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Study on the Prognosis of Tuberculous Meningitis Treated with Streptomycin in Children

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Since the introduction of streptomycin as an antituberculous agent, many reports of dramatic results in the treatment of tuberculous menigitis have appeared in the medical literature.

Cures have been reported, and in fatal cases the course of illness has been prolonged from three weeks to many months and in many instances to one or more years.

At the Faculty of Pediatrics of Kyoto University, 83 children admitted between July 1948 and March 1953 have completed treatment and most of them have been discharged with the diagnosis "tuberculous meningitis" written on their charts.

In March 1953, we collected the results of treatment of our patients with tuberculous meningitis. The results are reported below.

1) The scheme of treatment

It is now beyond discussion that streptomycin is the most effective drug in the treatment of tuberculous meningitis.

The following scheme was adopted here; streptomycin by the intramuscular route 0.5 g. to 1 g. according to the age and body-weight of the patient, divided in two, morning and night, during the first month, then only half a dose; streptomycin (not dihydrostreptomycin) intrathecally 50 mg. daily regardless of age and weight during two months, then every other day or once or twice a week

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for at least six months, and often longer, according to the state of the patient. PAS, Teben, Promin or INAH have been used in combination, but in this report, we don't mention these drugs.

2) *Prognosis according to the total dose of streptomycin* (Table 1).

As table 1 shows, no one who has received a dose less than 40 g. of streptomycin is clinically cured. The maximum dose of streptomycin employed in clinical cures, was 300 g., where as the dose for patients who died was only 87 g.

Table 1 Prognosis according to total dose of streptomycin.

total dose of S.M. employed	dead	alive	cured
less than 19 g.	27	0	0
20 – 39 g.	11	2	0
40 – 79g.	13	5	12
more than 80 g.	1	7	5
total	52	14	17

comment: "cured" means: survival time of more than one year since treatment was begun, and at present they have no mental of physical defects, that is, are quite healthy.
"alive" means: survival time has been less than one year since treatment was begun, or more than one year, but with some physical or mental defects.

3) *Prognosis according to age* (Table 2).

In our own series most of our cases were from 1 to 5 years old, and the rate of mortality for children less than 1 year old (7 of 10 i.e., 70 %) is not so higher than that of others.[1][2]

Table 2 Prognosis accoding to age.

age	number of cases	dead	alive	cured
<1 year	10(12%)	7(70%)	2	1(10%)
1 – 5 years	59(71%)	36(61%)	10	13(22%)
<6 years	14(17%)	9(64%)	2	3(21%)

4) *Survival time after treatment was started* (Table 3).

It should be pointed out that death occurred mostly during the first six months. Of the 17 patients who have been clinically cured, 3 have been well for more than 3 years.

Table 3 Survival time after treatment was started.

survival time	dead	alive	cured
>3 years	0	2	3
3-2 years	0	4	6
2-1 year	4	0	8
1-0.5 year	5	6	0
6-1 month	31 } 83%	2	0
<1 month	12 }	0	0

5) Prognosis according to date of treatment (Table 4).

We know the treatment of tuberculous meningitis will be effective only if started early, but the course of tuberculous meningitis, though regular as a whole, can be long or short, and there is not always a correlation between the duration of illness at the time of the diagnosis and the condition of the child on admission to the clinic. We can not often determine the first clinical signs, that is, fever, headache, drowsiness, vomiting, convulsions etc., in their anamnesis, and are unable to determine the exact onset, so we select the first signs suggestive of the disease.

Table 4 Prognosis according to date of start of treatment.

date of start of treatment	number of cases	dead	alive	cured	mortality
first week	21	12	6	3	57%
second week	33	22	4	7	67%
third week	21	14	3	4	67%
S.M. had been employed	8	4	1	3	50%

Table 4 shows the prognosis according to the date of treatment.

Contrary to our expectations and other author's assertions,[1][2][3] we found that during the first week mortality is high. Accordingly, we see the state of consciousness at the time of admission.

6) Prognosis according state of consciousness (Table 5).

We divide the state of consciousness into two groups "clear" and "not clear". We find the mortality rate in the former 52.5%, in the latter 72%, and the rate of clinical cures in the former is 30%, in the latter 11.6%.

The duration of an abnormal state of consciousness before treatment, in survivors is 2.5 days, in those who died, (it is) 4.9 days.

Table 5 Prognosis according to state of consciousness.

state of consciousness	number of cases	dead	cured
clear	40	21(52.5%)	15(30%)
not clear	43	31(72%)	5(11.6%)

This shows that the relationship between the mortality rate and the state of consciousness at the time of admission to the hospital is much closer than the relationships between the mortality rate and duration of illness at the beginning of the treatment. Next, we use vomiting, fever, convulsion and headache as the first signs of the disease. The results are shown in tables 6, 7, 8 and 9. Table 8 is especially interesting for us, since it shows that the prognosis of the patients who have convulsions before treatment is very bad. Loss of consciousness and convulsions mean a bad prognosis for tuberculous meningitis.

Table 6 Prognosis according to date of start of treatment. (using vomiting as the first sign of the disease)

date of start of treatment	number of cases	dead	alive	cured	mortality
first week	33	19	9	5	57.5%
second week	15	11	1	3	73.2%
third week	7	5	2	0	71.5%

Table 7 Prognosis according to date of start of treatment. (using fever as first sign of disease)

date of treatment	number of cases	dead	alive	cured	mortality
first week	11	5	5	1	45.5%
second week	15	8	2	5	53.2%
third week	21	14	1	6	66.7%

Table 8 Prognosis according to date of start of treatment. (using convulsion as date of onset)

date of treatment	number of cases	dead	alive	cured	mortality
first week	6	6	0	0	100%
second week	2	2	0	0	100%
third week	2	2	0	0	100%

Table 9 Prognosis according to date of start of treatment.
(using onset of headache as first symptom)

date of treatment	number of cases	dead	alive	cured	mortality
first week	13	8	3	2	61.5%
second week	6	2	0	4	33.3%
thirk week	2	2	0	0	100%

7) Complications and prognosis (Table 10).

Table 10 shows that the mortality, in patients with meningitis only is 53.7 %, and in those with complications 71.3 %.

Table 10 Prognosis according to tuberculous complications.

disease type of tuberculosis	number of cases	dead	alive	cured	mortality
tbc meningitis only	52	33	9	10	63.5%
+ tbc complication (not miliary)	9 (31)	6	2	1	66.7%
+ miliary tuberculosis	22 (31)	13	3	6	50.2%

The most frequent complication if naturally miliary tuberculosis (22 of 42 or 52.4 %). The mortality of tuberculous meningitis accompanied by miliary tuberculosis is 59.2 % (13 of 22), so there is no real difference between this group and those without miliary tuberculosis. But when accompanied by tuberculous complications, the prognosis is fatal (5 of 5 or 100 %). In regard to tuberculous complications we have only 4 cases of varicella, and we found no influence on the prognosis or on the cerebrospinal fluid.

8) Prognosis according to exposure to tuberculous infection (Table 11).

The presence of exposure to tuberculous infection has been estimated in 83 cases as follows. (Table 11) These results do not show any clear correlation between exposure and prognosis.

Table 11 Prognosis according to exposure of tuberculous infection.

exposure	number of cases	dead	alive	cured	mortality
known	43	23	9	11	53.5%
unknown	40	29	5	6	72.5%

9) Prognosis according to clinical symptoms and laboratory data.

To know as soon as possible, whether the streptomycin treatment is effective

or not, we compared and examined clinical symptoms in 42 cases (25 dead and 17 cured) in the first day of therapy and one month later.

Contrary to our expectations, we have poor harvest, and results are presented below.

a) Blood picture.

Anemia and leucocytosis were more severe at the begining of treatment in the patients who died than in the others, but one month later, they returned to normal in both groups. There were no differences in the ratio of neutrophiles and lymphocytes.

The percentage of patients who had eosinophiles in their blood was 50% in the cured cases and 31% in the others, and one month later, it increased to 90% in the former and 75% in the later. The percentage of monocytes did not differ between the two groups. It is of interest to us that the number of plasmacells was different in the two groups.

It averaged 13% in those who died and 35% in those who were cured.

b) Cerebrospinal fluid.

We were unable to assign any prognostic value to the number and variety of cells, or the concentration of sugar, protein or globulin in the cerebrospinal fluid. It has been maintained by Enzyozi[4] that the sign of hyperergie or normergie of meningeal reaction (that is, over 200 cells and over 100 neutrophiles per ml. of cerebrospinal fluid) indicates a good prognosis. However, we can not agree with him, because we noted this sign in 18% of those who died and in 17% of the cured cases in our series.

It seems to us that an increase in the number of cells in the cerebrospinal fluid indicates a good sign for the patients, because it was seen one month after the start of treatment in 31% of the cases who died, but in 64% those who recovered. Improvement in the concentration of sugar, protein and globulin one month later, has no relationship to prognosis. For instance, improvement of the concentration of sugar occurred in the dead and the cured cases.

c) Tubercle bacilli in the cerebrospinal fluid.

We find tubercle bacilli in the web between 2 and 29 days (average time 7 days) after treatment in the cured cases, and between 2 and 60 days (average 17 days) in those died. This shows that the longer the tubercle bacillus is in the cerebrospinal fluid, the worse is the prognosis. In 83 cases tubercle bacilli were found in the web.

d) General clinical condition.

Prognosis was not affected by any changes in the general condition which occurred between the onset and one month later i.e., fever pulse and frequency of respiration, vomiting, convulsions, stiff-neck, Kernig's sign, tendon-reflex, enlargement of liver and spleen, body-wheight, and blood sedimentation rate.

But improvment of appetite occurred in only 30% of the patients was later died and in 100% of those who were cured.

e) Tuberculin reaction (Mantoux reaction).

Many authors[5] have maintained that the intensity of the tuberculin-reaction decreased in proportion to recovery by streptomycin treatment, but we could not find this phenomenon in our series.

Both in those who died and those who survived, the intensity was constant throughout the course.

10) Tubercles in eye-ground (Table 12).

It was of interest to us, to know how frequently we could find tubercles in the eye-grounds in each group. We examined it for the last 20 years, and obtained the results stated in table 12. The number of cases is small, because before 1946, our seniors had not always examined the eye-grounds of their tuberculous patients for tubercles, even in cases of miliary tuberculosis and tuberculous meningitis.

Table 12 Relationship of type of tuberculosis and tuberculous changes (mostly tubercle) in eyeground.

type of tuberculosis	tbc changes in eye gorund		number of cases
	(+)	(−)	
miliary tbc	7(63.6%)	4	11
tbc meningitis	8(13%)	52	60
miliary tbc tbc meningitis	10(49%)	16	26
another type of tbc	0(0%)	1	

It is interesting and significant that we find tubercles in the eye-grounds more frequently in miliary tuberculosis than in tuberculous meningitis.

11) This fact suggests that tuberclous meningitis do not always occurred, even if tubercles are detected in the meninges.

Table 13 shows how soon clinical symptoms subsided in the cured cases. In all the cases who died after a long period of survival the cerebrospinal fluid did not return to normal. That is, when sugar concentration and cell number did not return to normal within 6 months, the prognosis was bad.

12) Permeability of streptomycin through the blood-cerebrospinal fluid barrier.

This is determined by measuring streptomycin concentration in the cerebrospinal fluid 4 hours after injection of 0.5 g. of streptomycin. In survivors, it ranges from 0.5 gamma to 1.22 gamma, almost always over 10 gamma on the first day

Table 13 Time of return to normal of various clinical signs and symptoms.

clinical sings and symptoms		time vequires to return to normal
c.s.f.	sugar	4—8 months
	cell counts	6--16 months
	protein concentration	6—4 years
	globulin reaction	10 months—4 years
	web	2—6 months
	vomiting	<1 month
	headache	<1 month
	appetite	<2 months
	fever	<3 months
	stiffneck	<3 months
	Kernig's sign	<3 months
	tendon-reflex	<4 months

admitted, and with treatment it decreases to under 0.9 gamma by the time of discharge. Some say that streptomycin permeability is a help in determining prognosis and when to stop treatment, but we do not think this is always so, having had a case who became worse a week after he had less than 1 gamma.

It is more suitable for early diagnosis than for prognosis.

13) The degree of resistance to streptomycin of tubercle bacilli isolated from cerebrospinal fluid (Table 14).

On first isolation from the cerenrospinal fluid, the tubercle bacilli are suspectible to streptomycin, and always inhibited by 1 gamma or less of streptomycin per ml. But they become resistant to streptomycin after treatment. Results of cultures grown in Kirchner's and Oka-Katakura media are shown in Table 14. It seems to us that tubercle bacilli in cerebrospinal fluid did not readily develop resistance to streptomycin.

14) Toxic effects of streptomycin.

All toxic effects were similar to those reported elsewhere.

Namely, we found generalized rashes, eosinophilia, albuminuria is some cases, and one child died of agranulocytosis. In one case a patient became deaf while under treatment, in another after treatment, and a third child became hard of hearing. It seems to us that vestibular disorder is clinically the most significant side effect of streptomycin.

15) The effect of streptomycin therapy.

31 patients are alive out of 83 treated. 17 of the 31 are in good general

Table 14 The degree of resistence of tubercle bacilli isolated from cerebrospinal fluid.

case number	S.M. dose (grams)	the number of days S.M. was employed	use of S.M.	Resistance of isolated tubercle bacilli (γ)	prognosis
1	64	160	i.m.△ i.t.○	12.0γ	dead
1	70	190	〃	12.0	dead
2	26	40	〃	1.4	dead
2	48	140	〃	111.0	dead
3	69	139	〃	5.0	dead
4	12.5	25	〃	4.0	cure
5	5	10	〃	12.0	〃
6	42	170	i.m.	4.0	alive
7	15	60	〃	1.0	〃
8	10	30	〃	5.0	dead

△ i.m.: intramuscular injection
○ i.t.: intrathecal injection

condition without any clinical manifestations of illness.

The value of streptomycin therapy in meningitis can perhaps be judged most correctly by the rate of survival and the physical and mental condition of survivors, so that, we distinguished complete cures from survivous. Cures have no physical or mental defects, namely, they are quite healthy. (Table 15) We find the mortality rate of tuberculous meningitis is considerably high (60–80% approximately 70%) in our country compared with the rate in foreign countries E. Lincoln[6] has reported the mortality as less than 30% and Cocchi[7] only 15% in his later series. Less good results (50%) have been obtained by Debé.

The best results that we know are those of Löffler[8] which is less than 10%. This difference is explained partially by the different method of chemotherapy.

We must endeavor to increase the number of cures of tuberculous meningitis devising ways to employ streptomycin combined with other antituberculous drugs.

Table 15 Observation of cases cured.

case no.	age (years, months)	total dose of S.M. employed (grams)	total number of times of S.M. intrathecal injection	survival time (months)	months since S.M. treatment was stopped	patients state at present
1	3,10	40.0	85 times	48 months	37 months	quite healthy; not very good student
2	3, 5	56.0	69	43	36	〃 ; very good student
3	2, 1	105.0	119	42	28	〃 ; varicella: II months after end of treatment pertussis: 12 months
4	7, 5	42.3	106	36	28	〃 ; not very good student
5	0, 7	62.0	34	34	26	〃 ; measles and varicella: 16 months after completing treatment
6	9, 3	70.0	48	30	22	〃 ; first in his class
7	1, 5	86.0	82	27	17	〃 ; pertussis: 2 months after completing treament
8	12, 1	49.0	86	26	16	quite healthy
9	4,11	300.0	76	25	2	〃 ; very good student
10	1, 6	70.0	51	23	17	quite healthy
11	1, 9	61.0	51	22	16	〃 ; pertussis: 6 months after completing treatment
12	3, 4	70.0	69	20	12	quite healthy
13	2, 0	74.0	87	19	12	quite healthy
14	4, 6	80.0	124	15	8	quite healthy
15	5, 1	80.0	150	15	9	quite healthy
16	1, 3	50.0	45	13	0	quite healthy
17	5, 3	76.0	67	13	5	quite healthy

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