ORIGINAL ARTICLE

Relationship Between Presenting Features and Outcome of Primary Childhood Meningitis

A C Tee, MRCP*
S P Puthucheary, FRCPath**
H Fatimah, MRCP*
* *Department of Paediatrics,*
** *Department of Medical Microbiology,*
University Hospital, 59100 Kuala Lumpur.

Summary

A study was undertaken to determine the relationship of presenting features and outcome in primary childhood meningitis at the Paediatric Department, University Hospital, Kuala Lumpur from January 1980 to December 1989.

A total of 177 cases of primary childhood meningitis admitted during the study period were analysed retrospectively. One hundred and nine cases (61.6%) had complete recovery, 49 cases (27.7%) recovered with residual complications and 19 cases (10.7%) died. The mean duration of illness of those with complete recovery, residual complications and acute mortality was 4.8 days, 9.6 days and 7.6 days respectively ($p<0.05$). Neurological signs were more common in those with mortality and morbidity i.e. 89% and 78% respectively as compared to those who had complete recovery (58%). There was significant correlation between outcome and haemoglobin level on admission (complete recovery 11 gm%, residual complications 10.4 gm%, mortality 9.6 gm% with $p<0.05$), mean CSF sugar content (complete recovery 2.2 mmol/l, residual complications 1.5 mmol/l, mortality 1.1 mmol/l, $p<0.00001$), and mean CSF protein level (complete recovery 168 mg%, residual complications 321 mg%, mortality 344 mg%, $p<0.001$). Gram positive organisms were associated with higher mortality and morbidity i.e. 24% and 40%, as compared to gram negative organisms 12% and 31% respectively. There was no significant correlation between age, sex, peripheral and CSF white cell count with outcome of illness. Our data show that prolonged duration of illness, presence of neurological signs, low haemoglobin level, low CSF sugar content, high CSF protein level, and gram positive organisms were associated with poorer outcome of childhood meningitis.

Key Words: Childhood meningitis, CSF sugar, CSF protein

Introduction

Meningitis is common, especially in children under one year of age. Without chemotherapy, the mortality of pneumococcal and *H.influenzae* meningitis is close to 100%[1]. With the introduction of antibiotics and sulphonamides, there was an initial dramatic improvement followed by a plateau of mortality and morbidity. At present, childhood meningitis still causes significant morbidity and mortality[2-9]. Neurological sequelae not only include sensory deficit like blindness or deafness but also physical and mental handicaps. Case fatality rates have remained significant and ranged between 5.4% -20% (Table I). A high index of suspicion is required for early diagnosis to reduce these complications.

This is a 10-year retrospective study of 177 cases of

childhood primary meningitis seen between 1980 and 1989 at the University Hospital, Kuala Lumpur (UHKL), a teaching and tertiary referral hospital for the country. The aims of this study are to study the outcome of the illness with respect to :-

(a) age of patient
(b) duration of illness
(c) clinical presentation
(d) results of diagnostic investigations
(e) causative organisms
(f) estimated interval between admission and the commencement of antibiotic therapy

Materials and Methods

Inclusion Criteria

All patients admitted to the Paediatric Unit, University Hospital between 1980 and 1989 were diagnosed to have bacterial meningitis or partially treated bacterial meningitis if any 3 of the following are present in the cerebrospinal fluid (CSF):

(1) Leucocyte count > 30 cells/ml (in neonates)
> 10 cells/ml (beyond the neonatal period)

(2) Glucose level < 1.1 mmol/l (in neonates)
or < 2.8 mmol/l (in the post-neonatal period)
or < 50% that of a simultaneously taken blood glucose level

(3) Protein > 90 mg/100ml (for neonates)
or > 45 mg/100ml (for the post-neonatal period)

(4) A positive gram-stain smear for bacteria
(5) A positive culture
(6) A positive detection of bacterial antigen

A total of 241 case records with a diagnosis of meningitis were reviewed. Only 177 cases fulfilled the inclusion criteria of primary childhood meningitis. Sixty-four cases were excluded for various reasons including failure to satisfy the inclusion criteria for meningitis in 16 ; incomplete data in 10; wrong diagnosis in 13 and ; contaminated CSF cultures in 2. Another 23 cases had secondary meningitis with obvious underlying predisposing factors eg, shunt infection or infected myelomeningocoeles.

Tuberculous and cryptococcal meningitis were included in the analysis. Cryptococcal meningitis was diagnosed either by presence of the cryptococcal antigen or by a positive Indian Ink stain. Tuberculous meningitis was diagnosed if there was CSF evidence of meningitis, and a positive Mantoux test > 15 mm.

Viral meningitis was considered if there was CSF pleocytosis as defined in bacterial meningitis, with normal or slightly increase CSF protein level, normal or slightly decrease CSF sugar level, no micro-organisms on direct smear and culture and absence of bacterial antigen.

Statistical Method

Statistical analyses were performed using the software epi-info 3 and STATA. Differences between proportions for qualitative data were tested using Chi-square (X^2) test. Statistical test of significance between means of quantitative data was performed with the Fisher's exact test or the Krukal-Wallis test where appropriate. Conventional p values of less than or equal to 0.05 were considered as significant.

Results

Tables II, III, IV and V summarise the initial features and outcome of illness. All the patients were started on antibiotics when meningitis was suspected. There was no significant association between age, sex, estimated interval between admission and commencement of antibiotic therapy and outcome of illness. There was a significant association between duration of illness and outcome. The longer the duration of illness, the more likely the occurrence of sequelae $p < 0.004$.

There was a significant correlation between neurological signs and outcome of illness $p < 0.004$. Patients were more likely to have sequelae or die in the presence of neurological signs. However there was no significant correlation between fever, neck stiffness, altered consciousness and fits with outcome of illness.

Table I
Case fatality rates in childhood meningitis
Published data

Authors	Year of study	Place	CFR	CMR
Bohr V.[2]	1966-76	Denmark	15.8%	
Goldacre[3]	1969-73	North-West, England	12.7%	
Lee E.L.[4]	1970-77	Malaysia	15%	
Low P.S.[5]	1977-83	Singapore	8.7%	31.6%
Louvois J.D.[6]	1985-87	England & Wales	Neonates 19.8%	
			Post-neonatal 5.4%	
William G[7]	1980-88	Alaska, USA	H. influenzae 5.9%	29%
Davidson[8]	1980-86	Alaska, USA	S. pneumoniae 26	

CFR = case fatality rate; CMR = case morbidity rate

Table II
Relationship of demographic characteristics with outcome of illness results in numbers
(% or S.D. where appropriate)

Demographic data	Outcome			Total	K. wallis	p=value
	*well	*sequelae	*Ac mortality			
Mean age in years	1.8 (2.8)	1.1 (1.8)	1.4 (2.1)	1.6 (2.5)	1.43	0.49
Sex male	69 (63)	23 (47)	11 (58)	103 (58)		
female	40 (27)	26 (53)	8 (42)	74 (42)	3.72	0.16
Mean duration of illness (days)	4.8 (5.4)	9.6 (14.3)	7.6 (9.0)	6.4 (9.2)	10.9	0.004
Estimated interval between admission & start of antibiotic (hrs)	9.9 (12.6)	12.2(15.0)	10.0(14.0)	10.6(13.4)	0.52	0.77

**well = complete recovery*
**sequelae = recovered with complication*
**Ac mortality = acute mortality*
S.D. = Standard Deviation

Although there seemed to be a correlation between low white cell (wbc) in the blood with morbidity and mortality, this was not statistically significant. There was no significant association between platelet count and outcome of illness. There was a significant association between haemoglobin (Hb) level and

Table III
Relationship between duration of illness and outcome results in numbers (%)

Outcome	Duration of illness	
	<=2 days	>2 days
*Well	43 (72)	66 (56)
*Sequelae	8 (14)	41 (35)
*Ac. mortality	8 (14)	11 (9)
Total	59 (100)	118 (100)

Chi squared = 8.87
p=0.01

outcome of illness with p=0.047. Those with acute mortality had the lowest mean Hb of 9.6 gm%.

Changes in CSF values showed a more significant association with outcome. Those with sequelae or acute mortality had a lower mean CSF sugar level (1.1 mmol/l and 1.5 mmol/l respectively) compared to those who were well (2.2 mmol/l) with $p < 0.001$. The higher the CSF protein value the more likely the presence of complications and acute mortality. The mean CSF protein level for the 3 groups were 168 mg%, 321 mg% and 344 mg% ,$p < 0.001$. Lower CSF white blood count appeared to correlate with outcome of illness but this was not statistically significant.

Table VI reveals the case fatality rate for various organisms. The case fatality was highest for *Staphylococcus aureus* and streptococcus species but the number of cases were small. The case fatality rate for *Streptococcus pneumoniae* (25%) and *Haemophilus influenzae* (8%) were quite comparable to those of other developing countries (Table I).

Of the 3 main groups of organisms as shown in Table VII, gram positive organisms had a higher rate of sequelae and mortality compared to gram negative organisms and others.

Table IV
Relationship of clinical features with outcome or illness results in numbers (%)

Clinical feature	Outcome					
	*well	*sequelae	*Ac mortality	Total	Chi squared	p=value
Fever						
present	62 (57)	18 (37)	10 (53)	90 (51)		
absent	47 (43)	31 (63)	9 (47)	87 (49)	5.52	0.06
Neck stiffness						
present	38 (35)	18 (37)	4 (21)	60 (34)		
absent	71 (65)	31 (63)	15 (79)	117 (66)	1.62	0.45
Altered consciousness						
present	61 (56)	34 (69)	15 (79)	110 (62)		
absent	48 (44)	15 (31)	4 (21)	67 (38)	5.14	0.08
Fits						
present	58 (53)	29 (59)	13 (68)	100 (56)		
absent	51 (47)	20 (41)	6 (32)	77 (44)	1.72	0.42
Neurological signs						
present	63 (58)	38 (78)	17 (89)	118 (66)		
absent	46 (42)	11 (22)	2 (11)	59 (32)	10.9	0.004

Table V
Relationship of results of investigations with outcome of illness results in numbers (S.D.)

Results of investigations	Outcome *well	*sequelae	Ac mortality	Total	Stat test	p=value
CSF						
wbc 1000/ml	2.1 (5.8)	1.7 (3.1)	0.5 (1.0)	1.9 (4.9)	H=4.8	0.08
glucose mmol	2.2 (1.4)	1.1 (1.2)	1.5 (1.5)	1.8 (1.4)	H=23.2	0.0001
Protein mg%	168 (204)	321 (253)	344 (380)	228 (251)	H=12.1	0.001
Blood						
Hb gm%	11.0 (2.4)	10.4 (2.1)	9.6 (2.3)	10.6 (2.3)	F=3.1	0.047
wbc 1000/ml	16.1 (9.3)	15.9 (9.2)	13.5 (10.5)	15.7 (9.4)	F=0.58	0.6
platelet 1000/ml	258 (171)	187 (151)	202 (237)	232 (177)	F=1.28	0.3

Table VI
Relationship between causative organisms and outcome of childhood meningitis results in numbers (%)

Causative agent	Outcome **Well	**Sequelae	Acute Mortality
Flavobacterium	2 (13)	11 (74)	2 (13)
Gp B streptococci	3 (50)	3 (50)	0 (0)
H. influenzae	30 (60)	16 (32)	4 (8)
Strept Pneumoniae	5 (31)	7 (44)	4 (25)
Salmonella species	3 (50)	1 (17)	2 (33)
Other GM + Orgn	1 (33)	0 (0)	2 (67)
Other GM - Orgn	5 (72)	1 (14)	1 (14)
Viral	35 (97)	0 (0)	1 (3)
*Partially treated	24 (75)	7 (22)	1 (3)
*Chronic meningitis	1 (17)	3 (50)	2 (33)
Total	109 (61)	49 (28)	19 (11)

* *Partially treated: cases with CSF changes characteristic of bacterial meningitis but culture negative; Chronic: Tuberculus & Crytococcal meningitis*

Flavobacterium had the highest percentage of post-meningitis sequelae (73%). This was followed by Group B Streptococcus (50%). Both of these caused mainly neonatal meningitis. Chronic meningitis which consist of tuberculous and crytococcal meningitis, *Haemophilus influenzae* and *Streptococcus pneumoniae* also gave rise to high sequelae rates of 50%, 32% and 44% respectively. In contrast, none of the patients with viral meningitis had any sequelae. The overall sequelae rate was 27.7% which was quite comparable to other published reports as shown in Table I.

Discussion

A causal relationship between sequelae of meningitis and duration of illness exists. The longer the duration of illness before admission the higher is the risk of sequelae which can occur before treatment is commenced. The risk of mortality was not directly related to the duration of illness. The mean duration of illness of patients with fatal meningitis was 7.6 days compared to 9.6 days in the non-fatal cases. A similar observation was made by Bohr[2]. It has been observed that there are 2 types of clinical presentations in childhood meningitis – one with a short history but with a severe fulminating illness and hence a higher mortality risk[10], and the other with an insidious onset and a higher tendency for a change to a subclinical infection resulting from the use of antibiotics.

The presence of neurological signs was found to be significantly associated with outcome with p = 0.004. It has been reported that those with focal neurological signs had a poorer prognosis[11]. Although altered consciousness such as irritability and drowsiness did

Table VII
Relationship of outcome of illness with organism-groups results in numbers (%)

	Outcome			
Types of organism	***Well**	***Sequelae**	**Ac. mortality**	**Total**
Gram positives	9 (36)	10 (40)	6 (24)	25 (100)
Gram negatives	40 (51)	29 (37)	9 (12)	78 (100)
Others	60 (81)	10 (14)	4 (5)	74 (100)
Total	109 (61)	49 (28)	19 (11)	177 (100)
	Chi 2 = 23.95 p<0.0001			

Gram pos = Gp B strept + S.pneumoniae + other gram positive organisms Gram negative = Flavo + H.influenzae + Salmonella + other gram neg organism Others = Viral + Partially Treated + Chronic

not appear to be significantly associated with outcome, those in the extreme state of altered consciousness such as who were comatose or in a semi-comatose state (6 patients) at diagnosis did poorly; 3 expired and 3 had multiple neurological sequelae. Similar findings had previously been published[2,12].

The severity of anaemia was significantly associated with outcome in this study. The prolonged antigenaemia in a severe infection like bacterial meningitis may result in haemolysis and thus anaemia. The anaemia may also be related to ineffective erythropoiesis secondary to hypoferremia which is frequently found in infections[13,14].

The CSF sugar and CSF protein levels were also associated with outcome. Reports by Taylor[15], Mustafa[16], and Fortnum[17], indicated that low CSF sugar and high CSF protein levels reflected a more severe illness and a poorer outcome. Current understanding on the pathophysiology of meningitis indicates that the CSF sugar and CSF protein values are related to inflammatory mediators such as tumour necrosis factor (TNF) and interleukin-1 (IL-1). The higher the CSF TNF, the lower the CSF sugar and the poorer the outcome[16]. The low CSF sugar can be attributed to decreased transport of glucose across inflammed choroid plexus and increased utilization of glucose by host tissue[11]. The high CSF protein level may be due to increased permeability in the inflammed meningeal vessels[18,19].

The type of causative organism was an important prognostic factor for outcome. Infections caused by gram-positive organisms such as *Streptococcus pneumoniae* had a poorer outcome compared to those caused by gram-negative organisms. However, it should be noted that Salmonella meningitis also had a high case-fatality rate of 33% in this series, probably because of the difficulty in eradicating this organism from the meninges. Generally, if no organism was identified, the outcome was better. This may either indicate that the organism was highly sensitive to the antibiotic used or there was a smaller load of organism in the meninges. However, it could also mean that the patients might actually have viral meningitis or meningism secondary to other causes.

In this study, there was no significant correlation between outcome of meningitis with age, sex, or the estimated interval between hospital admission and the commencement of antibiotics.

In conclusion, the outcome of meningitis in this study was significantly related to the :

(a) duration of illness before admission
The longer the duration of illness before admission, the higher the risk of neurological complications. However, this did not apply to risk of mortality.

(b) nature of causative organisms
Gram positive organisms resulted in higher mortality and morbidity rates than gram negative organisms. Viral meningitis generally had a good outcome.

(c) level of CSF glucose and protein
Patients with a low CSF glucose and a high CSF protein had a higher risk of complications and mortality.

(d) Neurological Signs
Patients with neurological signs had a higher risk of complications and mortality.

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