



Original Article

Clinical presentations, Laboratory analysis and Linear Growth in 50 Neonates and Young Infants with Acute Meningitis: One Year Experience of a Single Center in Qatar

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Competing interests: The authors have declared that no competing interests exist.

Abstract. Background: Meningitis frequently occurs in neonates and can lead to a number of acute, severe complications and long-term disabilities. Although, long term growth delay and abnormal weight gain appear to be risk factors following an acute attack of both bacterial and aseptic meningitis in children, especially during the fast phase of infantile growth, the long-term effects of acute meningitis occurring during the neonatal and early infantile periods on linear growth (length, weight and head growth) have not fully reported.

Aim of the study: The objective of this study is to describe the clinical presentation of neonates and young infants with acute meningitis with different etiologies and to determine the clinical impact of the effect of acute meningitis on growth parameters.

Material and methods: We analyzed the clinical data and the growth parameters of 50 newborns and young infants (age: 1.6 ± 0.9 months) admitted to our hospital (Al Wakhra Hospital, Department of Pediatrics, Doha, Qatar), between 1-1-2016 to 1-1-2017, with acute meningitis. Anthropometric measurements included weight, length, and head circumference. Length SDS (L-SDS) and body-mass-index (BMI) were calculated and recorded at every clinic visit, every 3 months for 8 ± 2 months.

Results: In this age group of neonates and young infants with acute meningitis fever (84%) and hypoactivity (64%) were the major presenting manifestations. Acute bacterial meningitis (n: 10) was associated with higher morbidity [shock (n: 1), subdural empyema (n: 1) and hydrocephalus (n: 1)]. Cerebrospinal fluid (CSF) examinations showed that infants with bacterial meningitis had significantly higher pleiocytosis of mainly polymorphic leukocytes and protein levels, compared to those with aseptic meningitis.

All infants showed normal linear growth and weight gain during the follow-up period (8 ± 2 months). The annualized growth rate of infants was 25.3 ± 3.5 cm per year. All had normal length standard deviation scores (LSDS) (-0.2 ± 0.9) and none of them had LSDS < -2 . All infants had a normal BMI (16.7 ± 1.8 kg/m²). Head circumference growth was normal in 49/50 infants (43.8 ± 1.8 cm) at 8 ± 2 months. One infant developed hydrocephalus after group B streptococcus (GBS) meningitis. There was no statistical difference in linear growth between infants with aseptic and bacterial meningitis.

Conclusion: Acute bacterial meningitis in newborns and young infants is still associated with considerably high morbidity and complications. Infantile linear growth appears to be normal in all newborns and young infants with both bacterial and aseptic meningitis.

Keywords: Acute meningitis; Newborns; Young infants; Growth; Length; Weight; Body-mass-index.

Citation: Abdelmaguid N., Seleem W.S., Soliman A.T., Mohamed R.S., Elgharbawy F.M., Yassin H., De Sanctis V. Clinical presentations, laboratory analysis and linear growth in 50 neonates and young infants with acute meningitis: one year experience of a single center in qatar. *Mediterr J Hematol Infect Dis* 2019, 11(1): e2019028, DOI: <http://dx.doi.org/10.4084/MJHID.2019.028>

Introduction. Meningitis frequently occurs in neonates and can lead to several acute, severe complications and long-term disabilities. Neonates are at higher risk of meningitis because of immaturity in humoral and cellular immunity, and the absence of specific clinical signs makes a diagnosis of meningitis more difficult in neonates than in older children. The causative organism varies with age, immune function, immunization status, and geographic region.^{1,2}

The rate at which the disease develops varies between patients. Those with more fulminant illness will be critically ill within the first 24 hours, leaving a very narrow window of opportunity to deliver life-saving treatment. Therefore, an early diagnosis of neonatal meningitis is essential to reduce mortality and to improve outcomes. Cerebrospinal fluid (CSF) examinations and cultures for bacteria as well as polymerase chain reaction (PCR) for viruses should be obtained prior to administration of treatment.^{3,4}

Complications of bacterial meningitis can be divided into systemic and neurologic. Systemic complications, such as septic shock, disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), and septic or reactive arthritis are usually the consequence of the bacteremia that frequently accompanies meningitis. Acute complications include cerebral edema (vasogenic and cytotoxic), increased intracranial pressure, ventriculitis, cerebritis, hydrocephalus, brain abscess, cerebral infarction, cerebral venous thrombosis, arterial stroke, and subdural effusion or empyema.⁵⁻¹⁰

Mortality and long-term complications in survivors are observed in 10-15% and 20-50%, respectively, depending on the term at diagnosis, type of identified organisms, and delay before treatment. Neurological deficits range from moderate-to-severe disabilities to more subtle problems including visual deficits, middle-ear disease, and cognitive and behavioural impairments. Intracerebral complications should be documented using magnetic resonance imaging.

Several studies of adults have shown that pituitary deficiencies can develop in a considerable proportion of subjects during the acute phase of meningitis or years after the infection has disappeared. Post-meningitis growth hormone (GH) deficiency has been described and confirmed by provocative tests in adults and children.¹¹⁻¹³

The objective of this study is to describe the clinical presentation, laboratory analysis of neonates and young infants with acute meningitis (with different etiologies) and to determine the outcome of this disease, especially

on growth parameters in a tertiary care center in Doha, Qatar.

Patients and Methods. All infants [4 preterms (36, 35, 35 and 28 weeks of gestation)] and 46 full-term newborns and young infants with acute meningitis, of different etiologies, who were primarily seen at Al Wakhra Hospital, Department of Pediatrics, Doha (Qatar), between 1-1-2016 to 1-1-2017 were included in the present study (23 girls and 27 boys, mean age: 1.6 ± 0.9 month).

Children with malnutrition, anemia, chronic or systemic disease, and skeletal abnormalities were excluded. Fifty infants, age and sex-matched healthy siblings, were randomly selected to serve as controls for anthropometric data.

The diagnosis of meningitis was based on clinical symptoms and cerebrospinal fluid (CSF) examinations (positive CSF bacterial antigen test, with latex agglutination counter immune electrophoresis, associated with neutrophilic pleocytosis, defined as absolute WBC ≥ 100 cells/mm³, with a decreased glucose level ≤ 40 mg/dL and an increased protein concentration ≥ 60 mg/dL), and cultures for bacteria as well as polymerase chain reaction (PCR) for viruses.

Anthropometric parameters including length (using a standard supine length stadiometer), weight and head circumference were measured during hospitalization and at every clinic visit for 8 ± 2 months, after discharge from the hospital.

Fenton Preterm Growth Chart was used for assessment of growth for preterm infants and WHO growth curves were used for evaluation of growth postnatally. Length and weight measurements were compared with the WHO gender- and age-related curves.¹⁴ The length standard deviation score (Ht-SDS) and body mass index (BMI; expressed in kg/m²) were calculated and compared to the control group.

The research protocol has been approved by the ethical committee of Hamad Medical Center before the study.

Data of patients are reported as mean \pm SD. The Student t-test was used to compare variables among the selected groups. Wilcoxon test was used to compare variables when the data were not normally distributed. The linear regression equation was used to investigate a possible correlation between variables. Significance was accepted at $p < 0.05$.

Results. Bacterial meningitis was diagnosed in 10/50 infants with positive CSF cultures: Group B Streptococcus (GBS) in 4 patients, Escherichia coli in 2

Streptococcus pneumoniae in 2, Streptococcus bovis in 1 and Klebsiella pneumoniae in another patient.

Forty infants had the diagnosis of aseptic meningitis (ASM) because of the presence of clinical manifestations of meningitis with CSF pleocytosis but without bacterial etiology detected in the CSF and/or blood. Of those, CSF virology CPR study diagnosed 19 cases with Enterovirus and 1 case with Adenovirus. ASM without viral identification occurred in 20 infants.

At the time of hospital admission, 42 infants were febrile ($> 38^{\circ} \text{C}$), four infants suffered from hypothermia ($< 36.6^{\circ} \text{C}$), and 8 were dehydrated, with serum sodium $> 135 \text{ mmol/L}$ and urine specific gravity > 1.030 .

Four out of 10 infants with bacterial meningitis were delivered by Caesarean section. They had a gestational age of 36 ± 3.7 weeks, birth weight of $2.52 \pm 0.29 \text{ kg}$ and birth length of $46.6 \pm 4.0 \text{ cm}$. Maternal age ranged from 28 to 32 years.

One infant (35 weeks of gestational age with premature rupture of membranes for $> 24 \text{ h}$ before birth) with a birth-weight of 2.56 kg had early onset meningitis. His mother had received antibiotic therapy for 2 days before delivery. Another infant (28 weeks of gestation), birth weight of 1.9 kg , with respiratory distress syndrome) had early meningitis. All the other 8 infants with bacterial meningitis had late-onset infection. Two infants were small for gestational age (SGA) (weight $<$ the 10th percentile). Their gestational age was 35 and 36 weeks, and birth weight of 2.4 and 1.9 kg , respectively. One infant with GBS presented

with status epilepticus and right-sided subdural empyema that responded to treatment with meropenem for 4 weeks. Another infant with GBS meningitis presented with shock (blood pressure $< 60 \text{ Torr}$ systolic). One infant had the syndrome of inappropriate diuretic hormone (SIADH) (defined as a serum Na concentration $< 125 \text{ mmol/L}$ and urine specific gravity > 1.022).

Ten of the 40 infants with aseptic meningitis were delivered by Cesarean section. Maternal age ranged from 25 to 36 years. They had a gestational age of 38.7 ± 1.6 weeks, a birth weight of $3.17 \pm 0.53 \text{ kg}$, and a birth length of $49.9 \pm 2.5 \text{ cm}$. Only 2 had an early onset disease. One infant had birth-weight = 2 kg . None of their mothers had premature rupture of membranes. Three mothers had a fever during the last trimester of pregnancy and received antibiotics.

During the follow up (8 ± 2 months) none of the infants developed cognitive or motor dysfunction. One infant with Streptococcus pneumoniae meningitis and bacteremia developed hydrocephalus (**Table 1**).

Laboratory showed that infants with bacterial meningitis had marked pleocytosis, with polymorphic leukocytes and protein higher levels than those with aseptic meningitis (**Table 2**).

Infants with bacterial meningitis received antibiotics for 18.2 ± 5.9 days.

On admission growth data, including length standard deviation score (L-SDS) and BMI, did not differ from those of healthy controls. During the follow-up, all infants had normal growth velocity and weight gain (BMI: $16.7 \pm 1.8 \text{ kg/m}^2$). Head

Table 1. Clinical presentations and laboratory analysis in 50 neonates and infants with acute meningitis.

Presentation	Total	Total	Aseptic	Aseptic	Bacterial	Bacterial	P value
	n= 50	%	n=40	%	n=10	%	
Fever	42	84%	33	82.5%	9	90%	0.58
Hypothermia	4	8%	2	5%	2	20%	0.12
Hypoactivity	32	64%	26	65%	6	60%	0.29
Poor feeding	10	20%	4	10%	6	60%	0.0004
Irritability	22	44%	17	43%	5	50%	0.42
Disturbed consciousness	4	8%	2	5%	2	20%	0.12
Shock	1	2%	0	0%	1	10%	0.043
Seizure	2	4%	0	0%	2	20%	0.004
Hyponatremia (Na $< 135 \text{ mEq/L}$)	10	20%	6	15%	4	40%	0.076
Hypernatremia (Na $> 149 \text{ mEq/L}$)	0	0%	0	0%	0	0%	NA
SIADH	1	2%	1	2.50%	0	0%	0.6
High CSF protein $> 1.4 \text{ g/dl}$	5	10%	2	5%	3	30%	0.018
CSF neutrophil/total cell count $> 60\%$	11	22%	5	12.50%	7	70%	0.0001
Complications (*)	3	6%	0	0%	3	30%	0.0003

Legend: CSF - cerebrospinal fluid, SIADH: inappropriate diuretic hormone. (*) Complications included: Shock, subdural empyema and hydrocephalus in 3 infants with bacterial meningitis (2 patients with Group B Streptococci and 1 with Streptococcus Pneumonia).

Table 2. Mean values of CFS components in neonates and infants with aseptic versus bacterial meningitis.

Diagnosis		CSF WBC (mm ³)	CSF Lymphocytes (%)	CSF Polys (%)	CSF Protein (mg/dL)	CSF Glucose (mg/dL)
Aseptic (n = 40)	Mean	581	46	33.8	82	64.1
	SD	279	27	29	42	12.5
Bacterial (n = 10)	Mean	873	15.6	67.9 (*)	136 (*)	57.6
	SD	1090	20.4	29.6	83	9.4

Legend: CSF - cerebrospinal fluid, WBC - white blood cell; Polys - polymorphs; (*) p < 0.05.

circumference growth was normal in 49/50 infants (43.8 ± 1.8 cm) at 8 ± 2 months. One infant developed hydrocephalus after GBS meningitis. There was no statistical difference in linear growth between infants with aseptic and bacterial meningitis (**Table 3**) No symptoms or signs suggesting thyroid or adrenal defects were present.

Infants did not have a visual impairment or hearing loss and clinically had normal developmental milestones during the first and second follow up visit as assessed by Pediatricians. We did not have a detailed neurodevelopmental assessment for all of them. Visual and Brainstem Auditory Evoked potential testing was used to evaluate all cases with bacterial meningitis and showed no abnormalities. None of the infants with aseptic meningitis had visual or hearing loss.

Discussion. Aseptic meningitis (including viral meningitis) is the most common infection of the central nervous system (CNS) in the pediatric population, occurring most frequently in children younger than 1 year.¹⁵ In agreement with this view, in our young infants (age: 1.6 ± 0.9 months), aseptic meningitis

constituted 80% of cases, while bacterial meningitis was diagnosed in 20 % of them.

In our study, fever (84%), hypoactivity (64%) and irritability (20%) were the most common presenting manifestations. However, the clinical signs of neonatal meningitis can be subtle and nonspecific. Meningitis signs such as convulsions, irritability, bulging fontanel, and nuchal rigidity are often late findings that are associated with poor outcomes.¹⁶

One infant with bacterial meningitis developed shock at presentation that responded to intensive care measures, another one developed subdural empyema, and a third one developed hydrocephalus. These complications confirm the high morbidity (30%) associated with bacterial meningitis in this age group of patients. Other studies reported mortality in 10% of affected infants. 20–50% of survivors developed seizures, cognitive deficiencies, motor abnormalities, and hearing and visual impairments.¹⁷⁻²²

All our infants had normal length and weight gain during the follow-up period of early infancy (not growth hormone (GH) dependent). No symptoms or signs suggested thyroid or adrenal defects. However, the fact that the young infants with meningitis in this

Table 3. Growth data (mean ± SD) of neonates and infants with aseptic versus bacterial meningitis.

Diagnosis	AGE at baseline (b)	Wt-SDS at (b)	BMI at (b)	L-SDS at (b)	HC at (b)	AGE at first follow-up	Wt-SDS at first follow-up	BMI at first follow-up	HC at first follow-up	AGE at second follow-up	L-SDS at second follow-up	BMI at second follow-up	GV	HC at second follow-up
	months				cm	months				months			cm/year	cm
Aseptic n = 40	1.49	-0.50	15.5	-0.50	36.5	4.88	0.29	17.38	41.5	8.27	-0.04	16.98	25.5	43.6
	0.87	1.07	1.88	1.07	2.94	1.68	1.08	2.04	2.03	2.86	0.93	2.36	3.89	1.72
Bacterial n = 10	1.18	-0.66	14.4	-0.66	36.0	3.94	-0.62	16.1	40.6	8.88	-0.70	16.4	24.7	43.2
	0.66	1.39	1.28	1.39	1.92	1.01	2.70	2.16	1.92	2.76	0.93	1.20	1.89	1.25
Controls n=50	1.25	-0.25	14.6	-0.12	36.8	4.50	0.19	16.5	41.2	8.90	-0.20	17.1	25.7	44.2
	0.52	0.50	1.20	0.50	1.00	0.70	0.70	1.50	1.20	1.50	0.40	1.80	2.30	1.10

Legend: Wt-SDS = weight standard deviation score, BMI = body mass index, L-SDS = supine length SDS, HC = head circumference, GV= growth velocity, expressed in cm/year.

study seemed to be completely “normal” with regards to length and weight may not be representative of infants with meningitis in other regions of the world. Long term growth delay and abnormal weight gain appear to be risk factors following an acute attack of both bacterial and aseptic meningitis in children especially during the fast phase of infantile growth.²³ Potentially, the inflammatory process associated with meningitis may involve the hypothalamic-pituitary area. Isolated and combined pituitary deficiencies, has been shown to develop in a considerable proportion of patients following acute infectious meningitis. These deficiencies may be either transient or permanent and may occur immediately or a few months later.²⁴⁻²⁵ Therefore, despite normal linear growth of our infants with meningitis during the first year of their life (not GH dependent) it is necessary to keep monitoring their growth during the childhood period (GH dependent period).

A limitation of the study is represented by the heterogeneous etiology of the cases as well as by the

fact that only patient presented with status epilepticus and right-sided subdural empyema. It could be possible that in complicated cases as tuberculous meningitis or in the presence of severe neurologic deterioration the results could be different. However, this population may offer opportunities for clinical observations in comparison with a similar population(s). Additionally, the delayed negative effect on linear growth still form a risk, and the growth of these children should be monitored periodically.

Conclusions. bacterial meningitis in early infancy is still associated with significant morbidity. However, our study showed normal linear growth and weight gain during the first 8 ± 2 months following treatment of infants with bacterial and aseptic meningitis. Long term follow-up for developing growth delay and delayed neurological sequelae is recommended. Invasive assessments should be reserved for selected cases where there is slow growth or another clinical suspicion of hypopituitarism.

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