ORIGINAL ARTICLE

WILEY

Clinical characteristics and post-discharge follow-up analyses of 10 infants with congenital tuberculosis: A retrospective observational study

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Funding source
This study was supported by the Special Fund of the Pediatric Medical Coordinated Development Center of Beijing Hospitals Authority (No. XTCX201816).

Received: 8 September, 2020
Accepted: 2 February, 2021

ABSTRACT

Importance: Congenital tuberculosis (TB) is a rare, potentially fatal disease. There is currently a lack of detailed clinical information available regarding this disease.

Objective: This retrospective study investigated the clinical manifestations, treatment, and long-term prognosis of congenital TB.

Methods: Patients were treated in Beijing Children's Hospital, Capital Medical University (Beijing, China) between 2009 and 2018. Their demographic data, maternal and family histories, symptoms and signs, treatment information, and follow-up data were retrospectively collected using the hospital's electronic information system.

Results: Ten infants with congenital TB were enrolled. The mean gestational age was 36.6 ± 2.2 weeks and mean birth weight was 2517 ± 487 g. All 10 patients exhibited fever, nine patients (90%) had anemia, and six patients (60%) had extrauterine growth retardation. On chest computed tomography scans, all 10 patients presented multiple pulmonary nodules and four patients (40%) had mediastinal adenopathy. Nine out of ten (90%) completed the T-spot test, and eight of them (8/9, 89%) were positive. Anti-TB treatment was initiated upon diagnostic confirmation. All patients (100%) received combined treatment with isoniazid (INH) and rifampicin (RIF). Eight of 10 patients (80%) received combined treatment with INH, RIF, and pyrazinamide. The survival rate was 100%. One patient was lost to follow-up and four patients are currently continuing treatment. Three of nine patients (33%) achieved normal developmental milestones at 6 months of age.

Interpretation: Early diagnosis based on maternal history, typical imaging results, and timely treatment can improve outcomes in infants with congenital TB.

KEYWORDS
Congenital tuberculosis, Infant, Newborn, Linezolid, Follow-up

INTRODUCTION

Congenital tuberculosis (TB) is a rare disease that is caused by *Mycobacterium tuberculosis* and carries a high mortality rate, especially in developing countries.[1] The mortality rate for congenital TB is 21.7%–100%; higher mortality is associated with delayed or inappropriate treatment.[2] However, it is difficult to diagnose congenital

DOI: 10.1002/ped4.12266

TB because the disease causes few or no symptoms in the fetus during pregnancy and nonspecific symptoms in infants. Clinical data concerning congenital TB are limited, possibly due to the rarity of the condition. In addition, the sensitivity and specificity of TB screening tests are poor in neonatal populations. Importantly, the outcomes of infants with congenital TB who have received prompt treatment is of considerable interest to clinicians. To provide additional guidance for clinicians, we performed a retrospective study of infants with congenital TB with the aim of identifying the clinical manifestations, treatment, and long-term prognosis of the disease.

METHODS

Ethical approval

This retrospective study was approved by the Ethics Committee of Beijing Children's Hospital (2018-k-124). The data are anonymous, and the requirement for informed consent was therefore waived.

Patients and treatment

All patients eligible for inclusion in this study were treated in the neonatal intensive care unit of Beijing Children's Hospital, Capital Medical University in China, between 2009 and 2018. The diagnostic criteria for congenital TB in this study were as follows: (1) onset of symptoms prior to 28 days of age; (2) at least one positive TB-specific test result; (3) positive response to anti-TB treatment (The patient's general condition and appetite were improved within 1 week. Fever was resolved. C-reactive protein (CRP) level was decreased. Respiratory support was weaned or lower.); and (4) postnatal transmission ruled out by thorough contact tracing. The exclusion criteria were as follows: (1) parent/legal guardian refusal of anti-TB treatment for the infant after a confirmed diagnosis and/or (2) infants placed under palliative care. Importantly, after an infant had been diagnosed with TB, all family members and caregivers were required to undergo complete TB investigations, including purified protein derivative (PPD) skin tests, chest X-rays, and blood T-spot assessments.

After confirmation of congenital TB, if the patient met specific subsets of the following criteria (either 1, 2, and 3, or 1, 2, and 4), they received additional linezolid (LZD) as a component of anti-TB chemotherapy[3,4]: (1) confirmation with recurrent TB infection in the mother (It was a risk factor for multidrug-resistant TB infection); (2) requirement for intubation due to respiratory failure; (3) worsening transaminitis during the infant's treatment.

Follow-up

The patients were first followed up at 1 month after discharge, then at 3-month intervals after discharge until 6 years of age. At each follow-up visit, the patients completed the following examinations: (1) measurements of physical growth and assessments of neurological development; (2) blood tests including whole blood counts, liver and renal function analyses, and T-spot assessment; and (3) chest X-ray and abdominal ultrasonography examinations. Computed tomography (CT) scans of lungs and/or head, as well as lumbar puncture, were optional depending on the patient's condition. Anti-TB treatments were discontinued if the results of all TB-specific investigations were negative and the length of anti-TB treatment was >1 year, or if liver function was severely damaged by anti-TB treatments.

Data collection

Information collected for analysis in this study included the infants' demographic data, their maternal and family histories, their symptoms and signs, their treatments, and all follow-up findings. These data were collected using the hospital's electronic information system. Categorical data are presented as numbers (%) and continuous data are presented as means and standard deviations for normally distributed data or medians and percentiles for non-normally distributed data.

RESULTS

Demographic data and maternal history

The infants' demographic data and maternal histories are shown in Table 1. In total, 10 infants with congenital TB (five boys and five girls) were enrolled in this study. Five patients (50%) were preterm infants. The mean gestational age was 36.6 ± 2.2 weeks (range: 33^{+2} to 40^{+1} weeks). The mean birth weight was 2517 ± 487 g (range: 1800–3350 g). Two patients (20%) were small for gestational age (i.e., birth weight below the 10th percentile of infants with the same gestational age and same sex[5]).

None of the 10 mothers received any anti-TB treatment during the pregnancy. Two of the 10 mothers (20%) were previously diagnosed with TB and had been considered fully recovered well in advance of pregnancy. Both were *in vitro* fertilization pregnancies and both mothers had been asymptomatic during pregnancy. These two asymptomatic mothers had been diagnosed with recurrent TB after their newborn infants had been diagnosed. The remaining eight mothers (80%) exhibited fatigue symptoms during pregnancy, which were not specifically regarded as TB-related symptoms. One out of the eight mothers with fatigue had been diagnosed with TB during pregnancy due to pleural effusion during late pregnancy, but she had refused anti-TB treatment because she considered herself to be asymptomatic and presumed that anti-TB medications were harmful to the fetus. One of the eight mothers with fatigue had genital TB alone. Six of the eight mothers with fatigue were confirmed to have miliary lung TB on the basis of chest radiography findings.

TABLE 1 Demographic data and maternal histories of infants with congenital tuberculosis

No.	GA (week)	BW (g)	Maternal age (y)	Maternal TB type	Pregnancy complication	GP	Delivery mode	PROM >18h	Breast feeding
1	35^{+2}	1800	33	Miliary, genital	None	G3P3	SVD	Unknown	No
2	35^{+0}	2400	27	Miliary	None	G2P2	SVD	No	No
3	40^{+1}	2300	32	Pleurisy	None	G2P2	SVD	No	No
4	33^{+2}	2100	29	Genital	GDM	G1P1	C/S	No	No
5	37^{+0}	2600	30	Infiltrative, pleurisy	None	G3P2	C/S	No	yes
6	36^{+1}	2500	30	Miliary	None	G3P1	SVD	No	No
7	39^{+2}	3350	35	Miliary	None	G1P1	SVD	No	yes
8	34^{+5}	2250	27	Miliary	None	G1P1	SVD	No	No
9	38^{+3}	2570	21	Miliary, pleurisy	None	G1P1	SVD	No	No
10	37^{+2}	3300	42	Pleurisy, genital	None	G1P1	C/S	No	No

BW, birth weight; GP, gestation parturition; C/S, caesarean section; GA, gestational age; GDM, gestational diabetic mellitus; PROM, prolonged rupture of membrane; SVD, spontaneous vaginal delivery; TB, tuberculosis.

Postnatal infection was ruled out in these 10 infants as follows: (1) none of the mothers exhibited cough, fever, or weight loss either during pregnancy or after delivery; (2) none of the infants' family members or caregivers had respiratory symptoms before the infants were admitted to the hospital; (3) after the infants had been diagnosed with TB, all of their family members and caregivers underwent complete TB investigations (e.g., PPD skin tests, chest X-rays, and blood T-spot assessments) and had negative results.

Patient history

Patient histories are shown in Table 2. Although one infant had fever on the day of birth, the other nine infants (90%) began to show symptoms at 13–28 days after birth. The mean onset age was 19.1 ± 7.9 days (range: 1–28 days). At the time of admission, all patients had fever (100%), six patients (60%) had extrauterine growth retardation (i.e., weight less than the 10th percentile for postmenstrual age[6]), five patients (50%) had cough, and four patients (40%) had seizure. One patient (1/10, 10%) did not have information of Bacillus Calmette-Guérin (BCG) vaccination, 5 patients (5/9, 55.6%) did not had BCG vaccination, and 4 patients (4/9, 44.4%) had BCG vaccination before diagnosis with TB.

TABLE 2 Medical histories of infants with congenital tuberculosis

No.	Onset age (d)	Symptoms at admission	BCG vaccination
1	24	Fever; cough; seizure; EUGR	No
2	15	Fever; tachypnea; seizure; EUGR	Unknown
3	22	Fever; cough; EUGR	No
4	25	Fever	No
5	13	Fever; cough; seizure	Yes
6	20	Fever; cough; anemia; EUGR	Yes
7	25	Fever; seizure	Yes
8	28	Fever; tachypnea; vomit; EUGR	No
9	18	Fever; cough; tachypnea; EUGR	Yes
10	1	Fever	No

BCG, Bacillus Calmette-Guérin; EUGR, extra-uterus growth retardation.

General laboratory findings

The findings of general and routine laboratory examinations are listed in Table 3. The white blood cell counts were elevated in all patients, ranging from 12.49 to 32.44 × 10^9 cells/L (mean: 21.45 ± 6.30 × 10^9 cells/L); neutrophils were the predominant (100%) cell type. The CRP levels were elevated in all patients, ranging from 36.0 to 163.0 mg/L (mean: 96.3 ± 41.4 mg/L). Nine of 10 infants (90%) and seven of 10 (70%) infants had complications of anemia and thrombocytopenia, respectively. Half of the patients had complications of hepatic dysfunction. The cerebrospinal fluid findings were abnormal in half of the patients, characterized by elevated levels of lymphocytes and protein, as well as reduced levels of glucose and chlorine.

Imaging findings

The imaging findings are summarized in Table 4 and some typical radiographic images are depicted in Figure 1. On chest CT scans, all patients (100%) exhibited multiple pulmonary nodules and four of 10 patients (40%) had mediastinal adenopathy. Abdominal ultrasonography showed hypoechoic nodules in the liver and spleen in four of 10 patients (40%); these nodules were strongly suspected to be TB lesions. In patient #7, who had symptoms and cerebrospinal fluid findings indicative of TB meningitis, magnetic resonance imaging showed severe brain damage with cerebral infarction, hydrocephalus, encephalomalacia, and cerebral atrophy.

TB-specific tests

The results of TB-specific tests are provided in Table 5. Among these tests, positive results were most common in the T-spot test (eight of nine patients, 89%). GeneXpert assessment was only completed in five patients, all of whom were diagnosed in the last 5 years; positive results were observed in four patients (80%). Furthermore, three of 10 patients (30%) had positive acid-fast bacilli (AFB)

TABLE 3 General laboratory findings among infants with congenital tuberculosis

No.	WBC ($\times10^9$/L)	Neutrophil (%)	Hb (g/L)	Platelet ($\times10^9$/L)	CRP (mg/L)	ALT (U/L)	HIV	CSF	Hearing screen	Eye exam
1	18.85	70.3	99	138	36.0	50.0	Unknown	Normal	Not done	Not done
2	19.75	83.8	77	200	104.0	8.9	Unknown	Pro↑	Not done	Not done
3	21.78	64.8	87	117	65.3	105.0	Unknown	Normal	Not done	Normal
4	22.80	60.5	73	218	58.6	110.7	Unknown	Normal	Not done	Not done
5	17.99	56.2	73	103	116.0	38.3	Negative	Glu↓	Passed	Normal
6	31.95	61.9	87	487	87.2	40.1	Negative	Normal	Passed	Suspected optic atrophy
7	17.39	81.7	71	87	163.0	119.7	Negative	Glu and Cl↓, Pro↑, WBC 326×10^9/L, L 72%	Not done	Not done
8	19.10	55.5	68	34	77.0	16.3	Negative	Glu and Cl↓, Pro↑, WBC 20×10^9/L, L 100%	Not done	Not done
9	32.44	78.7	93	106	163.0	41.3	Negative	Glu and Cl↓	Not done	Not done
10	12.49	62.9	70	20	96.0	57.0	Negative	Normal	Passed	Retinitis

WBC, white blood cell; Hb, hemoglobin; CRP, C-reactive protein; ALT, alanine aminotransferase; HIV, human immunodeficiency virus; CSF, cerebral spinal fluid; Glu, glucose; Cl, chlorine; L, lymphocytes; Pro, protein.

TABLE 4 Imaging findings among infants with congenital tuberculosis

No.	Chest CT scan	Abdominal ultrasonography	Brain MRI/CT
1	Multiple pulmonary nodules; bronchopneumonia; mediastinal adenopathy	Hypoechoic nodules in liver and spleen	Not completed
2	Multiple pulmonary nodules	Normal	Not completed
3	Multiple pulmonary nodules	Normal	Normal
4	Multiple pulmonary nodules; bronchopneumonia	Normal	Normal
5	Multiple pulmonary nodules	Hypoechoic nodules in liver and spleen	Normal
6	Multiple pulmonary nodules; mediastinal adenopathy	Normal	Not completed
7	Multiple pulmonary nodules; mediastinal adenopathy	Hypoechoic nodules in liver and spleen	Cerebral infarction, hydrocephalus, encephalomalacia, cerebral atrophy
8	Multiple pulmonary nodules	Normal	Normal
9	Multiple pulmonary nodules	Normal	Normal
10	Multiple pulmonary nodules; mediastinal adenopathy	Hypoechoic nodules in liver and spleen	Normal

CT, computed tomography; MRI, magnetic resonance imaging.

TABLE 5 TB-specific test results among infants with congenital TB

No.	PPD	AFB smear	TB culture	GeneXpert	T-spot
1	(−)	Gastric fluid & tracheal aspirates (+)	(−)	Not completed	Not done
2	(−)	Gastric fluid (+)	(−)	Not completed	(+)
3	(−)	Gastric fluid (−)	(−)	Not completed	(+)
4	Not done	Gastric fluid (−)	(−)	Not completed	(+)
5	(−)	Gastric fluid (−)	(−)	Not completed	(+)
6	Not done	Gastric fluid & tracheal aspirates (−)	Gastric fluid (+)	Bronchoalveolar lavage fluid: (+) for TB, (−) for Rifampicin resistance	(−)
7	(+)	Gastric fluid & CSF (+)	Gastric fluid (+)	CSF and gastric fluid: (+) for TB, (−) for Rifampicin resistance	(+)
8	(+)	Gastric fluid & tracheal aspirates (−)	(−)	Bronchoalveolar lavage fluid (−)	(+)
9	(−)	Gastric fluid & tracheal aspirates (+)	(−)	Tracheal aspirates: (+) for TB, (−) for Rifampicin resistance	(+)
10	Not done	Gastric fluid & tracheal aspirates (+)	(−)	Tracheal aspirates: (+) for TB, (−) for Rifampicin resistance	(+)

TB, tuberculosis; AFB, acid-fast bacilli; CSF, cerebral spinal fluid; PPD, purified protein derivative; (+), positive; (−), negative.

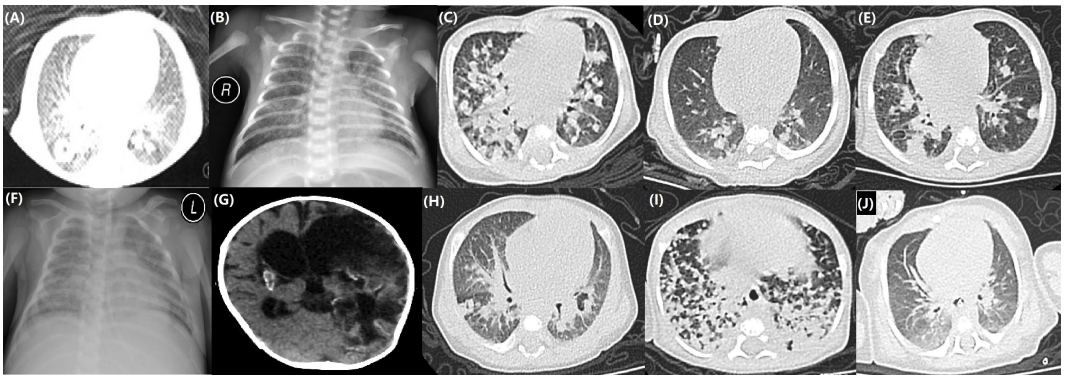

FIGURE 1 Imaging findings: (A) Chest CT scan of patient #1 exhibited multiple pulmonary nodules, bronchopneumonia and mediastinal adenopathy; (B) Chest X-ray of patient #2 exhibited extensive patchy and granular shadows in both lungs; (C) Chest CT scan of patient #3 exhibited multiple pulmonary nodules; (D) Chest CT scan of patient #5 exhibited multiple pulmonary nodules; (E) Chest CT scan of patient #6 exhibited multiple pulmonary nodules and mediastinal adenopathy; (F) Chest X-ray of patient #7 exhibited extensive patchy and granular shadows in both lungs; (G) Brain CT scan of patient #7 exhibited cerebral infarction, hydrocephalus, encephalomalacia and cerebral atrophy; (H) Chest CT scan of patient #8 exhibited multiple pulmonary nodules; (I) Chest CT scan of patient #9 exhibited multiple pulmonary nodules; (J) Chest CT scan of patient #10 exhibited multiple pulmonary nodules.

smear examination results for both gastric fluid and tracheal aspirates, one patient had positive AFB smear examination results for gastric fluid, and one patient had positive AFB smear examination results for both gastric fluid and cerebrospinal fluid. Samples of blood, cerebrospinal fluid, tracheal aspirates, gastric fluid, urine, and stool were cultured; positive TB culture results were recorded for two of 10 patients (20%), both in samples of gastric fluid. Two of seven patients (29%) had positive tuberculin skin test results.

Anti-TB treatment

Treatment approaches are summarized in Table 6. Lung tissue was involved in the disease in all patients. Two patients (patients #8 and #9) were intubated on admission and were extubated 4 and 7 days later, respectively. Seven of 10 patients (70%) had disseminated disease (≥2 organ sites involved). Anti-TB treatment was initiated following confirmation of the diagnosis. The median time between the development of symptoms and the initiation of treatment was 6.5 days (range: 3.0–15.2 days). All patients (100%) received combined treatment with isoniazid (INH) and rifampicin (RIF). Eight of 10 (80%) patients received combined treatment with INH, RIF, and pyrazinamide (PZA); however, PZA was discontinued in two patients (patients #7 and #10) because of elevated alanine aminotransferase levels. The daily dosage of anti-TB drugs was administered in accordance with guidance from the World Health Organization.[7] Additional corticosteroid treatment was administered to three patients, two of whom had TB infection complicated with meningitis. LZD was administered as a supplementary drug for seven patients (70%) at a dosage of 10 mg/(kg · dose), twice daily at 12-hour intervals or three times daily at 8-hour intervals, for 2–6 months. The total duration of anti-TB treatment varied from 2 months to 3 years. Evaluation of adverse effects revealed that three patients (30%) experienced side effects of drug treatment, such as hepatotoxicity. Treatments for patients #5 and #10 were discontinued at 6 months and 2 months, respectively, due to severe hepatotoxicity.

Outcome and follow-up

All patients were discharged in accordance with medical advice. The mean length of stay in the neonatal intensive care unit was 23.3 ± 17.2 days. Fever persisted for a median of 7.0 days (range: 4.5–20.0 days). Treatment with anti-TB drugs was continued after discharge. The follow-up rate was 90%; one patient was lost to follow-up at 2 months after discharge. The survival rate was 100% in the remaining nine patients. Five of nine patients (56%) fully recovered and showed gradual resolution on consecutive chest radiographs. Four patients (44%) were continuing to undergo treatment, four patients (44%) failed to thrive, and three patients (33%) had TB infection complicated with neurological sequelae. Patients #7 had persistent seizure and required ventricular shunt and physical therapy. Only three of nine patients (33%) exhibited normal growth and development at 6 months of age.

DISCUSSION

Congenital TB is defined as an infection that develops as a result of an encounter between a TB-infected mother and her infant during the intrauterine period or during birth. Cantwell et al[8] defined the initial criteria for congenital TB in 1994. Subsequent progress in medicine has led to more advanced investigation methods for disease diagnosis. The diagnostic criteria used in our study were established in accordance with the Cantwell criteria, with the following modifications: (1) onset time within 28 days of age, based on the universal definition of the neonatal period; and (2) at least one positive TB-specific test result was included (notably, the GeneXpert test of bronchoalveolar lavage

TABLE 6 Treatment approaches and outcomes among infants with congenital TB

No.	TB involved organs	Drugs and duration[†]	Drug side effects	Respiratory support on admission	Other treatments[‡]	Outcome
1	Lung; liver; spleen; CNS[§]	INH36 + RIF36	None	CPAP	None	Recovered
2	Lung; CNS	INH2 + RIF2 + PZA2 + Pred2	None in 2 months, but lost to follow-up	CPAP	Mannitol; hepatic protector	Lost
3	Lung	INH12 + RIF12 + PZA12	None	None	Hepatic protector	Recovered
4	Lung	INH18 + RIF18 + LZD2	None	Low flow O_2	Hepatic protector	Recovered
5	Lung; liver; spleen; CNS	INH6 + RIF6 + PZA6 + LZD6	Hepatotoxicity	Low flow O_2	Mannitol; hepatic protector	Recovered
6	Lung; endobronchial	INH18 + RIF18 + PZA18 + LZD3	None	None	Bronchoalveolar lavage once per month for 10 times; hepatic protector	Recovered
7	Lung; liver; spleen; CNS	INH14 + RIF14 + EMB14 + PZA3 + LZD4 + Pred3 (INH, RIF, EMB are still continued)	Hepatotoxicity	CPAP	Anticonvulsant; mannitol; hepatic protector	Improved
8	Lung; CNS	INH9 + RIF9 + PZA6 + LZD6 (INH, RIF are still continued)	None	SIMV	Mannitol; hepatic protector	Improved
9	Lung	INH6 + RIF6 + PZA6 + LZD6 + Pred1 (INH, RIF, PZA, LZD are still continued)	None	SIMV	Hepatic protector	Improved
10	Lung; liver; spleen	INH2 + RIF2 + PZA2 + LZD2 (all medications were D/C after 2 months due to severe hepatotoxicity)	Hepatotoxicity	None	Hepatic protector	Improved

[†]Presented by the abbreviations of the drug followed by the administration period (in months) of each drug. [‡]Hepatic protector refers to glutathione, ornithine and aspartate. [§]Suspected CNS involvement. TB, tuberculosis; CNS, central nervous system; CPAP, continuous positive airway pressure; INH, isoniazid; LZD, linezolid; Pred, prednisone; PZA, pyrazinamide; RIF, rifampicin; D/C, discontinued; SIMV, synchronized intermittent mandatory ventilation.

fluid and blood T-spot tests were not available when the Cantwell criteria were established). To the best of our knowledge, our study is the first that includes the complete clinical information regarding a case series of infants with congenital TB in China, including their treatment results and follow-up findings. We presume that our study provides valuable insights concerning congenital TB infection. Although LZD was considered a second line anti-TB treatment in this study, we believe that the criteria for addition of LZD were appropriate. The high survival rate is an important result in our case series, but we were unable to determine whether the application of LZD contributed to this outcome.

Because female genital TB and tuberculous endometritis are associated with infertility, congenital TB is rare. Our data showed that 20% of the mothers were diagnosed with TB before pregnancy and had undergone *in vitro* fertilization procedures. This suggests that the increasing availability of assisted reproductive technologies may contribute to increased prevalence of congenital TB, which was in consistent with literature report.[9]

The confirmation of TB infection for the mother might highly suggestive diagnosis of congenital TB for infant presenting relative symptoms and prompt TB-specific tests for infant. One study reviewed 170 infants with congenital TB and reported that 162 mothers were found to be active tuberculosis patients either during pregnancy or postpartum.[2] Unfortunately, it is difficult to clearly identify mothers who are likely to transmit TB infection to their fetus during pregnancy. A delay between symptom onset and disease diagnosis is frequently observed, due to the nonspecific symptoms at presentation, reluctance to perform radiography, and low level of suspicion.[10] It was not surprising that the diagnosis of TB in some mothers in this study was made only after the infants had shown symptoms of TB and were subsequently diagnosed. For those 170 infants with congenital TB reviewed in the other study, 121 mothers (71%) had been diagnosed during the postpartum period; of these 121 mothers, 39 mothers had been completely asymptomatic.[2] In our study, 90% of the mothers were diagnosed after delivery.

The symptoms of postnatal TB infection are usually observed 4 to 8 weeks after infection.[11] Cantwell et al[8] analyzed 29 patients with congenital TB and reported that the age at TB onset ranged from 1 to 84 days, whereas Patel et al[12] analyzed 21 patients with congenital TB

and reported the age at onset to range from 1 to 90 days. Congenital TB symptoms commonly manifest in the first 2 to 3 weeks after birth.[2] In our study, the age at onset varied from 1 to 28 days. Clinical manifestations of congenital TB can be diverse, nonspecific, and difficult to differentiate from neonatal bacterial or viral sepsis. In our study, fever was the most frequent symptom. Nonspecific markers identified in patients with congenital TB have included neutrophilia, thrombocytopenia, and elevated CRP levels.[2] In our study, all patients exhibited neutrophilia and elevated CRP levels. Moreover, 70% of the patients with congenital TB had complications involving thrombocytopenia.

The imaging results in our study indicated that the most frequent patterns of chest CT scans were multiple pulmonary nodules and mediastinal adenopathy; moreover, abdominal ultrasonography showed hypoechoic nodules in the liver and spleen in 40% of the patients. Liver and spleen nodules were similarly found in adult patients with TB, but the lung TB nodule features considerably differ from those in other lung diseases and could support a diagnosis of congenital TB when analyzed by an experienced radiologist or TB specialist.[2] Recently, multiple pulmonary nodules have been described as a new radiographical finding in some published studies.[13] Multiple pulmonary nodules on chest CT scans have been regarded as the progressive deterioration of miliary TB, consistent with caseating necrosis in a biopsy specimen.[14] Several pediatric TB specialists and radiologists in China reported that both patterns of miliary TB and pulmonary nodules were specific imaging characteristics in patients with congenital TB.[15,16] Accordingly, TB-specific investigations should be performed when there are suspicions of TB based on imaging results.

The confirmation of TB infection is often challenging in infants because TB-specific markers have poor sensitivity. Serial gastric fluid appears to be the most common specimen for TB pathogen identification in infants. Lower sensitivity and a longer interval before confirmation of culture-positive results frequently occurs in children because of reduced bacterial loads. In our study, the rate of positive AFB smear results was 50% when recorded within 24 hours. Furthermore, only 20% of the patients had a positive culture result by 13.5 to 16.0 days. The GeneXpert assay is a hemi-nested real-time PCR test that simultaneously identifies RIF resistance in *M. tuberculosis.* Its diagnostic accuracy is comparable with that of sputum sample culture and provides results within 24 to 48 hours.[7] The World Health Organization recommends GeneXpert for rapid diagnosis in communities with a high burden of TB.[7] In our study, GeneXpert had high positive rate and provided results within 24 hours. Currently, there are two types of commercially available IFN-γ release assays: QuantiFeron TB Gold (Cellestis) and T-spot TB (Oxford Immunotec).[17] Although there are concerns regarding the applicability of these assays to infants due to the low levels of IFN-γ production in infants, the T-spot assay also had high positive rate in our study and was one of the most robust assays for initial evidence of TB in our patients.

The standard regimen for treatment of congenital TB includes INH, RIF, PZA, and ethambutol for 2 months during the intensive phase, followed by INH and RIF for 7–10 months during the continuation phase. Chest X-ray examination is recommended at the end of treatment.[12,18] The overall mortality for infants with congenital TB is reportedly 100% if undiagnosed; delayed infant diagnosis carries a fivefold greater mortality rate than that associated with prompt diagnosis and treatment.[2] In contrast to the findings in a previous case report of patients with congenital TB,[8] our patients had a much higher survival rate as 100% survival rate. And this was in the first year from treatment and without mortality. We presume that this difference in outcomes might have resulted from early diagnosis and prompt anti-TB treatment in our study, including the introduction of LZD during the intensive phase of treatment. LZD is a member of the oxazolidinone class of antibiotics, which exhibit bacteriostatic activity against *M. tuberculosis,* including multidrug-resistant and extensively drug-resistant strains of *M. tuberculosis*.[19] Clinical trials in adults have revealed that LZD is an important component of treatment for patients with multidrug-resistant and extensively drug-resistant strains of *M. tuberculosis*.[20,21] Notably, LZD is a newer anti-Gram-positive antibiotic with excellent penetration to the central nervous system. Furthermore, published studies support its effectiveness and safety in treating infections caused by resistant pathogens, including staphylococcal bacteremia and cerebrospinal fluid infections, in both term and preterm infants in neonatal intensive care units.[22,23] Li et al[24] reported that LZD improved the early outcomes of childhood TB meningitis in 36 patients. Because China has a serious epidemic of drug-resistant TB[25] and the immune system is not fully developed in infants, our center has used LZD as a supplementary drug for patients with congenital TB since 2015. In our study, LZD was administered to seven patients, ranging in age from 4 to 70 days, for a duration of 2–6 months. To the best of our knowledge, this is the first report of the long-term use of LZD for treatment of congenital TB. The adverse events and side effects of LZD in our patients were monitored and evaluated on the basis of clinical symptoms, whole blood counts, and serum liver/renal function analyses at intervals of 1–2 weeks.

This study had some limitations. First, this was a single-center study with a small sample size, which limits the generalizability of the findings. Second, there was not extensive evidence for the application of LZD treatment as an anti-TB medication in infants; moreover, there was a lack of culture-based data to support this approach. Thus, its usage was mainly based on the experience of

neonatologists and TB specialists. A clinical guide for the standard treatment of patients with congenital TB is urgently needed.

In summary, congenital TB is a potentially fatal disease; however, affected patients can achieve good treatment outcomes in the context of careful evaluation and aggressive clinical management. Early diagnosis is crucial and should include considerations of maternal history and typical imaging findings; subsequent timely treatment is necessary. Multi-drug anti-TB treatment, including LZD, is safe and might be effective for reducing mortality in infants.

ACKNOWLEDGMENTS

We thank pediatric TB specialist Dr. Shunying Zhao and her team for the consultation of all patients. We also gratefully acknowledge imaging analysis support from experienced radiologists.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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How to cite this article: Du J, Dong S, Jia S, Zhang Q, Hei M. Clinical characteristics and post-discharge follow-up analyses of 10 infants with congenital tuberculosis: A retrospective observational study. Pediatr Investig. 2021;5:86-93. https://doi.org/10.1002/ped4.12266