A 5 YEAR FOLLOW-UP STUDY OF CHILDREN TREATED FOR TUBERCULOUS MENINGITIS WITH SHORT COURSE CHEMOTHERAPY*

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Summary : **A total of 215 patients with tuberculous meningitis were treated for a period of 9 months. Of these, 30 patients were excluded from analysis for various reasons. Of the remaining 185, 57 died during treatment leaving 128 patients (5 with severe sequelae, 43 with moderate, 18 with mild and 62 with complete recovery) for long term follow-up. The noteworthy features of the study are 100% coverage, low relapse rate and development of late sequelae in 10 patients during follow-up period.**

INTRODUCTION

Of all forms of tuberculosis, tuberculous meningitis (TBM) still carries a high mortality and morbidity. Infections of the central nervous system, unlike other infections cause irreparable damage unless diagnosed early and promptly treated. The resulting neurological sequelae can manifest either during treatment or subsequently. Long term follow up of treated TBM patients is therefore essential to find out the course of the residual lesions and also the relapse rates. This report gives the 5 year follow up status of 128 survivors out of 185 patients treated for TBM with short course chemotherapy. The study was undertaken by the Tuberculosis Research Centre in collaboration with the Institute of Child Health and Hospital for Children, Chennai from where the patients were drawn.

MATERIAL AND METHODS

A total of 215 patients aged between 1 and 12 years, who had not received more than 2 weeks of previous anti-tuberculosis chemotherapy and had no evidence of renal or hepatic disease and no optic atrophy were admitted to the study. They were treated for 9 months with one of the following regimens.

Regimen-I : 2 $SHER_3Z_3/7R_2H_2$: Patients received streptomycin, isoniazid and ethambutol daily supplemented with rifampicin and pyrarinamide thrice a week for the first 2 months followed by rifampicin and isoniazid twice a week for the next 7 months.

Regimen-II: $2SHER_2Z_2/7R_2H_2$: Patients were treated with streptomycin, isoniazid and ethambutol daily supplemented with rifampicin and pyrazinamide twice a week for the first 2 months followed by rifampicin and isoniazid twice a week for the next 7 months.

In addition to anti-tuberculosis drugs. non-specific therapy was also given in the form of intravenous fluids, anti-oedema measures, anti-convulsants and vitamins. Steroids were administered to all the patients for a period of 6 to 12 weeks.

The results (awaiting publication in *The Indian Journal of Tuberculosis)* were similar in both the regimens with a mortality rate of 31%. There was a clear association between the stage on admission and the mortality rate, the latter being highest in stage III patients and lowest in stage I. At the end of treatment, there were 128 survivors. 66 (36%) with neurological sequelae and 62 (34%) with complete recovery.

Neurological sequelae were classified as follows Patients classified as with severe residual damage either remained unconscious or even if they had regained consciousness, were incapable of independent existence. Moderate residual damage included defects like involuntary movements. hemiparesis and substantial mental impairment. Mild sequelae included hyperactivity, irritability, mild perceptual defects and limited motor impairment like facial weakness or monoparesis.

All the patients who completed 9 months of

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treatment were seen once a month till 24 months, once in 3 months till 36 months and thereafter once in 6 months till 60 months. The period of follow up was 51 months after completion of therapy. At all these visits, a complete neurological examination was done on all the patients. Lumbar puncture and CSF examination for cell count biochemical and bacteriological examination was repeatedly undertaken for those who had abnormal CSF findings at the end of treatment, till the results became normal.

RESULTS

Table 1 shows the status at the end of 5 years for the 128 patients who completed the treatment. Eleven patients died during the follow up period - 7 due to TBM sequelae and 4 due to non tuberculous causes. The remaining 117 patients were seen upto 60th month from the start of treatment.

Of the 5 patients with severe sequelae at the end of treatment, 4 patients died-all due to sequelae, in the 14th, 15th, 19th and the 44th months respectively, while the fifth patient showed improvement.

Of the 43 patients with moderate sequelae, 2 patients died of TBM sequelae in the 11 th and 30th months while 2 others died of non-tuberculous causes. In 36 patients the status remained the same while 2 patients improved to mild sequelae and one had complete recovery.

Of the 18 patients with mild sequelae, 2 patients died, the first patient due to non-tuberculous cause while, the second relapsed at the 12th month and died in the 31 st month despite intensive therapy for 9 months. Ten patients maintained their status while 3 other developed moderate sequelae, namely, secondary epilepsy. Three had a complete recovery.

Of the 62 patients who had complete recovery status quo was maintained in 54 patients, while 7 developed sequale-1 patient developed diabetes insipidus, 3 had secondary epilepsy. while the remaining 3 had behaviour problems. One patient died of a non-tuberculous cause.

Seven patients had CSF abnormality (increased protein level) at the end of treatment. All the 7 had hydrocephalus and 6 of them underwent ventriculo-peritoneal shunt surgery. In the surgery group, the CSF protein level became normal in all the patients. In the 7th patient whose parents refused surgery. the last CSF examination at the 47th month was still abnormal. Repeat lumbar puncture was no possible because of non-cooperation. The patient was alive at 60th month with moderate sequelae.

Relapses during follow-up

In all, 3 patients relapsed, 1 in regimen I and 2 in regimen II. All of them had clinical signs and symptoms of meningitis with abnormal CSF biochemical findings and bacteriological positivity. In the first patient who had mild sequelae at the end of treatment and relapsed in the 12th month, the CSF cultures (both initial and at the time of relapse) were sensitive to all the drugs. Despite retreatment with intensive therapy for 9 months, the patient died in the 31st month. The last CSF was normal biochemically and bacteriologically. The remaining 2 patients (1 with mild sequelae and the other with moderate) relapsed in the 11 th and 22nd month of follow-up (from the commencement of treatment) respectively. The first patient relapsed with organisms sensitive to all the drugs while the 2nd relapsed with organisms resistant to streptomycin and isoniazid (both initially and at the time of relapse). Both the patients were treated with

Table I. Status at 5 years in relation to status at the end of 9 months

Status at 9 months	No. of pts.	Deaths after 9 months		Status at the end of 5 years			
		TBM seq.	Non. TB	Sev. Seq.	Mod. Seq.	Mild Seq.	Comp. Rec.
Severe Seq.	5	4	0	0	1	0	0
Moderate Seq.	43	2	2	0	36	2	I
Mild Seq.	18	1	1	0	3	10	3
Comp. recovery	62	0	1	0	4	3	54
All	128	7	4	0	44	15	58

intensive chemotherapy and both recovered with moderate sequelae. The CSF at the end of retreatment was normal biochemically and bacteriologically.

DISCUSSION

There are very few reports available on long term follow-up of patients treated for tuberculous meningitis. In our earlier report on long term status (4½ - 8 years) of 119 survivors treated for TBM[2] the salient features were : out of 10 deaths due to TBM sequelae, 9 occurred in those who had severe sequelae at the end of treatment and of the 52 patients who were classified as fully recovered, 10 developed mild to moderate sequelae during follow-up period. Fitzsimons[3] treated 289 patients between the years 1946 and 1959. There were 198 survivors who were followed for a period of 2 to 15 years after discharge and the results showed that 122 patients (62%) had a complete recovery, 42 (21%) had minimal restriction, 19 (10%) had moderate disability and 15 (8%) severe disability. A follow up study on 100 survivors out of a total of 170 children treated for TBM between 1947 and 1955 is reported by Lorber[4]. He followed them for a period of 5 to 13 years and found neurological sequelae in 23 patients. In another study by Miller *et aI*[5] 116 patients were treated between 1947 and 1957 and the results showed that 36 (31%) patients died and 80 (69%) survived. The survivors were followed for a period of at least 2 years and residual neurological sequelae were found in 38 (48%) patients.

The salient feature of the present study is that the coverage was 100% despite 50% of the patients hailing from semi-urban and rural areas. This was possible because of initial and periodic subsequent motivation. The relapse rate was low and 10 patients (in the complete recovery and mild sequelae group) developed late sequelae during the follow up period stressing the necessity for long term follow up of treated TBM patients.

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