The Pediatric Infectious Disease Journal Publish Ahead of Print

DOI: 10.1097/INF.0000000000001830

Perinatal Tuberculosis: Is it a Forgotten Disease?

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Abbreviated Title: Perinatal Tuberculosis: A Forgotten Disease?

Running Head: Perinatal Tuberculosis

Disclosures: The authors have no conflicts of interest or funding to disclose.

Perinatal tuberculosis is an uncommon condition but with a high mortality and a challenging diagnosis. We present four cases of perinatal tuberculosis managed between 1991-2014 in a Spanish Tertiary Hospital. The infection should be considered in patients with progressive respiratory symptoms and with a poor response to conventional antibiotic therapy, especially in those with positive epidemiologic risk. Bronchoscopy can be a useful tool for diagnosis.

Key words: Perinatal tuberculosis, *Mycobacterium tuberculosis*, bronchoscopy.

INTRODUCTION

Tuberculosis (TB) continues to be one of the most prevalent infections worldwide. Perinatal TB is uncommon and its diagnosis and management remains a challenge[1]. The clinical manifestations in these patients are non-specific and manifest in a variety of ways. The diagnosis is based on two principles: the identification of *Mycobacterium tuberculosis* (MT) in cultures or a positive gene amplification/PCR from patient samples, and by imaging. There is limited data about therapeutic regimens at this early age[1-4], therefore treatment follows the same guidelines as that of older children.

Case 1

45-day-old premature infant (32 weeks gestation), from Morocco, transferred to our hospital after a slow resolution of a respiratory infection, with no response to antibiotics. Chest radiograph showed several areas of consolidation (figure 1, 1A). He required increasing respiratory support including intubation and assisted ventilation. Flexible bronchoscopy (FB) and bronchoalveolar lavage (BAL) were performed that revealed extrinsic compression of the airway. Chest CT showed numerous cavitating nodules (figure 1,1B). Tuberculin testing (TST) was 3 mm and QuantiFERON-TB Gold® test (QFT) was positive. The BAL smear microscopy showed acid-fast bacilli (AFB), confirmed by MT PCR. Treatment was initiated (isoniazid, rifampicin, pyrazinamide and ethambutol) along with systemic steroids. MT culture from the BAL was positive and the organism was pan-susceptible. On contact tracing, the mother was found to have symptoms and tuberculosis was confirmed. The infant made a good recovery.

Case2

A 5-month-old infant, of Moroccan origin, presented with a 3-month history of persistent cough, progressive shortness of breath, intermittent fever and failure to thrive. The infant was referred to our pediatric surgery department with a suspected diagnosis of congenital lobar emphysema (figure 1.2A). A chest CT excluded this (figure 1,2B). He underwent a FB which showed granulation tissue. BAL and gastric aspirate smear were negative, but MT PCR and culture were positive. TST was <5 mm. The mother had findings compatible with TB disease. Treatment was established with three drugs (isoniazid, rifampicin and pyrazinamide) as per current guidelines along with steroids the first month. He made a good recovery.

Case 3

Ex-preterm infant, from Morocco, transferred to our hospital at 20 hours of life. Intubated and ventilated after delivery, diagnosed with acute respiratory distress secondary to hyaline membrane disease. He made a clinical improvement and was weaned from ventilatory support. However, he had persistent tachypnea, intermittent low grade fever and sequential radiographs showing persistent atelectasis of superior right lobe (figure 1,3A). FB and BAL were performed at three months of age, showing granulation tissue. Bacilloscopy was negative, but MT culture in BAL and gastric aspirate was positive. TB treatment was initiated with systemic steroids for a month. His recovery was satisfactory, although residual atelectasis persisted after completion of treatment (figure 1, 3B).

Case 4

A 2-month-old-infant, transferred to our hospital from Morocco, due to persistent tachypnea since early days of life, and progressive respiratory failure. No evidence of parenchymal abnormalities on chest radiograph. FB and BAL were performed, showing moderate obstruction of the distal tracheal lumen and principal left bronchi with no evidence of granulation tissue or caseum. Bacilloscopy and MT culture of BAL were negative. CT scan showed mediastinal-subcarinal adenopathies. On contact tracing, mother's investigations were compatible with TB disease, strengthening the decision to begin TB treatment for the infant. Systemic steroids were added during the first month. The infection resolved without sequelae.

DISCUSSION

Perinatal TB refers to an infection with MT that occurs in utero, at birth, or during the early newborn period[1]. In 1994, Cantwell and collaborators, defined the diagnostic criteria of "congenital TB"[5,6]. These criteria required at least one of the following: onset of symptoms in the first week of life, a primary liver lesion or a caseous liver granuloma, tuberculous infection of the placenta or of the maternal genital tract[1,2-6].

Perinatal TB is an uncommon infection and its incidence is difficult to determine[2,3]. To date, there have been approximately over 300 reported cases published in the English language[4].

Neonates are extremely vulnerable to TB, due to the immaturity of the immune system. There are three routes of transmission: the hematologic path, via the umbilical vein, producing primary lesions in the liver or in the lung; by in utero aspiration of infected fluids, with primary lesions in the lung or digestive tract (congenital TB); postpartum by inhalation or ingestion from an infectious contact[1,3,6,7].

According to the literature, the symptoms in newborns usually occur from the second or third week of life, although its onset may be delayed until the fourth month of life[1] (as in cases 2 and 3). Clinical manifestations include hepatosplenomegaly (65-100 %), respiratory distress (70 %), fever (50-100 %), lymphadenopathy (38 %), poor weight gain, irritability and lethargy (20-40 %)[3,6,7]. TB should be considered in all cases of infants presenting with progressive pneumonia and poor response to conventional antibiotic treatment (cases 1 and 3)[1,7,8].

The diagnosis of TB in the infant is complicated. As soon as it is suspected, a tuberculin skin test and/or IGRAs (Interferon Gamma Release Assay) is indicated, along with a chest radiograph and cultures (gastric/broncho-aspirates or bronchoalveolar lavage and CSF)[7,8]. Tuberculin skin testing does not have adequate sensitivity in infants younger than 6 months because of their immunologic immaturity. IGRAs are an alternative diagnostic test, although there are doubts about its validity in newborns due to lower production of IFN-γ. Individual studies have suggested worse sensitivity and higher rates of indeterminate results in children <5 years of age compared with older ones[7,9]. In a recent meta-analysis assessing the diagnostic accuracy of IGRAs compared with TST, similar sensitivity was shown for both[9]. MT culture of gastric aspirate material establishes definitive diagnosis, with higher yield (70 %) in newborns than in infants or older children (30-40 %)[1,7].

Chest radiograph usually shows variable pathologic findings, depending on the transmission mechanism and time course of the disease. Different radiographic patterns include: (i) miliary or interstitial pattern (approximately 50 % of patients[3,8,10]; (ii) pneumonic forms; (iii) nodal forms; (iv) cavitated forms (although rare in children, it is referred to as "progressive primary TB" as seen in case 1) and (v) endobronchial forms (like cases 2 and 3)[8]. At the beginning of the infection, radiograph may be normal, and CT should be considered.

FB for perinatal TB might be indicated for the following reasons; the need for collection of respiratory samples; assessment of unclarified interstitial lung disease with poor response to conventional treatment (case 3); staging of endobronchial TB; and to aid decisions regarding the need for systemic steroids[8]. In all of our cases bronchial compression or a bronchial fistula were observed; hence, the decision to initiate steroids.

In the evaluation of a neonate with suspected TB, it is necessary to perform screening for other congenital infections and staging of the disease with diagnostic tests such as brain and abdomen ultrasound (MRI brain could be required) and fundoscopy[1,7].

Once the initial investigations are complete, treatment should be initiated. It must be based on the sensitivity of the maternal strain, if known[7,8]. The recommended treatment for newborns and infants includes 4 drugs for 2 months: isoniazid, rifampin, pyrazinamide and streptomycin/amikacin or ethambutol; followed by 4-10 months with only two drugs (isoniazid and rifampicin) depending whether the infant has pulmonary TB or tuberculous peripheral lymphadenitis (6 months total treatment)[11] or disseminated disease with CNS involvement (12 months)[7,11]. As perinatal TB is not a common disease, there are currently no therapeutic trials to determine the optimal type or duration of treatment, although an accepted regimen is maintenance treatment for 6-12 months, extending to 18-24 if resistance is observed[1,7]. Corticosteroid therapy is not routinely indicated, but is recommended in cases of central nervous system, miliary TB, pleural or pericardial or endobronchial involvement. The drug of choice is prednisone 1-2mg/kg/day oral for 4-6 weeks with gradual weaning[7,11].

Since there are no reported cases of TB transmission through breastmilk[4], breastfeeding is only contraindicated in mothers with an active lesion in the breast[1].

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Figure legend:

Figure 1. Radiological findings. Case 1: 1A. Chest radiograph: RUL condensation and RLL and ML. 1B. Chest CT: multiple cavitated parenchymal nodules. Case 2. 2A. Chest radiograph: right lung hyperinflation with collapsed RUL, ML and RLL with mediastinal shift to the left. 2B. Chest CT: right paravertebral adenopathic conglomerate with calcifications. Case 3. 3A. Chest radiograph (diagnosis): interstitial pattern (hyaline membrane disease) and atelectasis RUL. 3B. Chest radiograph: residual atelectasis in RUL (end of treatment). (RUL = Right Upper Lobe; LUL = Left Upper Lobe; ML = Middle Lobe; RLL = Right Lower Lobe; LLL = Left Lower Lobe).

Figure