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Major article

Nosocomial exposure to active pulmonary tuberculosis in a neonatal intensive care unit

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Background: Nosocomial transmission of tuberculosis (TB) in a neonatal intensive care unit (NICU) is a recognized risk. We investigated TB transmission to neonates and health care workers (HCWs) exposed to a nurse with active TB in a NICU.

Methods: A NICU nurse in a tertiary referral hospital in Seoul, Korea, developed pulmonary TB. The investigation included 108 infants and 75 HCWs. Tuberculin skin test (TST) and chest radiograph were performed at baseline. Isoniazid prophylaxis was started in neonates. After 3 months of prophylaxis, infants underwent repeat TST and chest radiograph. HCWs underwent a second TST after 3 months.

Results: Baseline chest radiographs were negative in infants and HCWs. Four (3.7%) of 108 infants screened had a positive TST, including 2 conversions, and received isoniazid for 6-9 months. Among the 59 HCWs screened, 27 (45.8%) had an initial positive TST result, and 6 (10.2%) had a positive TST result at 3 months. Four of the 6 HCWs with TST conversions received isoniazid treatment for 9 months. In the 2-year period after exposure, none of the exposed infants or HCWs developed active TB.

Conclusion: In this investigation, 4 (3.7%) of 108 infants exposed to a nurse with active TB developed latent TB infection. They were given isoniazid therapy without any adverse events and did not progress to TB disease in the 2 years after exposure.

Nosocomial transmission of tuberculosis (TB) is a recognized risk in medical facilities. In particular, nosocomial TB exposure in a neonatal intensive care unit (NICU) can lead to serious problems because infants can develop lethal and invasive disease after TB infection.[1] However, few data are available on the impact of TB exposure on infants in a NICU. Early diagnosis and treatment of TB infection is important to prevent disease development and secondary transmission in a NICU. We report the results of our investigation of the infants and health care workers (HCWs) who were exposed to a nurse with active TB in a NICU at a tertiary university hospital. The report has been written according to the ORION statement guidelines.[2]

METHODS

Index case

In April 2009, a 24-year-old nurse working at a NICU in a tertiary care children's hospital in Korea was evaluated for an abnormal chest radiograph performed as part of an annual employment screening. The index case had a 2-month history of cough, sputum, and intermittent fever. Chest radiograph revealed nodules and consolidation in the left upper lung field. A tuberculin skin test (TST) using 2 units of purified protein derivative yielded a 23-mm positive result. T-cell–based interferon-γ release assays were also positive. A sputum smear was negative for acid-fast bacilli, but *Mycobacterium tuberculosis* polymerase chain reaction was positive. The nurse was treated empirically with isoniazid (INH), rifampin, pyrazinamide, and ethambutol. *M tuberculosis* was confirmed by culture, fully sensitive to anti-TB agents tested. She stopped working for personal reasons on May 4, 2009. On the basis of her symptom onset, her infectious period was estimated as January 1, 2009-May 4, 2009.

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Conflicts of interest: None to report.

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Exposure investigation

The index patient had no household contacts during the infectious period. All of the infants and HCWs who had been in the NICU during the contagious period were considered to be exposed. We identified 108 infants and 75 HCWs with possible exposure to the index patient.

Exposed infants underwent a chest radiograph and TST. After screening, they were recommended to receive INH prophylaxis (10 mg/kg/d) for 3 months. After 3 months of preventive therapy, a second TST and chest radiograph were performed. All infants were observed for any adverse events from INH and for clinical symptoms of TB. According to the World Health Organization guidance,[3] serum liver enzyme levels were not monitored routinely, whereas investigation of serum liver enzyme levels and the immediate stopping of INH was performed in case of the occurrence of liver tenderness, hepatomegaly, or jaundice. Bacille Calmette–Guérin (BCG) vaccination was delayed in all exposed infants until they had negative results on second TST and chest radiograph.

HCWs involved in the index case were offered a chest radiograph and TST. If they had a positive TST or abnormal chest radiograph, they were referred to an infectious disease specialist. If initial TST and chest radiograph were normal, they underwent a second TST 3 months later.

TST was performed on the volar side of the forearm using the Mantoux method, with 2 tuberculin units of purified protein derivative RT23 (Statens Serum Institut, Copenhagen, Denmark), and any induration was measured after 48-72 hours using the ballpoint pen method. The largest transverse diameter of induration was read by 2 trained pediatricians on infants and several medical laboratory staff on adults. A positive TST was defined as an induration of $\geq$10 mm. A TST conversion was defined as an increase of $\geq$6 mm between the first and second TST.

All exposed infants were followed for development, growth, and clinical symptoms of TB by outpatient department visits and telephone over a period of 2 years. Exposed HCWs were observed for clinical symptoms of TB by the hospital infection management team during the follow-up period of 2 years. The study protocol was reviewed and approved by the Institutional Review Board of Severance Hospital.

RESULTS

Outcomes of neonatal investigation

Baseline characteristics of the exposed infants were summarized in Table 1. At the start of the investigation, the mean ± SD chronologic and corrected ages of exposed infants were 7.6 ± 5.1 and 4.0 ± 4.0 weeks, respectively. Of the exposed infants, 29% were neonates (0-28 days).

Figure 1 shows the investigation process and TB screening results of 108 exposed infants. At baseline screening, 2 infants had a positive TST. One was 14.7 weeks, hospitalized with prematurity. The other was 21.4 weeks, admitted with choledochal cyst. In them, congenital TB infection was excluded because they did not fulfill the Cantwell et al criteria.[4] They were treated with a 9-month regimen of INH. Of the remaining 106 infants with negative TST and chest radiograph, 102 received INH treatment for latent tuberculosis infection (LTBI) for 3 months (3 neonates did not complete the treatment because of guardian request), whereas 4 infants did not receive prophylaxis because of elevated liver enzyme levels (n = 3) and a medically unstable state (n = 1).

At 3-month follow-up, 2 infants had a TST conversion. One of them completed 9 months of INH treatment for LTBI and the other discontinued treatment at 6 months on parent request. The remaining infants with negative second screening results discontinued INH prophylaxis.

Table 1
Characteristics of infants exposed to the index case

Characteristic	Infants (N = 108)
Age at baseline (wk)	
Chronologic	7.6 ± 5.1
Corrected	12.0 ± 7.7
Sex	
Male	55 (50.9)
Female	53 (49.1)
Gestational age (wk)	35.6 ± 4.0
Birth weight (g)	2,487.3 ± 924.2
Main indication of NICU admission	
Prematurity	30 (27.8)
Neonatal jaundice	10 (9.3)
Acute gastroenteritis	7 (6.5)
Small for gestational age	6 (5.6)
Congenital heart disease	5 (4.6)
Other diseases*	50 (46.3)

NOTE. Values are mean ± SD or n (%).
NICU, neonatal intensive care unit.
*Other diseases include meconium aspiration syndrome, small intestine atresia, skin infection, anorectal malformation, esophageal atresia, atrial flutter, biliary atresia, bronchopulmonary dysplasia, choledochal cyst, cleft lip, pneumonia, pneumothorax, transient tachypnea of newborn, cystic lymphangioma, histidine metabolism disorder, Down disease, duplex kidney, epidural hemorrhage, hydrocephalus, hypoglycemia, birth asphyxia, neonatal seizure, sepsis, thrombocytopenia, and tracheoesophageal fistula.

None of the infants that received INH treatment showed clinical evidence of hepatotoxicity. In the 2 years after exposure, no children, including 4 infants with a positive TST and 4 infants in which INH prophylaxis was withheld, developed TB disease.

Outcomes of HCW investigation

Figure 2 summarizes the study process and outcomes of exposed HCWs. Of the 75 HCWs exposed to the index case, 16 were unavailable for screening tests because they no longer worked at the hospital. The remaining 59 HCWs were offered TST and chest radiograph screening because they had no previous TST results. Chest radiograph was normal in all of them, but 27 had a positive TST. The 27 HCWs with positive TSTs were referred to infectious disease specialists. They were not recommended to receive INH prophylaxis with close observation because it was assumed they were not newly positive based on the lack of clinical symptoms and chest radiograph results. The 32 HCWs with negative TSTs underwent a second TST after 3 months. Of these, 6 HCWs had TST conversion. Four HCWs with conversion received INH treatment for LTBI for 9 months, and 2 refused the medication. Of those who refused the treatment, one did not develop TB disease within the 2-year follow-up period, and the other was lost to follow-up. In the 2 years after exposure, no cases of TB disease developed in the exposed HCWs who completed follow-up.

DISCUSSION

Nosocomial TB transmission to hospitalized neonates occurred in 4 (3.7%) patients after exposure to a HCW with pulmonary TB disease. Most of the earlier studies have reported no evidence of nosocomial TB transmission in exposed infants.[5-10] However, some studies report conflicting data.[11-13] A study by Steiner et al reported TB infection in 2 of 1,668 neonates exposed to active TB.[12] In a study by Perry et al, 5 (2.9%) of 172 exposed infants developed LTBI.[13] In agreement with results of Perry et al, although low, 4 (3.7%) of 108 exposed infants had LTBI in our study. These data suggest that there