Isoniazid-Resistant Rifampicin-Susceptible Tuberculosis in Children☆

Tuberculosis resistente a isoniacida y sensible a rifampicina en niños

To the Editor,

Drug-resistant tuberculosis (TB) is a worldwide public health problem.[1] Many studies have focused on multidrug-resistant TB (resistant to isoniazid [H] and rifampicin [R]), but little attention has been given to isoniazid-resistant, rifampicin-sensitive (H^RR^S) TB.[2] H^RR^S is the most common form of resistance (8.5% of cases[1,3,4]) and is a risk factor for poor clinical progress if treatment is not appropriate.[5] Resistance rates to H in Spain are estimated at 5% among adults and 9.6% among children.[6] There are few pediatric studies of H^RR^S TB due to the difficulty of isolating the Bacilli, and those that are available are generally retrospective.[7,8]

During the period 2014–2016, 17 children were diagnosed with TB in our hospital, of whom 7 (41.2%) were considered H^RR^S (Table 1). The study was prospective, using the REDCAP on-line database created by the pTBred working group, and the children were treated by a single pediatrician. Clinical samples were collected before starting treatment, and sensitivity studies were conducted in the local laboratory and national reference laboratory.

The 7 children with probable H^RR^S TB were between 3 and 6 years of age, of Spanish nationality, and not BCG-vaccinated. They were all detected following the diagnosis and contact tracing of 4 adults with active TB who were subsequently found to have H-resistant disease: 2 had single resistance to H and 2 were also streptomycin-resistant, and the mutation study detected 2 cases with the *inh*A and 2 with the *kat*G gene mutation (Table 1). The Bacilli was isolated in only 1 child, confirming the resistance pattern of the source case. In the remaining 6 children the diagnosis of H^RR^S was based on the resistance of the source case and the absence of a different sensitivity pattern in the TB patients detected in the contact tracing study. Four of these 6 children had more than 6 h daily contact with the resistant adult and 1 was the brother of the child with the positive culture.

Changes were observed on the chest X-ray of 5 children at the time of diagnosis. Patient 7, whose X-ray was normal, began treatment for latent tuberculosis infection, but 1 month later presented persistent cough, doubtful X ray and pathological CT. Chest CT was performed in another 2 cases: 1 had clinical symptoms with normal X-ray and the CT was abnormal and the other because of a radiological deterioration during treatment. Fiberoptic bronchoscopy was performed in this patient and in another case, both of whom had endobronchial involvement and corticosteroids were prescribed.

All patients started treatment with HRZE and continued for 1-2 months, until resistance was determined, after which they continued with RZE up to a total of 7–12 months The reasons for administering longer treatment regimens to 2 children were a failure of treatment compliance and a slow-to-resolve endobronchial TB.

Ophthalmological monitoring due to the administration of ethambutol was normal and 4 patients had mild side effects, not requiring treatment discontinuation. Patients were followed up for at least 12 months after completing treatment; at discharge, 6 cases had a normal X-ray, and 1 showed a small residual lymphadenopathy.

TB is usually classified as monoresistant, polyresistant, multidrug-resistant or extesively drug resistant TB,[9] but the term H^RR^S TB is important because it is the most frequent form of drug resistant TB and its treatment must be appropriate.[5,8] In our study, diagnosis of the H^RR^S pattern by culture took 1–2 months, as only rapid resistance testing for rifampicin was performed (GeneXpert®). It would also be advisable to perform a rapid diagnostic test such as MTBDRplus® (Hain Lifescience, Nehren, Germany), which identifies most cases resistant to R and/or H.[10] However, the children were appropriately treated, since they started the treatment with 4 drugs because the sensitivity pattern of the source case was initially unknown and the rate of resistance to H in Spain is greater than 4% .[11,12] Furthermore, our hospital area has an unusually high prevalence of H^RR^S TB, mainly due to strains with a unique pattern suggestive of TB reactivations. After H^RR^S TB was diagnosed, RZE was continued for a total of 7–12 months[11,13] with good tolerance, and cure was confirmed without sequelae or reactivation in long-term follow-up.

The guidelines for initial treatment (2HRZE+4HR) and retreatment (2SHRZE+1HRZE+5HRZ) in cases of H^RR^S can lead to treatment failures, relapse, and acquired resistance, and the 6–9RZE combination has greater hepatotoxicity in adults.[5] A meta-analysis comparing different treatments for H^RR^S TB concluded that the addition of a fluoroquinolone improved treatment success, although it only included 37 children.[2,14] A retrospective study in children with H^RR^S TB, mainly with severe disease and administration of fluoroquinolones in 75% of cases, reported a treatment failure rate of only 4%.[8] In our study, patients did not have advanced disease and the 6–12RZE regimen was effective and showed no side effects.

It could be argued that some of the 6 children without bacteriological confirmation might not have been H^RR^S. The definition of probable resistant disease in children has been recommended when the source case is resistant.[9] This study was prospective and all the children were diagnosed following the contact tracing of an adult that caused an outbreak of TB with many secondary cases of TB infection and TB disease (with the same strain and sensitivity pattern) and having 6 of the children high probability of contagion from the source case (proximity, frequency of exposure and infectivity).[15] Moreover, the children were young, with little exposure to other TB patients outside of the family setting. In any case, the low rate of isolates in children means that the diagnosis of resistance is often made from the drug suscetibility testing of the source case. This, however, is a barrier to publishing pediatric studies of drug-resistant TB and proving the effectiveness of the different treatment regimens.

We conclude that it is important to determine resistance to H by performing a rapid drug sensitivity testing in the child and in their source case. Our patients responded favorably to 7–12RZE without side effects, sequelae or relapse.

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Table 1
Characteristics of patients and their sources of contagion.

	Source case 1		Source case 2	Source case 3	Source case 4		
TB type	Pulmonary TB Smear positive		Pulmonary TB Smear positive	Laryngeal and pulmonary TB Smear positive	Pulmonary TB Smear positive		
Resistance	H+S		H+S	H	H		
Mutation	*inh*A		*kat*G	*kat*G	*inhA*		
Number affected in the outbreak	0 TB infection 2 TB disease		7 TB infection 3 TB diseas	19 TB infection (1 conversion) 2 TB disease	18 TB infection (1 conversion) 5 TB disease		
	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5	PATIENT 6	PATIENT 7
Relationship with source case (contact time)	Mother (> 6 h per day)	Mother (> 6 h per day)	Cohabiting uncle (> 6 h per day)	Cohabiting uncle (> 6 h per day)	Mother's partner (< 6 h per day)	Mother's partner (< 6 h per day)	Occasional
Age	3 years	3 years	3 years	3 years	6 years	3 years	6 years
Tuberculin	15 mm	16 mm	20 mm	20 mm	20 mm	20 mm	20 mm necrosis and vesiculation
Quantiferon	Positive 9.4	Positive 4.57	Not requested	Positive 12	Not requested	Not requested	Positive 10
Symptoms	Pneumonia and persistent cough in previous months Asymptomatic at diagnosis	Cough Anorexia	Cough Night sweats	No	Slow-progressing pneumonia 2 months previously. Asymptomatic at diagnosis	Fever and pneumonia in previous months. Asymptomatic at diagnosis	Initially asymptomatic. Subsequently, coughing and sweating
Chest X-ray at diagnosis	Consolidation in right upper lobe	Consolidation in right upper lobe	Normal	Left hilar lymphadenopathy	Hilar and mediastinal lymphadenopathies. Infiltrate in right upper lobe	Right hilar lymphadenopathies and infiltrate in right lower lobe	Doubtful paratracheal lymphadenopathies
Complications	Middle lobe atelectasis	Right upper lobe atelectasis					
Chest CT	Right subcarinal and hilar lymphadenopathies. Middle lobe atelectasis	-	Pulmonary nodule Laminar atelectasis in right lower lobe. Left hilar lymphadenopathies	-	-	-	Lymphadenopathies and pulmonary infiltrate
Fiberoptic bronchoscopy	Granulomas and stenosis in the right upper lobe bronchus and intermediate bronchus	1st Granulomas in right upper and middle lobe bronchi 2nd Normal	-	-	-	-	-
Clinical samples	GA and IS × 3 BAL	GA and IS × 3 BAL	GA and IS × 3	GA and IS × 3	GA and IS × 3	GA and IS × 3	GA and IS × 3
Results	AFB neg. Culture neg. PCR neg.	AFB neg. Culture neg. PCR neg.	AFB neg. Culture neg. PCR neg.	AFB neg. Culture neg. PCR neg.	AFB neg. Culture neg. PCR neg.	AFB neg. Culture GA and IS × 2 *M. tuberculosis* resistant to H PCR IS × 1 *M. tuberculosis*	AFB neg. Culture neg. PCR neg.
Treatment administered	2HRZE+7RZE	2HRZE+10RZE	2HRZE+7RZE	2HRZE+5RZE	1HRZE+6RZE	1HRZE+6RZE	1HR+2HRZE+5RZE
Side effects of medication		Photosensitivity	Abdominal pain Hypertransaminases	Abdominal pain			Abdominal pain
Post-treatment follow-up	12 months	12 months	12 months	14 months	12 months	12 months	13 months
Other	Brother of patient 2		Residual hilar lymphadenopathy. Poor compliance		Brother of patient 6		Classmate of patient 5

AFB: acid-fast bacilli smear; BAL: bronchoalveolar lavage; CT, computed tomography; E: ethambutol; GA: gastric aspirate; H: isoniazid; IS: induced sputum; PCR: polymerase chain reaction; R: rifampin; S: streptomycin; TB: tuberculosis; Z: pyrazinamide.

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Do HIV-Infected Patients Die of Chronic Obstructive Pulmonary Disease in Western Countries?

¿En los países occidentales, los pacientes infectados con el VIH mueren de enfermedad pulmonar obstructiva crónica?

Dear Editor:

According to Global Burden of Disease estimates, at least 65 million people worldwide have moderate to severe chronic obstructive pulmonary disease (COPD). In addition to being globally prevalent, COPD was responsible for more than three million deaths in 2015 (5% of all deaths globally),[1] and from 1990 to 2015, the mortality rate increased 11.6%.[2] Furthermore, chronic respiratory diseases in the United States account for more than 155,000 deaths annually and are the third leading cause of death, surpassed only by heart disease and cancer.[3]

Recent systematic reviews report that up to 11% of people living with HIV (PLWH) have spirometric test results compatible with those for COPD.[4] Furthermore, although PLWH smoke tobacco and other products at higher rates than other groups at risk for COPD, they are relatively younger, and the frequency of COPD appears higher than would be expected from smoking only.[5] Proposed hypotheses have suggested that this increase in COPD prevalence could be due to several associated factors such as local inflammation, increased susceptibility to apoptosis and an altered antioxidant–oxidant balance.[6]

Currently, the presence of HIV infection is considered a risk factor for developing COPD, a finding just recently included in the latest GOLD document.[7] This increased prevalence of COPD among PLWH, consistently observed in several studies performed in western countries, would suggest that mortality due to COPD among PLWH could be at least similar to the rate observed in the general population, especially considering that recent studies from the same geographical environment have stated that COPD in PLWH can result in higher mortality rates than in the HIV-uninfected population.[8] Surprisingly, however, published data from current cohorts of HIV-infected patients report low rates of death attributed to COPD, even less than 1% in some nationwide studies.[9]

This observation could be explained by different factors. First, with regard to death certificate coding, it is worth remembering that the immediate cause of death in COPD patients is usually due to exacerbations (half of which are infectious) and cardiovascular events.[10] In both situations, actual codification systems, such as CoDe,[11] classify the events correctly as the immediate cause of death in HIV-infected patients, but probably tend to underestimate COPD as the underlying cause. Thus, when reporting causes of death in PLWH cohorts, COPD is usually not even reported to be within the top 10 causes. This misclassification phenomenon has previously been reported in the general population,[12] but some authors have suggested that it could be even more manifested in the HIV-infected population. The trend among practitioners who are not used to caring for PLWH is to codify infectious diseases as the cause of death, related or unrelated to HIV. As a consequence, could the number of deaths caused by infections unrelated to AIDS and cardiovascular disease be systematically reported more frequently in AIDS cohort studies?

Several examples might support this hypothesis. Recent data published from the Swiss HIV Cohort Study (SHCS) reported 1.7% of deaths due to COPD in 2005–2009, whereas the reported rates for non-AIDS-related infections and heart disease were 9.2% and 6.5%, respectively.[13] Similarly, Croxford et al. reported that 0.75% of deaths were caused by COPD (1.78% after excluding AIDS-defining illnesses) while deaths by cardiovascular disease (including stroke) and non-AIDS-defining infections accounted for 7.86% and 7.45%,