TUBERCULOUS MENINGITIS TREATED WITH A.C.T.H. AND ISONIAZID

A COMPARISON WITH INTRATHECAL STREPTOMYCIN

BY

WINIFRED C. M. BULKELEY, M.B., B.S., D.C.H.

Council for Scientific and Industrial Research, Tuberculosis
Research Unit, King George V Hospital, Durban

Until the advent of streptomycin, tuberculous meningitis was a fatal disease. With the use of intrathecal streptomycin the mortality was reduced to 40–50% by most workers (Cocchi and Pasquinucci, 1950; Smith and Vollum, 1950; Lincoln and Sifontes, 1953). A change in the intrathecal schedule to daily injections over a very prolonged period and the earlier diagnosis of the disease have reduced the mortality still further (Cocchi and Pasquinucci, 1950; Smith and Vollum, 1950; Lincoln and Sifontes, 1953). Cairns, Smith, and Vollum (1950), whilst experimenting with intrathecal tuberculin, found that this substance, given intrathecally, was able to aid the resorption of the thick basal exudate that is always present in fatal cases, and this, with the concomitant use of intrathecal streptomycin, has salvaged some of the cases that were hitherto considered incurable (Cairns *et al.*, 1950; Smith and Vollum, 1950).

In an attempt to prevent the formation of the thick basal exudate and to control the development of tuberculous endarteritis it was decided to try the effect of intramuscular or subcutaneous adrenocorticotrophic hormone (A.C.T.H.), using isoniazid (isonicotinic acid hydrazide) by mouth also, instead of intrathecal streptomycin. It has been demonstrated that isoniazid given by mouth enters the cerebrospinal fluid (C.S.F.) in high concentration (McDermott, 1952), and it was hoped that by controlling the cellular reaction with A.C.T.H. the tubercle bacilli would be left free for antibiotic attack instead of being enmeshed and inaccessible in the thick basal exudate.

This work was started with children at King George V Hospital, Durban, in March, 1952. In September, 1952, after we had satisfied ourselves of the efficacy of this treatment by treating 13 cases in this way, intramuscular streptomycin and oral *p*-aminosalicylic acid (P.A.S.) were added to the schedule to delay the development of resistant strains of tubercle bacilli. Many of these patients have extensive tuberculosis in other parts of the body.

In 1950 our overall mortality rate from tuberculous meningitis was 60%; this was reduced to 10% in 1951,

when earlier diagnosis was made and daily intrathecal streptomycin was given until the C.S.F. was normal for several months.

The mortality rate for the present series is 6.45%; this includes three patients who were having intrathecal streptomycin and who were changed to the new regime (the intrathecal streptomycin being discontinued); also five patients to whom intrathecal streptomycin was also given because of our inexperience with A.C.T.H. and isoniazid at this time, and our fear that the patients might suffer.

Classification of Cases

The streptomycin group (31 cases) and the present series (31 cases), though unselected, are fairly comparable in the numbers of early, intermediate, and late cases. The comparative mortality for the two groups is shown in Table I.

The following criteria have been used as a basis for our classification at time of diagnosis.

Early.—Fever, vomiting, headache, drowsiness, neck stiffness, and/or bulging fontanelle and/or positive Kernig sign in a known tuberculous patient with a raised C.S.F. cell count, protein, and globulin, and a variable chloride and sugar content.

Late.—As above, plus clouding of consciousness or coma, paralysis, and/or multiple fits and grossly abnormal C.S.F. findings.

Intermediate.—Cases lying between the two extremes.

Action of A.C.T.H.

Before the advent of isoniazid A.C.T.H. had been tried experimentally in three children suffering from tuberculous meningitis—two with hemiplegia, and one subject to multiple fits; two of these children were mentally abnormal. There was an obvious improvement in all three. Unfortunately the supply was adequate for only one week's trial. All children had been receiving intrathecal streptomycin for some months.

The action of A.C.T.H. is well demonstrated in the following case history (No. 53, Table III).

A Bantu girl aged 7 years was admitted on December 17, 1952, with tuberculous meningitis. She was emaciated and dehydrated, had a left facial paralysis, was drowsy but could be roused, and was doubly incontinent. She improved rapidly on our new regime, but on February 9, 1953, the C.S.F. was observed to be turbid, though no growth was obtained on culture for secondary organisms. By February 12 it was evident she was developing a partial spinal block, and A.C.T.H. was given again. Table II

TABLE II

Date	Cells perc.mm.	Protein (mg./ 100 ml.)	Chloride (mg./ 100 ml.)	Sugar (mg./ 100 ml.)	Pressure
2/2/53	76	158	—	44	Normal
9/2/53	184	248	640	36	Low
12/2/53 (lumbar fluid)	338	286	680	18	Very low
12/2/53 (cisternal fluid)	48	158	660	33	Raised
16/2/53 (lumbar fluid)	4	57	675	58	Normal

TABLE I

Date	Early			Intermediate			Late			Total Cases
	Cases	Deaths	Cause of Death	Cases	Deaths	Cause of Death	Cases	Deaths	Cause of Death	
1950	0	0	—	4	2	Both from tuberculous meningitis	6	6	4 tuberculous meningitis; 1 cerebral tuberculoma (one year later, meningitis healed); 1 hydro- cephalus (one year later, menin- gitis healed)	31
1951	11	2	1 tuberculous septicaemia; 1 extensive bilateral pulmon- ary tuberculosis and cere- bral tuberculoma and tuber- culous meningitis	3	0	—	7	3	1 tuberculous meningitis; 1 lobar pneumonia (meningitis healing); 1 superior sagittal sinus thrombo- sis (meningitis healing)	
Present series	8	1	1 cor pulmonale (meningitis healing)	6	0	—	17	5	2 tuberculous meningitis; 1 pyogenic meningitis; 1 cerebral tuber- culoma and cerebral softening (meningitis healing); 1 cause unknown (meningitis healing)	31

Table III gives a detailed analysis of these cases.

TABLE III.—Analysis of 62 Cases of Tuberculous Meningitis Treated Since 1950

Case No.		Age in Years	Pulmonary or Other Tuberculosis	Classification	Treatment	Result	Cause of Death
1	29/3/50	2½	Miliary tuberculosis	Late	1+1A	Death	Tuberculous meningitis
2	6/4/50	3	"	Intermediate	1+P.P.D.	"	"
3	5/6/50	10	Bilateral pulmonary tuberculosis	Late	"	"	"
4	17/6/50	5	Miliary tuberculosis + cervical adenitis	Intermediate	1+1A	"	"
5	22/6/50	2	Miliary tuberculosis	Late	1+1A	"	"
6	29/7/50	9/12	"	"	1+P.P.D.+1A	"	Tuberculoma. Meningitis healed
7	11/8/50	5	Miliary tuberculosis + cervical adenitis	Intermediate	1+3 (in 1952)	Recovery—deaf and precocious puberty	—
8	28/10/50	4	Miliary tuberculosis + tuberculous knee-joint	"	1	Recovery—deaf	—
9	20/11/50	20/12	Progressive primary pulmonary tuberculosis	Late	1+1A+P.P.D.	Death	Hydrocephalus. Meningitis healed
10	27/12/50	2	Miliary tuberculosis	"	1	"	Tuberculous meningitis
11	23/1/51	11/12	Primary pulmonary tuberculosis	Early	1+A.C.T.H. 1/52 in Feb., 1952	Recovery, but very retarded	—
12	27/1/51	5	Calcified primary pulmonary. Complex + spinal caries	"	1	Recovery—deaf	—
13	31/1/51	7	Gross bilateral pulmonary tuberculosis	"	1	Death	Tuberculoma of brain + tuberculous meningitis + extensive tuberculosis
14	25/2/51	7/12	Primary pulmonary tuberculosis	"	1	Recovery	—
15	4/3/51	12	Calcified primary pulmonary. Complex + spinal caries	Intermediate	1	Recovery—deaf	—
16	4/3/51	6	Progressive primary pulmonary. Tuberculosis + spinal caries with paraplegia	Late	1	"	—
17	6/4/51	1	Miliary tuberculosis	"	1+1A+P.P.D.+2	Recovery—deaf, blind, and hydrocephalic, quadriplegic	—
18	11/4/51	10/12	Miliary tuberculosis + unilateral pulmonary cavitation	"	1	Death	Superior sagittal sinus thrombosis, meningitis resolving
19	10/5/51	3	Miliary tuberculosis	Early	1	Recovery	Tuberculous meningitis
20	11/5/51	15/12	"	"	1	"	—
21	13/7/51	4	Progressive primary pulmonary tuberculosis	"	1	"	—
22	14/7/51	3	Primary pulmonary tuberculosis	Late	1+1A+P.P.D.+2 A.C.T.H. 1/52 in Feb., 1952	Death	Pneumonia. Meningitis resolving
23	31/8/51	8	Pleural effusion	Early	1	Recovery—deaf	—
24	20/9/51	13	Miliary tuberculosis + tuberculous septicaemia	"	1+2	Death	Jaundice and anaemia
25	26/10/51	5	Miliary tuberculosis + spinal caries	"	1	Recovery—deaf	—
26	7/11/51	4	Progressive primary pulmonary tuberculosis + cervical adenitis. Spinal caries developed under treatment	Late	1+A.C.T.H. 1/52 in Feb., 1952	"	—
27	10/12/51	5	C.S.F. relapse after 10 months	Early	4	Rapid response	—
28	14/12/51	7	Miliary tuberculosis	Intermediate	1	Recovery	—
29	20/12/51	9/12	Progressive primary pulmonary tuberculosis	"	1	"	—
30	31/12/51	Adult	Primary tuberculosis	Late	1	"	—
			Miliary tuberculosis	Intermediate	1+decompression of right lateral ventricle for sudden hemiplegia	Recovery—deaf	—
31	7/1/52	5	Bilateral pulmonary tuberculosis	Early	1	Recovery	—
32	7/2/52	3	Miliary tuberculosis	"	1 for 3/52 then isoniazid alone	"	—
33	7/3/52	2	"	Late	1+isoniazid	Recovery after partial spinal block	—
34	29/3/52	18/12	Primary pulmonary tuberculosis	Early	3+isoniazid alone for C.S.F. relapse	Recovery	—
35	1/4/52	5	Miliary tuberculosis + spinal caries	Intermediate	3	"	—
36	9/4/52	10	Bilateral pulmonary tuberculosis + calcified tuberculoma of brain	Early	3	"	—
37	30/4/52	3	Miliary tuberculosis	"	1→3	"	—
38	11/5/52	5	Primary pulmonary tuberculosis	Late	3	Death	Cause unknown. Meningitis resolving
39	6/6/52	14/12	Miliary tuberculosis	"	3+1	Death in 1 week	Tuberculous meningitis + disseminated tuberculosis
40	6/6/52	8	Primary pulmonary tuberculosis + spinal caries	Early	3	Recovery	—
41	14/6/52	2½	Primary pulmonary tuberculosis	Late	3+1	Death	Pyogenic meningitis
42	18/6/52	5½	Primary pulmonary tuberculosis + cervical adenitis	"	3+1	Recovery after coma lasting 5 weeks	—
43	23/6/52	6	Progressive primary pulmonary tuberculosis + cervical adenitis	Intermediate	3	Recovery	—
44	25/6/52	2½	Miliary tuberculosis	Late	3+1+tryptar	Recovery after spinal block	—
45	11/7/52	18/12	"	"	3	Recovery	—
46	22/8/52	2	Bilateral pulmonary tuberculosis	Early	4	Death	Cor pulmonale
47	8/9/52	3	Miliary tuberculosis	Late	4	"	Tuberculoma of brain, cerebral softening, meningitis resolving
48	12/9/52	10	"	"	4	Recovery	—
49	24/9/52	2	Progressive primary pulmonary tuberculosis + spinal caries	"	4	Death	Spinal caries with exposure of dura and tuberculous meningitis
50	14/10/52	16	Primary pulmonary tuberculosis	"	4→1→(1+4)	Admitted with paraplegia and retention of urine. Making slow progress. Deaf. Isoniazid omitted temporarily because of mental derangement	—
51	22/11/52	6	Healed miliary tuberculosis + active spinal caries	Intermediate	4	Recovering	—
52	26/11/52	6	Miliary tuberculosis	Late	4+2 extra courses A.C.T.H.	Recovering (see text)	—
53	17/12/52	7	Bilateral pulmonary tuberculosis	"	4+1 extra course A.C.T.H.	"	—

TABLE III.—*Analysis of 62 Cases of Tuberculous Meningitis Treated Since 1950. (Continued.)*

Case No.		Age in years	Pulmonary or Other Tuberculosis	Classification	Treatment	Result	Cause of Death
54	20/12/52	2½	Bilateral pulmonary tuberculosis + spinal caries	Early	4	Recovering	—
55	20/1/53	1	Primary pulmonary tuberculosis	Late	4	„	—
56	21/1/53	7	Miliary tuberculosis	Intermediate	4	„	—
57	26/1/53	15/12	„ „	Late	4	Recovering. Hemiplegic still	—
58	28/1/53	4	Miliary tuberculosis + spinal caries	Early	4	Recovery	—
59	12/2/53	10	Miliary tuberculosis	Late	4	Recovering after spinal block	—
60	3/3/53	21/12	„ „	„	4	Rapid deterioration, followed by slight improvement	—
61	24/3/53	9	Unilateral pulmonary cavitation	Intermediate	4	Recovering	—
62	27/3/53	22	Abdominal tuberculosis	„	4	„	—

1=Intrathecal streptomycin+intramuscular streptomycin (I.M.S.)+oral P.A.S. 1A=Intraventricular therapy. 2=Intravenous P.A.S. 3=A.C.T.H.+isoniazid. 4=A.C.T.H.+isoniazid+I.M.S.+oral P.A.S. Recovering=C.S.F. almost normal and patient apparently normal.

demonstrates its effectiveness. After this the fluid gradually returned to its previous state and has progressively improved.

Post-mortem examinations performed on patients with tuberculous meningitis who were treated with this regime, and who died of extensive tuberculosis in other organs or of other diseases, have not shown such gross basal exudate as we were accustomed to seeing, and some presented a "clean brain."

Scheme of Treatment

1. A.C.T.H., 6 to 25 I.U. six-hourly intramuscularly or 12 to 50 I.U. twice a day of the gel subcutaneously; this is given for one week if the patient makes steady progress. It is continued longer if the response is not as good as expected or if there is a block, partial or complete. A patient admitted in coma is usually able to answer questions and help to feed himself by the end of a week. It has been given for as long as five weeks, with no toxic effects or withdrawal symptoms, other than moon-face and some oedema.

2. Isoniazid is given by mouth in dosage of 4 mg. per lb. body weight per 24 hours, but the first two doses are equivalent to 8 mg. per lb.; the dose is increased as the weight increases, and very thin children are given the dose for their expected weight. Intramuscular isoniazid has been used, but does not seem any more effective, though it is of use in patients who are vomiting. Intrathecal isoniazid has also been tried and found to be both irritant and unnecessary, and, as this drug has no antibiotic action against the usual secondary organisms, the risk of a secondary septic meningitis is very great.

3. Streptomycin, 0.02 g. per lb. body weight per 24 hours to the nearest 0.5 g., but not exceeding 1 g., is given daily until the temperature settles and improvement is assured, and then every third day.

4. P.A.S., 0.1–0.15 g. per lb. body weight per 24 hours by mouth.

5. C.S.F. is collected weekly for examination—bi-weekly for the first two to three weeks.

Cerebrospinal Fluid Findings

Whilst A.C.T.H. is administered there is a marked fall in cells and protein in the C.S.F.; on discontinuing the drug the cells rise slightly, and the protein more so: this rise continues for a few weeks, and then there is a gradual fall until the whole C.S.F. picture returns to normal. The C.S.F. appears to return to normal more quickly than in the streptomycin-treated cases—that is, in one to four months.

Complications.—Complications which have been observed are (1) moon-face; (2) oedema; (3) septic complications—(a) pyogenic meningitis (Case 41); (b) acute otitis media (Case 55); (4) mental disturbances due to isoniazid in one adult patient.

Discussion

This form of treatment is simple to administer, but the A.C.T.H. or isoniazid can easily be forgotten. It is a maxim in dealing with tuberculous meningitis that the disease and

its complications must be treated early and adequately. A good deal of experience with cases of tuberculous meningitis is necessary when using this regime. Without daily lumbar punctures (as with intrathecal streptomycin therapy) one does not automatically inspect the C.S.F. daily for change in colour and turbidity or observe pressure changes. One must rely on one's clinical judgment to determine if additional punctures—lumbar, cisternal, or even ventricular—are necessary to control raised intracranial pressures or to diagnose complications. This is shown by the following case (No. 52, Table III).

An Indian girl aged 6 years was admitted in coma on November 26, 1952; she could be roused, but resented disturbance, and one could not communicate with her. She made a fair initial improvement, but on December 4, after the A.C.T.H. was discontinued, she relapsed slightly, and the lumbar C.S.F. pressure was very low; this necessitated an immediate cisternal puncture to eliminate the possibility of a spinal block. She later developed a left hemiparesis, and the A.C.T.H. was recommenced. On December 30 the C.S.F. was completely normal, and remained so for one week, but the child was very restless and had difficulty in swallowing.

On January 3, 1953, she became worse, possibly owing to toxicity of A.C.T.H. and/or isoniazid, but both these were discontinued without improvement until January 8, when isoniazid was again given. On January 7 she did not swallow, but either held the food in her mouth or let it run out. Bilateral prefrontal burr-holes were made and the lateral ventricles explored, but very little fluid was obtained. There was, however, a transient improvement. She soon relapsed and required tube feeding. On January 19 she could be fed by mouth again with very great difficulty. On January 28 she was becoming very noisy; the C.S.F. was only slightly abnormal, but sedatives and forced feeding were still necessary. On February 26 the C.S.F. pressure was raised and the fluid was markedly abnormal. A.C.T.H. was re-administered for three weeks with dramatic improvement, and by April 7 she was able to sit up, help to feed herself, laugh, and talk. She would sing an Indian song on request, and she also spoke in English. On May 21 she stood up alone for the first time.

Conclusion

The form of therapy described above is producing very gratifying results, and there have been no cases of deafness, and no clinical or radiological evidences of spread of pulmonary tuberculosis whilst A.C.T.H. was being administered.

As most of our patients are small children the avoidance of the ordeal and danger of the daily lumbar puncture is a great advance. Intrathecal streptomycin is now a thing of the past in this hospital.

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