

Acute bacterial meningitis in a developing country: diagnosis related mortality among paediatric patients

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Objectives: To evaluate the effect of late diagnosis and other factors on outcome of paediatric bacterial meningitis (BM) and recommend appropriate intervention.

Design: Case series.

Setting: University of Calabar Teaching Hospital, Calabar, Nigeria.

Subjects: 62 consecutive BM patients aged two months to 16 years admitted between 1991 and 1994.

Main Outcome Measures: Mortality rate.

Results: Diagnostic difficulties experienced in 58% of cases and other factors resulted in delayed diagnosis and high mortality (20 to 47%).

Conclusion: Only elimination of the identified inadequacies in management can significantly reduce the BM-related high mortality in developing countries.

Introduction

It is generally accepted that bacterial meningitis (BM)-related mortality is high,^{1,7} especially in developing countries (DC) and that optimal outcome depends on early diagnosis and prompt initiation of appropriate antibiotic therapy.^{8,21} But, unfortunately these aspects of management of emergencies are extremely difficult to accomplish in DC'S.

What are the specific factors that significantly contribute to diagnostic difficulties and high mortality? What is the role of self-medication or patronage of traditional healers and prayer houses (churches) or the high cost of hospital treatment?

Exactly, what is the BM-related mortality among paediatric patients in Nigeria? These and other BM-related problems of DC are not well documented in the literature. In this paper we report the results of a study of some aspects of BM-related mortality among paediatric patients.

Materials and Methods

To evaluate the effect of late diagnosis and other factors on the outcome of paediatric BM, the medical records of 62 consecutive BM patients (male: 29; female: 33) ranging in age from two months to 16 years (mean: 6.4 years), admitted

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to the University of Calabar Teaching Hospital (UCTH), Calabar, Nigeria, from 1991 to 1994, were identified and studied retrospectively. Based on age, the patients were divided into three groups:

1. Group A (n=21): age range = two to 11 months, mean = 3.9.
2. Group B (n=23): age range = one to 10 years, mean = 5.8.
3. Group C (n=18): age range = 11 to 16 years, mean = 13.4.

Only patients with acute illness (≤ 2 days) and probable or definite bacterial cause were included in the study.

Durand's¹ diagnostic criteria for BM were used in checking the accuracy of the diagnoses of the 62 patients. Where indicated the Widal test was done and blood was examined for malaria parasites. The presenting clinical manifestations, the daily medical records, results of laboratory and other relevant investigations and the diagnoses were analysed. The relationship between delayed (late) diagnoses and mortality was established by comparing the mortality rates of two groups of BM patients: those whose diagnosis was established promptly on admission and those whose diagnosis and appropriate antibiotic therapy were delayed for several days. Reasons for such delays and diagnostic difficulties in Nigeria were documented. Considered early was the clinical diagnosis of BM made on admission or within the first 24 hours in hospital, later confirmed by gram stain or CSF culture. The diagnosis was described as late if it came more than 24 hours after admission.

Data analysis: Chi square analysis was used to evaluate differences between the groups.

Results

Bacterial Findings.

Gram positive cocci (mainly *Streptococcus pneumoniae*) were the most common pathogens overall, causing 47% of the

62 cases: among Group A patients they caused 11, Group B, 8 and Group C, 10 of cases. Gram negative bacilli caused 35% of all cases [Group A (7); Group B (11) and Group C (4)]. In 18%, no pathogen was identified: Group A (3); Group B (4) and Group C (4) (they all received antibiotics before lumbar puncture - LP).

Clinical Manifestations.

Table I shows the most frequent presenting complaints and signs. The majority of patients were apparently well until the onset of fever (n=45). In the remaining 17 patients, predisposing factors were identified: sepsis (4); pneumonia (2); chronic *Otitis media* (3); sinusitis (1); other infectious conditions (7). As younger children could not express themselves, headache and neck stiffness were important complaints only in Group B and C, while bulging anterior fontanelle was important in Group A.

In all age groups, the most frequent presenting complaint was high fever (range: 38 to 40.5°C, mean = 39.2°C). Patients on average had five consecutive days of fever during the period of hospitalization (range: one to 15 days). Thirteen patients had prolonged fever of more than seven consecutive days. Thirty one percent of patients not known previously as epileptics, came to hospital with a 24 to 48 hour history of seizures [generalized (18%); focal (4%); not further characterized (9%)]. Six more patients developed seizures within the first 48 hours in hospital: generalized (4) and not characterized (2).

On admission (and during the period of hospitalization) 42 of the patients were unconscious: 26% of these were from Group A, 24% from B and 18% from Group C. Thirty two percent were normally alert through the period of illness; 55% of the 62 patients were brought to hospital already with impaired consciousness: confusion/arousable coma (34%) and deep unarousable coma (21%). Of Group A patients, on admission, 12 were unconscious, 14 of Group B and 8 of

Table I: The frequency of the most important presenting complaints and signs in paediatric BM on admission (n=62).

Group of patients	Most important presenting complaints		Most important presenting signs	
	Complaints	Frequency	Signs	Frequency
A n=21	* Fever	19	* Fever	19
	* Disturbed consciousness	12	* Bulging anterior fontanelle	15
	Loss of appetite	9	* Highly irritable child	14
	Convulsion	8	* Impaired consciousness	12
B n=23	* Fever	21	* Positive Kernig's sign	9
	* Disturbed consciousness	14	Seizures	8
	* Stiffness of neck	12	* Fever	21
	Convulsion	8	* Neck stiffness	20
	Loss of appetite	7	Impaired consciousness	14
C n=18	* Fever	16	Positive Kernig's sign	12
	* Stiffness of neck	15	* Fever	16
	* Headache	9	* Neck stiffness	16
	Disturbed consciousness	8	* Positive Kernig's sign	10
	Vomiting	8	Impaired consciousness	8
	Neck pain	6		

*The most important presenting complaints and signs on admission (i.e. occurring in >50% of patients in the group).

Table II: Diagnosis of 62 cases of BM on admission (before lumbar puncture).

Diagnosis on admission	Group A (n=21) Frequency	Group B (n=23) Frequency	Group C (n=18) Frequency
a. BM as the only diagnosis	9	8	9
b. BM as the most likely diagnosis, but rule out CM	5	7	5
c. Total number of cases (%) in which BM was considered as the only or most likely diagnosis (a + b)	14	15	14
d. Cases in which BM was not considered at all (on admission)	3	5	2
e. CM as the only diagnosis	3	4	—
f. CM as the most likely diagnosis, but rule out BM	4	3	2
g. Total number of cases in which CM was considered the most likely or alternate diagnosis (b + e + f)	12	14	7
h. Typhoid fever as the only diagnosis	—	1	2
i. Cases in which doctors experienced diagnostic difficulties	12	15	9

Table III: Factors influencing mortality among paediatric patients with BM (n=62).

Factors	Factor-related subgroups	Group of 62 patients	Main Study Groups		
			Group A n=21	Group B n=23	Group C n = 18
F1. I-Late diagnosis	F1. I-Early diagnosis	n = 26 M = 2	n=4 M = 1	n=9 M = 1	n=13 M = 0
	F1. II-late diagnosis	n = 36 MR = 33% II>I, p<0.05	n=17 M = 8	n=14 M = 3	n=5 M = 1
F2. I-Impaired consciousness	F2. I-Impaired consciousness	n = 42 MR = 31% I>II, p<0.05	n=16 M = 7	n=15 M = 3	n=11 M = 3
	F2. II-Normal consciousness	n = 20 M = 1	n=5 M = 1	n=8 M = 0	n=7 M = 0
F2. - Seizures 48 hours before and after admission	F3. I-With Seizures	n = 41 MR = 27%	n=19 M = 8	n=14 M = 2	n=8 M = 1
	F3. II-No Seizures	n = 21 M = 3	n=2 M = 0	n=9 M = 1	n=10 M = 2
F4. - Late admission (after 1st 3 days of illness)	F4. I-Early admission (1st 3 days of illness)	n = 25 M = 4	n=12 M = 2	n=9 M = 2	n=4 M = 0
	F4. II-late admission	n = 37 MR = 27%	n=9 M = 5	n=14 M = 2	n=14 M = 3

1. Where "P" is not indicated, the differences were not significant.

2. MR = Mortality Rate (%); M = Number dead.

3. The relationship between the different degrees of impaired consciousness and mortality could not be studied because of the relatively small size of unconscious patients.

Group C. Twenty eight of the 42 unconscious patients (the remaining 14 died) were in the state of impaired consciousness for one to nine days (mean: 3.8).

Because the majority of patients were unconscious on admission, Kerning's sign was absent in 44 (57%) of patients of Groups A, B, and C; CSF pressure visually found to be elevated in 79%; 74% had low CSF sugar (mean: 0.91 mmol/h) and 89% elevated CSF protein levels (mean = 320 mg/dl.)

Diagnosis.
On admission diagnostic difficulties were experienced in 36 (58%) of the 62 BM cases: among Group A patients 12, Group B 15 and Group C 9. This delayed the diagnosis for one to five days (mean: 2). Before lumbar puncture (LP) (Table II), cerebral malaria was seriously considered in the diagnostic process in 53% of the 62 cases and in the remaining 5%, typhoid fever was the diagnosis of choice. Only in 9 (Group A), 8 (Group B) and 9 (Group C) was the diagnosis of BM made promptly, not confusing it with any other disease condition. Where malaria was suspected (n=33) blood was examined for malarial parasites. In 29 cases the test was done

promptly: ring forms of *Plasmodium falciparum* were seen only in two cases. In 13 patients the test was delayed for two to five days, mainly because of financial difficulties.

In 19 cases (eight in Group A, seven in Group B and four in Group C), signs of meningeal irritation were not tested on admission. These were eventually tested 24 to 72 hours later, when the initial diagnosis of malaria and typhoid fever could not be substantiated. In 25 patients (mainly due to financial reasons) LP was not done on admission: this was delayed for several days (two to three) days in 17 cases and four to six days in eight cases). LP was repeated at least once in 29 cases.

Mortality.
Fourteen (23%) out of our 62 patients died. Most deaths occurred in the first 10 days of hospitalization (mean: seventh day). For meningitis caused by different bacterial pathogens we found no significant differences in mortality rates (MR).

The result of evaluation of the influence of four factors (late diagnosis, impaired consciousness, seizures and late admission on mortality is presented in Table III.

In the group as a whole (n=62) late diagnosis and the presence of impaired consciousness on admission) were

significantly ($p < 0.05$) associated with higher MR (12/36 compared to 2/26 and 13/42 against 1/20, respectively). Late admission and the presence of seizures 48 hours before and after admission did not appear to significantly influence mortality (although their MR were higher). Influence of the four factors on mortality in the individual subgroups (A, B and C) was also evaluated. Group A patients with history of seizures exhibited significantly ($p < 0.05$) higher MR than those of Group B. Similarly, the MR of Group A patients who were admitted to hospital late was significantly higher than those of Group B ($p < 0.01$) and Group C ($p < 0.05$). Although not statistically significant, each subgroup (A, B, C) demonstrated (with few exceptions) higher mortality in relation to each of the four factors.

The possible influence of complications (e.g. cerebral oedema and cerebellar herniation) and other variables on mortality could not be established as *post mortem* was not allowed by relations of the dead patients.

Discussion

Problems of Diagnosis.

Our data showed that in 58% of the 62 BM cases, due to diagnostic and financial difficulties, the correct diagnosis was not established on admission or during the first day in hospital (41% in another study²⁰). The diagnosis was confused mainly with cerebral malaria (CM) and typhoid fever - two disease conditions that frequently cause high fever among children in developing countries. In these countries, acute headache, disturbed consciousness and convulsion in a febrile patient frequently lead doctors, especially in paediatric practice, to the diagnosis of CM.^{12,20} Such mistakes are possible because the doctor working in the tropics thinks of malaria whenever he sees a febrile patient.^{20,21} This may prevent him from properly evaluating neurologic status (31% of our patients). If LP is also not done, it is possible that the diagnosis will be missed for several days.^{20,21} Only a good history and results of detailed neurological evaluation in suspected cases, blood and Widal tests and CSF examination can effectively rule out cerebral malaria or typhoid fever in favour of BM.

In 18% of our patients (in another study¹: 15%), the diagnosis was initially missed because no pathogen was identified in the CSF. In other cases (13 to 57%), signs of meningeal irritation were absent. In these two situations a compatible clinical picture and CSF neutrophilic pleocytosis may volunteer the clinical diagnosis of BM. If not, the diagnosis can be clarified by detection of bacterial antigen in the CSF using techniques such as countercurrent immunoelectrophoresis (CIE) and the limulus lysate and nitroblue tetrazolium dye tests.¹³ However, these sophisticated tests lack the sensitivity and specificity of CSF culture and are not widely available in developing countries.^{13,14} Where these tests are not available and the diagnosis is still in doubt a 48 hour antibiotic therapeutic trial may confirm the diagnosis.

Factors Contributing to High Mortality.

The overall mortality rates of BM as reported by other authors^{10,11} range from five to 15%, and for pneumococcal meningitis, 15 to 30%.^{1,5,10,11,20} Among our patients the rate was 23%, higher in some patients (Table III)

Although it is often impossible to explain the death of a critically ill BM patient or trace it to a single mechanism, it is generally accepted that some of the effects of overwhelming infection, with bacteraemia and hypotension or brain swelling and cerebellar herniation, especially in the initial 48 hours may explain the deaths of such patients.¹⁰ Our opinion is that such life threatening complications and fatal outcome are more likely when diagnosis and appropriate antibiotic therapy are delayed for several hours or days. Our data seems to confirm this: late diagnosis and impaired consciousness were significantly associated with higher MR in the whole study group of 62 patients. Of the 14 patients that died, 13 had at least one of these factors. The data shows that late diagnosis and admission (and the resultant high MR) were caused by:

- (i) The failure to establish early diagnosis (on admission), using available clinical and laboratory data; (ii) Failure to carry out proper neurologic evaluation of suspected cases; (iii) Failure to perform LP on admission;
- (iv) Patronage (by patients) of traditional healers and churches; and
- (v) Financial difficulties of patients that prevented proper and prompt investigation of these cases.

Frightened by the high cost of hospital treatment, 60% of patients delayed coming to hospital. First they tried self-medication (34%) or consulted traditional healers (15%) or churches (11%) or a combination of these (10%). It was only when it became apparent that approach would not effectively deal with the bacterial infection and especially when the patient's life became threatened that the decision to come to hospital was reluctantly taken. This delay also explains why a majority of our patients (55%) came to hospital already in a state of impaired consciousness which resulted in a significantly higher MR. Other studies associated mortality with age (60 years and above)^{1,11} obtunded mental state¹, seizures¹, absence of nuchal rigidity¹⁵ and hypoglycorrhachia.¹⁴

In relation to the four factors (Table III), Group A exhibited higher MR than Group B and Group C. These differences were statistically significant only in relation to late admission and presence of seizures. These differences between groups A, B and C can be explained using the fact that the levels of development, maturation and functional capability of the brain among patients of the three groups are not the same. Consequently, Group A is functionally less equipped to fight back and survive a serious disease condition: young patients are more likely to die in an emergency situation like BM, especially when diagnosis and therapy are delayed.

How to Improve Diagnosis and Reduce Mortality.

Although the diagnosis of BM is not difficult in a febrile patient with meningeal symptoms and signs developing in the setting of predisposing illness,¹¹ diagnostic difficulties are frequently encountered in paediatric practice. This does not mean doctors are ignorant of the clinical manifestations of this disease, which are excellently presented in standard medical textbooks and other sources.^{8-11,17-19} As stated earlier a wrong approach to management may be one of the important causes.

Consequently, we would like to remind general practitioners of the time tested simple step-by-step approach to the diagnosis of BM:

- Step 1.** Always be conscious of the fact that BM is a serious medical emergency: diagnosis and therapy must not be delayed even for a few hours.
- Step 2.** Take a good history: does this patient have the most frequently presenting symptoms (Table I)?
- Step 3.** Carry out a detailed physical and neurologic examination (including testing for signs of meningeal irritation): does the patient, considering his or her age group, have the most frequent presenting signs (Table I)?
- Step 4.** Prompt lumbar puncture, CSF examinations and blood culture: CSF with elevated pressure, numerous white cells with polymorph predominance, protein content elevated, glucose content reduced or absent.
(Steps 2 and 3 may suggest the clinical diagnosis and Step 4, especially CSF culture may confirm it.)
- Step 5.** Difficult cases (these include CSF culture-negative cases and those with no apparent signs of meningeal irritation): a compatible clinical picture, CSF neutrophilic pleocytosis or detection of bacterial antigens in CSF (see text) will volunteer the clinical diagnosis of BM.

Conclusion.

Our data shows that diagnostic difficulties and other related factors are contributing to the very high mortality among paediatric BM patients in Nigeria. We believe that only the elimination of the identified inadequacies in the management of these patients can significantly reduce this high mortality in developing countries.

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