Retrospective Assessment of Neuro Developmental Outcome of Neonatal Meningitis

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Research Article

Abstract: The survival of the "high risk" newborns has improved considerably in last few decades, with the setting-up of a number of well-equipped neonatal units. But mere survival is not enough, it is the quality of survival that is important. In a young infant, who is in a in a state of rapid growth, the dynamic process of rapid development is such that, any static parameter should and must alert the pediatrician- be it slowness or stagnation of acquisition of new skills. Following the infant's development closely at regular intervals provides the best key to judge the neurodevelopmental outcome. There are very few Indian studies available on this subject. Therefore this observational cross- sectional retrospective study was undertaken in a referral centre.

Keywords: Neonatal meningitis, neurological outcome, CSF analysis.

Introduction

Diseases involving the brain in the neonatal period not only have a high mortality, but also a high incidence of neurologic morbidity. Despite development of effective vaccines, tools for rapid identification of pathogens and potent antimicrobial drugs, neonatal meningitis contributes substantially to neurological disability worldwide. The persistence of neonatal meningitis results from increasing number of premature and extremely low birth weight (ELBW) surviving in the developed countries and limited access to medical facilities in the developing countries. In addition, the absence of specific clinical findings makes the diagnosis more difficult compared to older children. Moreover, a wide variety of pathogens are seen in infants because of the immaturity of their immune system. The incidence of neonatal meningitis is approximately 0.3 – 0.4 per 1000 live births in industrialized countries (1-2) and probably much more in developing countries. Neurological sequelae are reported to be about 50%, sequelae being more in meningitis due to gram negative organisms (3). With advanced care in tertiary units, the mortality rate has gone down, but the neurodevelopmental outcome is of great concern to neonatologists. Though there are many studies on follow up of other risk factors like birth asphyxia, hyperbilirubinemia, intraventricular hemorrhage etc., there are very few studies on outcome of neonatal meningitis. Since meningitis is notoriously one of the most serious infections of the newborn, this outcome study of neonates treated for meningitis in a tertiary care unit was undertaken, as there are hardly any Indian studies on this subject.

Aims and Objectives

1. To determine the neurodevelopmental outcome of neonatal meningitis.
2. To determine the mental and motor development using Developmental Assessment Scale for Indian Infants (DASII).
3. To find out correlation between CSF analysis and neurological outcome.

Material and Methods

This is a Observational Cross- Sectional Retrospective study in which the babies with neonatal meningitis discharged from the NICU of a tertiary care teaching hospital between 1st January 2006 – 31st December 2008 were selected for this study and were recalled for a single examination. At follow up examination, physical growth (head circumference, height, weight, etc.) were noted, milestones were also noted. On admission to the NICU, gestational age of all babies was determined using the Modified Ballard's Score (13) which is accurate to $\pm$ 2 weeks. All preterm neonates were given a corrected date of birth. All clinical data of the NICU stay was obtained from hospital records.

A diagnosis of meningitis was based on the following criteria (12).

(1) C.S.F. examination :

a. Increase in the number of cells (> 20 cells/cmm), predominantly neutrophils.

b. Increase in concentration of protein (>100mg/dL)

c. Reduction in the concentration of glucose (<50% of the concomitant blood sugar)

(2) Positive spinal fluid culture

(3) Definite bacteria on stained smear of C.S.F.

All patients were treated with antibiotics for a maximum of 21 days. Neonates with meningomyelocoele, congenital CNS infections, hydrocephalus and a previous history of surgical procedure of central nervous system were

excluded. All the patients were called for a special examination after the age of one year. Corrected age was used in preterm babies. At this visit, a complete physical examination was done. Routine advice regarding nutrition, immunization was given if necessary.

Neurodevelopment was assessed using

1 Development Assessment Scale for Indian Infants (DASII) (4-6).

2 Auditory and Ophthalmic check-up

Hearing was already assessed by otoacoustic emission (OAE) at the time of discharge from NICU. This was reconfirmed by BERA test at corrected age of 3 months.

Method

The Developmental Assessment Scale For Indian Infants (DASII) :

The baby was tested for mental and motor development using The Developmental Assessment Scale For Indian Infants (DASII) which is Indian adaptation of the Bayley Scales of Infant Development. Here the mental and motor quotients were calculated and scored normal, abnormal or suspect as follows: After calculating the mental and motor age, the developmental quotient (DQ) for both the mental and motor age are calculated as follows:-

$$DQ\ (\text{mental / motor}) = \frac{\text{Mental / Motor age}}{\text{Chronological age}} \times 100$$

DQ $\geq$ 85 is a normal score

71 – 84 is a suspect score

$\leq$ 70 is an abnormal score

The testing is carried out in a sound proof room with a one way mirror. The testing is done by 2 psychologists – one acting as a tester and the other an observed to reduce inter observation variability. As DASII is a performance test, it is a prerequisite that the baby should be in optimum health and alert. Many testings had to be abandoned if the baby was irritable, sleepy or sick. Also if the age of child is > 30 months , if clinical examination of the child was normal then Intelligent Quotient (IQ) was determined using Stanford Binet test. Also if the child had shown delayed development based on clinical examination and tone examination then DQ of that child was determined even if that child was older than 30 months. The children were classified as delayed, if milestones were delayed on the basis of tone abnormalities and / or with DQ/IQ less than 85. An ophthalmic check up was done at the same visit. An ophthalmic examination was also done including fundoscopy.

Sample Size Calculation

Purpose: To calculate sample size to be able to detect the statistical significance for determining the long-term neurological outcome among neonatal bacterial meningitis cases.

Design: Hospital based retrospective study.

Reference cited: Long term outcome of neonatal meningitis. J P Stevens, M Eames, A Kent, S Halket, D Holt, D Harvey, Arch Dis Child Fetal Neonatal Ed 2003;88: F179–F184

Fixed Parameters:

Incidence of bacterial meningitis in KEM NICU = 4.4%

Total admissions in KEM NICU per year (meningitis and others) = 800

Incidence of mortality in meningitis = 40%

Variable Parameters:

Alpha (Type I error): 0.05 (5%).

Power (Probability of correctly rejecting null hypothesis): 75%, 80%, 85%, 90%, 95%

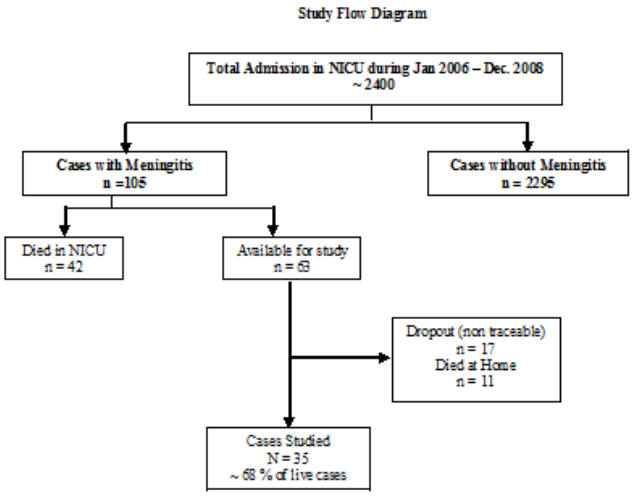
Sample Size Calculations:

		Power				
Alpha		75%	80%	85%	90%	95%
0.05 (5%)	Sample Size (n)	22	26	34	40	45

Thus a minimum sample size of 26 would give 80% power and 5% type I error probability (α=0.05) to be able to detect a true statistically significant association between developmental parameters (such as birthweight, gestational age etc) of meningitis cases with the neurological outcome measures.

About the Software used:

We used software called PS: power and sample size calculation software. It is an interactive program for performing power and sample size calculations. The program runs on the Microsoft Windows operating systems (Windows 95 and later). It can be used for studies with dichotomous (the present study), continuous, or survival response measures. The alternative hypothesis of interest may be specified either in terms of differing response rates, means, or survival times, or in terms of relative risks or odds ratios. Studies with dichotomous or continuous outcomes may involve either a matched or independent study design. The program can determine the sample size needed to detect a specified alternative hypothesis with the required power, the power with which a specific alternative hypothesis can be detected with a given sample size, or the specific alternative hypotheses that can be detected with a given power and sample size.



Data Analysis and Results

A total 2400 neonates were admitted in our NICU from January 2006 to December 2008. Out of that 105 patients were diagnosed as neonatal meningitis; 42 patients died during treatment in hospital and 63 patients discharged or went against medical advice from the hospital. We decided to do follow up with a neurological examination of these patients. 11 patients died at home and 17 patients were non traceable, so finally 35 cases (68% of live cases) were followed up, out of which 27 patients were male and 8 were females. Ten patients had birthweight $\geq$ 2.5kg and 25 patients had birthweight < 2.5kg. Only 4 babies were SGA (small for gestational age). These patients were followed up with a single examination for this observational cross sectional retrospective study. The follow up of these 35 cases was divided in two groups based on their age of follow up (in months) as follows. Group I – No. of cases seen between their ages from 12 months to 24 months of corrected gestational age. Twenty cases belonged to this age group. Group II – No. of cases seen between their ages older than 24 months to 36 months of their corrected gestational age. Fifteen cases (Patients) belonged to this age group. In Group I, out of 20 cases, 7 cases were found to have normal neuromotor development and 13 cases were delayed in the form of tone and developmental abnormalities determined by DASII testing. 9 cases were having spastic cerebral palsy (CP) while 2 cases were having dystonic CP. 2 cases showed only minimal developmental delay without tone abnormality. 4 patients suffered from seizure disorders which were confirmed by EEG and also microcephaly was found in one patient. In Group II, out of 15 cases, 12 cases were found to have normal neuromotor development, while 3 cases were delayed including 2 cases of spastic CP and 1 case of hypotonic CP. All CPs were mentally retarded, microcephaly was found in 2 patients. So, out of 10 cases who were having birthweight $\geq$ 2.5kg, 5 cases showed normal neuromotor development while 5 cases were delayed on tone examination and developmental assessment (including 4 cases of spastic CP, 1 of which also had microcephaly and seizure disorder, 1 case of hypotonic CP) and out of 25 cases who were having birth weight $\leq$ 2.5kg 14 cases shown normal neuromotor development, while 11 cases were delayed (including 7 cases of spastic CP 2 of which also had microcephaly and seizure disorder, 2 cases of dystonic CP, 1 of which also had seizure disorder). So, out of total 35 cases, 19 cases were found to have normal neuromotor development, while 16 cases (45.7%) showed delayed neuromotor development in the form of low DQ (mental and motor) and tone abnormalities (hypotonia / hypertonia). Radiological examination – MRI brain was done in total 4 cases, out of two patients with normal MRIs, one had CP and another one was normal neurodevelopment. In the two patients with abnormal MRI findings like periventricular leucomalacia and delayed myelination, outcome was CP. EEG was done in 4 cases suffering from seizures, all showed abnormal results consistent with seizure disorder (25%). In delayed neuromotor developmental group, 2 cases showed abnormalities in ophthalmic examination in the form of squint, visual acuity problems. Three children had impaired hearing which was confirmed by BERA, done already at 3 months corrected age (18.7%).

Table 1: The comparison of birth parameters and neonatal complications between normal and delayed cases Baseline characteristics of the patients are given Table I.

Parameters	**Neurological Outcome**		**P-value**
	Normal (n=19)	**Delayed (n=16)**	
Birth Parameters			
Gestational age (wks) ¥	34.7 (3.8)	35.7 (4.0)	0.502
Birthweight (Kg) ¥	1.94 (0.7)	2.09 (0.7)	0.567
Birthweight Groups			
<1.0 Kg	0	1 (6.3)	0.374
1.0 to 01.5 Kg	8 (42.1)	3 (18.8)	
1.51 to 2.49 Kg	6 (31.6)	7 (43.8)	
$\geq$ 2.5 Kg	5 (26.3)	5 (31.3)	

Weight for Gest age			
AGA	15 (78.9)	16 (100.0)	0.050
Sex			
Male	14 (73.7)	13 (81.3)	0.595
Female	5 (26.3)	3 (18.8)	
Neonatal complications			
Sepsis	19 (100.0)	16 (100.0)	--
Hyperbilirubinemia	11 (57.9)	8 (50.0)	0.740
RDS	6 (31.6)	3 (18.8)	0.460
Fungal Sepsis	0	3 (18.8)	0.086
Others	12 (63.2)	10 (62.5)	0.968
Age at follow-up (yrs) [¥]	2.3 (0.8)	1.8 (0.8)	0.048

[¥] Values are Mean (Standard Deviation), p-values by using Mann-Whitney U test. The rest of the values are n (%) whose p-values are obtained using Chi-square test. P-value less than 0.05 is considered to be statistically significant.

Comments: There was no statistical difference between normal and abnormal neurodevelopmental group with regards to sex, gestational age, birthweight. Also only four babies were SGA (small for gestational age) so it is not possible to compare between SGA and AGA (appropriate for gestational age). Also the distribution of neonatal complications such as sepsis, respiratory distress syndrome, hyperbilirubinemia and fungal sepsis were not significantly different between the two groups.

Table 2: Correlation of Cerebrospinal Fluid (Csf) Findings with Neurodevelopment

CSF Examination	**Neurological Outcome**		
	Normal (n=19)	**Delayed (n=16)**	**P-value**
CSF Proteins			
Normal (<100)	9 (47.4)	2 (12.5)	0.035
Abnormal (≥100)	10 (52.6)	14 (87.5)	
CSF Sugar			
Normal (≥50% of BSL)	15 (78.9)	3 (18.8)	0.001
Abnormal (<50% of BSL)	4 (21.1)	13 (81.3)	
CSF Gram staining			
Positive Cocci	0	3 (18.8)	0.175
Negative Cocci	4 (21.1)	1 (6.3)	
Positive Bacilli	0	0	
Negative Bacilli	3 (15.8)	2 (12.5)	
No Organism	12 (63.2)	10 (62.5)	
CSF Culture			
Sterile	5 (26.3)	4 (25.0)	0.841
Ecoli	2 (10.5)	1 (6.3)	
Pseudomonas	0	1 (6.3)	
Strept Pyogens	0	1 (6.3)	
H.influenza	1 (5.3)	1 (6.3)	
Enterococci	1 (5.3)	1 (6.3)	
Not Done	10 (52.6)	7 (43.8)	

The values are n (%), p-values are obtained using Chi-square test. P-value less than 0.05 is considered to be statistically significant.

Comments: In the group with normal neurodevelopmental outcome 52.6% babies had abnormal CSF proteins as compared to the group with abnormal neurodevelopmental outcome, where 87.5% babies had elevated CSF proteins. This difference was statistically significant (p=0.035). Similarly, 78.9% of babies from normal neurodevelopmental outcome group has normal CSF sugar while significantly less babies (18.8%) had normal CSF sugar in abnormal neurodevelopmental group (p=0.001). Because of the financial constraints CSF culture has not been done in all the patients. CSF culture was done in only 18 patients out of which 9 culture results were sterile while 9 patients showed organisms in CSF .We did not find any correlation between isolation of organism from CSF and abnormal neurodevelopment. Two infants who were neurologically normal was thought to have hearing impairment on the basis of OAE which was done at the time of discharge from NICU, but later on turned out to have normal BERA. In babies with delayed development 37.5% babies (6 out of 16) had abnormal OAE while 18.8% (3 out of 16) had abnormal BERA. Thus incidence of hearing disabilities were significantly high with delayed neuromotor development.

Table 3: The correlation of OAE and BERA with CSF Proteins in normal and delayed cases

		Normal CSF Proteins	High CSF Proteins	P-value
OAE	Normal	8	19	0.674
	Abnormal	3	5	
BERA	Normal	2	2	0.147
	Abnormal	0	3	

P-value by Chi-square test

The values are n, p-values are obtained using Chi-square test. P-value less than 0.05 is considered to be statistically significant.

Comment: There was no statistically significant correlation between abnormal CSF proteins and hearing impairment.

Table 4: The comparison of head size and Tone between normal and delayed cases

Parameters	Neurological Outcome		P-value
	Normal (n=19)	Delayed (n=16)	
Head Size at Birth (cm) ¥	31.7 (2.5)	32.8 (2.5)	0.271
Head Size at follow up			
Normal	19 (100.0)	4 (25.0)	0.000
Microcephali	0	11 (68.8)	
Hydrocephali	0	1 (6.3)	
Tone			
Normal	19 (100.0)	2 (12.5)	0.000
Abnormal	0	14 (87.5)	

¥ Values are Mean (Standard Deviation), p-values by using Mann-Whitney U test. The rest of the values are n (%) whose p-values are obtained using Chi-square test. P-value less than 0.05 is considered as statistically significant.

Comments: All babies who had normal neurodevelopment has normal head circumference and normal tone at follow up. In babies with delayed neurodevelopment only 25% babies had normal head circumference, 68.8% had microcephaly and 6.3% had hydrocephalus. Also 87.5% babies had tone abnormality in delayed development group. All babies with normal neurodevelopmental had normal vision while 12.5% babies with abnormal neurodevelopment had abnormal vision. Also, 3 babies (18.8%) had abnormal EEG, out of these 2 had abnormal MRI also.

Table 5: The multivariate independent determinants of neurological outcome (Multiple Logistic Regression Analysis)

Parameters in the model	Odds Ratio (Std Beta)	95% CI of Odds Ratio	P-value
Birthweight Groups			
<1.0 kg	--	--	--
1.0 to 01.5 kg	1.52	0.87 – 2.95	0.414
1.5 to 2.5 kg	1.41	0.82 – 2.88	0.356
≥2.5 kg (Reference)	1.0	--	--
Weight for Gest age			
AGA (Reference)	1.0	--	--
SGA	1.85	0.95 – 2.51	0.402
CSF Proteins			
Normal (<100) (Reference)	1.0	--	--
Abnormal (≥100)	2.31	1.11 – 3.82	0.029
CSF Sugar			
Normal (≥50% of BSL) (Reference)	1.0	--	--
Abnormal (<50% of BSL)	3.16	2.16 – 5.67	0.009
CSF cells			
20-100 (Reference)	1.0	--	--
100-500	2.65	1.11 – 3.98	0.020
>500	3.55	2.01 – 5.79	0.007

The parameters such as Gestation age, Sex, Neonatal complications are also included in the model, which were not statistically significant.

Comments: On applying Multiple Logistic Regression Analysis CSF proteins, CSF Sugar and CSF cells are independent determinants of abnormal neurological outcome after controlling for possible confounders such as birthweight and gestational age. In other words if CSF cells are more than 500 then there are approximately 3 to 4 fold odds of developing neurological delayed outcome.

Discussion

There are very few studies on outcome of neonatal meningitis in India. This prompted us to do this study. The

outcome was divided into two groups of normal neurodevelopmental outcome and delayed development. In our study, the hospital mortality was around 40% while other studies showed less mortality ranging from 17% to 21% (7-10). This could be probably due to majority of outborn sick cases being transferred to our NICU. Out of 35 patients, 16 (45.7%) patients had moderate to severe neurodevelopmental sequelae. While comparing other risk factors for adverse neurodevelopmental outcomes like gestational age, birth weight and weight for gestational age, there was no statistical difference between distribution of these risk factors in the two outcome groups. However many studies like that by Stevens JP et al have shown that very low birth weight infants with meningitis have more adverse outcome as compared to normal weight infants with meningitis, while the study done by Vera L Krebs et al did not observe any association between the occurrence complications and birth weight (11-12). In the study by Doctor et a has demonstrated despite a sparsity of abnormal spinal fluid findings (only 26%) patients. Culture proven neonatal meningitis among VLBW infants ha a detrimental effect on neurological outcome.In our study, where CSF culture positivity is 25.7%, we have found that high CSF proteins and low CSF sugars are significantly associated with adverse neurodevelopmental outcome (p value = 0.35 and 0.001 respectively).Edward et al has also demonstrated that CSF proteins >300mg/Dl is associated with severe neuromotor impairment. Klinger et al has also found correlation between high CSF proteins, low CSF sugar and adverse neuro developmental outcome (7,9). In other words one can say that normal CSF sugar and CSF proteins, in a case of meningitis will predict good neurological outcome. In our study, out of 16 delayed developed patients 3 patients (18.7%) had hearing impairment. Klinger et al has found an incidence of hearing loss as low as 8.3% in neonatal meningitis (7). In a study by Stevens et al, they found that hearing impairment was present in 3.6% of the patients with neonatal meningitis which is significantly low as compared to our study (11). We found that in normal outcome group head size and tone was normal while in delayed developmental outcome group 18.7% had microcephaly whereas 6.3% had hydrocephalus. However, in a study by Klinger et al 25% of patients had microcephali at the age of one year (7). In a study done by Stevens et al showed incidence of hydrocephalus requiring shunt surgery being 3% which is comparable to our study (11). All babies from normal outcome group had normal vision while from delayed development group, 12.5% had visual impairment. Similar results were seen with study by Stevens et al where the incidence of visual impairment was 17% (11). In our cohort, out of 16 delayed neurodevelopmental cases, 4 babies (25%) had seizures disorder. While in Klinger et al study, out of 12 delayed cases 3 cases (25%) had seizure disorder which is comparable to our study (7). The study by Stevens et al has also found incidence of seizure disorder being 15%, requiring anticonvulsants (11).

Conclusions

Mortality (40%) and morbidity (45.7%) of neonatal meningitis was high as compared to other studies.

1. Incidence of poor neurological outcome was high.

For total of 35 babies

a. Incidence of CP - 40%
b. Incidence of MR - 40%
c. Incidence of seizure disorder - 11.4%
d. Incidence of hearing problem - 08.60%
e. Incidence of vision problems - 5.7%

1. High CSF proteins and low CSF sugar was predictor of poor outcome
2. All babies with hearing impairment diagnosed on the basis of OAE, should be confirmed by BERA.

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