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Tuberculous Meningitis in Childhood

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Summary

Aderele WI and Nottidge V. Tuberculous Meningitis in Childhood. *Nigerian Journal of Paediatrics*, **1982; 9: 13.** Seventy-two cases of tuberculous meningitis in children were studied and 63% of these were aged 3 years and below. The major presenting symptoms of fever, weight loss, anorexia and repeated convulsions were similar to those in other series. Cough was also prominent and indicated associated pulmonary tuberculosis which was present in 78%. A majority (64%) of the children had various degrees of CNS depression at presentation and this, in addition to malnutrition in 93% of the cases, and delay in presentation, adversely affected mortality which was 50% in the series. Those who died had lower mean CSF cell counts, higher mean protein level and lower mean glucose level than the survivors. Steroid therapy was associated with a lower mortality rate. In order to reduce the mortality and morbidity, particularly in areas where facilities for rehabilitating those who survive with sequelae are inadequate, early diagnosis, based on a high index of suspicion, and prompt treatment of those at highest risk with the newer and more potent anti-tuberculous drugs, are recommended.

Introduction

IN 1961, Hendrickse[1] reported 50 cases of tuberculous meningitis (TBM) in children seen at the University College Hospital (UCH), Ibadan. Ten years later, Osuntokun, Adeuja and Familusi [2] updated that report by studying 194 cases. Although children below the age of 10 years constituted most of the latter report, there was no clear distinction in the presentation, between children and adults. In spite of improved standards of living and diagnostic facilities which ought to have a marked effect on the incidence of the disease and ensure early diagnosis respectively, our impression is that the incidence has not varied appreciably, while there are still delays in presentation and diagnosis. Since TBM is a predominantly childhood disease in Nigeria, [2] we have studied childhood cases seen at the same institution over an 8-year period, 1972-1979, examining the current clinical features, diagnostic problems and prognostic factors. It is hoped that the findings will provide guidelines for early diagnosis and management.

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Materials and Methods

The subjects consisted of children admitted to the paediatric wards of the UCH, Ibadan. The criteria for diagnosis of TBM included one or more of the following:

(1) Demonstration of *M. tuberculosis* in the cerebrospinal fluid (CSF)

(2) Post-mortem confirmation of TBM

(3) Clinical and laboratory evidence of meningitis which had failed to respond to antibiotics in association with evidence of active tuberculosis outside the nervous system

(4) CSF data compatible with TBM.

The patients were divided into three groups (Medical Research Council, UK, criteria[3]), based on the initial clinical assessment as follows:

Group I — Patients who were fully conscious and rational with no focal neurologic signs.

Group III — Patients who were deeply comatose or delirious or who had pareses.

Group II — Patients in a condition between those of groups I and III.

The clinical findings and results of relevant investigations were analysed, paying particular attention to factors which might have affected the outcome. Student's 't' and chi squared tests were used for statistical analysis.

Results

Sixty cases were studied prospectively and 12 others, retrospectively. In six of the latter 12 cases, the diagnosis of TBM was made during life while the remaining 6 cases were diagnosed at autopsy. *M. tuberculosis* was demonstrated in the CSF in 15 cases, while 15, 37 and 5 others fulfilled diagnostic criteria 2, 3 and 4 above, respectively.

Age and sex distribution

There were 39 males and 33 females, a M/F ratio of 1.2:1. Their ages ranged from 4 months to 11 years, with a peak in the second year of life (Table 1). Forty five (63%) of the 72 patients were aged, 3 years and below.

TABLE I

Age Distribution and Mortality in 72 cases of Tuberculous Meningitis

Age (years)	*No. of Cases*	*No. of Deaths*	*% Mortality*
<1	8	5	63
1	18	7	39
2	12	2	17
3	7	2	29
4	8	6	75
5	3	3	100
6	7	4	57
7	4	2	50
8	1	1	100
9	2	2	100
10	1	1	100
11	1	1	100
Total	72	36	50

Clinical Features

As shown in Table II, fever, convulsions, cough, anorexia and loss of speech were the most prominent symptoms. Fever had lasted for a period of 1 day to 5 months (mean, 19.6 days) in the survivors and for 1 day to 5 months (mean, 17.8days) among those who died (Table III). Similarly, convulsion, often severe and recurrent, occurred 1—14 days (mean, 3 days) before presentation in the survivors and 1—15 days (mean, 3·3 days) in those that died. Headache was complained of by 4 children, who were over 5 years old. Less common symptoms included confusion, unsteady gait, involuntary movements, inability to sit up or to walk. Cough was one of the five major symptoms (Table III); it lasted longest with a mean period of 30.8 days (range, 3—180 days) in 20 survivors in contrast to a mean of 76 days (range, 4—150 days) in 13 cases that died ($p < 0.001$). The differences in the mean duration of the other major

TABLE II

Presenting Symptoms in 72 cases of Tuberculous Meningitis

Symptom	*No. of Survivors*	*No. of Non-Survivors*	*Both groups*	*% of Total*
Fever	27	32	59	82
Convulsion	20	29	49	68
Cough	20	13	33	46
Anorexia	8	18	26	36
Weight loss	9	5	14	19
Vomiting	6	6	12	17
Lethargy	3	8	11	15
Inability to talk	3	8	11	15
Generalised stiffness	2	6	8	11
Irritability	1	4	5	7
Unconsciousness	1	4	5	7
Diarrhoea	0	5	5	7
Constipation	1	3	4	6
Headache	0	4	4	6

symptoms between survivors and non-survivors, were not statistically significant.

The salient physical signs are listed in Table IV. Thirty-one (86%) of 36 survivors and all the 36 who died, were malnourished. Fifty-eight (28 survivors and 30 non-survivors) of the 67 malnourished patients were marasmic or wasted, while 9 (3 survivors and 6 non-survivors) had kwashiorkor or marasmic-kwashiorkor. Pyrexia occurred in 63 of the 72 cases and hypothermia in three. Neurological signs, consisting mainly of changes in the sensorium, were present in 46 (64%) cases. There were four patients with facial palsy and impaired motor function in the limbs in 30 others. Neck stiffness and positive Kernig's sign were present in 58 (81%) cases while 4 infants had bulging anterior fontanelle and 2 others presented with nystagmus. Funduscopy revealed choroidal tubercles in only one (1.4%) case.

Other signs included phlyctenular keratoconjunctivitis in two patients, and stridor, jaundice and generalised lymphadenopathy in one case each. Twenty-eight cases, consisting of 13 survivors and 15 non-survivors, were dehydrated on admission, from prolonged anorexia associated with vomiting and diarrhoea. Respiratory signs, mostly crepitations, were present in 30 cases. These thirty cases, four of whom also had digital clubbing, were among the 56 patients who had associated pulmonary tuberculosis.

Previous immunisation and therapy

Nine (12.5%) children including 8 survivors, had scars of previous BCG vaccination. Seventeen, including 11 survivors, had been given locally prepared oral medication for convulsions, while 15, including 2 survivors, had had antibiotic therapy at the onset of their illness.

Associated findings

Sixty-three (88%) of the 72 cases also had extra-CNS tuberculosis. Of this number, 56 had pulmonary tuberculosis either alone (28 cases) or in combination with tuberculosis elsewhere (28 cases). Thus, 16 children had pulmonary tuberculosis as well as peripheral glandular tuberculosis while 8 had abdominal and pulmonary involvement. Two children had peripheral glandular, abdominal, and pulmonary infection, while two others had spinal and pulmonary lesions. Six children had peripheral glandular tuberculosis alone, and one child had associated abdominal tuberculosis. There was no direct statistical relationship between the type of extra-CNS involvement and mortality ($p > 0.3$).

Investigations

CSF

In 21 (32%) of the 66 cases diagnosed during life, there were no cells in the CSF while in 14 others, cells were less than 5×10^6/L (5/mm^3) (Table V). However, there were over 50×10^6/L (50 cells/mm^3) in 19 (29%) cases. Lymphocytosis occurred in 65% and neutrophilia in 35%. The

TABLE III

Duration of Major Symptoms in 72 Cases of Tuberculous Meningitis

Symptom	Survivors				Non-Survivors				P*	Total			
	No.	Mean (days)	SD	Range (days)	No.	Mean (days)	SD	Range (days)		No.	Mean (days)	SD	Range (days)
Fever	27	19.6	40.9	1–150	32	16.9	31.6	1–150	> 0.05	59	17.8	35.3	1–150
Convulsion	20	3.0	4.1	1–14	29	4.0	4.0	1–15	> 0.1	49	3.3	4.0	1–15
Cough	20	30.8	31.2	3–180	13	76	38.6	4–150	< 0.001	33	47.4	33.8	3–180
Anorexia	8	9.5	4.0	4–14	18	8.7	10.2	2–30	> 0.5	26	9.1	7.5	2–30
Weight loss	9	45.5	30.8	14–90	5	42.0	19.6	30–60	> 0.5	14	44.1	25.9	14–90

* Level of Significance
SD = Standard deviation

TABLE IV

Major Physical Signs in 72 cases of Tuberculous Meningitis

Sign	No. of Survivors	No. of Non-Survivors	Both groups	% of Total
General				
Malnutrition	31	36	67	93
Pyrexia	32	31	63	88
Abnormal chest signs	15	15	30	42
Dehydration	13	15	28	39
Hypothermia	1	2	3	4
Neurological				
Change in Sensorium				
Semicoma	9	8	17	24
Coma	6	9	15	21
Drowsiness	4	10	14	19
Others				
Neck stiffness	19	21	40	56
Positive Kernig's	10	13	23	32
Generalised rigidity	6	8	14	19
Spastic quadriplegia	4	6	10	14
Spastic paraplegia	0	4	4	6
Facial palsy	3	1	4	6
Nystagmus	0	2	2	3
Generalised hypotcnia	0	2	2	3

protein level was below 0.5g/L (50mg/100ml) in 8 cases (12%), between 0.5g/L and 1.0g/L (50mg/100ml - 100mg/100ml) in 30 (45%) cases while in 12 others, the level was greater than 10g/L (1,000mg/100ml). Spontaneous clotting occurred in two samples. The glucose level was 1.7mmol/L (30mg/100ml) in 40 (61%), but above 2.2 mmol/L (40mg/100ml) in 18 (27%), only 2 of whom died. The mean cell count and mean glucose level were higher, while the mean protein level was lower in survivors than in non-survivors. The differences between the means for survivors and non-survivors were significant in respect of cell count ($p < 0.001$), protein ($p < 0.01$) and glucose levels ($p < 0.05$).

Tuberculin skin test

This was performed in 65 cases and a negative reaction was obtained in 26 (38%).

Radiography

Chest X-ray, carried out in 63 patients, was normal in 10. The main findings in the other 53 patients, some of whom had mixed lesions, included miliary mottling (19 cases), mediastinal adenopathy (18 cases), bronchopneumonia/parenchymal infiltration (16 cases), segmental consolidation/collapse (5 cases) and pleural effusion in 3 cases. A significantly higher proportion (58%) of the 19 children with miliary mottling

TABLE V

Summary of Major CSF Changes in 72 Children with Tuberculous Meningitis

	Survivors	*Non-Survivors*	*Both groups*	*% of total*	*P value*
APPEARANCE					
Clear & colourless	21	16	37	56	
Turbid	7	7	14	21	
Xanthochromic	5	5	10	15	
Hazy	2	3	5	8	
Total	35	31	66	100	NS
CELLS					
No. of cases	35	31	66		
Mean ($x10^6$/L)	126.6	83.9	105.2		<0.001
Range ($x10^6$/L)	0 –780	0 –400	0 –780		
SD					
Differentials: Mean Polys %	37.4	25.7	31.8		
Mean Lymphs %	22.3	39.1	31.5		
PROTEIN	77.7	60.9	68.5		
No. of cases	35	31	66		
Mean (g/L)	3.55	4.57	4.02		<0.01
Range (g/L)	0.3 –> 10	0.4 –> 10	0.3 –> 10		
SD	1.37	1.27	1.31		
GLUCOSE					
No. of cases	35	31	66		
Mean (mmol/L)	1.96	1.29	1.64		<0.05
Range (mmol/L)	0.3 – 6.3	0.3 – 3.1	0.3 – 6.3		
SD	1.52	0.9	1.29		

SD = Standard deviation NS = Not significant

Conversion: *SI to traditional units*
Protein: 1g/L = 100mg/100ml
Glucose: 1mmol/L = 18mg/100ml

either alone (11 cases) or in combination with other lesions, died, compared with a mortality of 29% in the remaining 34 cases who did not have miliary mottling ($p < 0.05$). Skull X ray showed sutural diastasis in 8 cases, 6 of whom survived. There was no case of intracranial calcification.

Management

Thirty of the children received standard antituberculous drug therapy consisting of streptomycin, isoniazid and paraaminosalicylic acid while 2 others received isoniazid, streptomycin and rifampicin. Fifteen (47%) of these 32 patients died. Thirty-four other patients in whom the diagnosis of TMB was initially in doubt, received both antibiotics and antituberculous drugs. The antibiotics were however, discontinued within 3 weeks in all, when the diagnosis of TBM was confirmed, while the antituberculous drugs were continued. Fifteen (44%) of these 34 children, died. Six patients who received antibiotics alone for suspected pyogenic meningitis, died and diagnosis of TBM was made at autopsy. Prednisolone was also used in 43 patients, for periods ranging between 1 week and 24 weeks (mean, 8.3 weeks). Only 14 (33%) of the 43 patients died. By contrast, 22 (76%) of 29 who did not receive steroids, died ($p < 0.025$).

The average interval between admission and commencement of specific theapy in the 66 patients diagnosed during life, was 2.7 days (2.6 days in survivors; 2.8 days in non-survivors). Antituberculous therapy was commenced within 24 hours in 44 (67%) of these 66 cases and within 6 days in a further 19 (29%). Specific therapy was however, not commenced until 10 days after admission in 3 patients, only one of whom survived.

Progress

The clinical course of the children during treatment as well as the CSF changes were evaluated in the 66 cases diagnosed ante-mortem. Of these, 9 were comatose from the day of admission till they died within 8 days. There was no response to therapy nor did the CSF picture improve significantly in 21 others who died within 2 weeks of admission. The overall mortality was 50%. The remaining 36 patients made steady progress which was remarkable in the 6 who survived with no sequelae. The neurological sequelae in 30 of the survivors are shown in Table VI. Consciousness was regained between 8 days and 3 months (mean, 29.5 days) in 16 survivors who were comatose or semicomatose on admission. A fall in the number of cells was usually the first favourable CSF change, followed by a rise in the glucose level before a fall in the protein level. Thus, the CSF was usually regarded as normal when the protein level became normal. In none of those who died did the CSF protein return to normal. In 31 of the survivors, the protein levels were normal within an average period of 6.3 weeks (range, 4 weeks to 4 months).

TABLE VI

Neurological Complications in 30 Survivors of Tuberculous Meningitis

Complication	*No. of Cases*	*% of Total*
Cranial Nerve Lesions		
Facial palsy	9	30
Optic nerve damage	4	13
IIIrd nerve damage	4	13
8th nerve damage	3	10
Others		
Spastic quadriparesis/plegia	11	37
Spastic hemiplegia/paresis	6	20
Monoparesis	2	7
Seizures	6	20
Mental retardation	5	17
Involuntary movements	5	17
Hydrocephalus	3	10
Inability to sit	3	10

Among the 7 survivors in whom the initial CSF protein was greater than 10g/L (1,000mg/100ml), this fell to 0.4g/L (40mg/100ml) and below, within 6 weeks of therapy. The fall in the CSF protein was not always smooth and continuous. In 10 of the survivors and 3 of those who died, the CSF protein fell initially within an average period of 17.8 days (range, 5 days to 30 days) of therapy, but subsequently rose before falling again in the survivors.

Factors affecting prognosis

Age: Age was not statistically related to prognosis. However, all the 5 cases aged 8–11 years, died. These 5 cases were grossly wasted and dehydrated, on admission. They all had associated pulmonary tuberculosis which was miliary in type in two. Four of them were comatose on admission. All the 5 died within 3 days of admission, despite steroid, antituberculous drugs and intravenous fluid therapy.

Duration of symptoms: The mean duration of cough which was usually the symptom with the longest duration, was 76 days (range, 4–150 days) in 13 who died, and this was significantly longer than a mean of 30.8 days (range, 3–180 days) among 20 survivors ($p < 0.001$).

Nutritional state: All the well-nourished children survived, whereas only 31 (46%) of the 67 malnourished ones survived ($p < 0.025$).

Sensorium: Of 46 patients who were comatose, semicomatose, or drowsy on presentation, 27 (59%) died. By contrast, only 9 (35%) of the remaining 26 who were lucid, died ($p < 0.05$). However, by the classification above,[3] the differences between the mortality of 27.3% in the 11 cases in group I, the 40% mortality in the 15 in group II and 58.7% in the remaining 46 in group II, were not statistically significant ($p > 0.05$).

Chest radiography. Mortality was significantly higher in those with radiographic evidence of miliary tuberculosis than in those without ($p < 0.05$).

CSF changes. As shown in Table V, the mean CSF cell count, and glucose level were significantly lower and the protein level higher in non-survivors than in survivors.

Discussion

The common presenting symptoms of fever, convulsion, anorexia and weight loss in the present series, were similar to those reported by others,[1,2] while the prominence of cough indicated the high frequency of associated pulmonary tuberculosis. Mortality and morbidity from TBM remain high in developing countries where facilities for rehabilitating survivors with sequelae are often inadequate. The age incidence in the present study was similar to the findings by Lincoln, Sordillo and Davies[4] and Smith,[5] but in contrast to their findings, age was not significantly associated with prognosis. On the other hand, late presentation appeared to have adversely affected the prognosis. The duration of cough, which was indicative of associated pulmonary tuberculosis, was significantly longer in non-survivors than in those who survived. One probable reason for the delay in presentation is that prominent symptoms such as cough, weight loss and low grade fever, are not usually dramatic in their onset. By contrast, convulsion, one of the main immediate reasons for seeking medical care, is dramatic and frightening. Unfortunately however, this symptom usually occurs many weeks or months after the onset of the disease. The poor prognosis which was associated with a change in the sensorium in the present series, has been reported by others,[6] just as lucidity which was associated with a better prognosis in the present series has also been previously reported.[5] Malnutrition was a prominent feature in 93% of our patients and was significantly associated with a poor prognosis.

While it is difficult to influence appreciably, the delay in presentation, prompt diagnosis and initiation of specific therapy are considered important measures to improve the prognosis in TBM.

A high index of suspicion is the most important aid to an early diagnosis. Early manifestations of TBM in children include a change in behaviour or sensorium, in the presence of tuberculosis elsewhere in the body. It is also suggested that TBM should be strongly suspected and every effort made to confirm it in any child with features of meningitis and malnutrition. Although convulsion is usually a late manifestation, and therefore not very helpful in making an early diagnosis, the prolonged and often repetitive nature of the convulsion, distinguishes it from the brief episodes associated with febrile convulsion.

Confirmation of the diagnosis of TBM presents many difficulties. Although Lincoln, Sordillo and Davies[4] reported that positive cultures may be obtained up to two weeks after initiating specific therapy, our study and those of others[6 7] have shown that it is often not possible to isolate *M. tuberculosis* from the CSF. Consequently, reliance must be placed on other changes in the CSF. Unfortunately however, these changes may be unhelpful in the differential diagnosis if the findings are atypical. In such cases, and where doubt exists, chest radiographs and tuberculin skin test would usually provide useful information in the diagnosis, although these investigations may also be negative. Since miliary tuberculosis is frequently associated with TBM,[8] it is suggested that any child with radiological evidence of military tuberculosis should be presumed to have an associated TBM until otherwise proven.

The standard drugs for the management of TBM consist of streptomycin, isoniazid, paraaminosalicylic acid (PAS) and steroids. Most workers agree that steroids are useful in the management of TBM,[9] but the dosage of prednisolone used varies from 1 to 3mg/kg body weight/day, for 4–6 weeks.[6 9 10] Based on the present series, it is considered that a dose of 2mg/kg body weight/day for 6 weeks is adequate. The standard triple antituberculous drugs have been the drugs of choice until recently when there were indications that the prognosis of TBM could be improved by using the newer and more potent drugs such as rifampicin, in place of PAS.[9] Two survivors in the present series received rifampicin, but this number is too small for proper evaluation of its efficacy. A clinical trial of these newer drugs which are more expensive and not without toxic side effects, is indicated in patients before their routine use can be recommended. Meanwhile, the standard triple drug therapy should routinely be used while the newer drugs should be reserved for cases not responding to the triple therapy, as well as for those that are likely to have a poor prognosis.

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