A Retrospective Survey of Proven Cases of Tuberculous Meningitis in the Northern Region, 1970-1980

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Much of our knowledge of the clinical picture and treatment of tuberculous meningitis (TBM) is based on experience gained in earlier decades and on more recent reports from Asia[1,2]. The clinical experience abroad may not be directly applicable to the UK, as a different population with different medical facilities is involved[2]. Current principles of management of TBM are derived from extensive studies which followed the introduction of anti-tuberculous drugs[3,4]. Over the past 25 years the overall incidence of tuberculosis in the indigenous population of Britain has declined[5], BCG vaccination has been introduced, and new anti-tuberculous drugs have become available. These changes may have altered the clinical picture, morbidity and mortality of TBM, and the present study was undertaken to determine the extent of any alteration. The Northern Region is particularly appropriate for this analysis, having a relatively fixed population and only a small number of immigrants.

Methods

An effort was made to trace all cases of TBM in the Northern Region during the decade 1970–80. Records of cerebrospinal fluids positive on culture for *Mycobacterium tuberculosis* were available from the Regional Tuberculosis Reference Laboratory for the years 1975–80, making possible the identification of all bacteriologically proven cases for this period. Earlier cases were identified by means of the Regional Diagnostic Index.

Patients were included in the survey if the cerebrospinal fluid (CSF) was positive on culture for *M. tuberculosis*, or if, in addition to the typical CSF findings of TBM, there was definite radiological evidence of pulmonary or miliary tuberculosis and an appropriate response to anti-tuberculous therapy. Two patients were included in whom the diagnosis was verified at autopsy. Fifteen patients with a clinical diagnosis of TBM and a positive response to treatment were excluded due to lack of bacteriological confirmation and no radiological evidence of pulmonary or miliary tuberculosis.

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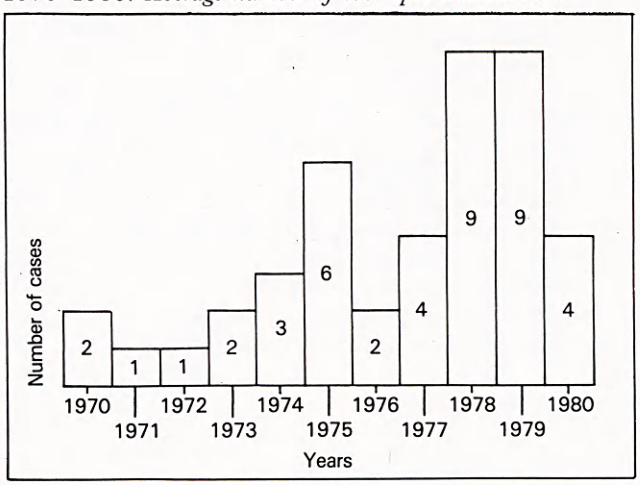
Results

Patients

Forty-three cases were identified, 25 females and 18 males. Two patients were immigrants from India, the rest being indigenous. One quarter of the patients were transferred from their hospital of admission to the Regional Neurological Centre at Newcastle for further management. The number of cases per year is shown in Fig. 1, which suggests that some cases in the earlier period of the study were not identified. During the more accurately documented years 1975–80, the average number of cases

Fig. 1. *Number of cases of tuberculous meningitis per annum, 1970–1980. Average number of cases per annum 4.3.*



per annum is 5.7, giving an incidence of 0.2 per 100,000 p.a. This compares with a figure of 0.15 predicted by extrapolation from the nationwide statistics recently reported[6]. In the majority of patients (74 per cent) the disease occurred before the age of 40, the mean age being 31, with a range of two to 74 years (Fig. 2). Details of exposure to tuberculosis and previous BCG vaccination were not available in sufficient patients to allow analysis.

Fig. 2. *Age distribution of cases of tuberculous meningitis. Mean age 31 years; range 2–74 years.*

Clinical Features

The severity of the disease before treatment was assessed in each case, using the Medical Research Council criteria[7] (Table 1). This classification of the cases shows that the majority fell into Groups II and III.

Table 1. Classification of severity of tuberculous meningitis prior to treatment (Medical Research Council, 1948).

Group	No. of patients	%
I	6	14
II	22	51
III	15	35

Group I: Patients with mainly non-specific symptoms, with little or no signs of meningitis, with no pareses, in good general condition, and fully conscious. Diagnosis established mainly on findings in CSF.
Group II: Patients in condition between those of Groups I and III.
Group III: Patients extremely ill, deeply stuporose or comatose, or with gross pareses.

In only 37 per cent of the cases was there a history of prior systemic upset, often comprising general malaise, anorexia, weight loss and night sweats. The average length of history of the meningitic illness before treatment was ten days (range 1–30 days). This was independent of the severity of the illness, being the same in each MRC group. Non-CNS tuberculous lesions were infrequent and were identified in only eight patients; Groups I and II each had one patient with pulmonary tuberculosis and Groups II and III each had three patients with miliary tuberculosis. Neurological abnormalities before treatment were common and 24 patients (58 per cent) had focal neurological signs in addition to altered level of consciousness and meningism. The most frequent were third or sixth cranial nerve palsies and cortico-spinal tract signs (Table 2).

Table 2. Neurological signs before treatment.

Sign	No. affected
Meningeal irritation	38
Altered level of consciousness	33
Cortico-spinal tract signs	11
Ocular palsy	9
Papilloedema	7
Tremor	1
Aphasia	1

Laboratory Investigations Before Treatment

Cerebrospinal Fluid

The CSF findings before treatment are summarised in Table 3. There were no instances in which the CSF was completely normal, but in three cases the CSF cell count was normal, in one the protein level was not raised, and in three there was no lowering of the CSF glucose content. Direct microscopy of the Ziehl–Nielson preparation revealed acid-fast bacilli in 22 per cent of cases and the CSF cell count revealed a combination of lymphocytes and polymorphs in over half the samples, the average polymorph count in these cases being 43 per cent.

Table 3. Cerebrospinal fluid findings before treatment.

	No. of patients	%
Cell count		
No. per mm^3		
0–3	3	7
4–99	25	58
100–399	14	33
400	1	2
mean 122		
cases with lymphoctes and polymorphs		53
average polymorph		43
Protein g/l		
0–0.45	1	2
0.46–0.99	9	21
1–5	28	65
5	5	12
mean 2.8		
Glucose mmol/l		
0–2	34	79
2.1–2.5	6	14
2.5	3	7
mean 1.4		
Acid-fast bacilli seen 9		22

Serum Sodium

Serum sodium measurements before treatment were available in 37 patients and hyponatraemia was present in all but four. The mean sodium was 127mmol/litre and Fig. 3 shows the distribution of these values.

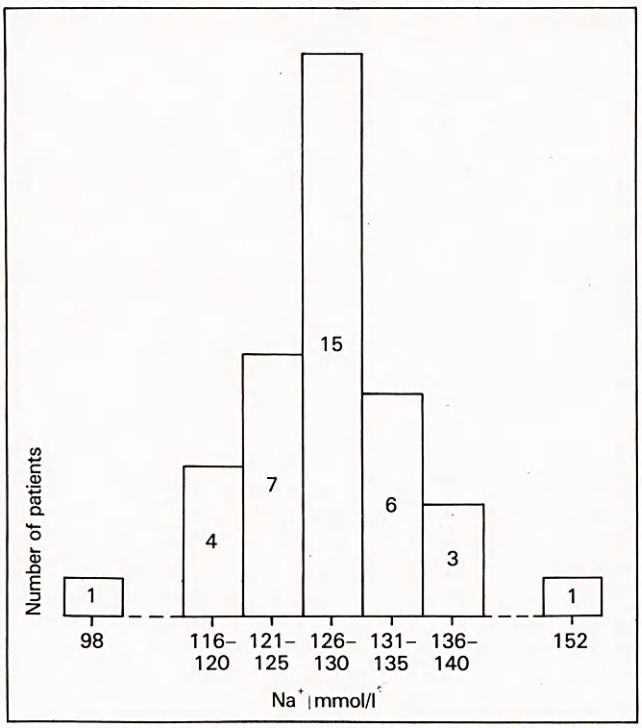


Fig. 3. *Serum sodium before treatment.*

Treatment

The majority of patients were treated with three or four anti-tuberculous drugs, the most frequent combination being rifampicin, isoniazid and streptomycin; ethambutol, ethionamide, PAS or pyrazinamide were used less frequently (Table 4). Intrathecal streptomycin therapy was given to 13 patients. Thirty-six patients (84 per cent) received parenteral or oral steroids for varying lengths of time. The treatment period varied from nine months to two years. In one patient treatment was given for one year and two years later he relapsed and died.

Table 4. Drug treatment. (Treatment period 9 months to 2 years).

Drug	No. Treated
Isoniazid	40
Rifampicin	33
Streptomycin	29
Ethambutol	18
PAS	8
Ethionamide	5
Pyrazinamide	6
3 drugs	23
4 drugs	20

Outcome (Table 5)

The overall mortality in this series was 23 per cent and a high proportion of survivors (36 per cent) had some degree of neurological disability as a consequence of their illness. This disability was variable and only four patients were incapable of independent existence.

Table 5 shows clearly that both mortality and morbidity are related to the severity of the disease at the start of treatment. Half the cases in MRC Group III died and only one individual in this group recovered without significant deficit. The frequency and type of neurological complication arising during treatment, including those which ultimately resolved, are shown in Table 6, which again emphasises the direct relationship between the severity of illness before treatment and subsequent neurological deficit.

Table 5. Results of treatment related to MRC group at start of treatment.

Group	No. of patients	%	Recovered	Disability	Mortality
I	6	14	5	1	—
II	22	51	12	7	3 (14%)
III	15	35	1	7	7 (50%)
Total (%)			41	36	23

Hydrocephalus is a well-recognised complication of tuberculous meningitis, and in this study was clinically evident in 17 patients. Ten patients were treated surgically with a ventricular shunting procedure; it was not clear from the case records why the other seven were not shunted, though the patients may have been considered too ill to benefit. The effect of shunting related to the outcome is shown in Table 7. The difference in mortality between the shunted and non-shunted patients is not statistically significant.

Discussion

Assuming that the findings of this regional survey are representative of Britain as a whole, the results suggest that a number of changes have occurred in the clinical picture of TBM in parallel with the diminished incidence of tuberculosis. Associated tuberculous lesions appear to be much less common than previously reported[8], and in most instances clinically evident tuberculous infection was confined to the central nervous system. Radiological evidence of pulmonary or miliary TB was seen in less than 20 per cent of cases (contrasted with 60 per cent in the 1948 MRC report[7]) and no other tuberculous lesions were identified in this survey. The mortality in those with miliary tuberculosis (66 per cent) was considerably higher than that of the group as a whole (23 per cent).

There may have been an increase in the proportion of cases falling into MRC Group III before treatment (35 per cent in this survey and 23 per cent reported by Smith *et al.*[3]). There are two possible reasons for this. With the decline in incidence of TBM, the diagnosis is likely to be

Table 6. Neurological complications during treatment. The total number of neurological complications is shown individually. Some patients suffered more than one complication. r = recovered.

Complication	Group I	Group II	Group III
Memory and intellectual impairment	1	2	3
Emotional lability and disinhibited		1	2
Epilepsy		2	
Hydrocephalus	1	7	9
Hypothalamic disturbance		3 — amenorrhoea; excess appetite (r); disturbed — sleep (r), temp., appetite (r)	
Extrapyramidal syndrome			1 (r)
Hemiparesis		3 (2r)	3
Spinal arachnoiditis		3—(1r) (mild 1) (mod 1)	1 (mod)
Ataxia		1	
Ocular palsy	2 (r)	3 (r)	3 (r)
Optic atrophy		2	
Optic tract lesion			1
Total	4	27	23

Table 7. Hydrocephalus and effect of shunting.

	No. of patients	Deaths
Shunted	10	3
Not shunted	7	6
Total	17	9

$P = 0.069$, NS

made less readily. However, this is not a sufficient explanation, since the average length of the meningitic illness is independent of the MRC group of severity, and if diagnostic delay were a major factor in accounting for the increase in cases falling into Group III, the length of the meningitic illness should be longer in this group. Although the broadness of the MRC groups would tend to conceal this so that patients may deteriorate without change of MRC group, it seems likely that, in addition to diagnostic delay, variable host resistance affects the severity of the disease.

Too great a reliance on typical CSF findings and the demonstration of acid-fast bacilli can lead to delayed or mistaken diagnosis. In seven cases in this study one of the CSF constituents was normal. A mixture of polymorphs and lymphocytes is more common than supposed and can make impossible the early laboratory differentiation of TBM from partially treated pyogenic meningitis. This is a familiar problem to the clinician and is exaggerated by the fact that acid-fast bacilli were identified in the initial preparation in less than a quarter of subsequently bacteriologically proven cases. Hyponatraemia was a common early feature in this study and its presence may be of some diagnostic help.

The outcome of treatment is disappointing since despite the introduction of new anti-tuberculous drugs, the mortality in this study is not appreciably different from results reported in earlier decades[3,9], and is comparable with recent reports from Glasgow[10] and the USA[11]. The morbidity among survivors remains high (36 per cent) and in most cases this involves a significant neurological disability. Some of the possible reasons for these poor results have been commented upon (diagnostic delay, variable host resistance and inherent severity of the disease), but it is doubtful whether chemotherapy and adjuvant therapy were used to their full potential.

This study shows that there is no unanimity about the best combination of chemotherapy, optimal duration of treatment or the need for intrathecal therapy with steroids, streptomycin or purified protein derivative (PPD). No patient in this series received PPD and in the 30 per cent in whom intrathecal streptomycin was used, this treatment was continued for a few days only. As the patients who received intrathecal treatment were usually more severely affected, it was not possible to draw any conclusions as to its effectiveness, although one patient with spinal arachnoiditis made a dramatic recovery following the introduction of intrathecal streptomycin. A similar confusion surrounds the use of parenteral or oral steroids in TBM[12,13]. In our series their use was

almost routine (84 per cent), but as the results are not appreciably different from those of Hockaday *et al.*[13], who reserved steroids for acute cerebral or pulmonary oedema and overwhelming tuberculous infection, it would appear that the benefit of routine steroids is questionable. The results of our study suggest that treatment of symptomatic hydrocephalus by early ventricular shunting may be beneficial but since these figures are not statistically significant, further studies are necessary[14].

As a result of extensive experience, Smith made very specific recommendations for the treatment of tuberculous meningitis[15]. Nevertheless, following the introduction of new anti-tuberculous drugs, the principles of management have become less clear, and it is evident that uncertainties about the optimum form of chemotherapy[16], the place of steroids and the need for intrathecal administration now exist. Since it is estimated that about 100 cases of TBM occur annually in England and Wales[6], it seems possible that these questions could be answered by multicentre trials.

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