Clinical characteristics and post-discharge follow-up analysis of 10 cases of congenital tuberculosis: a retrospective observational study

CURRENT STATUS: UNDER REVIEW

Juan Du
Beijing Children's Hospital, Capital Medical University
ORCiD: 0000-0001-7751-6994

Shixiao Dong
Beijing Children's Hospital, Capital Medical University

Shengnan Jia
Beijing Children's Hospital, Captial Medical University

Qiaoru Zhang
Beijing Children's Hospital, Capital Medical University

Mingyan Hei  heimingyan@bch.com.cn
Corresponding Author

DOI:
10.21203/rs.2.13513/v1

SUBJECT AREAS
Pediatrics
Abstract

Background Congenital tuberculosis (TB) is a rare disease with a high mortality. In this study, we reviewed patients with congenital TB that were promptly treated with an anti-TB regimen, including linezolid, based on new clinical diagnosis criteria. We described the clinical manifestations, treatment, and long-term prognosis of this disease in these patients. Methods This was a retrospective observational study that enrolled patients with congenital TB that were admitted to Beijing Children’s Hospital between 2009 and 2018. Results A total of 10 congenital TB patients were enrolled. Ninety-percentage of the mothers were diagnosed at postpartum; however, none of the mothers received anti-TB treatment during pregnancy. The onset age of congenital TB ranged from 1 to 53 days. Chest computed tomography scans demonstrated pulmonary nodules in 100% of the patients and mediastinal adenopathy in 40% of the patients. Abdominal ultrasonography showed hypoechoic nodules in the liver and spleen in 40% of the patients. The positive rate of GeneXpert and T-spot were relatively high—80% and 78%, respectively. Anti-TB treatment was started when congenital TB was confirmed for 1 patient based on TB-specific tests or clinically diagnosed for the other 9 patients based on confirmed maternal TB history and typical radiological findings. Beside isoniazid, rifampicin, and pyrazinamide, linezolid was also administrated in 70% of the patients for a period of 2–6 months. One patient was reported to present with spontaneously resolved thrombocytopenia. The survival rate was 100%, and 33% of the patients have thrived and reached normal developmental milestones since the last documented follow-up. Conclusion Congenital TB is a potentially fatal disease, but early diagnosis based on maternal history, typical imaging results, and timely treatment can improve the outcome. Linezolid is safe and might be effective in reducing the mortality of congenital TB.
Background

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (Mtbt). Despite advances in therapeutic and diagnostic techniques, TB continues to be a major infectious cause of morbidity and mortality worldwide, especially in developing countries [1]. Congenital TB infection by vertical transmission from infected mothers is rare, but carries a poor prognosis. The mortality rate for congenital TB is 21.7%-100%, with a higher mortality associated with delayed, or inappropriate treatment [2]. Furthermore, diagnosis in neonates is challenging because of non-specific manifestations.

The outcome of infants with congenital TB who have been promptly treated is of great interest for clinicians. In this study, we present 10 patients with congenital TB that were admitted to Beijing Children’s Hospital, Capital Medical University in China. Moreover, this study had access to the follow-up information of each patient after discharge. To the best of our knowledge, this is the first study analyzing cases of congenital TB with the follow-up data.

Methods

2.1 Patients and study design

This was a retrospective observational study based on the in-patient electronic records of patients admitted to Beijing Children’s Hospital between 2009 and 2018. All patients were confirmed with a first diagnosis of congenital TB. They were treated and followed up in Beijing Children’s Hospital.

2.2 Diagnostic criteria

Congenital TB was diagnosed according to the criteria revised by Cantwell et al [3]. Cantwell et al. proposed that in order for an infant to be diagnosed with congenital TB, the infant must have proven tuberculous disease and at least one of the following: 1) lesions
in the first week of life, 2) a primary hepatic complex or caseating hepatic granulomas, 3) tuberculous infection of the placenta or the maternal genital tract, and 4) exclusion of the possibility of postnatal transmission by thorough investigation of contacts.

2.3 Statistical analysis

Categorical data are presented as numbers (%) and continuous data as the mean and standard deviation for normal distribution data or median and percentiles for non-normal distribution data. SPSS, version 15.0 (SPSS Inc., Chicago, IL, U.S.) was used for all statistical analyses.

Results

3.1 Demographic data and maternal history

A total of 10 congenital TB patients were enrolled in this study from 2009 to 2018, with a male:female gender ratio of 1:1.5. Further, five (50%) of these patients were preterm. Gestational age was 35.8 (± 1.7) week. The average birth weight was 2517 (± 487) g. Two (20%) of the patients were small for gestational aged infants. There were two (20%) mothers that were diagnosed with TB, but were considered to have fully recovered prior to pregnancy. These women received in vitro fertilization (IVF) to become pregnant. TB symptoms were reported to have reoccurred during their pregnancy; however, no anti-TB treatment was given. A total of eight out of ten (80%) mothers presented with TB symptoms during pregnancy or immediately after delivery, of which only one out of the eight symptomatic mothers was diagnosed with TB during pregnancy. However, this mother was not treated, which was against all medical suggestions. Two out of ten (20%) mothers were completely asymptomatic and were not diagnosed with tuberculosis until their children were suspected of TB infection based on imaging results.
Thus, 90% of the mothers were diagnosed postpartum and not one of the ten mothers received anti-TB treatment during pregnancy. Most mothers were diagnosed with miliary TB by chest radiography, and only three out of ten (30%) of the mothers were confirmed to have genital TB.

3.2 Clinical manifestations

3.2.1 Patient history

The average onset day of life for congenital TB (DOL) was 25.6 (± 17.8) days with a range of 1—53 days. The most frequent clinical features were fever (100%), failure to thrive (60%), and cough (50%). Four out of nine (44%) infants received a BCG (Bacillus Calmette-Guérin) vaccination before diagnosis.

3.2.2 General laboratory findings

Common laboratory findings of each patient were analyzed. The white blood cell counts of all patients were elevated, ranging from 12.49 to 32.44 × 10^9 cells/L (an average of 21.45 (± 6.30) × 10^9 cells/L), with neutrophils being the predominant (100%) cell type. The C-reactive protein (CRP) levels of all the patients were elevated to 36—163 mg/L (96.3 ± 41.4) mg/L. Nine out of ten (90%) infants and seven out of ten (70%) infants had disease complicated with anemia and hepatic dysfunction, respectively. Half of the patients were complicated with thrombocytopenia. The cerebrospinal fluid of half of the patients was abnormal, with elevated levels of lymphocytes and protein and reduced levels of glucose and chlorine.

3.2.3 Imaging findings

Chest computed tomography (CT) scans were completed for all patients, which demonstrated pulmonary nodules in ten (100%) patients and mediastinal adenopathy in four (40%) patients. Abdominal ultrasonography (US) showed hypoechoic nodules in the
liver and spleen in four (40%) patients. The MRI analysis from one patient demonstrated severe brain damage with cerebral infarction, hydrocephalus, encephalomalacia, and encephalatrophy.

3.2.4 TB-specific tests
The positive rate of GeneXpert and T-spot were relatively high, with 4/5 (80%) and 7/9 (78%) positive rates, respectively. Further, 5/10 (50%) and 2/7 (29%) cases were positive for acid-fast bacilli (AFB) smear and tuberculin skin test, respectively. Samples of blood, cerebrospinal fluid, tracheal aspirates, gastric fluid, urine, and stool were cultured; however, only two (20%) cases were positive. The sample with the highest positivity rate of TB was gastric fluid followed by tracheal aspirates.

3.3 Diagnosis and treatment
Lung tissue was involved in the disease in all patients. Two patients required mechanical ventilation at admission and were extubated 4 and 7 days later, respectively. Seven out of ten (70%) patients had multi-organ lesions. Anti-TB treatment was started as soon as congenital TB was confirmed in one patient and clinically diagnosed in the other nine patients, based on proven maternal TB history and typical radiological findings (chest CT/abdominal ultrasonography) while TB was identified later for eight out of the nine patients. TB was not identified in one patient (patient number 3), who was diagnosed with congenital TB based on proven maternal TB history, typical chest CT findings, and efficacy of anti-TB treatment. The remaining nine patients met the criteria of Cantwell et al. AFB and T-spot analysis offered evidence for TB infection in 4/9 (44%) cases. The time between the development of symptoms and the initiation of treatment varied from 3 to 57 days, with a median time of 6.5 (3.0, 15.2) days. All of the patients received a treatment regimen consisting of isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA); however,
PZA was halted in two cases because of elevated alanine aminotransferase (ALT) levels. The daily dosage of anti-TB drugs used adhered to the Chinese National Formulary of Chemicals and Biological Products for Children. Corticosteroid was added to the regime for three patients, two of which had TB infection complicated with meningitis. Linezolid (LZD) was administrated as a supplementary drug for seven (70%) patients at a dosage of 10 mg/kg/dose, q12h (twice daily) to q8h (three times daily) for two to six months. The total duration for anti-TB treatment varied from two months to three years. The adverse effects were evaluated. Three (30%) patients experienced side effects, such as hepatotoxicity, from the drugs. The treatment for patients number 5 and number 10 was discontinued at six months and two months, respectively, due to severe hepatotoxicity. One patient presented thrombocytopenia during LZD treatment but recovered spontaneously without LZD withdrawal.

3.4 Outcome and follow-up

The survival rate was 100% at hospital discharge, with an improved health condition for all patients. The average hospital stay duration was 23.3 (± 17.2) days. Time of fever clearance ranged from 3–49 days, with a median time of 7.0 (4.5, 20.0) days. Treatment with anti-TB drugs was continued as an outpatient procedure for all the patients. The follow up rate was 90%. There were five (56%) patients that fully recovered, of whom consecutive chest radiographs showed gradual resolution. Four (44%) patients were still under treatment, four (44%) patients failed to thrive, and three (33%) patients had TB infection complicated with neurological sequelae. Only 3/9 (33%) patients thrived and achieved normal developmental milestones.

Discussion

Congenital TB is defined as infection that develops as a result of an encounter between a
TB-infected mother and her infant during the intrauterine period or during birth. Maternal TB can be transmitted to the fetus either transplacental or through the aspiration of infected amniotic fluid [3]. To our best knowledge, our study is the first that includes the complete clinical information of 10 congenital TB infants in China, including treatment and follow-up information. Our study provides valuable insights into congenital TB infection. Since female genital tuberculosis 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 received IVF. This suggests that the increasing availability of assisted reproductive technologies has a potential to increase the prevalence of congenital TB [4].

The mothers who transmit TB infection to their fetus during pregnancy are difficult to diagnose. A delay between the onset of symptoms and diagnosis occurs frequently, due to the non-specific symptoms at presentation, reluctance to perform radiography, and low index of suspicion [5]. It was not surprising that the diagnosis of some maternal TB cases was made only after the infants’ exhibited symptoms of TB and were subsequently diagnosed. One study reviewed 170 cases of congenital TB and reported that 121 (71%) mothers were diagnosed at postpartum, of which 39 cases were completely asymptomatic [2]. In our study, 70% of the mothers were diagnosed after delivery, among which two mothers were individually diagnosed by chest X-ray and T-Spot test after their babies were suspected for congenital TB. Thus, according to our study, if there is a strong suspicion of TB in the infant and the mother is not currently diagnosed with TB, then they should both be tested.

According to WHO guidelines for BCG vaccination, a single dose of the BCG vaccine should be given to all healthy infants as close to the time of birth as possible [6]. However in our study, five out of ten patients had not received BCG when they were admitted to the
hospital. One explanation is that the BCG vaccination is not given to preterm newborns, according to Chinese national protocol. Patients 1, 4, and 8 were preterm newborns that did not receive the BCG vaccine immediately after birth. Patient 10 presented with symptoms of TB on DOL 1, and as such, the BCG vaccination was delayed due to the uncertain TB status. The mother of patient 3 was diagnosed with TB during pregnancy, and as a result, the BCG vaccination was held for the newborn.

The symptoms of postnatal TB infection are usually exhibited 4 to 8 weeks after infection [7]. Therefore, the symptoms of congenital TB could theoretically be present within two months after birth. However, Cantwell et al. analyzed 29 patients with congenital TB and reported that the onset age of TB ranged from 1 to 84 days; whereas Sonal et al. reviewed 21 congenital TB cases and reported the onset age as 1 to 90 days [3, 8]. Congenital TB symptoms commonly present in the first 2 to 3 weeks of life [2]. In our study, the onset age varied from 1 to 50 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 found in patients with congenital TB included neutrophilia, thrombocytopenia, and elevated CRP levels [2]. In our study, all of the patients presented with neutrophilia and elevated levels of CRP. Moreover, 70% of the patients with congenital TB had complications with thrombocytopenia.

The imaging results of our study showed that (1) the most frequent patterns of chest CT scans were multiple pulmonary nodules and mediastinal adenopathy, and (2) abdominal US showed hypoechoic nodules in the liver and spleen in 40% of the patients. Liver and spleen nodules were similarly found in adult TB patients, but the lung TB nodule features are quite different from other lung diseases and could lead to the suspicion of congenital TB when analyzed by an experienced radiologist or TB specialist. Recently, multiple
pulmonary nodules have been described as a new radiographical finding in some published studies [9]. Multiple pulmonary nodules on chest CT scans were considered as the progressive deterioration of miliary tuberculosis, consistent with caseating necrosis in a biopsy specimen [10]. Several pediatric TB specialists and radiologists in China reported that both patterns of military TB and pulmonary nodules were specific image characteristics of congenital TB [11, 12]. 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 newborns because markers specific to TB have poor sensitivity. For neonates, serial gastric fluid appears to be the most common specimen for TB pathogen identification. Lower sensitivity and a longer time before confirmation of culture-positive results frequently occurs in children because of decreased bacterial loads. In our study, the positive rate of AFB smear was 50% with the results available within 24 hours. Furthermore, only 20% of the cases showed a positive culture result by 13.5 to 16 days. Because of the limitation of the laboratory environment, our hospital was unable to perform drug susceptibility testing for TB. The GeneXpert assay is a hemi-nested real-time PCR test that simultaneously identifies Mtb/RIF resistance. Its diagnostic accuracy is comparable to culture in sputum samples and provides results within 24 to 48 hours [13]. The WHO recommends GeneXpert for rapid diagnosis in communities with a high burden of TB [13]. Our study results showed that GeneXpert is the most sensitive test, with an 80% positive rate. Furthermore, the result could be obtained within 24 hours. The tuberculin skin test is mostly negative in newborns since the test takes at least four weeks to be positive. In our study, two cases showed a positive tuberculin skin test result at two to three months of age. Currently, there are two types of commercially available IFN-γ release assays—the QuantiFeron TB Gold (Cellestis) and T-Spot TB (Oxford Immunotec) [14]. The latter is an enzyme-linked immunospot (ELISPOT)
assay used in our hospital. Though there are concerns about the applicability of these assays to newborns due to the decreased IFN-γ production in newborns, in our study the T-Spot assay demonstrated a relatively high sensitivity and was one of the best results for initial evidence of TB in our cases.

Compared to the previous congenital TB case report [3], our patients demonstrated a much better outcome with a 100% survival rate. Based on literature analysis, we theorize that the better outcomes in our study were a result of the new clinical diagnosis criteria for congenital TB and the introduction of LZD in the treatment regimen during the intensive phase of anti-TB treatment.

It is understandable that maternal history and typical imaging findings might be the only basis for diagnosis of congenital TB. The clinical diagnosis criteria of congenital TB in our center was: (1) if an infant has fever, respiratory distress, hepatosplenomegaly, or other nonspecific symptoms within two months after birth, (2) if the infant’s mother was diagnosed with active TB infection perinatally, and (3) if the infant’s imaging showed miliary tuberculosis or multiple pulmonary nodules in chest CT scans or multiple focal lesions in the liver/spleen by abdominal US. Infants that meet the criteria were put into isolation, further TB investigation was started, and anti-TB treatments were initiated. This might partially explain the fairly good prognosis of the ten congenital TB patients in our study.

The standard regimen for congenital TB includes INH, RIF, PZA, and ethambutol during the intensive phase for two months, followed by INH and RIF for seven to ten months during the continuation phase. Chest X-rays at the end of treatment is recommended [8, 15]. Linezolid (LZD) is a member of the oxazolidinone class of antibiotics, which exhibits bacteriostatic activity against Mtb, including multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB strains [16]. Clinical trials in adults have revealed that LZD is an
important component for the treatment of MDR and XDR TB [17, 18]. As a newer anti-Gram positive antibiotic, LZD has excellent penetration to the central nervous system. Furthermore, published studies support its effectiveness and safety in treating infections caused by resistant pathogens, including staphylococcal bacteremias and cerebrospinal fluid infections, for term and preterm newborns in neonatal intensive care units [19, 20]. Li et al. reported clinical data, which demonstrated that LZD improved the early outcomes of childhood TB meningitis for 36 cases [21]. Since China has a serious epidemic of drug-resistant TB [22] and the immune system of neonates is not fully developed, our center has used LZD as a supplementary drug for congenital TB patients since 2015. In our study, LZD was administrated to seven patients, ranging in age from 4 to 70 days, for a duration of 2 to 6 months. This is most likely the first report of the long-term use of LZD for neonatal and infant congenital TB. The adverse events and side effects of LZD in our patients were monitored and evaluated by clinical symptoms, periodical whole blood counts, and serum liver/renal function analysis every one or two weeks. One patient presented with thrombocytopenia while receiving LZD, but recovered spontaneously without LZD withdrawal. Another two patients presented with hepatotoxicity during the intensive phase of treatment with INH, RIF, PZA, and LZD. However, it is difficult to differentiate the side effects induced by each drug. The low frequency of LZD-associated adverse side effects highlights the promising prospects of its use for the treatment of congenital TB. A LZD regimen during the intensive phase of anti-TB treatment might contribute to the improvement of outcomes of congenital TB.

It was reported that the overall mortality for infants with congenital TB is 100% if undiagnosed, and delayed infant diagnosis carries a 5-fold higher mortality rate in comparison with prompt diagnosis and treatment [2]. In our study, responses to anti-TB drugs were good in all patients who finished the treatment, with chest X-rays revealing no
infection at the end of treatment. However, only 33% of the patients in our study are currently thriving and have achieved normal developmental milestones.

This study has several limitations. First, this retrospective study was conducted in a single medical center, which makes applying the study results to the general population difficult. Second, the sample size was too small to demonstrate the effectiveness of new clinical diagnosis criteria and Linezolid in reducing the mortality of congenital TB. This issue may require further cooperation from multiple centers in the future for a comprehensive study. Furthermore, the clinical decisions of LZD administration was made according to the experience from neonatologists and TB specialists, which may result in practice variability. A clinical guide for the standard treatment of congenital TB is urgently needed.

In summary, congenital TB is a potentially fatal disease, but with a high index of suspicion and aggressive management, it can have a good outcome. Early diagnosis based on maternal history, typical imaging findings, and timely treatments are crucial. Multi-drug anti-TB treatment, including LZD, is safe and might be effective for infants and reduces mortality.

List Of Abbreviations

TB - Tuberculosis
Mtbb - Mycobacterium tuberculosis
BW - birth weight
IVF - in-vitro fertilization
DOL - day of life
WBC - white blood cell
CRP - C-reactive protein
CSF - cerebrospinal fluids
CT - computed tomography
AFB - acid-fast bacilli
INH - isoniazid
RIF - rifampicin
PZA - pyrazinamide
LZD - Linezolid
US - ultrasonography
MDR - multidrug-resistant
XDR - extensively drug-resistant

Declarations

Ethics approval and consent to participate

All patient information regarding diagnosis/differential diagnosis and treatment were stated as written consents and signed by the infants’ parents/legal guardians. Data in this study were de-identified after data collection. The protocols applied in this study were approved by the Ethics Committee of Beijing Children’s Hospital. The approval number is 2018-k-124.

Consent for publication

The patients’ parents have given their written consent to publishing patients’ clinical details and/or clinical images.

Availability of data and material

The datasets used and analysed during the current study are available from the authors on reasonable request.

Competing interests
The authors declare that they have no competing interests.

Funding
This study was supported by Canada Institutes of Health Research (CIHR). NICU Team of Maternal & Infant Care Program (Grant number: CTP87518)

Authors’ Contributions
Dr. Du, Dr. Jia and Dr. Zhang reviewed patients’ files, collected the data, carried out the analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Hei and Dr. Dong designed the study, supervised the cases review and critically reviewed the manuscript for important intellectual conten.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Acknowledgements
Not applicable

Author details
Juan Du Email: green.xm@163.com
Shixiao Dong Email: dongsx.hi@163.com
Shengnan Jia Email: jiashengnanno1@126.com
Qiaoru Zhang Email: qiaoruzhang1991@163.com

References
1. Global tuberculosis report 2017. Geneva: World Health Organization; 2017. Licence: CC BY-NCSA 3.0 IGO

2. Peng W, Yang J, Liu E. Analysis of 170 cases of congenital TB reported in the literature between 1946 and 2009. Pediatr Pulmonol. 2011;46:1215–24.
3. Cantwell MF, Shehab ZM, Costello AM, Sands L, Green WF, Ewing EP Jr, Valway SE, Onorato IM. Congenital tuberculosis. N Engl J Med. 1994;330:1051–4.

4. Flibotte JJ, Lee GE, Buser GL, Feja KN, Kreiswirth BN, McSherry GD, Nolan SM, Tolan RW Jr, Zhang H. Infertility, in vitro fertilization and congenital tuberculosis. J Perinatol. 2013;33(7):565–8.

5. Ormerod P. Tuberculosis in pregnancy and the puerperium. Thorax. 2001;56(6):494–9.

6. World Health Organization. BCG vaccines: WHO position paper. Vaccine. 2018;36(24):3408–10.

7. Lamb GS, Starke JR. Tuberculosis in infants and children. Microbiol Spectr. 2017;5(2):TNM17-0037-2016.

8. Patel S, Hermes DeSantis ER. Treatment of congenital tuberculosis. Am J Health Syst Pharm. 2008;65(21):2027–31.

9. Perez-Velez CM, Marais BJ. Tuberculosis in children. N Engl J Med. 2012;367:348–61.

10. Chen A, Shih SL. Congenital tuberculosis in two infants. AJR Am J Roentgenol. 2004;182(1):253–6.

11. Wang X, Xu F, Huang Q, Mei H, Xu C, Chen X. Clinical and Imaging Features of congenital Tuberculosis[J] Med Res. 2014; 43(2):127–30.

12. Wang Y, Zhao S, Peng Y, Hong T, Yin J, Wang W. Clinical and Imaging Features of congenital Tuberculosis[J] Chin J Radio. 2016;50(12):981–2.

13. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd edition; 2014.

14. Andersen P, Munk ME, Pollock JM, Doherty TM. Specific immune-based diagnosis of tuberculosis. Lancet. 2000;356(9235):1099-104.

15. Skevaki CL, Kafetzix DA. Tuberculosis in neonates and infants: epidemiology,
pathogenesis, clinical manifestations, diagnosis, and management issues. Paediatr Drugs. 2005;7(4):219–34.

16. Alcalá L, Ruiz-Serrano MJ, Pérez-Fernández Turégano C, García De Viedma D, Díaz-Infantes M, Marín-Arriaza M, Bouza E. In vitro activities of linezolid against clinical isolates of Mycobacterium tuberculosis that are susceptible or resistant to first-line antituberculous drugs. Antimicrob Agents Chemother. 2003;47(1):416–7.

17. Schecter GF, Scott C, True L, Rafery A, Flood J, Mase S. Linezolid in the treatment of multidrug-resistant tuberculosis. Clin Infect Dis. 2010;50(1):49–55.

18. Zhang L, Pang Y, Yu X, Wang Y, Gao M, Huang H, Zhao Y. Linezolid in the treatment of extensively drug-resistant tuberculosis. Infection. 2014;42(4):705–11.

19. Deville JG, Adler S, Azimi PH, Jantausch BA, Morfin MR, Beltran S, Edge-Padbury B, Naberhuis-Stehouwer S, Bruss JB. Linezolid versus vancomycin in the treatment of known or suspected resistant gram-positive infections in neonates. Pediatr Infect Dis J. 2003;22(9 Suppl):S158–63.

20. Langgartner M, Mutenthaler A, Haiden N, Pollak A, Berger A. Linezolid for treatment of catheter-related cerebrospinal fluid infections in preterm infants. BMJ Case Rep. 2009;2009:bcr11.2008.1217.

21. Li H, Lu J, Liu J, Zhao Y, Ni X, Zhao S. Linezolid is associated with improved early outcomes of childhood tuberculous meningitis. Pediatr Infect Dis J. 2016;35(6):607–10.

22. Zhao Y, Xu S, Wang L, Chin DP, Wang S, Jiang G, Xia H, Zhou Y, Li Q, Ou X, Pang Y, Song Y, Zhao B, Zhang H, He G, Guo J, Wang Y. National survey of drug-resistant tuberculosis in China. N Engl J Med. 2012; 366(23): 2161–70.

Tables
### Table 1 Demographic data and maternal history

| No. | gender | GA (wk) | BW (g) | type of newborn | maternal age (yr) | TB history before pregnancy | symptoms during pregnancy | maternal diagnosis time | maternal TB type       |
|-----|--------|---------|--------|-----------------|-------------------|-----------------------------|---------------------------|-------------------------|------------------------|
| 1   | male   | 35      | 1800   | SGA             | 33                | no                          | yes                       | after delivery          | military, genital      |
| 2   | male   | 35      | 2400   | AGA             | 27                | no                          | yes                       | after delivery          | military               |
| 3   | female | term    | 2300   | SGA             | 32                | no                          | yes                       | after delivery          | pleurisy               |
| 4   | female | 33+2    | 2100   | AGA             | 29                | yes                         | no                        | after suspicion of TB   | genital                |
| 5   | female | 37      | 2600   | AGA             | 30                | no                          | no                        | after suspicion of TB   | infiltrative, pleurisy |
| 6   | male   | 36+     | 2500   | AGA             | 30                | no                          | yes                       | after delivery          | military               |
| 7   | female | term    | 3350   | AGA             | 35                | no                          | yes                       | after delivery          | military               |
| 8   | male   | 34+5    | 2250   | AGA             | 27                | no                          | yes                       | after delivery          | medical, pleurisy      |
| 9   | male   | 38+3    | 2570   | SGA             | 21                | no                          | yes                       | after delivery          | medical, pleurisy      |
| 10  | female | 37+2    | 3300   | AGA             | 42                | yes                         | yes                       | after delivery          | genital, pleurisy      |

GDM: Gestational Diabetes Mellitus; IVF: in-vitro fertilization; SVD: Spontaneous Vaginal Delivery; C/S: Cesarean Section

### Table 2 Patient history

| No. | onset age (DOL) | Symptoms | BCG vaccination |
|-----|-----------------|----------|----------------|
| 1   | 40              | fever; cough; seizure; failure to thrive; fever; tachypnea; seizure; failure to thrive | no |
| 2   | 15              | unknown |
| 3   | 32              | fever; cough; failure to thrive | no |
| 4   | 25              | fever   | no |
| 5   | 13              | fever; cough; seizure | yes |
| 6   | 31              | fever; cough; anemia; failure to thrive | yes |
| 7   | 53              | fever   | yes |
| 8   | 28              | fever; tachypnea; vomit; failure to thrive | no |
| 9   | 18              | fever; cough; tachypnea; failure to thrive | yes |
| 10  | 1               | fever   | no |

### Table 3 General Laboratory Findings
| No. | WBC \((\times 10^9/L)\) | Neutrophil \(\%\) | Hb \((g/L)\) | Platelet \((\times 10^9/L)\) | CRP \((mg/L)\) | ALT \((U/L)\) | HIV | CSF | hearing screen | fundus examination |
|-----|----------------|-----------------|--------|----------------|----------------|---------|-----|-----|----------------|------------------|
| 1   | 18.85          | 70.3            | 99     | 138            | 36             | 50      | unknown | normal | not done       | not done          |
| 2   | 19.75          | 83.8            | 77     | 200            | 104            | 8.9     | unknown | pro ↑   | not done       | not done          |
| 3   | 21.78          | 64.8            | 87     | 217            | 65.3           | 105     | unknown | normal  | not done       | normal            |
| 4   | 22.8           | 60.5            | 73     | 218            | 58.6           | 110.7   | unknown | normal  | not done       | not done          |
| 5   | 17.99          | 56.2            | 73     | 103            | 116            | 38.3    | neg      | normal  | not done       | normal            |
| 6   | 31.95          | 61.9            | 87     | 487            | 87.2           | 40.1    | neg      | normal  | passed         | suspecter optic atrophy |
| 7   | 17.39          | 81.7            | 71     | 87             | >160           | 119.7   | neg      | glu ↓   | not done       | not done          |
| 8   | 19.1           | 55.5            | 68     | 34             | 77             | 16.3    | neg      | glu ↓, pro ↑ | not done       | not done          |
| 9   | 32.44          | 78.7            | 93     | 106            | 163            | 41.3    | neg      | normal  | not done       | not done          |
| 10  | 12.49          | 62.9            | 70     | 20             | 96             | 57      | neg      | normal  | Passed         | retinitis         |

WBC: white blood cell; N: neutrophils; Hb: haemoglobin; PLT: platelet; CRP: C-reactive protein; glu: glucose; Cl: chlorine; pro: protein; L: lymphocytes

**Table 4 Imaging Findings**

| No. | chest CT                                                                 | abdominal ultrasonography                          | brain MRI/CT                                        |
|-----|----------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
| 1   | multiple pulmonary nodules; bronchopneumonia; mediastinal adenopathy      | hypoecho 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                                                 | hypoecho nodules in liver and spleen                 | normal                                               |
| 6   | multiple pulmonary nodules; mediastinal adenopathy                         | normal                                               | not completed                                       |
| 7   | multiple pulmonary nodules; mediastinal adenopathy                         | hypoecho nodules in liver and spleen                 | cerebral infarction; hydrocephalus; encephalomalacia; encephalatrophy |
| 8   | multiple pulmonary nodules                                                 | normal                                               | normal                                               |
| 9   | multiple pulmonary nodules                                                 | normal                                               | normal                                               |
| 10  | multiple pulmonary nodules; mediastinal adenopathy                         | hypoecho nodules in liver and spleen                 | normal                                               |

CT: computed tomography; MRI: magnetic resonance imaging
| No. | TST     | AFB smear      | culture     | gene Xpert | T-spot     |
|-----|---------|----------------|-------------|------------|-----------|
| 1   | Neg     | gastric fluid/ | neg         | not completed | not done |
|     |         | tracheal       |             |            |           |
|     |         | aspirates      |             |            |           |
| 2   | Neg     | gastric fluid  | neg         | not completed | pos |
|     | neg     |                | neg         | not completed | neg |
| 3   | not completed | neg     | neg         | not completed | pos |
| 4   | not completed | neg     | gastric fluid | not completed | neg |
| 5   | neg     | gastric fluid  | gastrc fluid| broncoalveolar lavage fluid: pos for TB; neg for Rifampicin resistance | pos |
| 6   | not completed | neg     | gastrc fluid| CSF and gastric fluid: pos for TB; neg for Rifampicin resistance | pos |
| 7   | pos     | gastric fluid  | gastrc fluid|                | pos |
| 8   | pos     | neg            | gastrc fluid|                | pos |
| 9   | neg     | gastrc fluid/   | neg         | tracheal aspirates: pos for TB; neg for Rifampicin resistance | pos |
|     |         | tracheal       |             |             |           |
|     |         | aspirates      |             |             |           |
| 10  | not completed | gastrc fluid/ | neg         | tracheal aspirates: pos for TB; neg for Rifampicin resistance | pos |
|     |         | tracheal       |             |             |           |
|     |         | aspirates      |             |             |           |

TST: tuberculin skin test; AFB: acid-fast bacilli

| No. | Final diagnosis (involved organs) | time of suspected DOL | time of initiation treatment DOL | time between onset and treatment | evidence for clinical diagnosis |
|-----|----------------------------------|-----------------------|----------------------------------|---------------------------------|--------------------------------|
| 1   | lung; liver; spleen; meningitis? | 50                    | 52                               | 12                              | mother’s history/chest CT/abdominal ultrasonography |
| 2   | lung; meningitis                 | 17                    | 19                               | 4                               | mother’s history/chest CT |
| 3   | lung                             | 42                    | 42                               | 10                              | mother’s history/chest CT |
| 4   | lung                             | 45                    | 50                               | 25                              | mother’s history/chest CT/T-spot |
| 5   | lung; liver; spleen; meningitis? | 69                    | 70                               | 57                              | mother’s history(X-ray)/chest CT |
| No. | Fever clearance time (d) | Total hospital stay (d) | Outcome | The latest F/U age | General Growth | CNS long term outcome |
|-----|--------------------------|-------------------------|---------|-------------------|----------------|-----------------------|
| 1   | unknown                  | 4                       | recovered | 9y                | normal         | cognitive delay       |
| 2   | 4                        | 11                      | lost     | none              | unknown        | normal                |
| 3   | 6                        | 9                       | recovered | 4y                | failure to thrive | normal               |
| 4   | 12                       | 20                      | recovered | 3y                | normal         | normal                |
| 5   | 7                        | 47                      | recovered | 2y                | normal         | normal                |
| 6   | 5                        | 17                      | recovered | 2y                | normal         | language delay        |
| 7   | 49                       | 51                      | improved | 1y2m              | failure to thrive | normal               |
| 8   | 8                        | 8                       | improved | 9m                | normal         | developmental delay    |
| 9   | 3                        | 25                      | improved | 6m                | failure to thrive | normal               |
| 10  | 28                       | 41                      | improved | 3m                | failure to thrive | normal               |

INH: Isoniazid; RIF: Rifampin; PZA: Pyrazinamide; LZD: Linezolid; EMB: Ethambutol; D/C: discontinued

Table 7 Outcome and follow up

Figures
Figure 1

Imaging Findings: (A) No.1 Chest CT; (B) No.2 Chest X-ray; (C) No.3 Chest CT; (D) No.5 Chest CT; (E) No.6 Chest CT; (F) No.7 Chest X-ray; (G) No.7 Brain CT; (H) No.8 Chest CT; (I) No.9 Chest CT; (J) No.10 Chest CT