

Congenital Tuberculosis

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Abstract

This is a retrospective study of congenital tuberculosis in Queen Sirikit National Institute of Child Health from 1979 to 1998. There were 9 patients with a mean birth weight of 2,500 grams (range 1,800-3,300). The onset of symptoms and age of diagnosis ranged from 7 to 42 (mean, 21) days and 14 to 75 (mean, 54) days after birth, respectively. The presenting signs and symptoms were fever (100%), poor feeding (100%), irritability (100%), failure to gain weight (100%), hepatomegaly (100%), splenomegaly (77.8%), cough (88.9%), respiratory distress (66.7%) and abdominal distension (77.8%). The tuberculin skin test reaction with ≥ 10 mm induration was found in 2 of 8 patients. Their abnormal chest radiographs revealed bronchopneumonia 66.7 per cent, miliary pattern 33.3 per cent and multiple cystic lesion 11.1 per cent. The bacteriological study from gastric aspirate content for acid-fast bacilli (AFB) staining and culture were positive in 62.5 and 71.4 per cent respectively. Fatality rate was 33.3 per cent with no sequelae found in the survivors. Congenital tuberculosis is a rare entity and difficult to give an early diagnosis. There should be a high index of suspicion for tuberculosis in those who had pneumonia and were unresponsive to aggressive antibiotics or had unexplained etiology.

Key word : Tuberculosis, Congenital, Young Infants

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Congenital tuberculosis (TB) is an infection acquired during intrauterine or sometime intrapartum life, reported rarely in approximately 60 cases after the introduction of isoniazid (INH) from 1952 to 1997⁽¹⁻

5). Six cases of congenital tuberculosis were recently reported from a mother with tuberculosis and human immunodeficiency virus (HIV) co-infection in a one year study (1996-1997) from South Africa⁽⁵⁾. Due to

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the HIV pandemic, there were upward trends of total notification of new TB cases in Thailand in 1992 and 1993, of 83 and 85 per 100,000 population compared to that of 76 per 100,000 population in 1991. However, in 1994 and 1995 the trend decreased a little and became stable which corresponded with the slower increasing trend of HIV infection of the country. The overall HIV prevalence rate at antenatal clinics in Thailand is around 1.5-2 per cent. The risk of tuberculosis in pregnancy might also increase, leading to an increased risk of congenital tuberculosis. The authors describe here nine cases of congenital tuberculosis, their outcomes, and the condition of their mothers.

METHOD

Inpatient records of neonates and young infants admitted to Queen Sirikit National Institute of Child Health (Children's Hospital), Bangkok, Thailand, from 1979 to 1998 in whom a differential diagnosis of tuberculosis was made, were reviewed. The neonate/young infant was confirmed to have congenital tuberculosis if he/she fulfilled the standardized criteria described by Beitzke(6) as follows. 1) The tuberculous nature of the lesions must be proved in both mother and infant. 2) A primary complex in the liver is proved. 3) In the absence of primary hepatic complex, the infection is congenital if tuberculous lesions are found in the fetus *in utero*, at birth, or a few days afterwards. Nine patients met the inclusion criteria. Clinical and laboratory profiles of the nine patients were analysed. Descriptive statistics were used for data analysis.

RESULTS

Clinical profile of the nine patients with congenital TB is shown in Table 1 and 2. There were five males and four females. Three of them were pre-term newborn infants, three had evidence of intra-uterine growth retardation, and three had normal range of birth weight. Their mean birth weight was 2.5 kg. All had good condition at birth except one who had asphyxia. The onset of symptoms and age of diagnosis ranged from 7 to 42 (mean, 21) days and 14 to 75 (mean, 54) days after birth, respectively. The time lapse from onset of the symptoms to diagnosis ranged from 4 to 63 days, with a mean of 33 days. The time lapse from admission to suspicion of tuberculosis in the seven cases who were diagnosed and treated with anti-tuberculous drugs ranged from 2 to 58 days, mean 20 days. The time lapse from admission to diagnosis of case no. 5 was the longest, 58 days. He had

Table 1. Clinical profile of nine children with congenital tuberculosis.

Patient no. (years)	Birth Wt (kg)	Normal or IUGR* or preterm	Age on Admission (day)	Day of onset (day of diagnosis)	Pneumonia	Hepatomegaly (size, cm)	Splenomegaly (size, cm)	Pyrexia	Cerebrospinal fluid	Gastric aspirate AFB† stain	Gastric aspirate culture	TB confirmed biopsy/autopsy	Outcome: Live or died (day)
1 (1979)	1.8	Preterm	0 (Birth)	30 (63)	Yes	Yes (2)	Yes (3)	Yes	Normal	ND‡	ND	Autopsy	Died (63)
2§ (1981)	1.8	IUGR	30	15 (36)	Yes	Yes (2)	No	Yes	Normal	Negative	ND	Autopsy	Died (36)
3 (1985)	3.1	Normal	60	30 (75)	Yes	Yes (4)	Yes (4)	Yes	Normal	Negative	Negative	LnII	Live
4 (1991)	2.9	Normal	20	18 (30)	Yes	Yes (4)	Yes (3)	Yes	Normal	Positive	Positive	Liver	Live
5§ (1994)	2.0	IUGR	12	7 (70)	Yes	Yes (4)	Yes (3)	Yes	ND	Positive	Positive	Autopsy	Died (85)
6 (1995)	2.7	IUGR	12	10 (14)	Yes	Yes (4)	Yes (2)	Yes	Normal	Positive	Positive	None	Live
7 (1996)	2.1	Preterm	56	42 (60)	Yes	Yes (3)	No	Yes	ND	Positive	Positive	Liver	Live
8 (1996)	3.3	Normal	70	21 (75)	Yes	Yes (5)	Yes (4)	Yes	ND	Negative	Negative	Liver	Live
9¶ (1998)	2.6	Preterm	15	12 (62)	Yes	Yes (5)	Yes (3)	Yes	Normal	Positive	Positive	None	Live

* = Intrauterine growth retardation, † = Acid-fast bacilli, ‡ = Not done, § = Patient had jaundice, mother development TB meningitis, ¶ = Inguinal lymph node biopsy, ¶ = Bronchoalveolar aspirate positive for acid-fast bacilli staining.

Table 2. Patient characteristics.

Characteristics	No. (n = 9)	%
Patients		
Prematurity	3	33.3
Intrauterine growth retardation	3	33.3
Normal	3	33.3
Birth weight < 2,500 g	4	44.4
Birth weight \geq 2,500 g	5	55.6
Condition at birth		
Good	8	88.9
Asphyxia	1	11.1
Age of onset		
Range (d)	7-42	-
Mean (d)	21.6	-
Age of diagnosis		
Range (d)	24-75	-
Mean (d)	58.1	-
Mothers		
Diagnosis of TB at or before delivery	0	0
Symptoms of TB at time of delivery	7	77.8
TB Diagnosis of mother		
Pulmonary TB	7	77.8
Miliary TB	2	22.2
TB effusion	2	22.2
TB meningitis	2	22.2
Tuberculosis and HIV co-infection	1/6	16.7

been admitted to two other hospitals before admission to the Queen Sirikit National Institute of Child Health. He had the most severe clinical features and expired after 5 days of anti-tuberculous drugs therapy.

The presenting signs and symptoms of the patients are shown in Table 3. All the patients had elevated body temperature, abnormal chest radiograph, hepatomegaly with or without splenomegaly, lethargy/irritability, poor feeding, and failure to gain weight. Other common features included cough (8 of 9), abdominal distention (7 of 9), and respiratory distress (6 of 9). Two patients (no. 1 and 3) had generalized lymph nodes enlargement, the mother of case no. 3 noticed that the inguinal lymph node of her child had been enlarged since birth. Two patients (no. 2 and 5) had severe clinical features with jaundice on admission (direct bilirubin of 4 and 5 mg% and SGOT of 216 and 92 unit, respectively).

The results of diagnostic procedures of the patients are shown in Table 4. Chest radiographs revealed miliary infiltration (3 of 9), pneumonia/bronchopneumonia (4 of 9), bronchopneumonia with pulmonary hemorrhage (1 of 9), bronchopneumonia with multiple cystic lesions (1 of 9). Two of 5 had BCG scars after BCG vaccination at birth. Tuberculin

skin reaction with 5 T.U. of PPD-S or its equivalent was positive (\geq 10 mm induration) in 2 of 8 and both of them were aged more than two months at the time of testing. Gastric aspirate for acid-fast bacilli (AFB) staining was positive in five of eight (62.5%) patients tested. While gastric aspirate for *M. tuberculosis* culture was positive in five of seven (71%) patients. Liver and inguinal lymph node biopsies were performed in three patients and one patient, respectively. Tissues from biopsies of the four patients showed caseating granuloma and positive AFB staining. Autopsies were performed on three patients who died (33%), sections of tissues from liver, spleen, lung, bone marrow and lymph nodes of all three showed caseating granuloma and positive AFB staining. In addition, tissues from patient no. 5 also showed pulmonary hemorrhage and evidence of disseminated intravascular coagulopathy. All laboratory parameters of cerebrospinal fluids obtained from six children were within normal limits and sterile on culture for *M. tuberculosis*.

Seven patients (78%) (no. 1-6 and 9) were initially treated with antibiotics without improvement. Two patients (no. 1 and 2) died without receiving anti-tuberculous therapy, the disease was diagnosed post-

Table 3. Presenting signs and symptoms of nine cases with congenital tuberculosis.

	No	%
Fever	9	100
Hepatomegaly	9	100
Splenomegaly	7	77.8
Poor feeding	9	100
Lethargy/irritability	9	100
Failure to gain weight	9	100
Cough	8	88.9
Abdominal distension	7	77.8
Respiratory distress	6	66.7
Lymph node enlargement	2	22.2

mortem. Anti-tuberculous drugs were given to five children after failure from aggressive courses of anti-biotic. One patient (no. 7) born to an HIV infected mother and another (patient no. 8) with chest radiograph showing miliary infiltration with pleural effusion were diagnosed as congenital tuberculosis and given anti-tuberculous drugs shortly (days 4 and 5, respectively) after admission. Patient no. 7 was subsequently declared HIV negative when she was 18 months old.

A short course of anti-tuberculous drugs was prescribed. A combination of streptomycin, isoniazid and rifampin (SIR) for 2 months followed by a combination of IR for 4 months were given to patient number 3. A combination of streptomycin, isoniazid, rifampin and pyrazinamide (SIRZ) for 2 months followed by IR for 4 months were given to four patients. One patient received IRZ for 6 months. All recovered fully. However, one patient (no. 5) died after receiving SIRZ for 5 days. The cure rate of those who received

anti-tuberculous therapy was 86 per cent (6 of 7).

One of the six mothers tested (mother of patient no. 7) was found to have HIV infection (positive HIV antibody for both enzyme-linked immunosorbent assay testing, Abbott Laboratories, and particle gel agglutination test) before delivery. None of the nine mothers was diagnosed with tuberculosis before giving birth. However, careful history re-taken retrospectively revealed that all the mothers had some symptoms of tuberculosis at a certain period of time before giving birth. All were diagnosed with pulmonary tuberculosis after giving birth and subsequently two of them (mothers of patient no. 1 and 5) also developed tuberculous meningitis. The mothers' chest radiographs showed pulmonary TB (7 of 9), miliary TB (2 of 9), and pleural effusion (2 of 9) as shown in Table 2.

DISCUSSION

This study reports nine cases of congenital tuberculosis. The affected infant is frequently born prematurely^(7,8), although term delivery is usually associated with intrauterine growth retardation⁽⁹⁾, which is more or less similar to the authors' experience. Signs and symptoms of disease usually do not appear for several days or weeks⁽¹⁰⁾, the presented patients had a mean age of onset of illness of 21 days. In the pre-antituberculous drugs era, congenital tuberculosis was always associated with fatality. At that time, the most common presenting symptoms and signs were failure to thrive, jaundice and central nervous system involvement⁽¹¹⁻¹³⁾. In contrast, the present study showed that fever, hepatomegaly, failure to gain weight, poor feeding and respiratory distress were the common findings which were very similar to

Table 4. Results of diagnostic procedures in nine cases of congenital tuberculosis.

Finding	No. positive/No. tested	%
Gastric aspirate for AFB staining	5/8	62.5
Gastric aspirate for <i>M. tuberculosis</i> culture	5/7	71.4
Bronchoalveolar aspirate for AFB staining	1/1	100
Bronchoalveolar aspirate for <i>M. tuberculosis</i> culture	1/1	100
Tuberculin test (≥ 10 mm)	2/8	25
Biopsy/autopsy specimen (7 cases)	7/7	100
Liver : caseating granuloma and AFB staining	6/6	100
Lymph node : caseating granuloma and AFB staining	3/3	100
Chest radiograph		
Bronchopneumonia	5/9	55.6
Miliary infiltration	3/9	33.3
Bronchopneumonia with multiple cystic lesions	1/9	11.1

reports from Hageman et al in 1980⁽¹⁾ and Abughali et al 1994⁽⁵⁾. In the present study, jaundice was observed in two cases who had severe clinical manifestations and none had central nervous system involvement. The serious findings seem to have occurred more frequently in the pre-antituberculous drug era than in recent years. This change probably reflects earlier recognition of infection in the post-antituberculous drug era, whereas almost all previous cases were diagnosed in the terminal stages of disease⁽⁵⁾. Chest radiographs in previous studies were abnormal in 73-83 per cent of cases^(1,2,14), while all of the presented patients showed lung involvement with either bronchopneumonia or miliary infiltration. Positive tuberculin skin test is not uncommon in these young infants, although the reaction is usually negative at presentation and it could not exclude the diagnosis of congenital tuberculosis^(1,14-16). This is either due to the anergy to the severe disease or because of their immunology immaturity especially in preterm infants⁽¹⁷⁾.

Mycobacterium tuberculosis can be transmitted to the fetus by hematogenous spread *via* the umbilical vein or by the aspiration or ingestion of amniotic fluid contaminated by placental or genital tract infection. Hematogenous dissemination leads to the primary complex in the liver and lungs, whereas the aspiration or ingestion of infected amniotic fluid results in primary complex in the lungs and gastrointestinal tract, respectively^(5,12,13,17). The AFB staining and culture for *M. tuberculosis* can often be positive from gastric aspirate, liver biopsy, lymph node biopsy, endotracheal aspirate or bone marrow aspirate. Gastric aspirate, a practical and inexpensive procedure, provides the most utilized test. In the present study gastric aspirate was positive for *M. tuberculosis* culture and AFB staining in 71 per cent and 57 per cent, respectively. Bronchoalveolar aspirate was

performed in one patient and was positive for both AFB staining and culture. Although histology findings of liver biopsies from all three cases in the present study demonstrated both caseating granuloma and positive AFB staining, it is an invasive procedure that could not be performed in all cases.

The presented data suggest that the longer the lapse from onset of symptoms/admission to diagnosis i.e. patient no. 5 the more severe clinical manifestations and the poorer the outcome. In the present study, diagnosis of tuberculosis was not made in two cases, and was delayed more than one week in four cases. Modern antituberculous agents are highly effective in the therapy of tuberculosis in young infants and early diagnosis has become critical to effect a favorable outcome. The difficulty in making an early diagnosis of congenital tuberculosis in the present study was partly due to the lack of a maternal history of tuberculosis before delivery and the unawareness of health care providers. As nearly all of the mothers (8 in 9) had some symptoms of pulmonary tuberculosis, a thorough history evaluating the risk of tuberculosis in the mother is essential. There should be a high index of suspicion for tuberculosis in those who had pneumonia with no response to aggressive antibiotics, progressive clinical course with unexplained etiology, especially in areas where tuberculosis is known to be prevalent. A prescription of antituberculous agents to these suspicious infant, whether or not a history of maternal illness is obtained, could be life saving.

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วัณโรคตั้งแต่กำเนิด

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การศึกษาโรควัณโรคตั้งแต่กำเนิด ในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี (โรงพยาบาลเด็ก) ตั้งแต่ปี พ.ศ. 2522 ถึง ปี พ.ศ. 2541 โดยทำการศึกษาลงข้อมูลพื้นฐานของผู้ป่วย อายุ ลักษณะทางคลินิก การตรวจทางห้องจุลชีววะ การเพาะเชื้อโรค ผลการรักษา และประวัติความเจ็บป่วยและการตั้งครรภในมารดาของผู้ป่วย จากเวชระเบียนของผู้ป่วย 9 ราย ผู้ป่วยมีน้ำหนักเฉลี่ยแรกคลอด 2,500 กรัม อายุเฉลี่ยเริ่มมีอาการป่วย 21 วัน (พิสัย 7-42) อายุที่วินิจฉัยได้เฉลี่ย 54 วัน (พิสัย 14-75) อาการสำคัญของผู้ป่วย คือ ไข้ (100%) กินน้อย (100%) หงุดหงิด (100%) เลี้ยงไม่โต (100%) ตับโต (100%) ม้ามโต (77.8%) ไอ (88.9%) หายใจหอบ (66.7%) ฯลฯ ตรวจพบปฏิชีวนาเบอร์คูลินให้ผลบวก (≥ 10 มม) เพียงร้อยละ 25 ของผู้ป่วยที่ทำการศึกษา ตรวจภาพรังสีทรวงอกพบความผิดปกติแบบ bronchopneumonia 66.7% miliary 33.3% และมีลักษณะ cystic lesion 11.1% การตรวจลึกลับหลังจากกระเพาะอาหาร พบ AFB จากการย้อมสี 62.5% และเพาะเชื้อวัณโรคได้ 71.4% ผู้ป่วยเสียชีวิต 3 ราย หายปกติดี 6 ราย อัตราตายป่วยจากยาด้านวัณโรค 6 ใน 7 ราย (86%) วัณโรคตั้งแต่กำเนิด พบได้น้อย การวินิจฉัยโรคน่ายากและมักล่าช้าเกินไป ดังนั้นแพทย์ควรเพิ่มความสงสัยในทารกอายุอ่อนที่มีอาการของปอดบวมที่ไม่ตอบสนองต่อการรักษาด้วยยาปฏิชีวนะหรือหาสาเหตุไม่ได้ ควรค้นหาประวัติความเจ็บป่วยในมารดาหรือถ่ายภาพรังสีทรวงอกในมารดา จะทำให้สามารถวินิจฉัยและรักษาด้วยยาด้านวัณโรคได้เร็วขึ้น

คำสำคัญ : วัณโรค, กำเนิด, ทารก

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