

Neonatal Bacterial Meningitis: Single Reference Center Experience and Review of Current Literature: A Retrospective Cohort Study

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ABSTRACT

OBJECTIVE: Despite improvements in neonatal care, neonatal bacterial meningitis is still an emerging problem worldwide with high rates of mortality. The present study evaluates data on suspected- and culture-proven neonatal bacterial meningitis in the light of a single tertiary reference center experience in Turkey in comparison with the globe.

STUDY DESIGN: In this retrospective cohort study newborns admitted to Hacettepe University Ihsan Dogramaci Children's Hospital Neonatal Intensive Care Unit during a 5-year-period between April 2014-May 2019 and who underwent atraumatic lumbar puncture were included.

RESULTS: Two hundred sixty-four patients fulfilled the inclusion criteria. Most common symptoms in all patients raised suspicion in favor of NBM and resulted in lumbar puncture were fever (34.5%, n=91), respiratory distress (31.1%, n=82), lethargy (31.1%, n=82), and apnea (26.1%, n=69). The incidence of culture-proven NBM among suspected patients was 5.7% (n=15/264); while the incidence is 3.1 per 1000 (15/4574) at all Neonatal Intensive Care Unit admissions. Respiratory distress (60.0%, n=9/15) and apnea (40.0%, n=6/15) were the most common symptoms in patients with NBM; which may be due to the predominance of premature newborns in the NBM group. The most common microorganisms in CSF cultures were coagulase-negative Staphylococci with Methicillin-resistant Staphylococcus epidermidis being most common among all.

CONCLUSIONS: The present study underlines high rates of culture-proven neonatal bacterial meningitis among suspected newborns despite improvements in modern health care, which raises attention to careful evaluation of these patients and early administration of properly-selected antibiotics. Our incidence rates are in keeping with studies from the developed world.

Keywords: Bacterial meningitis, Epidemiology, Neonatal, Newborn

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Introduction

Meningitis, which is characterized by inflammation of meninges due to various pathogens, has great importance in

the neonatal period due to its higher incidence and mortality compared to any other age (1-8). The incidence and mortality rates of culture-proven neonatal bacterial meningitis (NBM) in developed vs. developing countries range between 0.2-0.3 vs. 0.8-6.1 per 1000 live births and 10-15% vs. 11-58%, respectively (5-15). Despite a declining trend in incidence and rates of mortality due to improvements in neonatal care, morbidity is still a great concern among surviving neonates which are subject to many short- (ventriculitis, cerebritis, and brain abscess) and long-term complications (loss of hearing and vision, focal neurological deficits, convulsions, delays in neurocognitive development) (1-3,10,12,13).

Appropriate treatment of NBM depends on early suspicion and accurate diagnosis, which may only be achieved by a comprehensive evaluation of symptoms (fever, lethargy, feeding difficulty, apnea, respiratory distress, convulsions, etc.) followed by a detailed examination of cerebrospinal fluid (CSF) (microscopic, biochemical, and microbiological properties) (1-3,10-13). While Group B Streptococci and

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Escherichia coli are the most emerging pathogens in early-onset meningitis (postnatal <3 days of age), Coagulase-negative Staphylococci are the most common pathogens among late-onset meningitis (postnatal >3 days of age) (1-3,8,9,11). Empirical and definitive antibiotic regimens vary according to postnatal age, accompanying risk factors, isolated microorganisms, and antimicrobial resistance patterns (1,2).

While numerous in-depth studies have addressed the aspects of NBM, large studies demonstrate that the epidemiology, etiology, treatment strategies, and outcome of NBM may vary with the changing setting; which is of importance in short-term care and long-term follow-up of newborns. In this study, we aimed to analyze suspected- and culture-proven NBM in the light of a single large tertiary reference center in Turkey, in comparison with other studies around the globe.

Material and Method

This retrospective cohort study included all newborns (chronologic age in 0-28 days, or corrected post-conceptual age under 40 weeks) who were admitted to Hacettepe University Ihsan Dogramaci Children's Hospital Neonatal Intensive Care Unit (NICU) during a 5-year-period between April 2014-May 2019, who underwent atraumatic lumbar puncture (LP) and successful withdrawal of CSF proceeding a suspicion of meningitis. Patients who were beyond the age limits and who had traumatic LP with blood contamination were excluded. Demographical features, clinical symptoms, culture findings (CSF, blood and urine samples), empirical antibiotic regimens, and duration of therapy were analyzed in a retrospective manner with Statistical Package for Social Sciences (SPSS) for Windows 20.0. The study was reviewed and approved by the ethics committee of Hacettepe University (ethics approval reference number: 2019/23-08). All procedures were performed according to the Declaration of Helsinki.

Results

Within the study period, 4,574 newborns were admitted to NICU for different causes; 646 of them underwent an LP proceeding with suspicion of meningitis at admission or during the stay. Of these, 264 of them fulfilled the inclusion criteria owing to an atraumatic LP with the successful withdrawal of CSF. Among the patients included in the study, 48.1% (n=127) of them were female with the median week of gestation (GW) 36 (24-42) weeks, median birth weight (BW) 2500 (500-4.920) grams, and the median duration of stay 22 (2-144) days. There was no significant variability regarding the demographical profile of the patients (Table I).

All lumbar punctures were performed during the investigation of late-onset sepsis/meningitis. The majority of the presentations were in a hospital setting (64.4%, n=170) with median timing of LP 16 (3-70) days (Table II). Most common symptoms which raised suspicion in favor of NBM and resulted in LP were fever (34.5%, n=91), respiratory distress (31.1%, n=82), lethargy (31.1%, n=82), apnea (26.1%, n=69) and difficulty in feeding (in patients with GW>34 weeks, 29.0%, n=47) (Table III). The most preferred empirical antibiotic regimens included wide-spectrum regime [Ampicillin/ Meropenem/ Gentamycin/Fluconazole (prophylaxis)] (59.1%, n=153) and Ampicillin/Gentamycin (35.9%, n=93). The median duration of antibiotics due to suspicion of NBM was 10 (2-39) days.

The incidence of culture-proven NBM among patients who had an atraumatic LP was 5.7% (n=15/264); while the incidence is 3.1 per 1000 (15/4574) at all NICU admissions (Table I). Among the patients diagnosed with meningitis, 46.7% (n=7) of them were female with the median GW 34 (25-41) weeks, median BW 2500 (500-4920) grams, and the median duration of stay 37 (16-130) days. The majority of the presentations were at the hospital setting 73.3% (n=11) with

Table I: Demographical profile of the patients included in the study

Variable	Non-meningitis n (%)	Meningitis n (%)	All Patients n (%)	p
Female	120 (48.2)	7 (46.7)	127 (48.1)	0.56
Cesarean section	197 (79.1)	12 (80.0)	209 (79.0)	0.61
Gestational diabetes mellitus	25 (10.0)	2 (13.3)	27 (10.2)	0.46
Gestational hypertension	31 (12.4)	4 (26.7)	35 (13.3)	0.12
Urinary tract infection during last trimester of pregnancy	61 (24.5)	1 (6.7)	62 (23.5)	0.09
Hypothyroidism at mother	31 (12.4)	1 (6.7)	32 (12.1)	0.43
Premature rupture of membranes	14 (5.6)	3 (20.0)	17 (6.4)	0.06
Chorioamnionitis	3 (1.2)	0 (0)	3 (1.0)	0.83
Resuscitation during labor	64 (25.7)	6 (40.0)	70 (26.5)	0.18
Congenital CNS* defects+	35 (14.1)	3 (20.0)	38 (14.4)	0.37
Congenital non-CNS* defects++	54 (21.7)	3 (20.0)	57 (21.6)	0.59
CNS* risk factors	17 (6.8)	3 (20.0)	20 (7.6)	
Ventriculoperitoneal shunt	12 (70.6)	2 (66.6)	14 (70.0)	0.09
External ventricular drainage	5 (29.4)	1 (33.4)	6 (30.0)	
Total	249 (94.3)	15 (5.7)	264 (100)	-

*CNS: Central nervous system, +Includes meningomyelocele, and hydrocephalus. ++Includes congenital cardiac and gastrointestinal defects.

Table II: Outcome of the patients included in the study

Variable	Non-meningitis	Meningitis	All Patients	p
Presentation in hospital setting [n (%)]	159 (63.9)	11 (73.3)	170 (64.4)	0.32
Lumbar puncture timing (median, days)	16 (3-67)	25 (5-70)	16 (3-70)	0.97
Duration of antibiotics due to suspected/proven of late-onset neonatal meningitis (median, days)	10 (2-39)	20 (14-32)	10 (2-39)	p<0.001
Duration of stay (median, days)	22 (2-144)	37 (16-130)	22 (2-144)	0.02
Exitus [n (%)]	11 (4.4)	2 (13.3)	13 (4.9)	0.16
Total [n (%)]	249 (94.3)	15 (5.7)	264 (100)	-

Table III: Symptoms at the time of presentation and preferred antibiotic regimens

Variable	Non-meningitis, n (%)	Meningitis, n (%)	All Patients, n (%)	p
Fever	87 (34.9)	4 (26.7)	91 (34.5)	0.36
Respiratory distress	73 (29.3)	9 (60.0)	82 (31.1)	0.02
Lethargy	78 (31.3)	4 (26.7)	82 (31.1)	0.47
Apnea	63 (25.3)	6 (40.0)	69 (26.1)	0.17
Abdominal distension	31 (12.4)	4 (26.7)	35 (13.3)	0.12
Brady-tachy arrhythmia	25 (10.2)	2 (13.3)	27 (10.2)	0.46
Convulsion	26 (10.4)	1 (6.7)	27 (10.2)	0.53
Vomiting	24 (9.6)	1 (6.7)	25 (9.5)	0.57
Irritability	21 (8.4)	1 (6.7)	22 (8.3)	0.63
Hypotension	13 (5.2)	0 (0)	13 (4.9)	0.45
Difficulty in feeding*	44 (28.8)	3 (33.3)	47 (29.0)	0.51
Initiation of antibiotics due to suspicion of late-onset neonatal sepsis/meningitis	244 (98.0)	15 (100)	259 (98.1)	-
Wide-spectrum+	143 (58.6)	10 (66.7)	153 (59.1)	
Ampicillin/Gentamycin	90 (36.9)	3 (20.0)	93 (35.9)	
Cefotaxime/Gentamycin	10 (4.1)	0 (0)	11 (4.2)	
Other	1 (0.4)	2 (13.3)	2 (0.8)	
Total	249 (94.3)	15 (5.7)	264 (100)	-

median timing of LP 25 (5-70) days (Table II). The median duration of antibiotics was 20 (14-32) days. The most preferred empirical antibiotic regime was the wide-spectrum regime [Ampicillin/Meropenem/Gentamycin/Fluconazole (prophylaxis)] (66.7%, n=10) (Table III). Most common symptoms included respiratory distress (60.0%, n=9), apnea (40.0%, n=6), lethargy (26.7%, n=4), abdominal distension (26.7%, n=4), and feeding difficulties (in patients with GW>34 weeks, 33.3%, n=3) (Table III).

Meningitis (n=15) and non-meningitis (n=249) groups did not differ significantly regarding demographical, epidemiological, and clinical profile (Table I and III); although respiratory distress as the preceding clinical symptom was more prominent in the meningitis group (60.0% vs. 29.2%, p=0.02) (Table III).

Table IV outlines the features of cultures of patients sampled from different sites. Blood culture negativity in patients with NBM was 53.3% (n=8/15), while 63.3% (n=168/264) of all investigated patients were culture-negative for both CSF, blood, and urine cultures with undefined etiology. CSF cultures revealed the most common microorganisms as coagulase-negative Staphylococci (53.3%, n=8/15) with Methicillin-resistant Staphylococcus epidermidis (33.3%, n=5/15) being the most common among all (Table V).

Although statistically not significant, the rate of mortality was higher in the meningitis group (13.3%, n=2 vs. 4.4%, n=11); while the overall mortality at all NICU admissions during the study period being 5.3% (Table II).

Table IV: Culture positivity of blood and urine samples

Patients	Culture positivity, n (%)				Total
	Blood	Urine	Blood + Urine	None	
Non-meningitis	63 (25.3)	16 (6.4)	2 (0.8)	168 (67.5)	249 (94.3)
Meningitis	7 (46.7)	0 (0)	0 (0)	8 (53.3)	15 (5.7)
Total	70 (26.5)	16 (6.1)	2 (0.7)	176 (66.7)	264 (100)

Table V: Cerebrospinal fluid and blood culture findings of patients with meningitis

Case	GW	BW	PN Age	Presentation	CSF culture	Blood culture
1	25	730	70	Hospital	<i>Klebsiella pneumoniae</i> (ESBL+)	<i>Klebsiella pneumoniae</i> (ESBL+)
2	27	980	53	Hospital	MRSE	MRSE
3	28	1060	28	Hospital	<i>Streptococcus sanguinis</i>	----
4	28	1170	10	Hospital	MRSE	MRSE
5	30	790	6	Hospital	<i>Klebsiella pneumoniae</i> (ESBL+)	<i>Klebsiella pneumoniae</i> (ESBL+)
6	30	1530	11	Hospital	MRSE	MRSE
7	34	1310	12	Hospital	<i>Enterococcus faecium</i>	----
8	34	1500	5	Hospital	MRSE	MRSE
9	35	2750	41	Hospital	MRSE	MRSE
10	36	2950	29	Community	<i>Escherichia coli</i>	----
11	37	3200	26	Community	<i>Staphylococcus haemolyticus</i>	----
12	39	3970	18	Hospital	<i>Acinetobacter baumannii</i> complex	----
13	39	3580	9	Community	<i>Staphylococcus hominis</i>	----
14	39	2990	27	Hospital	<i>Enterobacter cloacea</i>	----
15	41	3940	25	Community	<i>Staphylococcus hominis</i>	----

GW: Gestation week, BW: Birth weight, PN: CSF: Cerebrospinal fluid, ESBL: Extended spectrum betalactamases, MRSE: Methicillin-Resistant *Staphylococcus Epidermidis*

Discussion

Despite improvements in neonatal routine- and intensive-care, neonatal bacterial meningitis (NBM) is still a great concern worldwide due to its higher incidence and mortality compared to any other age (1-3,10,12,13). This recent retrospective cohort evaluates culture-proven NBM while presenting data over patients with clinically-suspected NBM, in the light of a single tertiary reference center experience in Turkey in comparison with the globe.

The present study included some important data that was not encountered in other studies during our routine literature review. The most common symptoms which raised suspicion in favor of NBM and resulted in LP were found to be fever, respiratory distress, lethargy, and apnea. While interpreting this finding, we realized that these symptoms led us to be more of a priority in making an LP decision in late-onset NBM. Among patients clinically suspected of NBM, the incidence of culture-proven NBM was 5.7%. We appraised this incidence to be high, which draws attention to being more attentive while evaluating a newborn suspected of NBM. This also further underlines the importance of early administration of properly-selected antibiotics whenever needed.

Literature reveals that the incidence and mortality rates of culture-proven NBM range between 0.2-0.3 vs. 0.8-6.1 per 1000 live births and 10-15% vs. 11-58% in respect to developed vs. developing countries (1-8,13-15). Direct comparison of the present study with the world in terms of NBM incidence was not possible due to the fact that our NBM incidence was calculated from NICU admissions rather than live births. On the other hand, the incidence of 3.1 per 1000 at all NICU admissions in the present study was in keeping with a recent study from Canada (2.2-3.5 per 1000 NICU admissions) and lower than a native study from Turkey (9 per 1000 admissions) (11,12). Mortality rates among patients with NBM in

the present study (13.3%) were in concurrence with the developed world (13.3% vs. 10-15%) (1-3,8).

Many variables have been shown as risk factors of NBM in multiple studies; which in turn affect the site of presentation (community- or hospital-based), the most common symptom at presentation, most preferred empirical antibiotic regimen, and most commonly isolated microorganisms in CSF cultures (1-3,9,12). The patients diagnosed with NBM in the present study were predominantly composed of premature newborns [GW 34 (25-41) weeks] with a relatively long duration of stay [37 (16-130) days]. Many of them had concomitant congenital CNS (meningomyelocele, hydrocephalus) or non-CNS (cardiac, gastrointestinal) defects with multiple invasive procedures (Table I). In our understanding, this may explain the relatively high rate of hospital-based NBM (73.3%). Respiratory distress and apnea were found to be the most common symptoms in patients with NBM; which may also be explained by prematurity and which is also in concurrence with current knowledge of NBM in premature newborns (1,2).

Wide-spectrum with multiple antibiotics was the regime of choice, as the patients were suspected of late-onset meningitis with a possible risk of resistance patterns. The most common bacteria isolated in CSF cultures (coagulase-negative *Staphylococci*) were in concurrence with the current literature and also with microorganisms related to late-onset meningitis (1,2,9,11). A variety of studies reported up to 50.0% of blood culture negativity in patients diagnosed with NBM and some of them even suggested multiple blood samples to be withdrawn to increase sensitivity (1-6,11,12). The present study has also detected a comparatively high rate of negative blood cultures (53.3%) parallel to previous studies.

An important limitation was the difficulty encountered during the comparison of the present study with other studies

around the globe owing to varieties in study design. A forthcoming new prospective study would address this issue by evaluating NBM incidence at live births by means of a new study architecture.

In conclusion, NBM continues to be a great concern both in our country and around the globe. The appropriate treatment depends on prior, early, and high clinical suspicion; where CSF cultures still stand to be the gold standard for definitive diagnosis. Our findings regarding incidence are in keeping with studies from the developed world. Despite improvements in neonatal health care in recent years, the rate of culture-proven NBM is still high among suspected newborns, which raises attention to careful evaluation of patients with apparent symptoms and early administration of properly-selected antibiotics.

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Authors' contributions: AA, HTC, GH: Raised the presented idea. SY, MY: Have designed the study. AA, HTC: Conducted the analyses and developed the first draft of the manuscript and the final review was conducted by GH, SY, and MY: All authors contributed to the writing of the paper, and have read and approved the final manuscript.

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