SPSS v. 26.

Results

In the period between 2006 and 2019, we treated 30 neonates with enteroviral meningitis. Maternal risk factors and neonate characteristics are detailed in Table 1.

Table 1. Clinical Characteristics of Neonates with Enterovirus Meningitis, Treated at the Department of Neonatology, Division of Paediatrics, University Medical Centre Ljubljana, during the Period from 2006 to 2019. Data Are Shown as Frequencies and Percentages If Not Indicated Otherwise

Clinical characteristics	Neonates (n=30)
Maternal risk factors	
Prolonged rupture of membranes	0 (0)
Chorioamnionitis	0 (0)
Fever	3 (10)
Antibiotic treatment	5 (16.7)
Signs of acute respiratory infection	6 (20)
Diarrhea	1 (3.3)
Neonate characteristics	
Male gender	19 (63.3)
Preterm	2 (6.7)
LBW	1 (3.3)
Apgar score at 5 min ≤ 6	0 (0)
Meconium stained amniotic fluid	0 (0)
Median (range) age at onset of disease (days)	16.5 (5-29)
Siblings	27 (90)
Siblings with signs of viral disease	17 (56.7)
Clinical status	
Axillary temperature ≥38 °C	25 (83.3)

Continuation of Table 1.	
Axillary temperature <36 °	1 (3.3)
Heart rate >160 beats/minute	18 (60)
Respiratory rate >60 breaths/minute	10 (33.3)
Prolonged capillary refill time (>3 s)	1 (3.3)
Feeding difficulties	20 (66.7)
Jaundice	6 (20)
Diarrhea	17 (56.7)
Rash	7 (23.3)
Signs of acute respiratory infection	2 (6.7)
Apnoea	4 (13.3)
Cyanosis	1 (3.3)
Neurological status	
Irritability	29 (96.7)
Seizures	3 (10)
Disturbance of consciousness	1 (3.3)
Laboratory parameters	
Median (range) CRP (mg/L)	9 (5–86)
Median (range) PCT (qg/L)	0.5 (0.14–0.78)
Median (range) AST qkat/L	0.67 (0.4–1.6)
AST>0.86 qkat/L	5 (16.6)
Median (range) ALT qkat/L	0.41 (0.22–1.29)
ALT>0.42 qkat/L	11 (36.7)
Median (range) Gama-GT qkat/L	1.5 (0.48–8.41)
Gama-GT>2.2 qkat/L	9 (30)
Mean (SD) urea mmol/L	3.52 (1.03)
Median (range) creatinine qmol/L	28 (15-53)
Hemoculture negative	30 (100)
Median (range) WBC (x 10^9/L)	8.88 (4.2–18.4)
CSF parameters	
Median (range) leucocyte count /mm^3	12 (2–1739)
Median (range) proteins g/L	0.815 (0,24–1.26)
Median (range) glucose mmol/L	2.6 (1.9–5.1)
Treatment	
Antibiotics	24 (80)
Median (range of) days receiving antibiotics	1.5 (1–7)
Antivirals	3 (10)
Median (range of) days receiving antivirals	2 (1–3)
Phototherapy	4 (13.3)
Diagnostics	
EEG	3 (10); all abnormal
Head US	23 (77); 1 abnormal
ECHO	1 (3); normal
Brain MRI	1 (3); abnormal
Median (range of) days of hospitalization	3 (1–19)

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, CSF: Cerebrospinal fluid, ECHO: Echocardiogram, EEG: Electroencephalogram; Gamma-GT: Gamma-glutamyltransferase, GBS: Group B Streptococcus, MRI: Magnetic Resonance Imaging, PCT: Procalcitonin, US: Ultrasound, WBC: White blood cell.

Maternal and Neonatal Risk Factors

Six mothers had signs of acute respiratory infection and one had diarrhoea (in all less than one week before delivery or while still at the maternity hospital). Five mothers received peripartum antibiotics, one received steroids.

Seventeen neonates (57%) were in contact with siblings who had signs of viral disease. In 8 (27%) patient's epidemiological situation was unremarkable.

Patient's Clinical Characteristics

Our patients were predominantly male (63%). All but one had appropriate birth measures, the birth weight being from 1430 g to 4240 g. Two neonates were twins, where only one of the siblings was affected. Six infants were born by caesarean section, others were born vaginally.

Nine (30%) neonates presented with early-onset disease, between 5^{th}-7^{th} DOL. Majority (73%) of patients presented with infection during the summer and autumn months (Fig. 1).

Twenty-six neonates (87%) presented with increased or decreased axillary temperature. Fever ceased in 4 – 72 hours in all patients. Seven (23%) had raised heart and respiratory rate; one also had prolonged capillary refill time. Out of 6 (20%) patients with jaundice, 4 (13%) needed phototherapy. The leading clinical sign was irritability (29 patients, 97%), 20 (67%) neonates presented with feeding difficulties, 17 (57%) with diarrhoea and 23% with a nonspecific rash. Three (10%) neonates had seizures, one neonate only had disturbance of consciousness.

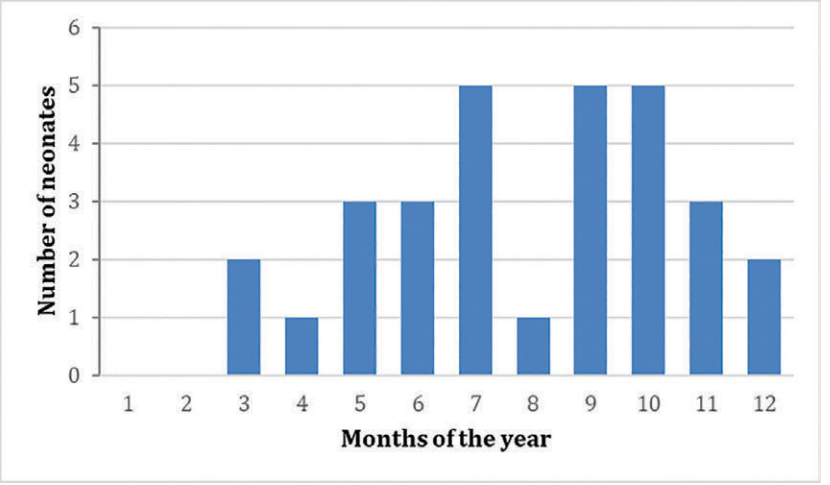

Fig. 1. *Months of Disease Presentation.*

Diagnostic and Laboratory Parameters

Seven (23%) patients had elevated CRP and PCT, 17 (56.6%) only had elevated CRP, 11 (36.7%) patients had only an increased concentration of PCT. Two patients (6.7%) had leukopenia, none had neutropenia and one (3.3%) had thrombocytopenia. Sixteen (53%) patients had clinical or laboratory signs of SIRS.

Fourteen (47%) patients had abnormalities in liver function tests, 3 (10%) patients had all liver enzymes levels elevated. None had hepatitis with coagulopathy and none had myocarditis.

Twelve (40%) had elevated leukocyte count in the CSF (20-1739 x 10^6/L). All neonates tested positive for EV in CSF with the PCR technique. In one patient PCR for EV was also positive in stool and in 5 (17%) in the nasopharynx.

Therapies and Outcome

In 24 (80%) neonates antibiotics were started, the median time of treatment was 1.5 days. Three patients were treated with acyclovir (1 – 3 days). During treatment, none needed cardiovascular support. The duration of hospital stay was 1 – 19 days (median 3 days) (Table 1).

During the acute phase of the disease, one infant had abnormal findings on brain ultrasound, with increased periventricular echogenicity. Three infants had seizures and abnormal electroencephalogram (EEG). Two of those needed antiepileptic treatment. One patient had signs of encephalitis on brain magnetic resonance imaging (MRI) and was transferred to the intensive care unit and also treated with antiepileptic drugs.

At follow-up, the patient with encephalitis had ischemic changes of white matter on brain MRI. Antiepileptic therapy was discontinued after 6 months and his neurological development at seven months of age was normal. In other patients antiepileptic therapy was discontinued after 2 and 9 months, respectively, and their neurological development was also normal. One patient is followed in the outpatient clinic because of hydrocephalus (which is most likely not a consequence of enteroviral meningitis). He does not need any therapy and neurological development is normal. Sixteen (53%) patients were followed in our clinic for a median time of 11 months. Their course was uneventful. Eleven (33%) more were followed regularly only at primary care and also had uneventful course.

Early- vs. Late-Onset Meningitis

Clinical characteristics and laboratory parameters of two groups of neonates according to the time of disease onset are presented in Table 2.

Jaundice, slightly higher values of urea, creatinine and value of thrombocytes are significantly associated with the time of the onset of enteroviral meningitis. Neonates with early-onset enteroviral meningitis more often presented with jaundice in comparison with late-onset group. The odds for the neonates with early onset enteroviral meningitis for having jaundice are 25 – times (95% CI: 2.27 - 275.7) higher in comparison to neonates with late

Table 2. Clinical Characteristics and Laboratory Values of Neonates with Early vs. Late-Onset Enterovirus Meningitis and Results of Logistic Regression (data Are Shown as Frequencies and Percentages If Not Indicated Otherwise)

Characteristic	Early-onset (n=9)	Late-onset (n=21)	OR (95% CI)	P
Median (range) axillary temperature	38.7 (37.5 – 39.2)	38.5 (35.2 – 39.5)	2.03 (0.43 – 9.71)	0.374
Heart rate >160	3 (33.3)	15 (71.4)	0.2 (0.04 – 1.07)	0.06
Respiratory rate >60	4 (44.4)	6 (28.6)	2 (0.4 – 10.11)	0.402
Prolonged capillary refill time (>3 s)	0 (0)	1 (4.8)	–	0.394*
Feeding difficulties	8 (88.9)	12 (57.1)	6 (0.63 – 57)	0.119
Jaundice	5 (55.6)	1 (4.8)	25 (2.27 – 275.7)	0.009†
Median (range) CRP	14 (1.2 – 50)	9 (5 – 111)	1 (0.96 – 1.03)	0.766
Median (range) PCT	0.6 (0 – 2)	0.4 (0.1 –- 2)	2.24 (0.59 – 8.45)	0.235
Mean (SD) urea	4.1 (0.9)	3.3 (1)	2.77 (1.03 – 7.46)	0.043‡
Median (range) creatinine	34 (24 – 53)	24 (15 – 53)	1.09 (1 – 1.18)	0.047‡
Median (range) WBC	9 (4.2 – 18.4)	7.9 (4.5 – 17.8)	1.05 (0.86 – 1.29)	0.635
Median (range) lymphocytes %	25 (7 – 43)	38 (13 – 70)	0.94 (0.88 – 1)	0.055
Mean (SD) thrombocytes	209.9 (53.6)	335.2 (87.1)	0.97 (0.94 – 0.99)	0.013‡
Median (range) CSF leucocyte count	10 (3 – 107)	13 (2 – 1739)	0.99 (0.98 – 1.01)	0.26
Mean (SD) CSF proteins	0.9 (0.2)	0.8 (0.4)	2.66 (0.24 – 29.78)	0.426
Median (range) CSF glucose	2.7 (1.9 – 3.3)	2.5 (2 – 5.1)	0.94 (0.28 – 3.11)	0.921

*Likelihood ratio test; †P<0.05; ‡P<0.01; CRP=C-reactive protein; CSF=Cerebrospinal fluid; PCT= Procalcitonin; WBC=White blood cell.

onset of the disease. Neonates with early-onset enteroviral meningitis had higher plasma urea (OR [95% CI]: 2.77 [1.03 - 7.46]) and creatinine concentration (OR [95% CI]: 1.09 [1 - 1.18]) and lower thrombocyte count (OR [95% CI]: 0.97 [0.94 - 0.99]).

Discussion

In a 14-year period we have treated 30 neonates with enteroviral meningitis, being the most common cause of aseptic meningitis, and due to the vulnerability of this population, it is important to timely recognize and treat this infection. Nine (30%) of them presented with early-onset disease, between 5-7 days of postnatal age. Neonates with early-onset meningitis had a comparable grade of clinical signs and concentration of proinflammatory parameters in comparison to the group with late-onset meningitis which might reflect similar grade of infection. Also, the outcome of both groups of neonates was favourable and did not differ. Our findings confirm that enteroviral meningitis carries a good prognosis in the majority of neonates.

We used the cut off age of 7 days to investigate possible differences in clinical features and outcome in neonates with enteroviral meningitis because of previous findings that infections with EV and hepatic necrosis have a more severe outcome in infants that contract the virus vertically or early (less than 7 days of age) after birth (15). Studies in the past have consistently shown, that infection within the first week of life (probably through vertical transmission) is associated with higher mortality than disease of later onset (probably through postnatal transmission) (16). In comparison to neonates who contracted EV later in the neonatal period, neonates who acquired the infection vertically were more ill (17). In a case series study Lin et al. involving 146 patients with enteroviral disease and 42 with hepatic necrosis coagulopathy features, WBC (15×10^9/L or greater) and low haemoglobin (107 g/L of lower) were independently and significantly associated with severe course of infection (18). Since none of our patients had hepatitis with

coagulopathy maybe this was the reason for good outcome in our group of neonates (15, 19).

Three mothers of neonates with early onset meningitis (33%) had signs of viral disease just before delivery or shortly after (while still in maternity hospital). In our study, 23% of mothers had signs of acute respiratory infection or diarrhoea, and 57% of neonates were in contact with siblings who had signs of viral disease. The big majority of our patients had siblings, who could be a potential source of infection albeit one third of them did not have apparent signs.

Leading signs in the clinical picture in our patients were irritability, fever, feeding intolerance and diarrhoea. Clinical signs of enteroviral meningitis in neonates are often nonspecific and similar to those in nonspecific febrile illness or sepsis-like illness. Clinical or laboratory signs of SIRS were present in 53% of patients. Three of our patients had epileptic seizures with abnormal EEG and needed antiepileptic treatment. One patient had also signs of encephalitis on brain MRI and was transferred to the intensive care unit. He was intubated, needed antiepileptic therapy but no vasoactive support. Because of a severe course of disease, he was treated with intravenous immunoglobulin (IVIG). On the seventh day of disease, EV was not detectable in CSF anymore.

Clinically, neonates with early-onset meningitis had jaundice more often than neonates with late-onset disease, neonatal jaundice maybe being a sign of infection, although it might be physiological or due to other reasons (20). In laboratory parameters, the early-onset group had a higher serum urea and creatinine concentration and lower thrombocyte numbers. Urea and creatinine typically decrease rapidly in the first days after birth, reaching the nadir until 2 weeks of life (21). In the first few days of life, the neonatal serum creatinine reflects maternal renal function or the maternal creatinine (22). The mean thrombocyte number in neonates increases slightly from birth to 4 weeks of age, being similar to that in older children and adults, ranging from 150 000 to 450 000/mm^3 (23). Thrombocytopenia, being a late sign of infection, was present in only one of our patients. Taken together, albeit not unexpected in the first week of life, jaundice, higher urea, creatinine, and/or thrombocytopenia, could indicate a possible neonatal infection. Neonates with early-onset enteroviral meningitis did not differ in any of the inflammation parameters in the blood nor in the CSF in comparison with the late-onset group, so we might suspect the immune reaction to the infection being of the same magnitude in both groups.

Different types of EVs have marked differences in tropism, virulence and also clinical manifestations. Enteroviral infection may manifest as one of the following clinical pictures: a nonspecific febrile illness, sepsis, myocarditis, hepatitis with coagulopathy, aseptic meningitis and encephalitis (4, 7, 24, 25). EVs are an important cause of aseptic meningitis in neonates and are probably underdiagnosed because the presentation is mild in most cases and specific testing is not performed (7, 24). In our cohort, 40% of patients had pleocytosis in the CSF.

Eighty percent of our patients were in contact with mothers or siblings with signs of viral disease. However, our neonates presented with a more serious clinical picture - with signs of sepsis or meningitis. Cautious collecting of epidemiological data is necessary.

Infections caused by EVs in neonates are more severe than in older children and adults. Causal mechanisms are not yet understood. Insufficient transplacental passage of antibody and diffuse dissemination of large inoculum of the virus in neonates that develop illness in the first week of life are possible reasons (26). Lin et al. described the risk factors associated with severe enteroviral infections in neonates. Prematurity, maternal history of illness, earlier age of onset, higher WBC and lower haemoglobin were identified as significant factors associated with hepatic necrosis with coagulopathy. Furthermore higher total bilirubin and concurrent myocarditis were most significantly associated with fatal outcomes (18), what was not the case in our rather small group of neonates. Soudée et al. suggested that systematic serotyping of neonatal enteroviral infections and biological

monitoring of liver function could be useful for early identification of children at high risk of clinical severity and fatality (27).

At our unit 80% of neonates were treated with antibiotics, the median time of treatment was 1.5 days. Three patients were treated with acyclovir (one to three days), due to suspicion of herpetic infection. The duration of hospitalization was 1-19 days (median 3 days) (Table 1). Currently, there are no therapies approved for enteroviral infection. IVIG have been used, because they may provide neutralizing antibodies for faster virus clearance, but randomized studies have not been done (28). We used IVIG only in a patient with life-threatening infection and the outcome was favourable. None of the patients in our cohort had signs of hepatitis, coagulopathy, and/or myocarditis.

Enteroviral meningitis is diagnosed by detection of EV by PCR in the CSF (29, 30). Disease in neonates tends to be generalized, therefore multiple samples should be collected (throat, stool, urine, blood and CSF) (26). Detection of EV in nasopharyngeal samples and stool samples can also be used to indirectly confirm EV as cause of meningitis. In one of our patients EV was found in stool and in five in the nasopharynx. Eichinger et al. showed that using PCR testing reduces the use of antimicrobials in properly selected cases (31). King et al. performed a retrospective study at The Children's Hospital of Philadelphia which showed that positive CSF EV PCR resulted in shorter hospitalization and duration of antibiotic use for young infants (30). The same holds true for our group of patients. We have a relatively short duration of antibiotic therapy (median 1.5 days) due to early PCR testing in appropriately selected patients. Shorter hospitalization reduces the risk of nosocomial infection and with appropriate instructions neonate can be discharged early.

Infections are most common during summer and fall. The majority (73%) of our patients presented with clinical signs during the summer and autumn months, which is consistent with previous studies. That supports the routine testing for EV during periods of peak EV prevalence. Routine evaluation of a neonate with possible sepsis, meningitis or seizures of unknown cause should include PCR for EV (26). A rapid diagnosis could have a beneficial impact by reducing the length of antibiotic therapy. Reinforcing hygiene measures to prevent nosocomial infections should be emphasized.

The Limitations of the Study

Our study limitations are missing EV serotyping due to a lack of financial resources and a long study time period. A few articles have been published in the literature addressing the genotyping of EV in meningitis, but only for epidemiological purposes at the national level and not at the level of a single department (32, 33). Otherwise, genotyping of EV is potentially important only in the detection of new genotypes or variants that could be associated with major outbreaks of meningitis.

Conclusion

Enteroviruses are an important cause of meningitis in neonates, especially during the summer and autumn months. Neonates present with persistent fever, irritability, feeding intolerance, diarrhoea, and normal or mildly elevated CRP and/or PCT values. Particularly, a positive history of contact with persons with signs of viral disease should prompt testing for EV in order to reduce treatment with antibiotics. Neonates with early-onset enteroviral meningitis did not differ in any of the inflammation parameters in the blood nor in the CSF in comparison with the late-onset group, so we might suspect the immune reaction to the infection being of the same magnitude in both groups. Our findings confirm that enteroviral meningitis carries a good prognosis in the majority of neonates.

Conflict of Interest: The authors declare that they have no conflict of interest.

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