

Mycobacterium tuberculosis Beijing – prevalence, diagnostics and treatment

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ABSTRACT

Mycobacterium tuberculosis (MT) is a widespread bacterium which usually attacks the lungs causing tuberculous pneumonia, but it can also occupy any other part of our body. One of the MT strains discovered in 1995 in China, known as the Beijing type, is extremely dangerous because of its increased antibiotic resistance. The most efficient method to properly identify this strain is genotyping which is based on the analysis of the MT genome. Symptoms of tuberculosis caused by the Beijing type

may be similar to normal MT strain; however, there are some discrepancies. The most significant step in the diagnostic process is to determine the range of antibiotic resistance. These strains usually show a multi-drug resistant or extremely drug resistant phenotype.

Keywords: *Mycobacterium tuberculosis*; *Mycobacterium tuberculosis* Beijing; tuberculosis treatment; tuberculosis diagnosis; tuberculosis management.

INTRODUCTION

Tuberculosis is a worldwide infectious disease caused by *Mycobacterium tuberculosis* (MT). The disease most commonly affects the lungs, but it can also affect virtually all other human organs. There are several genotypic groups of tuberculosis – one of them is the Beijing type discovered and described for the first time in 1995 in China, near Beijing. Further research on this variety revealed its genetic similarity with other strains found in East Asia and spread around the world. Importantly, this type is associated with species with increased drug resistance. The available comparisons also show that the course of tuberculosis caused by the MT Beijing is different from other MT strains. In our study, we will focus on collecting information on the origin, spread around the world and ways to fight MT Beijing.

been observed as a dominant genotype in the countries that were part of the Soviet Union (such as Russia, Estonia, Latvia, Lithuania, Belarus, Ukraine, Moldova, etc.), in southern African countries, as well as in South and East Asia [1, 4, 6, 7]. It is supposed that it may be an 'escape variant' after widespread Bacillus Calmette-Guérin (BCG) vaccination of the population [8]. The study of >29,000 clinical cases of patients from 35 countries allowed isolating 4 models of tuberculosis associated with the above-mentioned strain. The first was an epidemic model in which bacteria showed resistance to treatment, in particular in Cuba, Vietnam, South African countries, the former Soviet Union, as well as in Western Europe. Other models, unrelated to treatment resistance, were noted in particular in East Asian countries, fewer cases in the United States, and drug-sensitive type in Argentina and Malawi. The last of the 4 mentioned models is of marginal importance; its cases have been described in the vicinity of Africa and Europe [5].

DISCOVERY AND SPREAD OF MYCOBACTERIUM TUBERCULOSIS TYPE BEIJING

The MT genotype that we are discussing was first isolated in Beijing in 1995, hence the current name of this strain [1, 2, 3, 4]. In the same year, it was reported that >80% of tubercule bacillus (TB) cases in the Beijing area were caused by the Beijing-type strain [5]. It was distinguished by its high similarity of the IS6110 RFLP pattern and the display of an identical polymorphism in the direct repeat region of the MT genome between the tested *mycobacteria* [2, 4]. It can also be noted that the MT Beijing has

DIAGNOSTICS

There are many methods of distinguishing the Beijing type, based on the analysis of the genome of *mycobacteria* and identification of insertion sequences or specific genes – genotyping. This process makes it possible to distinguish genetic profiles – fingerprints for individual strains of MT, and thus also the relationship between them. Some of these methods were repeated in the studies we compare. Molecular methods are an extensive group of tests, including the analysis of the length of the restriction fragment

length polymorphism (RFLP) that contains the IS6110 insertion sequence. The specific location of this sequence on the genome and the number of its copies are used as a marker in the RFLP assay, which allows the differentiation of individual MT complex strains.

Genetic typing uses, among others, nucleic acid amplifications – fragments of DNA or RNA are cloned *in vitro*, resulting in amplicons which are then analyzed after their electrophoretic separation or dot-blot hybridization. One of the techniques in this category is Spoligotyping – a method that has been gaining popularity recently. It is based on PCR and the detection of chromosomal polymorphisms of the DR region in the MT complex. The advantages of this method are the ease of its implementation and the stability of the results. It can be used to identify the MT complex directly from a clinical specimen without prior cultivation of the organism. However, this method is not able to distinguish strains having the same spoligo-types, in this case other techniques should be used [9].

DISEASE SYMPTOMS AND FACTORS AFFECTING THE COURSE OF TUBERCULOSIS CAUSED BY THE BEIJING STRAIN

In studies comparing 2 groups of patients infected by Beijing and non-Beijing strains, the main difference in the course of the disease was the appearance of fever after the start of treatment in patients infected by Beijing strains [8, 10]. It has been theorized that the cause of fever is most likely due to a different reaction of the immune system to Beijing TB strains compared to the reaction triggered in response to non-Beijing strains. Symptoms such as shortness of breath, cough or weight loss were observed with similar frequency and intensity in both groups of patients [8]. The X-ray images of the lungs taken in patients in the study groups did not show any significant differences [10, 11]. On the other hand, chest pain was more frequent in patients infected by non-Beijing strains [8]. Contradictory information is available regarding the occurrence of haemoptysis, because depending on the study, either no differences in the incidence of this symptom were noted, or it occurred more often in patients infected by non-Beijing strains. Patients more predisposed to developing Beijing tuberculosis were young people (slightly more often patients aged <25 than >25), people living in cities and those who had already been treated for tuberculosis [12, 13]. Gender, economic status or previous contact with tuberculosis-infected patients did not affect the risk of contracting the disease [8]. A case of a 29-year-old pregnant woman was described in which non-specific symptoms of Beijing MT infection, such as weakness, weight loss and high fever, caused a delay in making an accurate diagnosis, resulting in intrauterine fetal infection and premature delivery [14].

TREATMENT

The standard in the treatment of tuberculosis is a 6-month therapy divided into 2 phases. The first stage, called the intensive treatment phase, lasts 2 months. The patient receives 4 basic medications,

isoniazid, rifampicin, pyrazinamide and ethambutol or streptomycin. The second stage is a 4-month maintenance phase during which 2 antibiotics, isoniazid and rifampicin, are administered. The introduction of this treatment regimen has contributed to a decrease in mortality among tuberculosis patients, and the introduction of preventive vaccinations has helped decrease the incidence rate [15].

Beijing tuberculosis is characterized by greater virulence and increased drug resistance – it usually shows a type of resistance, called multi-drug resistant, i.e. simultaneous resistance to isoniazid and rifampicin, or extremely drug resistant, simultaneously resistant to isoniazid and rifampicin, and additionally to at least one fluoroquinolone and at least one injectable drug, i.e. capreomycin or aminoglycoside [15]. It has also been proven that the BCG vaccine is much less effective against it than against other subtypes, and the treatment of strains that are not even drug-resistant is more difficult than non-Beijing tuberculosis [8, 15]. It becomes necessary to use more toxic and less effective second-line drugs, including fluoroquinolones (to which this type of tuberculosis is more often resistant), aminoglycosides or bedaquiline [16]. Second-line drugs are also used in standard therapies of infections with bacteria other than *Mycobacterium* spp., hence the risk of generating resistance mechanisms to these antibiotics raises justified concerns about future therapeutic failures in the entire medicine of infections. All this contributes to the greater spread of strains belonging to the Beijing type, long-term persistence in the population and higher mortality. In addition, the current geopolitical situation also significantly contributes to the consolidation of the presence of more virulent strains in our area.

CONCLUSIONS

Tuberculosis is one of the most widespread diseases in the world that can affect both the lungs and virtually any other organ. One of its types is the so-called Beijing, widespread all over the world, and associated with the IS6110 insertion sequence of polymorphic fragments. There are a number of methods to identify this type of tuberculosis, including Spoligotyping, which has recently gained popularity. There is a particular feature in the clinical course of Beijing MT infection, consisting in the onset of fever after the start of treatment, which may be associated with a different reaction of the immune system than in relation to non-Beijing types. Unfortunately, this type of MT also causes increased resistance to classic tuberculosis treatment regimens, which necessitates the introduction of second-line drugs, also used in the treatment of infections with other bacteria, which raises concerns about the development of resistance mechanisms. Long-term persistence of MT Beijing in the population and higher mortality can also be expected.

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