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SHORT-COURSE THERAPY IN TUBERCULOUS MENINGITIS. A STUDY OF 16 PATIENTS

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ABSTRACT

From 1986-1989, sixteen patients suffering from TB meningitis aged 12-58, with CSF smear or culture positive for *Mycobacterium tuberculosis* were hospitalized and treated with rifampin (RIF), isoniazid (INH), pyrazinamide (PZA) and ethambutol (ETB) for nine months.

In all patients, ETB and PZA were withdrawn after three months and INH and RIF were continued for the next six months. 81.2 percent of patients were in stages 2 and 3 of this illness, and steroids were added to their treatment regimes. In two patients whose liver enzymes and blood uric acid levels increased during the second week of therapy, INH was discontinued temporarily and PZA was replaced with streptomycin. In the remaining patients, side effects of drugs and central, peripheral and other complications were trivial. Mortality rate was 25%, follow-up of the patients continued for 12-24 months.

According to the mortality and morbidity of classic 12-18 months therapy with three drugs and results obtained in this study, treatment with four drugs for nine months showed some advantages to the other protocols.

We look forward to finding more documents and similar studies from other centers. Confirmation of results of this study could be a suggestion for short-course therapy in TB meningitis, and this is the first report of short-course therapy in TB meningitis from Iran.

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INTRODUCTION

Tuberculous meningitis is one of the most serious complications of tuberculous infections. The mortality of this entity remains unacceptably high, with case fatality rates of up to 50% in some countries.[1,2] The difficulties of rapidly diagnosing TB meningitis in many hospitals are well known,[3] and delays in diagnosis result in a poorer outcome. A substantial proportion of the patients who survive are likely to suffer from neurological sequelae which can manifest during the treatment course or after its completion.

METHODS AND MATERIAL

From 1986-1989, sixteen patients suffering from TB meningitis, living in the northwest of Iran (provinces of Azarbaydjan & Kurdestan) aged 12-58 years were hospitalized. In all patients, C.S.F. smear, culture and routine blood biochemestry, LFT, RFT, PPD, chest x-ray, skull CT scan and other laboratory measures were performed.

All patients recieved INH, RIF, ETB and PZA (four drugs) for three months, then INH and RIF was continued for another six months (two drugs). 18.8%

Table I. Criteria for steroid therapy

1- Patient in coma or sub-coma
2- Signs of paralysis
3- Signs of intracranial hypertension
4- Signs of blockage in CSF channel
5- TB meningitis+ arachnoiditis
6- C.S.F. protein 4 gr/100 ml or higher
7- Concomittant brain tuberculoma

Table II Main Features In 16 Patients

No-Ages / Stage	Ages 12-58, Averuge 30.6	
	No: 16	Stages(%)
I	3	18.8
II	10	62.4
III	3	18.8
Total	16	100

were hospitalized in stage I and 81.2% in stage II or III of this illness, for whom prednisolone 1 mg/kg/ day was added to their treatment regimen (in three comatose patients, hydrocortisone 2 gr/day for the first two weeks) for four to six weeks. Our criteria for steroid therapy in the patients is shown in Table I.

RESULTS

Main features of the sixteen patients are illustrated in Table II. Age of patients was 12-58 years, with a mean of 30.6 years. Nine patients out of 16 were female and seven were male. Except in two patients whose liver enzymes and blood uric acid serially increased during the second week of therapy, INH was discontinued temporarily and PZA was replaced with streptomycin. In the remanining patients, side effects of drugs, peripheral and other complications were negligible.

The most significant CNS complications that were seen in our patients included paralysis of cranial nerves VI, VII, III, VIII, IX, X, XII and papilledema, optic disc atrophy, hemiplegia and hemiparesis. These complications were seen in 50% of the patients alone or concomitantly. Mortality rate in this study was 25 percent and complete recovery with some CNS deficit was seen in 75% of the patients. All patients were followed for 12-24 months.

According to the results obtained from this study and comparison with mortality and morbidity rates of standard treatment regimens,[1,2,4,5] including treatment with three to four first line antituberculous drugs

Table III. Treatment of TB Meningitis (Back ground)

Used Agents	Duration of therapy (months)	Mortality (%)	Recovery with some C.N.S Deficit(%)	Complete Recovery (%)	Comment Ref: No.
PAS-ST 1942-52	24-36	40-50	30-40	10-20	11
INH PAS ST	18-24	30-40	20-30	20-30	12
INH- RIF PZA or ETB	12-18	Nearly 25	25	Nearly 50	4,5
INH- RIF ETB- PZA	12	23	27	50	—
INH- RIF ETB- PZA	9	25	25	50	ourstudy

Table IV. Ratio of C.S.F.to Blood Level (%) of Drugs

Agent	Normal Meninges	Inflamed Meninges
ETB	+	25
ETN	+	100
INH	+	20-90 Reported
RIF	+	25
PZA	+	100
ST	Nil	+
PAS	Nil	Minimal

for 12-18 months[4] which is presently followed by many centers, treatment with four drugs for nine months shows an advantage to the other protocols (Table III).

We are looking forward to finding more documents about similar studies from other centers (with respect to the lack of such studies at the present time in other institutions).

DISCUSSION

Although tuberculosis is an uncommon disease in some developed countries (with respect to the increasing rate and number of AIDS patients)[7-9] but in areas with low socio-economical conditions it is a very common infectious disease.[10] On the other hand, the outlook for patients with tuberculous meningitis has gradually changed from certain death to survival with severe disability, to a prospect of full recovery (see Table III for treatment of TB meningitis background).

In the Department of Infectious and Tropical Diseases of Tabriz University of Medical Sciences, TB meningitis is the fifth cause of mortality in our hospitalized patients.

The basic requirements of a successful regimen are however very simple. As in any other form of the disease, at least three drugs (even four drugs) must be

Table V. Antibacterial Activity of some Anti-TB Preparations

Drug	Antibacterial Activity	Extracellular Activity	Intracellular Activity	Miscellaneous Activity
INH	Bactericidal	Yes	Yes	Cavitary Caseous Tissue
RIF	Bactericidal	Yes	Yes	Slowly metabolized. Dorman Organism?
PZA	Bactericidal	No	Yes	AcidpH (macrophage)
ST	Bactericidal	Yes	No?	Neutral on Alkaline pH
ETB	Bacteriosta-tic?	Yes	Yes	Prevents Emergence of INH Rif, PZA ST Resistance

given initially to cope with the possibility and prevent the development of resistant organisms, and also obtain optimal results.

Obviously in patients with TB meningitis, there are two additional requirements, the drugs chosen should cross and continue to cross the blood brain barrier, and treatment should be started early in the disease to prevent or minimize the formation of adhesions (Tables IV, V reflect the ratio of CSF to blood level and properties of some of the main anti-TB preparations).

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