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Original Article

Outbreak of Multidrug-resistant Tuberculosis in Two Secondary Schools☆

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ABSTRACT

Objectives: To describe an outbreak of multidrug-resistant tuberculosis (MDR-TB) in two schools.
Methods: This was a prospective, observational study of an outbreak of MDR-TB in 2 schools located in the towns of Onda and Nules, in the Spanish province of Castellon, from the moment of detection in November 2008 until November 2014, including patient follow-up and contact tracing.
Results: Five cases of MDR-TB were diagnosed. Overall attack rate was 0.9%, and among the contacts traced, 66 had latent tuberculous infection, with an infection rate of 14.4%. Molecular characterization of the 5 *M. tuberculosis* isolates was performed by restriction fragment length polymorphism (RFLP) analysis of the IS6110 sequence. In all 5 patients, cultures were negative at 4-month follow-up, showing the efficacy of the treatment given. No recurrence has been reported to date.
Conclusions: In the context of globalization and the increased prevalence of MDR-TB, outbreaks such as the one presented here are only to be expected. Contact tracing, strict follow-up of confirmed cases, the availability of fast diagnostic techniques to avoid treatment delay, and chemoprophylaxis, together with the molecular characterization of strains, are still essential.

Brote de tuberculosis multirresistente en dos colegios de educación secundaria

Palabras clave:
Tuberculosis multirresistente
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RESUMEN

Objetivos: Descripción de un brote de tuberculosis multirresistente (TB-MDR) en el medio escolar.
Métodos: Se ha realizado un estudio prospectivo y observacional de un brote de TB-MDR en 2 colegios de Onda y de Nules de educación secundaria, en la provincia de Castellón, desde su detección en noviembre de 2008 hasta noviembre de 2014, con seguimiento de los casos y estudio de los contactos.
Resultados: Se diagnosticaron 5 casos de TB-MDR, con una tasa global de ataque de la enfermedad del 0,9% y en el estudio de contactos se detectaron 66 con infección latente tuberculosa, con una tasa de infección del 14,4%. Los 5 aislamientos de *M. tuberculosis* se estudiaron mediante el análisis del polimorfismo de los fragmentos de restricción (RFLP) de la secuencia IS6110 para su caracterización molecular. En los 5 pacientes el cultivo se negativizó a los 4 meses, demostrando la eficacia del tratamiento pautado, sin recaídas hasta la actualidad.
Conclusiones: Con la actual globalización y el aumento de la TB-MDR no es extraño la presentación de un brote como el que presentamos y sigue siendo fundamental el estudio de los contactos, el seguimiento estricto de los casos y la disponibilidad de las técnicas de diagnóstico para no demorar el inicio del tratamiento y la quimioprofilaxis, así como la caracterización molecular de las cepas.

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Introduction

In the 1980s, the emergence of HIV/AIDS led to a dramatic increase in the incidence of tuberculosis, primarily in countries with fewer resources, initially sub-Saharan Africa, followed several years later by south-east Asia. In 1993, the World Health Organization (WHO) declared tuberculosis to be a global health emergency.[1]

Epidemics of multi-drug resistant tuberculosis (MDR-TB), defined as *Mycobacterium tuberculosis* infection resistant to isoniazid and rifampicin, were first described in the United States and Europe at the beginning of the 90s. MDR-TB occurs mainly in HIV-infected patients, the transmission pattern is explosive, attack rates are high and incubation periods are short due to the immunosuppressed status of the host and the lack of adequate preventive measures against tuberculosis transmission in hospitals and penitentiary institutions affected by these outbreaks. Healthcare personnel are not exempt from risk.[2–4]

In 1994, the WHO, together with the International Union against Tuberculosis and Lung Disease, set up their Surveillance of Drug Resistance in Tuberculosis program. Until then, drug resistance had been a minor problem, usually related with poor treatment adherence, and primary multi-drug resistance was very rare.

Poverty, overpopulation, lack of economic resources for obtaining second-line drugs, the absence of effective programs for the management of tuberculosis, the HIV epidemic, and moving populations; all are reasons for the appearance and international dissemination of multi-resistant strains of *M. tuberculosis.* This has become a worldwide health problem, but one that is unequally distributed – countries such as Brazil, China, India, the Russian Federation, and South Africa are much more severely affected.[5]

Confirmation of diagnosis in a patient with suspected MDR-TB and the considerable delay in starting treatment was an additional problem, since cultures and sensitivity studies had to be performed. This particularly affected the start of second-line treatment.[6] The situation has improved, thanks to new techniques that detect *M. tuberculosis* DNA in respiratory specimens, allowing the diagnosis and detection of isoniazid and/or rifampicin resistance in a matter of hours.[7,8]

Tuberculosis epidemics in schools are not uncommon, and when they occur, contact tracing is essential to diagnose secondary cases, to initiate prompt treatment of patients and carriers who require it, and to identify the real index case.[9]

This is a description of an outbreak of MDR-TB in a school setting and the difficulties we encountered in managing both patients with disease and carriers.

Methods

We conducted an observational, prospective study of an MDR-TB outbreak detected in November 2008 in 2 schools in Onda (O) and Nules (N) in the province of Castellón (Spain). A microepidemic or epidemic outbreak was defined as the appearance of 3 or more cases of tuberculosis related in space and time, or the diagnosis of at least 2 patients generated by the same index case.[9,10]

The index case was the first patient diagnosed, and the source case, or real index case, was the patient who was most likely to be the origin of the outbreak. A contact was any person who had shared enclosed spaces with a tuberculosis carrier.

After the index case was detected, contact tracing was performed, in accordance with previously published guidelines,[9,10] using the concentric circles or "stone-in-the-water" model.[11]

The Castellón Public Health Center worked with the health centers in O and N to coordinate contact tracing in the 2 schools in which the index case was employed as a teacher, and among family members. They were also responsible for providing information to the parents of pupils at the school.

Tuberculin testing was performed using the Mantoux technique with 2TU PPD RT 23.

Latent tuberculosis infection was defined as a positive Mantoux test with a 5 mm induration at 72 h. An initial Mantoux test was performed and repeated 2 months later in cases which were initially negative. Individuals aged over 50 years with a negative result repeated the test 7 days later, to determine the booster effect.

All individuals with a positive Mantoux test had a chest X-ray.

If mycobacteria were cultured, the intraspecific differentiation was identified using restriction fragment length polymorphism (RFLP) analysis of the IS6110 sequence.[12]

Statistical Analysis

Tuberculosis infection and disease attack rates were estimated in contacts and compared using Chi-squared and Fisher statistical tests in the different risk groups. Odds ratio (OR) was used to estimate the association between contacts according to exposure to MDR-TB cases and the 95% confidence interval was calculated. *P*-values <.05 were considered significant and the Epi-info program version 5 was used for all statistical calculations.

Results

Contact Tracing

The index case taught second year secondary pupils (10 h a week) in school O. The previous year he had taught first year pupils. The 2 secondary cases also taught all year grades in school O; their pupils were aged between 11 and 15 years.

After detecting 3 cases among the teachers, we decided to include all pupils, teachers, and non-teaching staff in the contact tracing. A total of 205 of the 207 secondary school pupils (99%) and 200 of the 205 primary and infant school pupils (97.5%) participated. There was a significant increase in positive Mantoux tests between the 1st year and 4th year of secondary school (*P*<.001).

The index case also taught first and third year secondary school pupils in school N (4 h a week). All exposed cases participated (93/93, 100%) in contact tracing, including all the pupils that case 1 had taught the previous year. Table 1 shows the results from the pupils of both schools.

No significant differences were observed in the risk of developing infection among secondary pupils at both schools [OR 0.63 (95% CI 0.28–1.42), *P*=.223]; nor was any significant difference observed when pupils attending classes given by the index case were examined separately [OR 0.51 (95% CI 0.15–1.66), *P*=.22].

Table 2 shows the results of all contacts that were studied.

If we compare the risk of infection among teachers from both schools, teachers at school O show a higher risk [OR 3.43 (95% CI 0.76–17.48) *P*=.069], probably due to greater exposure. It is interesting to note that none of the 3 teachers who contracted the disease had received BCG vaccination, and if vaccinated contacts (10) are compared to unvaccinated contacts (21), the OR of developing the disease is 0.51 (95% CI 0.0–5.13). This difference is not statistically significant (*P*=.59), but it may indicate some protective effect from vaccination. Table 3 compares the results in cases exposed and not exposed to MDR-TB cases. The OR of contracting infection was 6.12 (95% CI 2.58–17.59), which is statistically significant (*P*<.001). The overall rate of disease attack was 0.9% and rate of infection 14.4%.