RECURRENT TUBERCULOSIS IN A YOUNG CHILD

Alexandra Dreesman, MD, Oriane Stévart, MD,* Catherine Adler, MD,* Vanessa Mathys, PhD,† and Françoise Mouchet, MD**

Abstract: A young child, 19 months of age, presented with a second episode of tuberculosis after full recovery from initial tuberculosis disease 6 months earlier. *Mycobacterium tuberculosis* strains isolated from both episodes were genotyped and differed from one another. We present the first case of proven tuberculosis reinfection in a likely immunocompetent child, living in a high-risk environment favorable for exposition to *M. tuberculosis* but in a low-incidence country.

Key Words: mycobacterium tuberculosis, recurrence, infant, culture confirmation, genotyping

Accepted for publication March 11, 2020.
From the *Pediatric Department, CHU Saint Pierre University Hospital, Université Libre de Bruxelles, Brussels, Belgium and †National Reference Centre of Tuberculosis and Mycobacteria, Infectious Diseases in Humans, Sciensano, Brussels, Belgium.
The authors have no funding or conflicts of interest to disclose.
A.D. and O.S. have equal contributions and would like to be first co-authors.
Address for correspondence: Alexandra Dreesman, MD, Pediatric Department, CHU Saint Pierre University Hospital, Université Libre de Bruxelles, Brussels, Belgium. E-mail: Alexandra_Dreesman@stpierre-bru.be.

DOI: 10.1097/INF.0000000000002685

Recurrent tuberculosis (TB) can occur as either relapse of the original infection or as exogenous reinfection with a new *M. tuberculosis* strain. Reinfection may suggest a failure to develop protective immunity after the first episode and is often associated with HIV infection. TB relapse and reinfection have been mentioned in 19.6% of a series of immunocompromised children.[1] On the other hand recurrence of TB in healthy children seems to be rare and is seldom reported.[2]

We describe confirmed TB reinfection in an immunocompetent child, based on molecular analysis of *M. tuberculosis* isolates from 2 distinct episodes of TB.

CASE REPORT

A 2-month-old boy was admitted with a 4 weeks history of recurrent pyrexia. He was born in Belgium, with a weight of 2320 g, after 34 weeks of pregnancy because of premature rupture of membranes without proof of infection. He did not receive Bacille Calmette-Guérin vaccination. His parents originated from Guinea, were non-related and arrived in Belgium 4 years earlier. No recent travel history was reported.

Physical examination revealed an alert but febrile baby: his weight was 3.770 kg, his length was 52 cm, rectal temperature was 38.5°C and he presented with moderate tachypnea. The rest of his physical examination was unremarkable. Admission chest radiograph (CXR) demonstrated diffuse bilateral micronodular pattern highly suggestive of miliary TB. C-reactive protein was 70 mg/L and erythrocyte sedimentation rate was 25 mm/h. HIV serology was negative. Cerebrospinal fluid analysis was normal. Brain magnetic resonance imaging showed one small nodular frontal lesion and one cerebellar deep parenchymal nodule. Abdominal and hepatic ultrasounds were normal. Polymerase chain reaction for *M. tuberculosis* on bronchoalveolar lavage (BAL) was positive. Gastric aspirate and BAL cultures identified *M. tuberculosis* susceptible to all first-line anti-TB drugs. Cerebrospinal fluid analysis mycobacterial culture was negative. The child underwent 2 months of intensive phase anti-TB therapy with isoniazid (INH) 10 mg/kg/day, rifampicin 15 mg/kg/day, pyrazinamid 35 mg/kg/day and ethambutol 20 mg/kg/day. Daily methylprednisolone (2 mg/kg) was administered for the first month and progressively tapered for the next 2 months. The child had been followed-up at monthly intervals. Brain magnetic resonance imaging at 3 months of age demonstrated resolution of abnormalities. Family screening demonstrated that both parents were infected by *M. tuberculosis* but without active disease. Mothers' clinical and gynecological examinations were normal. INH therapy was prescribed for both parents. Among other household contacts, no case of active TB was detected. Congenital TB was considered but could not be proved. Child's treatment was fully completed with INH and rifampicin for another 9 months. At the end of the treatment (11 months in total), the patient had a normal physical examination with a weight of 9.8 kg and a length of 76 cm and normal CXR.

Six months after completion of child's treatment, both parents were admitted to the Department of Infectious Diseases because of cough, fever and weight loss. Both parents' sputum were smear positive for acid-fast bacilli. They admitted having not taken their preventive treatment. Due to the close contact with 2 contagious parents, despite a previous episode of active TB, and despite being asymptomatic, the 19-month-old child was again screened for TB disease. Clinically, he was afebrile with an unremarkable examination except for a mild rhinorrhea, his weight/length were, respectively, 11.2 kg and 81 cm. CXR showed left upper lobe consolidation. Tuberculin skin test revealed an induration of 17 mm. C-reactive protein was 5.3 mg/L and erythrocyte sedimentation rate was 15 mm/h. Interferon-gamma release assay indicated a cellular immune response to *M. tuberculosis.* polymerase chain reaction for *M. tuberculosis* was positive in the BAL. Xpert MTB/RIF assay (Cepheid) did not identify resistance to rifampicin. Gastric aspirate and BAL cultures grew *M. tuberculosis* susceptible to all first-line anti-TB drugs. He was started on standard 4-drug first-line therapy daily and responded well. Since birth and throughout the diseases, the child showed normal weight and length gain according to World Health Organization Child Growth Standards. On account of this repeated disease, further immunologic investigations were performed and revealed normal lymphocyte counts and subsets, normal T-cell response after phytohemagglutinin stimulation, and normal age-adjusted serum immunoglobulins. In addition, assessment of the interleukin-12—interferon-gamma pathway was normal. Vitamin D value was normal.

M. tuberculosis strains isolated from the father, the mother and the child's two episodes were submitted to MIRU-VNTR typing[3] and spoligotyping which concordantly revealed fully matching genotypes between the mother's strain and the strain isolated during the first TB episode of the child while the genotype of the child's strain isolated during the second TB episode was fully identical to that of the father's strain (see Fig. 1). These genotyping results clearly proved two distinct infectious episodes in this child caused by different *M. tuberculosis* strains.

We postulated that this boy and his mother had been infected by the same source case and that the child developed a second episode after having been infected again, this time by his father.

DISCUSSION

Bacteriologic confirmation of TB is difficult in children, however, in this child *M. tuberculosis* was cultured from gastric aspirate fluid and from bronchoalveolar lavage during both episodes of TB disease. The use of genotyping methods led to the identification of distinct *M. tuberculosis* strains and allowed us to prove reinfection

A

	MIRU 04	MIRU 26	VNTR 1955	MIRU 40	MIRU 10	VNTR 2163b	MIRU 16	MIRU 31	VNTR 0424	VNTR 0577	VNTR 4052	VNTR 2165	MIRU 02	MIRU 23	VNTR 2401	MIRU 39	MIRU 20	MIRU 24	VNTR 4156	MIRU 27	VNTR 2347	VNTR 2461	VNTR 3690	VNTR 3171
Mother	2	5	3	1	3	4	3	3	2	4	5	4	2	5	2	2	1	1	2	3	4	2	-	3
Child - first TB episode	2	5	3	1	3	4	3	3	2	4	5	4	2	5	2	2	1	1	2	3	4	2	-	3
Father	2	4	3	3	3	4	2	3	4	2	3	2	2	6	2	2	2	1	2	3	4	2	1	1
Child - second TB episode	2	4	3	3	3	4	2	3	4	2	3	2	2	6	2	2	2	1	2	3	4	2	1	1

B

	Spoligotype	SIT	Genetic family
Mother	■■■■■■■■■■■■■■■■■□□■■□□□■■■■■■■□□□□■■■■■■■	57	LAM10
Child - first TB episode	■■■■■■■■■■■■■■■■■□□■■□□□■■■■■■■□□□□■■■■■■■	57	LAM10
Father	■■■■■■■□□□■■■■■■■■□□□□■■■■■■■□□□□■■■■■■■	33	LAM3
Child - second TB episode	■■■■■■■□□□■■■■■■■■□□□□■■■■■■■□□□□■■■■■■■	33	LAM3

FIGURE 1. MIRU-VNTR genotyping results of four *M. tuberculosis* isolates. MIRU-VNTR (**A**) and spoligotyping (**B**) patterns. Correspondences with isolates are indicated. – indicates non-amplified marker after multiple assays; LAM, Latin American Mediterranean; SIT, spoligotype international type.

with a genetically different strain.[3] To our knowledge, this is the first case of proven *M. tuberculosis* reinfection with detailed bacteriologic confirmation for 2 consecutive episodes in a child.

This child first presented at the age of 2 months, with culture-confirmed miliary TB. The strain involved in this episode was fully susceptible to standard drugs and likely to have been eliminated by treatment: the child was treated efficiently and clinically recovered entirely. Subsequently, lobar pulmonary disease occurred 6 months after the end of first-episode treatment, at the age of 19 months.

Exogenous reinfection or endogenous reactivation are forms of recurrent TB that are clinically indistinguishable.[4] In areas of low TB incidence, recurrence is usually due to endogenous reactivation and occurs shortly after cure of the first episode. Recurrence due to reinfection is mostly seen in areas of high TB incidence where relapse incidence can reach 75%, and it is a constant risk with time.[5] However, in low TB incidence countries, the risk of reinfection persists if the patients remain in a social environment where they are re-exposed to *M. tuberculosis*.[6]

At the time of onset of the second disease episode, at first sight, several factors were in favor of relapse rather than reinfection: living in a low-incidence country, the absence of traveling, no known reported contact outside the family and recurrence after a short interval.

Moreover, the risk of endogenous reactivation could have been increased in case of non-adherence to the prescribed regimen by his parents.[7] Directly observed therapy is not routinely available in Belgium and is used, if necessary, on an individual basis. In this case, during the continuation phase of treatment, daily dosing was prescribed, and medications were administered by the parents without daily supervision. But the parents did not fail to attend any scheduled visit, regimen comprehension was correct, no communication problem was noted and no adverse effects to treatment were reported. For these reasons, we assumed non-adherence as unlikely, however, we need to consider that parents failed to take their own preventive treatment appropriately.

Another mechanism for relapse could theoretically have been linked to the persistence of dormant bacilli after treatment completion, as bacillary load was high during the first episode, and to a mechanism that could theoretically involve the development of drug resistance. However, a posteriori drug susceptibility testing was available for both episodes and excluded resistance, making this line of enquiry irrelevant at that stage.

Furthermore, this child did not present any of the other risk factors which promote TB recurrence,[8] and he demonstrated optimal cellular immune responses and good containment of the organisms.

As pediatric TB cases provide evidence of recent TB transmission, reinfection by a different strain was also considered.[9] Source-case investigations potentially identified both parents as possible index cases for the second episode, whereas no transmission source was identified during the child's first TB episode. Genotyping supported evidence of the transmission link of infection: the child had most probably been infected, in the first instance, by his mother or the same source as his mother, and matching genotypes revealed the father as the source of his second episode.

Although Belgium is a low-incidence country, the environmental incidence of TB in the local community of this family with a migration background is likely to have been significantly higher, generating the same risk to develop recurrent TB as in high incidence settings.

ACKNOWLEDGMENTS

The authors thank the parents for giving them the opportunity to publish the case.

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