SHORT COURSE CHEMOTHERAPY STUDY IN TUBERCULOUS MENINGITIS IN CHILDREN

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Summary : **A total of 215 patients with tuberculous meningitis were treated for nine months with one of the following two regimens : The first regimen consisted of 5 drugs namely Streptomycin, Isoniazid and Ethambutol given daily, supplemented with Rifampicin and Pyrazinamide thrice a week for the first two months, followed by Rifampicin and Isoniazid twice a week for the next seven months. Regimen II was similar to Regimen I excepting that Rifampicin and Pyrazinamide were given twice a week during the first two months of intensive phase, instead of thrice a week. As a general policy, steroids were administered to all the patients for a period of 6 to 8 weeks. On admission. 56% of the patients were aged less than 2 years and 75% less than five years. Forty five patients (21%) were classified as stage I, 160 (74%) as stage II and only 10 (5%) as stage III. Cerebrospinal fluid culture was positive for tubercle bacilli either by smear, culture or both in 47%. Smear was negative and culture alone was positive in 74 patients and in 14 patients both smear and culture were positive. Of the 88 culture positive patients, in 7 (8%) the cultures were resistant to Streptomycin alone, in 12 (14%) to INH alone, in 11 (12%) to both Streptomycin and INH, while in 2 (2%) patients, they were resistant to all the three drugs.**

The response to therapy was similar in both the regimens. The mortality was very high, namely 31%, despite using intensive regimens. There was a strong association between the stage on admission and the mortality rate, the latter being highest in stages II and III. This emphasises the need for early diagnosis and treatment in tuberculous meningitis.

INTRODUCTION

Short course chemotherapy (SCC) is now widely accepted as the treatment of choice for adult pulmonary tuberculosis but there is relatively little information on the value of the same in childhood tuberculosis, in particular tuberculous meningitis. The results of the earlier 3 chemotherapy studies on tuberculous meningitis in children, conducted by the Tuberculosis Research Centre, Chennai[1] showed that the mortality was very high. Hence, the Centre undertook the short course chemotherapy study where patients were treated with more intensive regimens, with 5 drugs in the initial phase. followed by two bactericidal drugs during the follow up phase. This paper presents the results of the above study.

Plan and conduct of the study

A total of 215 patients, aged between 1 and 12 years, who had not received more than 4 weeks of previous anti-tuberculosis chemotherapy, bad no evidence of renal or liver disease and bad no optic atrophy or pallor of optic discs, were admitted to the study.

Criteria for diagnosis

The diagnosis was based on clinical symptoms and signs like fever, vomiting, irritability. apathy, anorexia, constipation, refusal to play, in the initial stages followed by presence of meningeal signs and impaired consciousness. coma and widespread paralysis. The cerebrospinal fluid (CSF) findings were also taken into consideration. A CSF protein value of more than 40 mg% plus cell count more than 10/cmm (predominantly lymphocytes) was taken as confirmatory.

Investigations

Tuberculin test with 1TU (PPD Batch. RT 23 with tween 80) was done on admission and read after 2 or 3 (occasionally 4) days. Urine tests for

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Acetyl Isoniazid, bile salts, bile pigments, urobilinogen, albumin and deposits were done on admission, at 1 and 2 months and, thereafter, tests for albumin and Acetyl Isoniazid were done every month. Anteroposterior chest radiographs were taken on admission and at the end of treatment. Routine haematological investigations, including liver function tests, urea and creatinine were done on admission, at 1 and 2 months and end of treatment. Biochemical, cytological and bacteriological examinations of the CSF were done on admission and once a month subsequently till the results became normal.

On admission, the patients were classified into 3 stages according to severity, using the classification suggested by the British Medical Research Council[2] :

Stage I : Patients were conscious and had mainly non-specific symptoms, with or without signs of meningeal irritation, but no focal neurological signs. Diagnosis was established mainly on CSF findings.

Stage II : Patients were mentally confused and/or had neurological signs.

Stage III : Patients were comatose and had gross neurological signs.

Patients found suitable were randomly allocated, after stratification according to the stage of the disease. in equal proportion to the two regimens :

Regimen I : $2S_7H_7E_7R_3Z_3/7R_2H_2$

Streptomycin, Isoniazid and Ethambutol daily supplemented by Rifampicin and Pyrazinamide thrice a week for 2 months followed by Rifampicin and Isoniazid twice a week for the next 7 months.

Regimen II : $2S_7H_7E_7R_2Z_2/7R_2H_2$

Regimen II was the same as regimen I except that Rifampicin and Pyrazinamide were given twice instead of thrice a week during the first 2 months.

Dosage of Drugs

Streptomycin was given in a dosage of 40 mg/kg body weight. Isoniazid 12 mg/kg and Ethambutol 20 mg/kg for 2 weeks, followed by 15 mg/kg for the next 6 weeks. Pyrazinamide was administered in a dose of 30 mg/kg in the thrice weekly regimen and 40 mg/kg in the twice weekly regimen. Rifampicin was given in a dose of 12 mg/kg. In addition to the anti-tuberculosis drugs, the patients received supportive therapy like I.V. fluids, anti-oedema measures, anti-convulsants and vitamins. Steroids were administered to all the patients. Seriously ill patients were given dexamethasone by the intra-muscular route in a dosage of 2-3 mg every 6-8 hours for the first 3-4 days followed by oral Prednisolone in a dosage of 1-2 mg/kg.

General Management

Patients were hospitalised for a minimum period of 2 months or more, if necessary. However, those who showed very good improvement were discharged at request before completing the intensive phase of two months treatment (mostly stage I patients) and asked to attend daily until they completed 2 months of treatment. After two months, the patients attended twice or once a week (or once in 15 days if they lived outside Chennai city) to collect drugs. They were given the drugs under supervision on the days they attended. The progress was assessed by monthly examination.

Surgery

Patients who developed clinical symptoms of hydrocephalus and those who did not show any improvement within 6 weeks of starting anti-tuberculosis treatment were subjected to a C.T. Scan and a ventricular operational shunt was performed if the diagnosis of hydrocephalus was confirmed.

Bacteriological procedures

CSF specimens were examined by fluorescence microscopy and cultured on multiple media namely Lowenstein Jensen medium with and without pyruvate, a selective 7H11 medium and selective liquid Kirschner medium. Tests of sensitivity to Streptomycin, Isoniazid, Rifampicin and Ethambutol, were performed. All positive cultures were subjected to identification tests.

Definitions of drug resistance

Streptomycin : A resistance ratio (RR) of 8 or more on 1 culture, or 4 followed by 8 or more on a repeat test.

Isoniazid : (a) Growth (defined as 20 colonies or more) on 1 mg/L or a higher concentration, or growth on 0.2 mg/L followed by the same result on a repeat test.

Rifampicin : Growth on 64 mg/L.
Ethambutol : Growth on 4 mg/L.

RESULTS

A total of 215 patients were admitted to the study. On admission, 56% of the patients were aged less than 3 years and 75% less than 5 years. Approximately half the patients were males. Most of the patients belonged to the lower socio-economic group. Fifty percent of the patients hailed from semi-urban and rural areas while the remaining 50% came from urban areas.

The nutritional status of the patients was very poor. Using growth standards set up by the Indian Council of Medical Research, only 4% of the patients were considered normal while 56% had mild to moderate malnutrition and 40% had severe malnutrition, based on deficit in weight for age: There was no association between the nutritional status and mortality. Only 5 patients had received previous anti-tuberculosis chemotherapy for a period ranging between 2 and 5 days. The time interval between the onset of symptoms and admission to hospital was 1-14 days in 53 (29%) patients, 2 weeks to 4 weeks in 108 (58%) and 1-3 months in 24 (13%) patients. There was no association between the duration of symptoms before admission and the stage of the disease. On admission, 4.5 (21%) patients were classified as stage I, 160 (74%) as stage II and 10 (5%) as stage III.

Tuberculin test with 1 T.U. was positive with an induration of 10 mm or more in 73 (34%) patients; a history of contact with a known case of pulmonary tuberculosis was elicited in 137 (64%) patients and an abnormal chest radiograph suggestive of tuberculosis was present in 111 (52%) patients. BCG scar was present in 47 (22%) patients. CSF was positive for tubercle bacilli either by smear, culture or both in 101 (47%) patients. CSF smear was positive in 74 patients and in 14 patients, both smear and culture were positive. Culture was, thus, positive in 88 patients (41%). Out of these, in 7 patients (8%) the cultures were resistant to Streptomycin alone, in 12 (14%) to INH alone, in 11 (12%) to both Streptomycin and INH and in 2 (2%) to Streptomycin, INH and Rifampicin.

Response to treatment

Of the 215 patients admitted to the study, in 10, the prescribed treatment was modified, 1 patient died of a non-tuberculous cause and 29 patients were discharged against medical advice before treatment was completed. Of these discharged patients, 10 were reported to have died within 4 days of discharge. Since their general condition was very poor at the time of discharge and the cause of death was most likely to be tuberculous meningitis, they were included in the analysis. Thus, the analysis of response to treatment was based on 185 patients.

Table 1 gives the response to treatment in the two regimens. Of the total 18.5 patients, 57 (3 1%) died of tuberculous meningitis, 66 (36%) recovered with neurological sequelae and the remaining 62 (34%) recovered fully without any sequelae. The neurological sequelae were classified as severe. moderate and mild.

Mild residual damage implied such sequelae as hyperactivity, irritability, mild perceptual defects and limited motor impairment such as facial paresis or monoparesis.

Moderate residual damage included such defects as hemiparesis, involuntary movements and substantial mental impairment. Severe residual damage included patients who either remained

Table 1. Response to treatment and status at 9 months according to treatment regimen

Regimen	No. in analysis	Died		Residual damage					Complete recovery	
		No.	%	Total		Severe	Moderate	Mild	No.	%
				No.	%					
$2SEHR_3Z_3/7R_2H_2$	89	26	29	31	35	4	21	6	32	36
$2\ SEHR_2Z_2/7R_2H_2$	96	31	32	35	36	i	22	12	30	31
ALL	185	57	31	66	36	6	43	18	62	34

unconscious or were conscious but were incapable of independent existence.

Table 2 shows the response to treatment according to stage. There was a clear association between the stage on admission and the mortality, the latter being highest in stage III patients (43%) and lowest in stage 1 patients (10%) (statistically significant with p = 0.002). There was no association between the age of the patient and death due to tuberculosis.

Table 3 shows the interval between admission and death according to stage on admission. Of the 57 deaths, 29 (5%) occurred within the first month, 7 (12%) in the second month, 7 (12%) in the third month, 13 (23%) between the fourth and sixth months ard only one (2%) between the seventh and ninth months of treatment. The last available CSF result was biochemically abnormal in 50 of 57 patients who died and bacteriologically positive in 26. Table 4 shows that there was a clear association between g resistance and response to treatment (significant with p = 0.007).

Complications while on therapy

Hydrocephalus : In seventy four patients hydrocephalus was suspected. Of these. C.T. Scan could not be done in 6 patients due to various reasons. On follow-up of these patients, 3 died while the remaining 3 recovered with neurological sequelae. The Scan was done in 68 patients and the diagnosis was confirmed in all of them. Of these, in 38 patients, a ventricular-operational shunt was performed while in the remaining 30, no surgery was undertaken either because the parents were not willing to subject their children to surgery or because the patient died before the scheduled date. Twenty five patients in the surgery group and 13 in the non-surgery group died.

Blindness and optic disc changes

Five patients developed mild pallor of optic disc while on treatment. In 4 of them, the changes reverted to normal while in 1 patient it persisted till

Table 2. Response to treatment and status at 9 months according to stage on admission

Stage on admission	No. in analysis	Died		Residual damage					Complete recovery	
		No.	%	Total		Severe	Moderate	Mild	No.	%
				No.	%					
I	41	4	10	7	17	0	3	4	30	73
II	137	50	36	56	41	5	37	14	31	23
III	7	3	(43)*	4	(43)	0	3	0	I	(14)
ALL	185	57	31	66	36	5	43	18	62	34

* Figures in brackets indicate percentages based on a total fewer than 25 cases

Table 3. Interval between admission and death, according to stage of disease on admission

Stage of disease	No. in analysis	Died of tuberculosis									
		Total	Week of treatment				Month of treatment				
			1	2	3	4	2	3	4	5	6	7-9
I	41	4	0	0	1	0	0	0	2	0	I	0
II	137	50	14	5	2	5	7	6	4	I	5	I
III	7	3	1	1	0	0	0	1	0	0	0	0
ALL	185	57	15	6	3	5	7	7	6	1	6	I

the end of treatment.

Optic atrophy with blindness developed in 7 patients; 4 of these died and had the abnormal finding till death, while the remaining 3 recovered with moderate sequelae but the ocular changes persisted till the end of therapy.

Discharge against medical advice before completing treatment

Of the 215 patients started on treatment, 29 patients were discharged against medical advice; of these, on follow up, 20 patients died (10 within 4 days of discharge) and the remaining 9 were alive.

Non-TB deaths

Only 1 patient (stage II) died of acute gastro-enteritis in the third month of treatment.

Hepatic toxicity

This analysis is based on 205 patients after excluding the 10 patients who had their treatment modified. Table 5 shows that 10 patients (10%) in regimen 1 and 3 patients (3%) in regimen II developed clinical jaundice with abnormal liver function test values (difference not statistically significant). All except 1 patient developed jaundice during the first 2 months of intensive therapy. Five other patients developed only increase in the enzyme levels with no clinical jaundice. Rifampicin and Pyrazinamide were terminated in these patients and the other drugs were continued.

DISCUSSION

Tuberculous meningitis is still the most serious form of tuberculosis and carries a high mortality In the earlier three studies conducted by the Tuberculosis Research Centre[1], Rifampicin containing regimens with and without Pyrazinamide were used during the first 2 months of intensive phase followed by Isoniazid and Ethambutol daily for the next 10 months. The mortality was very high in these studies and ranged between 27 and 33%. It was felt that the drugs given in the follow-up phase in these 3 studies were not adequate. Hence, the regimens in the present study were intensified by administering 5 drugs namely Streptomycin, Isoniazid, Rifampicin. Pyrazinamide and Ethambutol during the first 2 months followed by 2 bactericidal drugs namely Isoniazid and Rifampicin for the next 7 months. However, the results showed that despite using intensive regimens, the mortality remained high (31%). **This indicates that in this form of tuberculosis, early diagnosis and prompt**

Table 4. Culture and sensitivity results related with response to treatment

Initial Culture/ Sensitivity	Total no. in analysis	Died		Complete recovery	
		No.	%	No.	%
Culture negative	110	30	27	39	35
Sensitive to S,H	47	11	23	18	38
Resistant to S,H or SH	28*	16	57	5	18

* Of these 2 had resistance to R also

Table 5. Occurrence of jaundice during treatment

Regimen	No. of patients admitted	Patients who developed jaundice		Week of onset					
		No.	%	1	2	3	4	5	6-8
$2SEHR_3Z_3/7R_2H_2$	103	10*	10	0	4	0	2	I	2
$2SEHR_2Z_2/7R_2H_2$	102	3	3	0	1	0	1	0	I
ALL	205	13	6	0	5	0	3	I	3

* Includes 1 patient who developed jaundice in the 3rd month

treatment are more important than the drug regimen. The results of the present study showed that there was a direct relationship between the stage of the disease on admission and the death rate, the latter being highest in stage III patients and lowest in stage I patients. Similar observations were made by us in our first three studies, as well as by other workers. The high mortality in the present study could be due to various reasons like majority of patients (79%) getting admission in the advanced stage of the disease, inclusion in analysis of deaths from day one of admission before the drugs could start acting and also inclusion of the patients who were discharged against medical advice in a critical condition and died within 7 days of discharge. In the present study, 29 of 57 (51%) deaths occurred within 1 month of admission and 21 (37%) within 2 weeks.

In this study, Ethambutol was used only during the first 2 months of intensive phase of therapy mainly to prevent the emergence of further resistance in patients with initial resistance to one or more anti-tuberculosis drugs. Ethambutol has been extensively used in the treatment of childhood tuberculosis in India[3-5]. In all these studies the dosage employed was 25 mg/kg for the first 2 months followed by 15 mg/kg and the reported ocular toxicity was negligible. A study by Leibold[6] suggests that, on a short term basis, it is safe to prescribe as much as 45 mg/kg. In the present study, Ethambutol was used only for 2 months in a dosage of 20 mg/kg for 2 weeks followed by 15 mg/kg for the next 6 weeks. This dose and the short duration are very unlikely to have produced ocular changes. Also, optochiasmatic arachnoiditis resulting in visual impartment or even blindness, with or without associated hydrocephalus, is a common complication of tuberculous meningitis. All the 7 patients who developed optic atrophy with blindness in the present study had moderate to severe neurological damages and this is most likely to be the cause of blindness.

In this study, clinical jaundice with abnormal liver function test values was higher in those who received Rifampcin thrice a week compared to those who received the same drug twice a week. This is in conformity with the findings of the other studies undertaken in our Centre[7].

The results of the present study show that despite using intensive regimens, the mortality was very high, specially in stages II and III patients, and it was lowest in stage I patients. This emphasises the need for early diagnosis and prompt treatment. Since the results were similar in both the regimens and the occurrence of jaundice was low in the group where Rifampicin and Pyrazinamide were administered twice a week, this regimen appears more suitable for the treatment of tuberculous meningitis.

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