Research Article

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Isoniazid-Resistant *Mycobacterium Tuberculosis*: A Global Problem

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ABSTRACT

Introduction: Tuberculosis is an infection that mainly affects the lungs, caused by three main pathogens of the genus Mycobacteria, there are a variety of factors, both exogenous and endogenous, that facilitate its development, as well as the presence of several host variables that play a role. important in disease behavior and susceptibility to it, current treatments for sensitive TB include isoniazid, rifampicin, ethambutol and pyrazinamide, poor adherence to therapy and misadministration of these leads to the emergence of drug-resistant strains.

Results: Different studies carried out have shown that there are mutations in different Mycobacterium genes that confer resistance to certain anti-tuberculosis drugs, such as isoniazid, where it was reported in a study carried out in Lima, Peru, that in patients with genetic mutations that conferred resistance to isoniazid in a sample of 777 patients evaluated, likewise >50% of patients resistant to isoniazid were reported.

Methodology: A bibliographic search was carried out in databases, selecting original articles, case reports and bibliographic reviews from 2006 to 2022, using the documents that will deal with Mycobacterium resistant to isoniazid, obtaining 22 articles for the realization of this document.

Conclusion: Tuberculosis greatly affects the lungs, treatments based on anti-tuberculosis drugs have reduced effectiveness due to genetic alterations of Mycobacterium that confer resistance to drugs such as isoniazid, which suggests a major public health problem when it comes to treating this.

KEYWORDS: Bacterial resistance; *Mycobacterium tuberculosis*; Resistance to isonizide; Resistant mycobacterium

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INTRODUCTION

Tuberculosis is considered a disease with great potential for infection that mainly attacks the lungs. It is spread through the spread of droplets of saliva containing the bacteria that cause tuberculosis which travel through the air when sneezing or coughing. The progression of the disease is related to external (exogenous) and internal (endogenous) risk factors [1].

Exogenous factors can accentuate the progression of exposure to infection, among which the bacillary load in the sputum and the proximity of an individual to a case of infectious tuberculosis are key factors. Similarly, endogenous factors lead to the progression of infection to active tuberculosis. Along with well-established risk factors (such as human immunodeficiency virus (HIV), malnutrition, and young age), emerging variables such as diabetes, indoor air pollution, alcohol, use of immunosuppressive drugs and tobacco smoke play an important role in both factors at the individual and population level. Additionally, socioeconomic and behavioral factors increase susceptibility to infection [1].

Specific groups such as health workers and the indigenous population are also at increased risk of tuberculosis infection and disease. Today, tuberculosis (TB) remains the number one cause of human death from a single infectious agent, causing approximately 10.4 million new cases and 1.7 million deaths per year [2]. The genus Mycobacteria comprises more than 170 species, most of which are environmental organisms. Traditionally, mycobacterial species have been divided into fast-growing and slow-growing, with the three major mycobacterial pathogens of humans (ie, MTBC, Mycobacterium leprae, and Mycobacterium ulcerans) belonging to the slow-growing group. In addition, several of the so-called non-tuberculous mycobacteria (NTM) can cause disease in immunosuppressed people. These include Mycobacterium abscess (a fast-growing) and the slow-growing Mycobacterium avium, Mycobacterium marinum, Mycobacterium xenopi, Mycobacterium gordonae and Mycobacterium kansasii [3].

The currently recommended treatment for drug-sensitive TB is a 6–9-month regimen combining four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide, however, non-compliance with the drug regimen, misuse of Mismanagement of TB drugs often leads to the emergence of drug-resistant strains. Other factors that predispose to drug-resistant TB include low socioeconomic status (such as employment, education, income, poor nutrition), alcohol abuse, smoking, immigrant status, coinfection with other diseases (HIV/AIDS, diabetes, infection by fungi), presence of TB patients in the house, etc.

However, the emergence of drug-resistant TB remains a challenge for TB treatment and effective disease management, and is a major threat to global public health, drug resistance in Mtb evolves through of various mechanisms including compensatory evolution, epistasis, clonal interference, cell envelope impermeability, efflux pumps, drug degradation and modification, target mimicry, and phenotypic drug tolerance [4]. Drug-resistant TB strains that emerge in hospital and community settings exhibit different levels of drug resistance, such as rifampicin resistance (RR), MDR, and extensive drug resistance (XDR). RR-TB is resistance only to rifampicin and not to other first- or second-line drugs. MDR-TB is defined as resistance to at least two of the most potent anti-TB drugs, isoniazid and rifampicin [4].

Resistance to first-line drugs is a major problem for tuberculosis care. During 2018, 500,000 cases of rifampicin-resistant TB (RR-TB) were registered, of which 78% presented concomitant resistance to isonazid (MR-TB); [5]. Isoniazid (H) is a first-line treatment anti-tuberculosis drug, with potent bactericidal activity that inhibits enoyl-ACP reductase, an enzyme required for the synthesis of mycolic acid [6-8]. According to the World Health Organization (WHO), tuberculosis (TB) with resistance to isoniazid (Hr-TB) refers to strains of *M. tuberculosis* with resistance to H and susceptibility to rifampicin confirmed in vitro [9,10].

METHODOLOGY

To carry out this article, a bibliographic search was carried out in various databases such as Elsevier, Scielo, Medline, pubmed, ScienceDirect and Ovid, thus selecting original articles, case reports and bibliographic reviews from 2006 to 2022, in Spanish and English. using MeSH terms: Bacterial resistance, mycobacterium tubeculosis, isonizide resistance, resistant mycobacterium and the Boolean operators and or. Thus, including all the documents that will deal with Mycobacterium resistant to isoniazid, the data found were between 15-35 records, thus using 22 articles for the preparation of this document.

RESULTS

In a cross-sectional study of 194 cases with isolation of *Mycobacterium tuberculosis* resistant to INH, RIF, or both, from the department of Atlántico, Colombia, it was found that 97.94% (190) corresponded to pulmonary tuberculosis; 68.04% (132 cases) were untreated and 31.96% (62 cases) previously treated. It was found that 6.19% (12 patients) were contacts of patients with TB/RF. The global resistance of *Mycobacterium tuberculosis* to quinolones and injectable drugs in the 132 untreated cases, in the 4 years studied, was 1.52% for OFX (95% CI 0.18-5.33), followed by amikacin and kanamycin with 0.76% (95% CI 0.02-4.12) and capreomycin that did not show global resistance. No TB/XDR cases were found, nor combinations between them.

Resistance of *M. tuberculosis* to quinolones and injectable drugs in cases of resistant tuberculosis, not treated with second-line drugs, 2013-2016 in the department of Atlántico102 cases were found resistant to INH, 98 (96.1%) were sensitive to second-line drugs; one (0.98%) presented resistance to kanamycin, one (0.98%) to amikacin, and two (1.96%) to OFX. There was no resistance to capreomycin or combined resistance to quinolones and injectable drugs (Table 1). Resistance of *M. tuberculosis* to quinolones and injectable drugs was also evidenced in untreated patients with resistant tuberculosis, 2013-2016. In previously treated cases, among the 30 INH-resistant in Barranquilla, only one case was detected (3.3%) resistant to kanamycin. In the 8 resistance to RIF, there was also evidence of one case (12.5%) with combined resistance to amikacin, capreomycin and ofloxacin [11]. In a study carried out to study the resistance of *Mycobacterium tuberculosis* in Peruvian strains to second-line drugs in patients, in 2004, from a total of 444 patients examined with pulmonary tuberculosis, 14 strains resistant to isoniazid and rifampicin were obtained from patients who had not previously received treatment for TB, with resistance to all injectables in 4 strains (36.4%); [12] A study presents a total of 324 patients treated in the Program against Tuberculosis by the jurisdiction of Lima Norte, of the registered patients, only 148 presented resistance to anti-tuberculosis drugs and isoniazid (46%), and only 12% [13] only resistant to isoniazid and also found a higher prevalence in men 31.6% finding a (59.37%), and (52.6%); [14,15].

Table 1: Atlantic Public Health Laboratory.

Casos no Tratados					
Perfil De Resistencia	**Resistentes a Isoniacide (N=102)**	**Resistentes a Rifampicina (N=11)**	**Multidrogorresistence (N=19)**	**Total (N=132)**	**IC 95%**
	N%	**N%**	**N%**	**N%**	
Sensible a quinolonas Y farmacos inyectables	98(96,1)	11(100)	19(100)	128(97)	92,5-99,2
Resistencia a Un Medicamento					
Kanamicina	1(0,98)	0	0	1(0,76)	0,02-4,12
Amicacina	1(0,98)	0	0	1(0,76)	0,02-4,12
Capreomicina	0	0	0	0	0
Ofloxacina	2(1,96)	0	0	2(1,52)	0,18-5,33
Resistencia Global Por Medicamento					
Resistencia a Kanamicina	1(0,98)	0	0	1(0,76)	0,02-4,12
Resistencia a Amicacina	1(0,98)	0	0	1(0,76)	0,02-4,12
Resistencia a Capreomicina	0	0	0	0	0
Resistencia a Ofloxacina	2(1,96)	0	0	2(1,52)	0,18-5,33

Between January 2006 and December 2018, 32 patients with Hr-TB were included in the study, out of a total of 528 cases of confirmed *M. tuberculosis* infection (6%). 78% (n=25) were classified as new cases (without previous exposure to anti-TB drugs, primary resistance) and 22% (n=7) corresponded to previously treated cases (acquired resistance); [16]. At the end of treatment, 63% (n=20) had successful treatment. On the other hand, 2 deceased cases were reported, which were related to meningeal TB. Most of our cases were new and presented coinfection with HIV as comorbidity; however, most alarming was the evidence for 24 different treatment regimens for this condition (Figure 1).

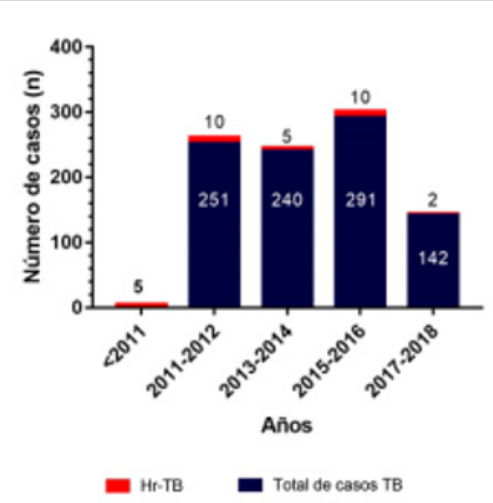

Figure 1: Isoniazid-resistant (Hr-TB) cases between 2006 and 2018 (n=32).

A study carried out in Lima, Peru reports the frequency of KatG and inhA genetic mutations that confer resistance to isoniazid in a sample of 777 patients with resistance to isoniazid. The GenoType® MTBDRplus test and the conventional sensitivity test by the agar plate method were used. It was found that 54% presented a mutation in the KatG gene; this was associated with resistance to streptomycin 76.6% (p<0.05), rifampicin 66.7% (p<0.05) and ethionamide in 33% (p<0.05). The mutation in the inhA gene had a frequency of 46% and was associated with resistance to ethionamide in 68.1% (p<0.05), rifampicin 47.2% (p<0.05) and streptomycin 33% (p<0.05). <0.05). In these patients, the presence of genes that confer resistance to isoniazid was associated with resistance to other anti-TB drugs [17-22].

DISCUSSION

Tuberculosis represents a public health problem worldwide due to its presentation, the symptoms it presents in patients, the increase in cases of HIV coinfection, and its rigorous treatment, where we have another problem due to the appearance of strains of *M. tuberculosis* resistant to specific treatment; In the results of

this article, the resistance of *Mycobacterium tuberculosis* against the drugs that are used for its treatment has been raised, where we can see that isoniazid is one of the drugs that most presents resistance in patients who had not previously received treatment of the pulmonary tuberculosis, as we can see in the study carried out in Colombia and published in 2020, where out of a total of 528 cases of infection by a study published in 2020 and conducted in South Africa shows the genetic diversity of *M. tuberculosis* strains has been demonstrated across Africa, implying that diverse genotypes are driving the epidemiology of drug-resistant TB across the continent, and raises that various factors influence the spread of treatment-resistant TB, such as socioeconomic level, incomplete treatment regimens, and some genes related to resistance; as well as it was shown in a study carried out in Peru where it is reported that the KatG and inhA genetic mutations that confer resistance to isoniazid, in a sample of 777 patients with resistance to isoniazid, it was found that 54% presented mutation in the KatG gene; this was associated with resistance to other drugs such as streptomycin 76.6% (p<0.05).

In a study carried out in Peru, a marked correlation was found between the presence of the C-15T mutation within the inhA promoter region and resistance to ETH; These mutations are associated with resistance because isoniazid and ethionamide are prodrugs activated by mycobacterial catalase-peroxidase, encoded by the katG gene, and act by inhibiting the activity of the enzyme enoyl-ACP-reductase, responsible for resistance. synthesis of cell wall mycolic acid. Therefore, mutations in the inhA promoter region, causing overexpression of this enzyme, lead to cross-resistance between these 2 anti-tuberculosis drugs; This finding suggests that there are 50 times more chances of finding an isolate resistant to ETH and, in turn, presenting the C-15T mutation.

CONCLUSION

Tuberculosis affects the lungs in a great way, its contagion is given by saliva drops of the infected that contain the Mycobacterium, giving this infection a high transmissibility, the susceptibility, progression and severity of this are influenced by the various endogenous and exogenous factors described. above, as well as factors present in the host itself such as diseases and other characteristics that suppress the host's immunity; The treatment for this entity is based on anti-tuberculosis drugs which have had great functionality for a long time, however the efficacy of treatment with these drugs such as isoniazid, rifampicin, ethambutol and pyrazinamide mainly.

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