TREATMENT OF TUBERCULOUS MENINGITIS

BY

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(RECEIVED FOR PUBLICATION JANUARY 27, 1959)

When isoniazid is used for the chemotherapy of tuberculous meningitis the need for intrathecal therapy is controversial. A Scottish Joint Committee (1957) concluded from a comparative trial, including both adults and children, that intrathecal streptomycin is not now an essential part of the treatment. But, in fact, all the patients reported did receive intrathecal streptomycin for at least one week. Lincoln (1958) and Gaisford (1958) have abandoned intrathecal therapy but Smith, Vollum, Taylor and Taylor (1956) and Lorber (1956) maintain that some, not necessarily prolonged, treatment by the intrathecal route should be given and Miller (1958) concurs with this opinion. Since February, 1954, routine intrathecal therapy has been abandoned by one medical unit in the Royal Hospital for Sick Children, Glasgow, but retained by the other. In both units, however, the alternative method of treatment has occasionally been used when the clinician in charge judged this advisable. The purpose of the present paper is to compare the results obtained with these two methods of treatment.

Case Material

The material comprises 41 cases of tuberculous meningitis admitted to the Royal Hospital for Sick Children, Glasgow, between February 1, 1954, and December 31, 1957. In one case no treatment was given as the child died shortly after admission to hospital and the diagnosis was only established in the post-mortem room. Twenty cases received intrathecal streptomycin (Group 1) and 20 had no intrathecal therapy (Group 2). The age distribution of these patients and the stage of their disease at the start of treatment is shown in Table 1. The stage of the disease has been assessed on the patient's clinical condition as early, medium and advanced in the way described by the Medical Research Council (1948).

Three patients in Group 1 and five patients in Group 2 had a snowstorm appearance of the lungs on radiography and in five there were choroidal

TABLE 1
AGE DISTRIBUTION AND STAGE OF DISEASE OF THE 40 TREATED CASES OF TUBERCULOUS MENINGITIS

Age (yr.)	Group 1			Group 2		
	E	M	A	E	M	A
0-2 ..	3	6	0	1	5	2
3-4 ..	0	5	1	4	1	0
5-10 ..	1	4	0	1	5	1
Total ..	4	15	1	6	11	3

E=early; M=medium; A=advanced

tubercles. One patient in each group had active spinal caries.

Bacteriological confirmation of the clinical diagnosis by smear, culture or guinea-pig inoculation of the cerebrospinal fluid was obtained in 17 cases in Group 1 and 15 cases in Group 2. Post-mortem examination confirmed the diagnosis in a further two cases in Group 2. One of the remaining three cases in each group had 'snowstorm lungs'.

Methods of Treatment

Group 1 (with Intrathecal Therapy)

Intrathecal Streptomycin. Dosage ranged from 25 to 50 mg. per injection according to age. Injections were given daily for a week, except in two cases where intrathecal therapy was stopped on the fifth and sixth days respectively. After the first week, injections were given on alternate days, twice weekly or weekly according to the physician's appraisal of the patient's progress. The number of intrathecal injections in the patients of this group ranged from five to 36.

Intramuscular Streptomycin. The daily dose was 20 mg. per lb. body weight (40 mg. per kg. body weight), given either as two divided doses (17 cases) or as a single injection (three cases). This was continued for five to seven months in 14 cases and for three to four months in five cases. One patient died in the fifth week of treatment.

Oral Isoniazid. The daily dose varied from 10 to 20 mg. per kg. body weight (5 to 10 mg. per lb. body weight). This was continued for between five and 10 months in 15 cases and for three to four months in four cases. The remaining patient was the one who died in the fifth week of treatment.

Additional Drug Therapy. Three patients were given para-aminosalicylic acid (P.A.S.). This was continued for one week in one, four weeks in another and 20 weeks in the third. One patient was given cortisone for four weeks and another prednisolone for 20 weeks.

Group 2 (without Intrathecal Therapy)

Intramuscular Streptomycin. The daily dose was 20 mg. per lb. body weight (40 mg. per kg. body weight), given either as two divided doses (one case) or as a single injection (19 cases). This was continued for five to six months in 14 cases and for three months in one case. Five patients died during their course of treatment. The duration of illness after the start of treatment in these cases was five days, three weeks, three months (two cases) and five months respectively.

Oral Isoniazid. The daily dose varied from 10 to 20 mg. per kg. body weight (5 to 10 mg. per lb. body weight). Except in the five cases where death intervened this was continued for six months to one year.

Additional Drug Therapy. P.A.S. was given to one patient for six weeks and to another for six months. Four patients received prednisolone. One patient was given intramuscular A.C.T.H. and intrathecal streptomycin (10 injections) during the last 17 days of his life. This patient is included in Group 2 as the intrathecal streptomycin did not alter the course of the illness.

Results

Recoveries. Seventeen patients in Group 1 and fifteen patients in Group 2 survived. Fourteen of the survivors in each group are well and have no detectable sequelae.

Relapses. Five patients in Group 1 had a relapse of the disease. In three, anti-tuberculous drugs were given initially for less than six months. One of these cases ended fatally. No patient in Group 2 has relapsed.

As a relapse can be regarded as a complication of the treated disease, the outcome of the relapse has been taken as the result of treatment in these cases.

This has been done although one of the relapses was treated without intrathecal therapy.

Deaths. Three patients in Group 1 and five patients in Group 2 died. Of the five deaths in Group 2, one occurred from status epilepticus on the fifth day of treatment, one was in the case of a low-grade primary ament, while in the third case the tuberculous meningitis was the termination of advanced spinal caries and resulted from the rupture into the spinal subarachnoid space of a large paravertebral cold abscess.

Disabilities. Four survivors, three in Group 1 and one in Group 2, are disabled. All show mental retardation and various types of spastic palsy. One in Group 1, a girl, also has frequent convulsions and premature hypertrophy of the breasts.

One other child in Group 2, aged 2 years and admitted in the medium stage of the disease, had a right hemiplegia at the time drug treatment was completed. Eighteen months later he had made a complete recovery.

Factors Influencing Results

Stage of Disease. It is generally accepted that, apart from the nature of the therapy used, the most important factor governing the prognosis in tuberculous meningitis is the stage of the disease at the start of treatment. In both groups of the present study (Table 2) patients with advanced disease either

TABLE 2
EFFECT OF STAGE OF DISEASE ON RESULTS OF TREATMENT

Stage of Disease	Group 1			Group 2		
	Healthy	Disabled	Dead	Healthy	Disabled	Dead
Early	3	1	0	5	0	1
Medium	11	1	3	9	0	2
Advanced	0	1	0	0	1	2

died or had residual disabilities, whereas the majority (74% in Group 1 and 82% in Group 2) of patients in the early and medium stages made a complete recovery. The death of a boy in the early stage of the disease treated without intrathecal therapy (Group 2) was unexpected. However, he was a known low-grade mental defective which may have contributed to the fatal outcome. Comparison of the two groups shows that the preponderance of deaths in the group treated without intrathecal therapy was due to the death of two children who were in the advanced stage of the disease when

treatment was started. One of these was the case associated with advanced spinal caries.

Age. When the results of treatment are related to the age of the patients at the onset of their illness it is seen that with one exception the deaths and disabilities were confined to children under 5 years of age (Table 3). The exception is again the case

TABLE 3
EFFECT OF AGE ON RESULTS OF TREATMENT

Age Group (yr.)	Group 1			Group 2		
	Healthy	Disabled	Dead	Healthy	Disabled	Dead
0-2	6	1	2	4	1	3
3-4	3	2	1	4	0	1
5-10	5	0	0	6	0	1

of the boy with advanced spinal caries. The less favourable prognosis of children under 3 years of age is recognized and has been shown to be due, at least in part, to delay in diagnosis (Medical Research Council, 1948; Lorber, 1954). In the present series the children under 5 years of age did tend to be in a later stage of the disease at the start of treatment than the older children. This is not apparent from Table 1 because of the wide range in the clinical condition of the patients included in the medium stage of the Medical Research Council classification.

Associated Miliary Tuberculosis. In neither group did an associated miliary tuberculosis of the lungs adversely affect the prognosis (Table 4). Indeed all

TABLE 4
EFFECT OF ASSOCIATED MILIARY TUBERCULOSIS ON RESULTS OF TREATMENT

	Group 1			Group 2		
	Healthy	Dis-abled	Dead	Healthy	Dis-abled	Dead
With 'snowstorm' lungs	2	1	0	4	1	0
Without 'snow-storm' lungs	12	2	3	10	0	5

the children with this association survived. This contrasts with the disproportionately high fatality rate in tuberculous meningitis associated with miliary tuberculosis when streptomycin was the only effective drug available (Russell and MacArthur, 1950).

Spinal Block. Two children in Group 2 had a spinal block and both had prednisolone added to

their therapy when the block was recognized. One had a spinal block on admission and recovered completely. The other, whose spinal block appeared during treatment, developed a progressive hydrocephalus and died. During prednisolone therapy, however, both showed clinical improvement and a fall in the protein content of the cerebrospinal fluid obtained by lumbar puncture.

Duration of Therapy. Five patients in Group 1 were treated with anti-tuberculous drugs for less than six months. Three of these had a relapse which was confirmed bacteriologically and one died. The fourth was given a further course of chemotherapy 15 months after the completion of his initial treatment because the radiological appearances in the chest showed deterioration. The fifth patient died. He was deeply unconscious with a progressive hydrocephalus after three months' treatment and, as the prognosis was regarded as hopeless, chemotherapy was stopped.

The short period of chemotherapy in these cases was probably responsible for the high relapse rate. Continuing daily intramuscular streptomycin for six months and daily oral isoniazid for a similar or an even longer period seems to be advisable if relapses are to be reduced to a minimum.

One patient in Group 2 was treated with intramuscular streptomycin for three months only but isoniazid was continued for nine months and this patient has remained well.

Method of Treatment. As complete recovery is the rule in the early stage of the disease and the exception in the advanced stage, Smith *et al.* (1956) consider that the results obtained in the medium stage are the most valuable for comparing the effectiveness of different methods of treatment. In the present series the recovery rate in the medium stage was 80% in the group receiving intrathecal therapy and 82% in the group treated without intrathecal therapy. By this criterion, therefore, the results of treatment were as good without intrathecal therapy as with it.

Discussion

There were 15 survivors from a group of 33 cases treated in this hospital with streptomycin alone (Russell and MacArthur, 1950). This is a survival rate of 45% and contrasts with 80% in the present series. As the proportion of early, medium and advanced cases is similar in the two series the higher survival rate in the present series is not due to earlier diagnosis and must be attributed to the inclusion of isoniazid in the therapeutic regime. It is disappoint-

ing that a decade has seen no progress in establishing the diagnosis at an earlier stage. In the present series the deaths and residual disabilities were almost entirely confined to children under 5 years of age, so that if improved results in the future are to be achieved by earlier diagnosis this disease must be constantly included in the differential diagnosis of unexplained illness in early childhood. The falling incidence of primary tuberculosis throughout the country may, in fact, tend towards delay in the diagnosis of tuberculous meningitis if doctors should fail to keep the possibility in mind in the case of young children with 'minor' symptoms of only a few days' duration.

Comparison of the two groups in the present study suggests that the results to be obtained without intrathecal therapy are as good as those obtained when a small number of intrathecal injections are included in the treatment. The Scottish Joint Committee (1957) has pointed out that if a schedule of chemotherapy was ineffective an excessive mortality in the first 28 days of treatment and a high relapse rate would be expected. In the group treated without intrathecal therapy there have been no relapses and only one child died during the first 28 days of treatment. As this child became unconscious the day after treatment was started and died in status epilepticus on the fifth day of treatment it is unlikely that his death would have been prevented by intrathecal streptomycin. By these criteria therefore a combination of intramuscular streptomycin and oral isoniazid has proved in the present study to be effective treatment for tuberculous meningitis.

Conclusion

These findings are considered to indicate that daily

intramuscular streptomycin for six months and daily oral isoniazid for a similar or an even longer period is the treatment of choice in the routine treatment of tuberculous meningitis in childhood at the present time. Adoption of this policy would avoid the hazards and discomforts of intrathecal streptomycin therapy in many cases of this disease. However, as superior results have not been shown to follow the withholding of intrathecal streptomycin, a limited number of intrathecal injections of streptomycin may still be advisable in children who are in the late stages of the disease when the diagnosis is established, and possibly in children whose disease does not show an early response to intramuscular and oral treatment.

Summary

Forty cases of tuberculous meningitis are reviewed. All of them were treated with intramuscular streptomycin and oral isoniazid. Twenty were also given intrathecal streptomycin in a minimum of five and a maximum of 36 injections. The results of treatment were as good without intrathecal therapy as with it. None of the children treated without intrathecal therapy had a relapse of the disease.

I wish to thank Professor Stanley Graham and Dr. J. H. Hutchison for helpful advice and criticism and for permission to publish this study of patients treated in their wards.

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