Neonatal bacterial meningitis in Turkey: epidemiology, risk factors, and prognosis

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Abstract

Introduction: We aimed to determine the incidence, etiology, risk factors and outcome of bacterial meningitis in neonates.

Methodology: Neonates who developed bacterial meningitis between 2003 and 2010 in a tertiary hospital in Turkey were included in the study. Patients born in our hospital were defined as Group 1 and patients referred from other centres were defined as Group 2.

Patients with evidence of congenital infections or central nervous system malformations were excluded. Demographic features, delivery type, time of onset of meningitis, co-morbidities, clinical features, blood and cerebrospinal fluid (CSF) analysis, cranial sonographic findings, and outcome of patients were recorded.

Results: The study comprised 325 meningitis cases identified from 38,023 hospitalised patients in the neonatology unit among 11,8091 live births. Mean gestational age, birth weight, and hospital stay were 36.8±3.7 weeks, 2.480±924 g, and 26±12.4 days, respectively. Almost half (48%) of the patients were diagnosed in the first seven postnatal days and 52% at 8-30 days after birth. CSF culture findings were positive in 59 (18%) patients (28 in Group 1 and 31 in Group 2). Gram-positive bacteria were the responsible agents in 30 (51%) patients, whereas 26 (44%) patients had Gram-negative bacterial meningitis and 3 (5%) had *Candida* meningitis**.** Gram-negative bacteria were predominant in Group 1 whereas Gram positive bacteria were predominant in Group 2. Transfontanel ultrasonography revealed pathologic findings in 17.5% of patients. The total mortality rate was 2.5%.

Conclusion: This large-scale study provides essential information about the etiology, characteristics, and outcome of neonatal bacterial meningitis in Turkey.

Introduction

Neonatal meningitis is the inflammation of the meninges typically occurring within the first 30 days of life [1]. It may be classified as early-onset (EOM) and late-onset meningitis (LOM) according to the time of diagnosis [2-5]. Symptoms and clinical findings usually appear during the first week of life in EOM [2,5-8]. Some authors define the disease that begins within the first three days as very early onset meningitis (VEOM) [8]. Late-onset meningitis occurs between postnatal 8th and 30th days [2,5-8].

Despite the advancements in neonatal intensive care units (NICU) and increased availability of antibacterial and supportive medications, neonatal meningitis is still a serious disease with high morbidity and mortality rates. Antibiotic resistant nosocomial infections pose significant risk to premature neonates [9-15]. Infection appearing at 48 to 72 hours of hospitalization that was not present or incubating at the time of admittance of the mother to hospital is defined as nosocomial [16]. Diagnostic criteria for nosocomial origin in neonatal meningitis is debatable; they are usually defined according to duration of hospitalization.

The overall incidence of neonatal bacterial meningitis has not changed during the last 20 years: 0.22 cases per 1000 live births between 1985 and 1987 versus 0.21 cases per 1000 live births between 1996 and 1997 [17]. These data are consistent with data from developed countries [18-20]. A recent review on the incidence of neonatal meningitis infections reported 0.8 to 6.1 cases in every 1,000 live newborns [21]. A well-designed, large-scale randomised controlled trial on neonatal meningitis is lacking in Turkey. The aim of our study was to evaluate neonatal meningitis cases treated during a seven-year period between 2003 and 2010 in a large neonatal centre. We investigated risk factors, clinical features, etiological

agents and prognosis of neonates with meningitis retrospectively.

Methodology

This study involved neonates with meningitis born in Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, or those referred to our centre from nearby hospitals, between 2003 and 2010. The study was approved by the local Ethics Board.

Patients with serological and clinical evidence of congenital infections, central nervous system malformations causing contraindications for lumbar puncture (LP), and inconsistent microbiological results of cerebrospinal fluid (CSF) due to contamination (more than one agent in the same culture) were excluded.

We recorded demographic features, birth weight, gestational age, gender, time to onset of meningitis, delivery type, symptoms, co-morbidities, risk factors, incidence, etiology, clinical findings, CSF and blood analysis, and cranial sonography results. CSF analysis included protein and glucose levels, CSF glucose/blood glucose ratio, cell counts, microscopic examination, and culture.

Preterm birth was defined as birth before 37 weeks of gestation [22]. New Ballard Score for the gestational age assessment [23], and Lubchenko's charts [24] of intrauterine growth were used.

Meningitis was diagnosed based on clinical and laboratory findings and CSF abnormalities. The indications for LP included suspicion of sepsis and/or meningitis and non-defined infectious focus. Patients with meningitis were classified into two groups as follows: patients born in our hospital were defined as Group 1 and patients referred to our hospital from other centres were defined as Group 2. Cases were further categorised as EOM and LOM according to time to onset of the disease. Presentation during the first week of life was defined as EOM, while LOM included presentation between postnatal 8th and 30th days. Infection was considered as nosocomial if it was diagnosed after 48 hours of maternal hospitalization and subsequent birth or after 48 hours of hospitalization of the newborn [5].

Coexisting disorders such as respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), history of hospitalization in NICU, and maternal risk factors (premature rupture of membranes, *etc*.), were also investigated. RDS was defined by the presence of two or more of the following criteria: evidence of respiratory compromise shortly after delivery and persistent oxygen requirement for more than 24 hours; administration of exogenous pulmonary surfactant; and/or radiographic evidence of hyaline membrane disease [25].

NEC was diagnosed according to Bell Staging Criteria [26].

BPD was defined as the need for supplemental oxygen (O2) for $\geq$ 28 days in terms or $\geq$ 36 weeks corrected gestational age in preterms [27]. Premature rupture of membranes (PROM) was defined as rupture of the membranes prior to 18 hours before delivery [28].

Clinical findings such as lethargy, dyspnea, irritability, alterations in body temperature, and inadequate feeding were noted.

Laboratory features such as blood count, sedimentation rate, CRP, differential leukocyte count in peripheral blood, CSF analysis, blood and CSF culture results were evaluated. White blood cell count <5000/mm3 and > 20.000/mm3 were accepted as pathologic [29]. Immature to total neutrophil ratio (I/T) was also recorded. The maximal I/T ratio in uninfected neonates was accepted as 0.16 in the first 24 hours, decreasing to 0.12 by 60 hours. The upper limit for neonates at 32 weeks' gestation or less was slightly higher; 0.2 [30].

CRP was measured by nephelometric inhibition immunoassay method. Levels above 1mg/dl were considered as pathologic. Poly-optic GMbH thoma glass was used for measurement of CSF cell count. Leukocytes > 32/mm^3, > 29/mm^3, glucose < 34 mg/dl, < 24 mg/dl, CSF/ blood glucose ratio < 0.44, <0.55 and protein > 170 mg/dl, > 150 mg/dl were compatible with the diagnosis of meningitis in term and premature babies, respectively [30]. Eosin methylene blue and chocolate agar were used for CSF and blood culture analysis. The etiologic agents responsible for EOM and LOM were noted.

All patients with meningitis were examined with transfontanel ultrasonography (Acuson cypress with 7V3c and 3V2c ultrasound probe). Presence of structural intracranial abnormalities, intracranial hemorrhage and periventricular leukomalacia were investigated. Papille's classification [31] was used for evaluation of intracranial hemorrhage.

Patients with hydrocephalus and/or planned shunt surgery underwent computed tomography (CT) and magnetic resonance (MR) imaging for further evaluation.

Mortality rate was also calculated. The results were analysed by arithmetic mean and standard

deviation. SPSS 16 pocket programme (IBM, Chicago, USA) was used for statistical analysis.

Results

Between January 2003 and June 2010, out of 11,8091 neonates who were born in our hospital 38,023 neonates were hospitalized due to various clinical problems. Of these, 344 patients were diagnosed with meningitis. Eight patients with congenital malformations (meningomyelocele in six patients and spina bifida in two). Eleven patients with unobtained protocol variables were excluded from the study. Among 325 patients who received a diagnosis of meningitis (325/3,8023) 161 were assigned to Group 1 and 164 were assigned to Group 2. The calculated incidence of neonatal meningitis was 1.3 in Group 1 and 2.7 in both groups per 1,000 live births. Group 1 included 84 patients (52%) with EOM and 77 patients (48%) with LOM, whereas Group 2 included 66 patients (40.2%) with EOM and 98 patients (59.8%) with LOM. Forty-three percent of the patients were female. Group 1 included 46 term and 115 preterm patients, whereas Group 2 included 123 term and 41 preterm patients. In the study population, mean gestational age was 36.8 ± 3.7 weeks and mean birth weight was 2480 ± 924 g. Fifty-two patients (16%) were preterm with a birth weight less than 1500 grams. Distribution of patients according to gestational age is shown in the Figure.

In Group 1, maternal risk factors such as PROM and chorioamnionitis were present in 10.8% and 1.5% of patients, respectively. Neonatal risk factors included

prematurity (71%), low birth weight (33%) and history of interventional procedures, specifically, exchange transfusion in three patients (1%) and endotracheal intubation in thirty (19%) patients. In Group 2, prematurity (20%) and delivery at home (1.8%) were the major neonatal risk factors, while cervical infections (1.5%) and urinary tract infections (2%) were the major maternal risk factors. Maternal cervical and urine culture results were available in 150 patients; 13 (8.6%) of them were positive (Gram-negative organisms [69%] including *Escherichia coli* as the most commonly detected pathogen [23%], *Enterococcus* spp. [23%], and methicillin sensitive *Staphylococcus aureus* [8%]).

The most common clinical features were fever (39%), poor clinical status (25%), and poor feeding (16%) in term-delivered patients, while poor clinical status (74%), hypotonia (11%), and cyanosis (7%) were commonly observed in preterm babies with meningitis. Other clinical findings of meningitis were apnea, convulsions, hypoglycemia, nausea, diarrhoea and jaundice. Seizure was observed in 29 (8.9%) patients, 11 at the time of admission and 18 during hospitalization.

Mean leukocyte count in CSF was 143 ± 235 (0-1000) cells/ mm^3. CSF leukocyte count was more than 1,000/mm^3 in 20 (6.2%) patients. Seventeen (5.2%) patients had no leukocytes in CSF examination; however, all had abnormal CSF findings (decreased glucose, increased protein) and/or pathologic bacterial growth in CSF or blood culture. Mean glucose level, CSF glucose/blood glucose ratio and protein levels

Figure1. Distribution of patients according to gestational age
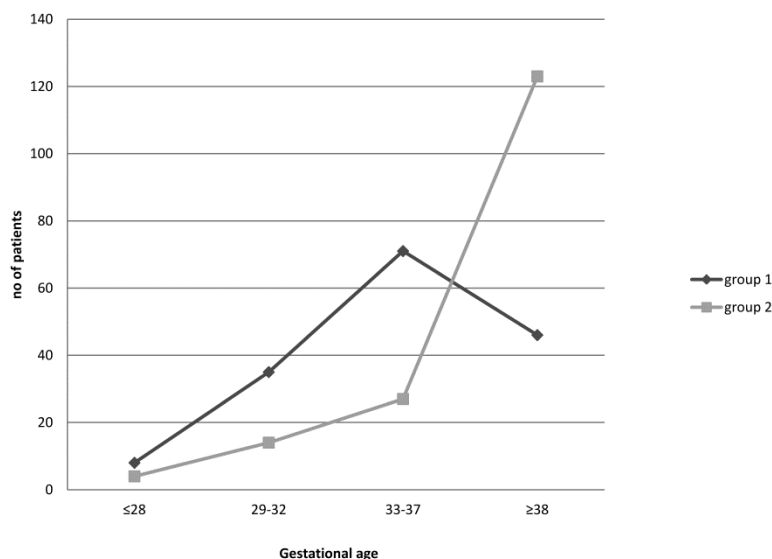
were 57 ± 27 (6-271) mg/dl, 0.53 ± 0.06 (0.2-1.5), and 92 ± 72 (10-641) mg/dl, respectively.

Positive CSF culture findings were detected in 59 (18%) patients (28 in Group 1 and 31 in Group 2). Gram-positive bacteria were detected in 30 (51%) patients, whereas 26 (44%) patients had Gram-negative bacterial meningitis and 3 (5%) had *Candida* meningitis**.** Gram-negative bacteria were predominant in Group 1, whereas Gram-positive bacteria were dominant in Group 2. Distribution of bacterial pathogens in Groups 1 and 2 is shown in Table 1.

Blood culture was examined in all patients; 17 of them had positive results. Table 2 shows the comparative results between blood and CSF culture findings.

Transfontanel ultrasonography revealed pathologic findings in 17.5 % (n = 57) of the patients (Table 3). The most common finding was ventricular dilatation. Cranial CT/MR was performed in 17 patients with evidence of hydrocephalus and/or planned shunt surgery; 6 patients had pathological findings (severe hydrocephalus and/ or intraventricular hemorrhage)

and were referred to the neurosurgery clinics for further evaluation.

The mortality rate was 2.5%. Half of the fatal cases had a history of preterm delivery. Mortality was higher in patients with LOM (77.5 %). Table 4 summarizes the characteristics of fatal meningitis cases in NICU.

Finally, other serious diseases that accompanied meningitis in this cohort are listed in Table 5.

Discussion

This study on confirmed cases of meningitis at a tertiary centre in Turkey with a large number of participants aimed to learn about the realities of this devastating disease in developing countries, which is difficult to diagnose during the neonatal period. We evaluated the incidence and mortality rate, causative organisms, maternal and neonatal risk factors, and complications of neonatal meningitis.

A vast majority of new technological, antimicrobial and supportive therapeutic advancements have been introduced in health-care

Table 1. Distribution of bacterial pathogens detected in CSF culture in group 1 and 2

Etiological agent	Group 1	(n = 28)	Group 2	(n = 31)
	EOM	LOM	EOM	LOM
Gram positive organisms	**5**	**7**	**4**	**14**
Staphylococcus epidermidis	4	7	4	14
Streptococcus spp.	1	-	-	-
Gram negative organisms	**9**	**5**	**4**	**8**
Serratia spp.	3	3	-	1
Klebsiella spp.	2	2	-	2
Gram negative rods	2	-	3	2
Enterobacter spp.	2	-	-	1
Pseudomonas auroginosa	-	-	1	-
E. coli	-	-	-	2
Fungi	**1**	**1**	**1**	**-**
Candida albicans	1	1	1	-
Total	**15**	**13**	**9**	**22**

CSF: cerebrospinal fluid; EOM: early onset meningitis; LOM: late onset meningitis
Group 1: Patients born in our hospital; Group 2: patients referred from other centers

Table 2. The comparative results between CSF and blood culture findings

CSF C. & Blood C.	Positive B.C.*	Positive B.C.**	Negative B.C.	Total
Positive CSF C.	**11**	**6**	**42**	**59**
Gram negative organism	4	3	19	26
Gram positive organism	6	3	21	30
Fungi	1	-	2	3

B: blood; C: culture; CSF: cerebrospinal fluid
*Different organisms were isolated compared to CSF results
**The same organisms were isolated both from the blood and CSF culture

Table 3. Cranial ultrasonography findings

Sonographic findings of CNS system	Number of patients	%
Ventricular dilatation	20	6.2
Grade 1 intracranial hemorrhage	10	3.1
Hydrocephalus	9	2.8
Periventricular leukomalacia	5	1.5
Grade 2 intracranial hemorrhage	3	0.9
Grade 3 intracranial hemorrhage	3	0.9
Grade 4 intracranial hemorrhage	1	0.3
Cerebral edema	1	0.3
Anatomical anomalies*	**5**	**1.5**

CNS: central nervous system

*Anatomical anomalies: plexus coroid cyst, cavum septum pellicidum, cavum verge, mega cisterna magna, interventricular septum agenesia

Table 4. Etiologies of the mortality in 8 patients

Patient	Etiology	Preterm	Term
1.	Early-onset sepsis/meningitis	36 g.a.*	-
2.	Late-onset sepsis /meningitis + intracranial hemorrhage	25 g.a.	-
3.	Late-onset sepsis /meningitis + ventriculitis	31 g.a.	-
4.	Late-onset sepsis /meningitis + CHD #	35 g.a.	-
5.	Late-onset sepsis/meningitis + fungal sepsis + CHD	-	40 g.a.
6.	Late-onset sepsis/meningitis + suspected metabolic disease	-	40 g.a.
7.	Late-onset sepsis /meningitis +perinatal asphyxia	-	40 g.a.
8.	Late-onset sepsis /meningitis + icthyosis	-	40 g.a.

*g.a: gestational age
CHD: Congenital heart disease

Table 5. The list of a variety of diseases accompanying meningitis in the study population

Diseases	n	%
Prematurity	81	24
Neonatal jaundice	39	12
Respiratory distress syndrome	25	7
Congenital heart disease	17	5
Transient tachypnea of newborn	15	4
Anemia	13	4
Necrotizing enterocolitis	13	4
Intracranial hemorrhage	12	3
Pneumonia	10	3
Uriner tract infection	8	2
Bronchopulmonary dysplasia	8	2
Others*	84	30

*Others: Perinatal asphyxia, hypocalcemia, retinopathy of prematurity

systems in recent years; however, neonatal infections are still important causes of morbidity and mortality [9-15].

In all decades, the incidence of meningitis was highest during the neonatal period [19]. The incidence of neonatal meningitis was reported as 0.72 per 1,000 live births in a previous study [9-11]. A recent study from Africa and South Asia reported that incidence of neonatal meningitis ranged from 0.8 to 6.1 per 1,000 live births [21]. In our study, incidence of neonatal meningitis was 1.3 in Group 1 and 2.7 in both groups per 1,000 live births.

Maternal risk factors in EOM include PROM, chorioamnionitis, recto-vaginal colonization of Group B streptococci, urinary tract infections, and bacterial vaginitis [2-5,7,32,33]. Neonatal risk factors are preterm delivery before 32 weeks of gestation, low birth weight, multiple births, prolonged internal fetal monitoring, male gender, low Apgar score, and history of resuscitation [2-4,33]. In the present study, PROM was present in 12.5% of the EOM cases; 8.6% of these patients had positive bacterial growth in maternal urinary or cervical cultures. Altuncu *et al*. [34] also had reported PROM as a major risk factor for sepsis in preterm delivery.

Maternal risk factors do not play a significant role in the pathogenesis of LOM, and the majority of affected newborns are full-term [2,3,5]. The most common predisposing factors for development of late-onset sepsis include invasive procedures such as endotracheal entubation, mechanical ventilation, frequent venipunctures, central and peripheral vascular catheter interventions, transcutenous oxygen measurement, enteral tube insertion, and prolonged parenteral nutrition [2,3,35-37]. Additionally, prolonged antibiotic treatment increase the risk of infection with resistant organisms [2,35-37]. In the present study, half of the patients were delivered before 37 weeks of gestation. Sixteen percent of the patients had a birth weight less than 1500 g. Patients with underlying illnesses such as RDS, pneumonia, NEC, BPD and other diseases leading to hospitalization in the NICU are at increased risk for development of sepsis and meningitis [5].

Delivery at home is a common practice in developing countries [38]. In a recent study from the Philippines, it was reported that out of 873 infants enrolled, 463 (53%) were delivered at home, 73 (8%) at small health centre and 286 (33%) at hospitals. Among 35 bacteriologically confirmed cases, 21 (60%) were delivered at home, including 16 out of 26 cases (62%) with Gram-negative sepsis [39]. In the present study, there were six home-delivered neonates (1.8%) and four of them (66 %) had EOM.

Presenting signs and symptoms of neonatal meningitis are nonspecific. The most frequently observed symptoms include lethargy, feeding intolerance, vomiting, respiratory distress, irritability, and temperature instabilities [30]. In the present study, fever (39%)**,** poor clinical status (25%) and poor feeding (16%) were the most commonly observed clinical features in term-delivered patients, whereas poor clinical status (74%), hypotonia (11%), and cyanosis (7%) were more common in premature babies. Other clinical findings were apnea, convulsion, hypoglycemia, nausea, diarrhoea and jaundice.

Laboratory features of neonatal bacterial meningitis include increased CSF WBC count with a predominance of polymorphonuclear leukocytes, elevated CSF protein concentration, decreased CSF glucose, and isolation of a bacterial pathogen from CSF [40].

In the present study, the mean CSF leukocyte count was 143 ± 235 (0-1000) cells/mm^3. Twenty (6.2%) patients had a CSF leukocyte count of more than 1000/mm^3. Mean glucose level and protein levels were 57 ± 27 (6-271) mg/dl and 92 ± 72 (10-641) mg/dl, respectively. Smith *et al*. [41] reported similar CSF findings except that they detected higher protein levels.

Etiologic agents and clinical course dictate duration of treatment in neonatal meningitis. A 10-day to 21-day treatment is usually adequate for group B streptococcal infection. It may take longer to sterilize the CSF with Gram-negative bacillary meningitis, and three to four weeks of treatment is usually necessary [42]. In our study, the mean age at the time of diagnosis was 26 ± 12.4 days and the mean duration of antibiotherapy was 22 ± 8.6 days.

The incidence of culture-confirmed meningitis cases differs according to geographic region, and even in the same centre [2-5,7]. The most frequently reported etiologic agents in EOM are group B *streptococci* and *Escherichia coli* [2-4,7,32,33] originating from maternal vaginal and rectal flora [2,7,33]. Group B streptococci colonization in pregnant women is reported as 2% to 7% in Turkey [43,44]; GBS is not a major pathogen in early sepsis in contrast to reports from developed countries [45]. In our study, culture-confirmed meningitis contributed to 18% of the cases. Gram-positive bacteria were the etiological agents in 59.6% of cases. *S. epidermidis* was detected in 29 patients and 21 of them were diagnosed as LOM. The most frequently detected

pathogens responsible for EOM were *Klebsiella spp.* and *S. epidermidis*. Gram-negative bacteria were predominant in Group 1, whereas the Gram-positive bacteria were more common in Group 2. Other studies from Turkey have also shown that the most frequently detected pathogens responsible for late-onset sepsis were coagulase negative staphylococci [45,46]. *Serratia spp.* and *Klebsiella spp.* were the most commonly detected Gram-negative bacteria. Garges *et al.* [47] reported that Group B *Streptococci* and *E. coli* were the most common etiologic agents in neonatal meningitis. In another study, Aletayeb *et al.* [48] reported *Klebsiella pneumonia* and *Enterobacteria* spp. as the most common pathogens involved in neonatal bacterial meningitis. However, several studies in Turkey have reported that coagulase-negative staphylococci played an important role in the pathogenesis of early- and late-onset neonatal sepsis [45,46].

The sensitivity of blood culture in neonatal sepsis is 50% to 80% [33]. Significant bacterial growth accompanying clinical findings suggests sepsis in neonates, but negative results do not exclude the diagnosis [2,33]. Meningitis frequently occurs in the absence of bacteremia and, for that reason, lumbar puncture is an important part of the diagnostic investigation in cases of suspected sepsis since it may be the only positive test [47].

Although there is a close relationship between bacterial sepsis and meningitis, it has been estimated that 15% to 30% of the infants with CSF-proven meningitis have negative blood cultures [49]. Garges *et al.*, in 2006, reported that 96.8% of the patients with a positive CSF culture had a blood culture examination and 62% had a positive bacterial growth. The organisms isolated in CSF and blood cultures were discordant in only 3.5% of cases [47]. A positive blood culture was detected in 19% of our patients and the same microorganism was isolated from both blood and CSF cultures in six patients [*S. epidermidis* (50%), *Klebsiella spp.* (35%), and *Candida* (15%) *spp.*].

In our study, maternal cervical and urine cultures were examined in 150 patients and 13 patients (8.6 %) had positive results. The most frequently detected pathogens were *E. coli* (23%), other unclassified Gram-negative bacteria (46%), *Enterococcus spp.* (23%), and methicillin-sensitive *Staphylococcus aureus* (8%).

Sonographic abnormalities are reported in approximately 65% of the infants with acute bacterial meningitis [50]. Sonography may play an important role in the detection of postinfectious hydrocephalus,

determination of the level of obstruction, and evaluation of intracranial compliance. Han *et al.* [51] stated that none of the infants with normal findings on initial sonographic examination developed complications. Some authors suggest that cranial sonographic examination should be performed in all patients with meningitis whether complications are present or not. Yikilmaz *et al.* recommended that cranial sonography should be performed as a baseline study in every infant with an adequate fontanel size and suspicion of bacterial meningitis [50]. Sonography is a safe diagnostic method and can be repeated if required. A second sonographic study should be performed if any clinical deterioration occurs, including an increase in head circumference, detection of new neurological findings, and inadequate response to therapy. In patients with complicated bacterial meningitis, MRI should be the next study of choice [50]. In our study, all patients were screened with transfontanel ultrasonography as a first-line diagnostic tool for investigation of intracranial hemorrhage, hydrocephalus, cerebral edema, periventricular leukomalacia, and other related pathologies. Pathological sonographic findings were detected in 17.5% of the patients. The most frequently detected findings were ventricular dilatation, hydrocephalus, and intracranial hemorrhage (Table 3).

While the mortality rate of meningitis is approximately 2% in childhood, this can reach up to 20% to 30% in newborns [52]. Early-onset meningitis has a 15% to 70% mortality rate, whereas it is 10% to 20% in patients with late onset of the disease. In our study, eight patients (2.4%) died during follow-up; seven of the fatal cases (87%) had received the diagnosis of LOM. We think that early diagnostic and therapeutic interventions could have played a major role in reducing mortality rates.

The present study has several limitations: it was retrospective and only a single centre was involved. Furthermore, the number of microbiologically confirmed cases was relatively small. However, a considerable number of neonates with meningitis was included.

Conclusion

Neonatal bacterial meningitis continues to be a major cause of morbidity and mortality in developing countries. Early diagnosis and treatment of established disease is essential. Although the ratio of microbiologically confirmed cases was relatively small, we believe that this study, with a significant number of cases with neonatal meningitis, will provide

essential information about the etiology, patient characteristics, and prognosis of neonatal meningitis. Multicentre studies are needed to determine the exact burden of neonatal meningitis in our country.

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