

Clinical Review of Miliary Tuberculosis in Korean Children

— 84 Cases and Review of the Literature —

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ABSTRACT

Tuberculosis is still one of the most serious infectious diseases in Korea. Tuberculosis in childhood is a serious problem to Korean pediatricians. Miliary tuberculosis, a form of extrapulmonary tuberculosis, has been frequently observed in out-patient dispensaries or in-patient wards in Korea.

Only one clinical review by Min et al (1969) was reported. We have summarized another eighty four pediatric patients who were observed during a nine years and three months period from Jan. 1960 to March of 1969, at Wonju Union Christian Hospital, Wonju, Kang Won Do, a branch hospital of our Severance. The following results were obtained;

1). During nine years and three months from Jan. 1960 to March of 1969, eighty four cases of miliary tuberculosis were observed which was 1.7 per cent of the total admission of pediatric patients (4,991) during the above period.

2). The youngest one was a five month old female infant and the oldest was a thirteen year old boy. The age group of three to six years included 40.5 per cent while 10.7 per cent were under one year.

3). Only eighteen per cent of the patients had a definite contact history with tuberculosis in the family.

4). Their chief complaints on admission were fever, cough, vomiting, loss of appetite, abdominal

pain, fatigue, in order. All eight convulsive patients had complication of meningitis.

5). Negative tuberculin responses were found in more than fifty per cent of patients.

6). Tuberculous meningitis was the most frequent complication (28.5 per cent) in miliary tuberculosis. Tuberculous complications were found in fifty per cent of all patients.

7). Death rate was twelve per cent. Six out of ten deaths occurred within three days after admission. Eight out of ten deaths were complicated cases of tuberculous meningitis. Seven out of ten deaths were male patients.

8). In improved cases, improvement on X-ray and by clinical symptoms appeared after two weeks or several months.

9). The patients were treated by triple chemotherapy and addition of corticosteroid, but we did not find a remarkable effect of steroid.

10). The prevention must precede treatment and doctor's and patient's attention to miliary tuberculosis must be emphasized.

INTRODUCTION

Kim (1966) reported recently that the prevalence of active pulmonary tuberculosis in the whole country was 5.1 per cent of the population and the estimated number of patients was 1.24 million. In his survey of tuberculosis prevalence in South Korea, 1965, 0.94 per cent of smears for acid fast

bacilli were positive. These statistics indicated the very serious problem in Korea compared with the prevalence rate of 0.025 per cent in Denmark and 0.07 per cent in Great Britain. (Franks, 1959)

Kim (1966) also reported the incidence rate of tuberculin reactors was 64.5 per cent in the whole country. The rate was 66.2 per cent in males and 63.1 per cent in females, 1.6 per cent under one year, 12.0 per cent under four years, 72.1 per cent in ten to fourteen years, and over 90 per cent in all over thirty years of age.

The incidence rate of tuberculin reactors was 33.3 per cent in the first year class of primary school children and it increased by 3 to 4 per cent per year to 75.1 per cent in high school boys (Kim, 1966). This report showed a tremendous difference in comparison of the 1.7 per cent rate in 4,027 children from the age of nine months to five years in America (Anderson and Grabau, 1966) and 5 per cent under ten years of age in America (Myers, 1965). Thus tuberculosis is a very serious Korean Public Health problem at the present. Some specialists of public health, Won and Kim (1963), Kim and Han (1956), and Park and Pyun (1958) reported tuberculosis prevalence survey in Korean school children. Bang (1967) reported the mortality rate of tuberculosis in Seoul, Korea as follows. In Seoul from 1963 to 1966 the tuberculous mortality rate was 41.3/100,000 population, as the second cause of death (9.7 per cent). The first cause of death was CNS diseases (13.4 per cent). One of every ten deaths was caused by tuberculosis and mortality of the total children in Seoul from tuberculosis was 19.1 per cent. So public health administrators, doctors and private citizens must pay more attention to prevention of tuberculosis.

Tuberculosis is not only a regional infection but also a systemic infection. Miliary tuberculosis is an example of the systemic spread.

Although there are many patients with miliary tuberculosis in Korea, clinical review of this problem is rare. One clinical review of fifty six patients was reported by Min et al in 1969.

We have summarized the case histories of another eighty four pediatric patients who were observed at Wonju Union Christian Hospital, Wonju, Kang Won Do, a branch hospital of our Severance Hospital.

RESULTS

1. Cases;

Eighty four patients with miliary tuberculosis were observed for nine years and three months from Jan. 1960 to March of 1969, which was 1.7 per cent of the total admitted pediatric patients (4,991) during the above period.

2. Age and sex incidence;

The youngest patient was a five month old female infant and the oldest was a thirteen year old boy. 40.5 per cent (thirty four patients) of the total were between three and six years of age. 10.7 per cent (nine patients) were under one year of age. 73.8 per cent (about three quarters) were in the preschool age group. The total number of male patients was forty nine (58 per cent) and female patients was thirty five (42 per cent) and the ratio of male to female was 1.4 to 1. (Table 1)

Table 1. Age and sex incidence of miliary tuberculosis

Age \ Sex	Male	Female	Total number	%	
Under 1 yr.	(6/12)	5 (5/12)	4	9	10.7
1~3 yrs.	11	8	19	22.6	
3~6 yrs.	19	15	34	40.5	
6~12 yrs.	13	7	20	23.8	
Over 12 yrs.	(13)	1 (12)	1	2	2.4
Total number	49(58%)	35(42%)	84	100	

Sex ratio 1.4 : 1

* Parenthesis indicates the youngest and the oldest ages in each group.

3. Seasonal incidence;

Fifty four patients (64 per cent) were observed during the spring and summer. Incidence order was summer, spring, winter and autumn. (Table 2 and Fig. 1)

4. Contact history with tuberculous family;

Only eighteen per cent (fourteen) of the patients had definite contact history with active tuberculosis

Table 2. Seasonal incidence of miliary tuberculosis

Sex \ Mon.	Dec.	Jan.	Feb.	Mar.	Apr.	May.	Jun.	Jul.	Aug.	Sept.	Oct.	Nov.
Male	0	2	4	8	5	4	8	6	2	3	5	3
Female	2	5	3	4	3	2	4	5	3	1	0	2
Total number	2	7	7	12	8	6	12	11	5	4	5	5
	Winter 16			Spring 26			Summer 28			Autumn 14		
%	19			31			33			17		

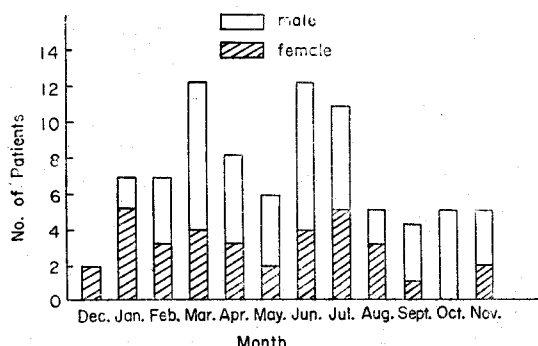


Fig. 1. Seasonal incidence of miliary tuberculosis.

in the family and nine patients had parents with pulmonary tuberculous disease. Eighty two per cent of them had no knowledge of tuberculous patients in their family or relatives. (Table 3)

Table 3. Contact history with tuberculous family

F.H.*	Sex	Male	Female	Total No. of Patients	%
Positive	Parents	6	3	9	18
	Siblings	2	1	3	
	Relatives	2	0	2	
Negative		38	32	70	82
Total No. of Patients		48	35	84	100

* F.H.: Family History

5. Chief complaints on admission;

Their chief complaints on admission were fever, cough, vomiting, loss of appetite, abdominal pain, fatigue, in that order. The eight patients with convulsions had also tuberculous meningitis. (Table 4)

6. Results of tuberculin skin test;

Tuberculin skin test was performed with O-T (1:2,000) intradermally and repeated with O-T

Table 4. Chief complaints on admission

C.C.	Number of Patients	%
Fever	63	75.0
Cough	43	51.2
Vomiting	23	27.3
Loss of appetite	13	15.4
* Abdominal pain	13	15.4
* Fatigability	12	14.2
Dyspnea	10	11.9
Convulsion	8	9.5
Night sweating	7	8.3
* Headache	7	8.3
Sputum	5	5.9
Diarrhea	4	4.7

* These are complaints of bigger children who can express his symptoms by themselves.

(1:500) for the patients with a negative reaction. 51.2 per cent of the patients showed negative tuberculin skin test. The death rate of the O-T negative patients was fourteen per cent which was higher than O-T positive patients (9.8 per cent). (Table 5)

Table 5. Result of tuberculin skin test*

Results	Positive	Negative
Numbers	41(4)	43(6)
%	48.8(9.8)	51.2(14.0)

* O-T 1 : 2,000 dilution (5T.U.)

* Read at 48 hrs. after injection.

Parenthesis indicates No. of deaths and %.

7. Complications;

Tuberculous complications were found in 50 per cent (forty two patients) of all patients. Non-tuberculous associated lesions occurred in 7.1 per cent of the patients.

There was no relation between complication and sex. The pure pulmonary miliary disease spread was found in thirty eight patients (45.2 per cent).

Table 6. Complications and associated diseases among miliary tuberculous patients

Sex		Male	Female	Total No. of patient	%	Total %
Complications						
Tuberculous	Meningitis	12	12	24	28.5	50
	Peritonitis	3	3	6	7.1	
	Cervical lymphadenitis	3	3	6	7.1	
	Intestinal t.b.	2	1	3	3.6	
	Renal t.b.	1		1	1.2	
	Bone t.b.	1		1	1.2	
	Pleural effusion	1		1	1.2	
	Total number	*23	**19	42		
Non-tuberculou	Glomerulonephritis	1	2	3	3.6	7.1
	O.M.P.C.	1		1	1.2	
	Osteomyelitis	1		1	1.2	
	Optic neuritis	1		1	1.2	
	Total number	4	2	6		
Lung t.b. only		+23	++15	38		45.2
Total No. of patient			49	35	84	

*(m) 46.9% *(f) 54.3% *(m) 46.9% *(f) 42.8%

Tuberculous meningitis (28.5 per cent, twenty four cases) was the most frequent complication in miliary tuberculosis and other complications in high incidence were cervical lymphadenitis (six cases), renal tuberculosis (one case), bone tuberculosis (one case) and pleural effusion (one case). (Table 6)

8. Treatment and prognosis;

Treatment was carried out with triple chemotherapy for all patients and corticosteroid was added in the forty four patients. Principle dosage: INH; 20 mg/kg/day; PAS, 200 mg/kg/day; Streptomycin, 20-40 mg/kg/day and prednisolone, 1-2 mg/kg/day, were given to hospitalized patients and INH and PAS were continued for one and a half or two years. Streptomycin was given by intramuscular injection daily for one month and two times per week for the next three months and prednisolone was given for six to eight weeks.

Under the above treatment, twenty six patients improved in the first two weeks clinically and radiologically. Complicated miliary tuberculous patients with renal tuberculosis, bone tuberculosis, tuberculous peritonitis and several meningitis patients required treatment for more than six weeks before improvement was observed.

Ten patients died during the hospitalization.

Few patients were discharged against advice during the treatment or failed to return for clinic visits. (Table 7)

Table 7. Improvement and prognosis

Prognosis	Discharge against advice	Expired	Improved
Duration			
Under 2 wks	9	9	4
2~4 wks	1		11
4~6 wks			6
Over 6 wks		1	9
Unknown	34		
Total	44	10	30

9. Death rate;

Death rate was twelve per cent. Six out of ten deaths occurred within three days after admission, eight out of ten deaths were cases complicated with tuberculous meningitis. Of twenty four cases complicated with tuberculous meningitis eight patients died, so the death rate of miliary tuberculosis with meningitis was 33.3 per cent.

Tuberculous meningitis was the most common complication of miliary tuberculosis and had the highest death rate and most serious prognosis. There

was no death in the patients with pulmonary miliary tuberculosis only. There were no deaths in the age group of three to six years and over twelve years.

The death rate was higher in the group of patients who did not receive steroids. However it was impossible to obtain a statistical difference.

Seven out of ten deaths were of male patients. (Table 8 and 9)

Table 8. Effect of steroid treatment

Age	Used group			Not used group		
	No. of patient	Death	%	No. of patient	Death	%
Under 3 yrs.	15	2	13.3	11	3	27.2
3~6 yrs.	16	1	6.3	22	0	0
6~12 yrs.	8	1	12.5	10	3	30
Over 12 yrs.	1	0	0	1	0	0
Total	40	4	10*	44	6	13.6*
Male	24	4		25	3	
Female	16	0		19	3	

* 0.7>P>0.6

Table 9. Relationship between the expired cases and the complication

	No. of death	%
T.B. meningitis	8	80
T.B. lymphadenopathy and t.b. intestine	1	
Osteomyelitis with lung cavity	1	

* Death rate among the complicated t.b. meningitis: 8/24=33.3%

DISCUSSION

Rosenberg and Gottlieb (1968) said the incidence of tuberculin reactors was nineteen per cent in the whole American population. Among children negroes were one seventh of the total.

One-half of all tuberculous patients were colored people. Rosenberg and Gottlieb (1968) said that tuberculosis was closely related to the socioeconomic and educational conditions. Kim et al (1967) analysed all tuberculous pediatric patients including hilar lymphadenopathy, bone and joint tuberculosis, cervical lymphadenitis, tuberculous meningitis, tuberculous pleurisy and miliary tuberculosis (4.3 per

cent) in the order of highest incidence in his clinical and statistical analysis of eight hundred and thirty tuberculous patients in Korean children.

This report suggests there may be many miliary tuberculous patients in Korea but from our survey of the literature we found only a report by Min et al (1966) which reviewed fifty six cases over twelve years from 1954 to 1966.

The lowest age was five months and oldest patient was fifteen years. Our youngest patient was five months old but Lee et al (1970) reported three patients with miliary tuberculosis of three months of age.

We found a remarkable incidence of miliary tuberculosis in the infant group. Our infant patients were 10.7 per cent and Min et al (1969) reported 16.7 per cent and the highest incidence rate in the three to six year age group was the same in our study and in that of Min et al (1969).

Min et al (1969) reported the sex ratio of male to female was two to one but it was 1.4 to 1 in our observed cases. Min et al (1969) said there was no relation of season to incidence, but we observed more patients in the warm season.

We found a contact history with active tuberculosis in the family in eighteen per cent of all cases which were obtained by history taking alone but Lee (1964) found 85.4 per cent, Cho et al (1968) 64 per cent, and Min et al (1969) 26.8 per cent. We did not check chest X-ray on all of the families.

The patients whose source of contact was their parents are most common and Min et al (1969) agreed with it. Min et al (1969) reported negative tuberculin reactors were thirty per cent and positive reactors fifty per cent but negative reactors were slightly higher than positive in our results.

Min et al (1969) also reported the mortality rate in negative reactors was three fold more than in positive reactors. In our report, six out of ten deaths occurred in negative reactors, so prognosis of negative reactor was bad.

Authors observed meningitis (28.5 per cent)

was the most common complication. But Min et al (1969) reported 7.1 per cent had complicating meningitis and Cho et al (1968) ten per cent. These rates were lower than the authors but Mayock (1966) agreed with our results that meningitis was the most common complication of miliary tuberculosis. Contrariwise Cho et al (1968) reported miliary tuberculosis was in 10.7 per cent of tuberculous meningitis patients, Shin et al (1964) 10.9 per cent and Park et al (1959) 36.8 per cent.

Besides tuberculous meningitis, there were serious complications of peritonitis, bone tuberculosis, renal tuberculosis and intestinal tuberculosis which were not treated easily. So we have had to pay attention to the complication in miliary tuberculosis.

Treatment was carried out with triple chemotherapy (INH, PAS, SM) and corticosteroid as have the other authors. In tuberculous diseases steroid therapy was recommended aside from pulmonary miliary tuberculosis in endotracheal, pleurisy with effusion, cervical lymphadenitis, meningitis etc. (Rosenberg and Gottlieb, 1968). The dosage of prednisolone was recommended as 1-2mg/kg/day and to a total dose of sixty miligram (Rosenberg and Gottlieb, 1968) or up to forty miligram (Mayock, 1966), and by Durfee et al (1969) 2 mg/kg/day. Durfee et al (1969) used prednisolone only in the acute stage and others discontinued it when respiratory difficulties had disappeared (Rosenberg and Gottlieb, 1968).

According to the above principle we treated our patients with a death rate of twelve per cent. Eighty per cent of deaths was complicated by meningitis. The patients with meningitis had a poor prognosis.

There was no difference in the death rate between the steroid treated group and the non-steroid group ($0.7 > P > 0.6$). Pure pulmonary miliary tuberculosis had a rather good prognosis. Authors experienced no death in pure pulmonary miliary tuberculous patients. Min et al (1969) reported 5.3 per cent which was a lower death rate in pure pulmonary miliary tuberculosis than other compli-

cated miliary tuberculosis. One out of ten deaths was complicated with osteomyelitis of left femur and lung cavity. Lung cavity is rarely found in miliary tuberculosis but in extremely severe case, cavity may develop.

But before discussing prognosis on death rate we had to think more about the elimination of tuberculosis because it can be prevented. Frank (1959) said the greatest cause of rapid decrease in the number of tuberculous patients in Denmark was the excellent principle of governmental administration. Strict registration, strict mass examination of patients by chest X-ray and generalized BCG vaccination were the most important contents of the principles.

In Korea three months old patients with miliary tuberculosis was reported, so we must give attention to the baby from birth. Cohen and Weber (1969) recommended that the baby whose mother had active tuberculosis must be given INH from two months after birth and said the baby under one month had no enzymes for acetylating INH in the liver and the high blood level of INH was toxic, so INH should be deferred until two months of age.

Potts (1966) said complete diagnostic procedures of 1) tuberculin skin test, 2) epidemiologic survey on the family and the environment of children, 3) chest X-ray and 4) test for tuberculous bacteria must be performed before treatment. The chemoprophylaxis by the Committee on the treatment of tuberculosis in children of American Society, Medical section of National Tuberculosis and Respiratory Disease Association was as follows;

1. When tuberculin skin test changed to positive within a recent one year, INH 20 mg/kg/day was given for at least one year regardless of age.
2. Whoever had a definite contact history with a tuberculosis patient, without relation to the tuberculin skin test, was given INH for one year with or without PAS.

Doctors and patients tended to disregard tuberculosis in our country which has a high incidence of tuberculous patients. Prevention of tuberculosis

is very important and should be of greater concern than the treatment of complications of tuberculosis.

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