IL-12Rβ1 Deficiency in Two of Fifty Children with Severe Tuberculosis from Iran, Morocco, and Turkey

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Abstract

**Background and Objectives:** In the last decade, autosomal recessive IL-12Rβ1 deficiency has been diagnosed in four children with severe tuberculosis from three unrelated families from Morocco, Spain, and Turkey, providing proof-of-principle that tuberculosis in otherwise healthy children may result from single-gene inborn errors of immunity. We aimed to estimate the fraction of children developing severe tuberculosis due to IL-12Rβ1 deficiency in areas endemic for tuberculosis and where parental consanguinity is common.

**Methods and Principal Findings:** We searched for IL12RB1 mutations in a series of 50 children from Iran, Morocco, and Turkey. All children had established severe pulmonary and/or disseminated tuberculosis requiring hospitalization and were otherwise normally resistant to weakly virulent BCG vaccines and environmental mycobacteria. In one child from Iran and another from Morocco, homozygosity for loss-of-function IL12RB1 alleles was documented, resulting in complete IL-12Rβ1 deficiency. Despite the small sample studied, our findings suggest that IL-12Rβ1 deficiency is not a very rare cause of pediatric tuberculosis in these countries, where it should be considered in selected children with severe disease.

**Significance:** This finding may have important medical implications, as recombinant IFN-γ is an effective treatment for mycobacterial infections in IL-12Rβ1-deficient patients. It also provides additional support for the view that severe tuberculosis in childhood may result from a collection of single-gene inborn errors of immunity.

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Introduction

“...The occurrence of tuberculosis in families led to the view that it was an inherited disease. The demonstration of a characteristic bacterium by Koch in 1882 disposed of this view.” Theobald Smith [1]

Tuberculosis (TB) is typically caused by Mycobacterium tuberculosis (Mtb) and has probably claimed more lives than any other single infectious disease in human history. It continues to be responsible for almost two million deaths each year [2]. Two main forms of clinical disease have been historically observed in endemic areas, at least until the advent of the first antibiotics, and the further blurring of the overall picture that occurred with the HIV pandemic. The disseminated form in children is acute and results from the hematogenous spread of Mtb during primary infection, whereas the chronic pulmonary form in adults, results from the reactivation of latent Mtb infection [3,4].

A few decades after the discovery of Mtb by Robert Koch in 1882, it became apparent that most people in endemic areas were infected with this bacterium but remained asymptomatic. These findings, obtained at the turn of the twentieth century, were based on both hypersensitivity to subcutaneously [5] and intradermally (Mantoux) administered tuberculin [6] and the growth of Mtb from the lungs of patients dying from other causes [7]. Indeed, only a small fraction of individuals infected with Mtb develop clinical TB in their lifetime. Mtb remains latent in most infected individuals. One century later, the phenomenon of latency, and reactivation thereof, remains largely unexplained, implying that the pathogenesis of adult TB itself is unclear. This is also true for pediatric TB, which occurs in about 5% of infected children during primary infection.

In line with a long tradition of thought, we hypothesize that TB is not only an infectious disease, but also a bona fide genetic disorder; more specifically, we hypothesize that TB results from inborn errors of immunity [3,8–12]. The genetic theory of TB, which predates the discovery of Mtb [1,13], was supported from the 1910s onwards by genetic epidemiology surveys, initially based on correlation studies [14,15] and twin studies [16]. Studies in the mouse model conducted from the 1920s onwards also provided strong support for the genetic theory of TB [17]. Finally, over the last decade, adult TB susceptibility chromosomal regions were mapped by candidate gene and genome-wide linkage and association studies [3,8–12,18–20].

The human molecular genetic dissection of pediatric TB was facilitated from 1996 onwards by the dissection of genetic etiologies of the syndrome of Mendelian susceptibility to mycobacterial disease (MSMD), which is characterized by clinical disease caused by weakly virulent mycobacteria, such as BCG vaccines and environmental mycobacteria (EM), in otherwise healthy children who are normally resistant to most other infectious agents [8,21]. In the last 12 years, as many as 15 disorders have been discovered, involving eight genes that control the IL-12-IFN-γ circuit [21–24].

These studies paved the way for the identification of the first children with Mendelian predispositions to bona fide TB: autosomal recessive IFN-γR1 deficiency in a child not vaccinated with BCG, autosomal recessive IL-12p40 deficiency in a child who also had disseminated BCG disease (known as BCG-osis), XR-MSMD1 (NEMO) in a child without BCG vaccination [21] and XR-MSMD2 (CYBB) in a child not vaccinated with BCG [23]. More convincingly, in three unrelated families from Morocco, Spain, and Turkey, children bearing two loss-of-function alleles of IL12RB1 were found to suffer from severe TB in the absence of any signs of MSMD, despite vaccination with BCG and clear exposure to EM [25–27]. The proband in the Moroccan family suffered from BCG-osis [25], leading to the investigation of a sibling with TB, whereas the other two families had no family history of MSMD [26,27]. Indeed, IL-12Rβ1 deficiency has been shown to display incomplete clinical penetrance for the case-definition phenotype of MSMD [28,29].

Based on these studies, the proportion of children with disseminated TB due to monogenic predisposition in endemic areas was proposed, by purely theoretical calculations, to be far from negligible (3% to 30%) [3]. These data and calculations raised two key, general questions: What proportion of children with disseminated TB have a predisposition conferred by single-gene variations? And what are these inborn errors of immunity? As a first approach to tackling this fundamental problem, we attempted to estimate the proportion of children with severe TB due to autosomal recessive IL-12Rβ1 deficiency in three countries endemic for TB, where HIV infection is infrequent, and where consanguineous marriages are common, including Iran, Morocco, and Turkey.

Results

In 48 patients, no rare variations were found. However, we identified two patients carrying homozygous mutations in IL12RB1: a mutation in exon 9 in Moroccan P1, leading to the introduction of a stop codon at position 305 (K305X), and a mutation in exon 5 in Iranian P2, leading to the replacement of an arginine residue with a tryptophan residue at position 173 (R173W) (Figure 1). These mutations were previously shown not to be polymorphisms by sequencing control samples from various ethnic groups [28,29] and had been further shown to be loss-of-expression and loss-of-function in other patients with MSMD [28,29]. Both mutations lead to complete IL-12Rβ1 deficiency and render the patient’s cells completely unresponsive to IL-12.

Two of these patients came from unrelated families, each of which was consanguineous, originating from and living in Morocco (P1) and Iran (P2).

P1 had been vaccinated with BCG at birth, with no adverse reaction. He developed severe pulmonary TB at 13 years of age, leading to his death after three months despite treatment with rifampin, isoniazid, pyrazinamide and streptomycin. The presence of Mtb was confirmed bacteriologically by culture from sputum. The patient was the only member of this family homozygous for the mutant allele of IL12RB1 (his older brother is heterozygous) (Figure 1).

P2 was diagnosed with severe pulmonary tuberculosis at seven months of age, which was bacteriologically confirmed (from gastric lavage), and treated with isoniazid and rifampin (Figure 1). A paraspinal abscess due to Mtb was diagnosed at six years of age, and was treated by surgical resection and antmycobacterial drugs (isoniazid, rifampin and clarithromycin). P2 also had cutaneous leishmaniasis at the age of five years, successfully treated with Glucantine (meglumine antimoniate) for 20 days. An older brother was found to be homozygous for the mutant allele of IL12RB1. This brother had been vaccinated with BCG, with no adverse effect, and developed cutaneous leishmaniasis at the age of seven years and scrofuloderma of the neck at the age of 12 years, which was successfully treated with antmycobacterial drugs (rifampin and isoniazid supplemented with streptomycin for the first two months). Unfortunately, no pathological and microbiological investigations were carried out to ascertain the probable Mtb-linked etiology of scrofuloderma. Another IL-12Rβ1-deficient patient with visceral leishmaniasis has previously been described [30]. All the children of this Iranian family, including
Discussion

This study shows for the first time, at the population level, that in at least two countries with a high rate of consanguineous marriages (Morocco and Iran) severe TB may result from autosomal recessive IL-12R\(\beta\)1 deficiency, in at least some children. We investigated 50 patients, two of whom were found to carry homozygous loss-of-function mutations in IL12RB1, giving an overall estimated prevalence of 4%. Given the small size of the sample, this estimate is only a rough one; however, it is quite remarkable that we were able to detect two IL-12R\(\beta\)1-deficient patients in a sample of only 50 children. It is difficult to assess the actual prevalence of IL-12R\(\beta\)1 deficiency as a genetic etiology of pediatric TB in Morocco (1 in 35 samples); however, P1 is the second child to be diagnosed with TB and IL-12R\(\beta\)1 deficiency in this country [25]. P2 is the first IL-12R\(\beta\)1-deficient child with TB diagnosed in Iran; however, this is probably not unique, as a young adult patient with TB and IL-12R\(\beta\)1 deficiency has also recently been identified in this country [31]. Finally, although we found no IL-12R\(\beta\)1-deficient Turkish children with TB in this study, we did identify one such child in a previous study [27]. Overall, IL-12R\(\beta\)1 deficiency does not seem to be an exceedingly rare genetic etiology of TB, at least in children from Morocco, Turkey, and Iran. We now need to test more children from these countries, as well as children with severe TB from other regions of the world where parental consangunuity is less common. Our previous identification of two Spanish siblings with TB and IL-12R\(\beta\)1 deficiency, born to non-consanguineous parents, suggests that there may be other cases around the world [26]. Overall, our study suggests that IL-12R\(\beta\)1 deficiency should be considered in selected children with severe TB, at least in areas with a high prevalence of parental consangunuity. This is important clinically, not only for genetic counseling, but also because recombinant IFN-\(\gamma\) is an effective treatment for mycobacterial disease in patients with IL-12R\(\beta\)1 deficiency displaying impaired IFN-\(\gamma\) production [21,32,33].

In this study, we investigated only one gene, IL12RB1, because mutations in this gene had previously been found in three unrelated children with TB [25–27]. We focused on its coding region, yet there may be children carrying non-coding and TB-causing mutations in IL-12RB1. Moreover, other genes are known to be associated with MSMD and even with childhood TB. Indeed, one child with partial recessive IFN-\(\gamma\)R1 deficiency, and others with IL-12p40 deficiency, XR-MSMD1 (NEMO deficiency) and XR-MSMD2 (CYBB deficiency) associated with clinical TB have been identified [21,23]. Mutations in these genes may be responsible for TB in other children, particularly if the morbid alleles concerned display incomplete penetrance for the case-definition phenotype of MSMD, such as IL12B and IL12RB1. Mutations in other genes possibly but not necessarily related to IFN-\(\gamma\)-mediated immunity, may also be involved. This study adds weight to the hypothesis that severe TB may be attributable to a collection of single-gene mutations, in at least some children. It is not surprising that recessive traits are frequently involved in countries in which the rate of consangunuity is as high as 20% (Morocco and Turkey) or 38% (Iran). However, in our recent large series of 102 families with an IL-12R\(\beta\)1-deficient proband with MSMD [29], only 58 families (57%) were clearly consangunous and 14 probands were compound heterozygous, indicating that complete IL-12R\(\beta\)1 deficiency may also occur in non-consangunous families. Dominant traits may also be involved, consistent with the identification of various dominant MSMD-causing mutations in IFNGR1, IFNGR2, and STAT1 [34–37]. We are currently trying to improve our estimate of the percentage of children suffering from genetically determined severe TB by collecting more samples from these three populations (Iran, Morocco and Turkey). We intend to use a genome-wide hypothesis-generating approach, sequencing the ‘whole exome’ and ‘whole genome’ of children with TB enrolled in this study [38–40]. The genetic dissection of pediatric TB should have a major impact on our understanding of the pathogenesis of TB and may lead to new therapeutic interventions based on a rational understanding of the pathogenesis.

Methods

We investigated the IL12RB1 gene in 50 children from three countries in which tuberculosis is endemic: 11 children from Turkey, 4 from Iran, and 35 from Morocco. These countries were selected because they have a high prevalence of consangunous marriages (around 20% in Morocco and Turkey [41,42] and 38% in Iran [43]), a very low prevalence of HIV (less than 0.1% in Morocco and Turkey and less than 0.15% in Iran) [WHO 2010], a high-quality pediatric care and microbiological diagnosis and a high incidence of TB (25–30 per 100,000 persons/year in Turkey and Iran, and 98 per 100,000 persons/year in Morocco) [WHO 2010]. This incidence is slightly higher in urban areas such as 40 per 100,000 persons/year in Istanbul and 122 per 100,000 persons/year in Casablanca. In addition, the Arabs and Berbers in Morocco, the Turks in Turkey, and the Persians in Iran form distinctly different ethnic groups. Our study was conducted in accordance with the Helsinki Declaration, with written informed consent obtained from each patient or the patient’s family. The
Table 1. Table indicating the clinical presentations of TB recorded in the fifty patients.

| N | Sex | Age | Origin | BCG | Miliary TB | TB Meningitis | Peripheral TB | Mediastinal TB | TB osteitis | Pulmonary TB | Urinary TB |
|---|-----|-----|--------|-----|------------|----------------|----------------|----------------|-------------|--------------|------------|
| 1 | F   | 0.5 | Morocco| yes | yes        | yes            |                |                |             |              |            |
| 2 | M   | 0.25| Morocco| yes | yes        |                |                |                |             |              |            |
| 3 | M   | 1.5 | Morocco| yes | yes        |                |                |                |             |              |            |
| 4 | F   | 3   | Morocco| yes | yes        |                |                |                |             |              |            |
| 5 | F   | 0.83| Morocco| yes | yes        | yes            | yes            |                |             |              |            |
| 6 | M   | 6   | Morocco| yes | yes        | yes            | yes            |                |             |              |            |
| 7 | F   | 7   | Morocco| yes | yes        |                |                |                |             |              |            |
| 8 | F   | 1.16| Morocco| yes | yes        | yes            | yes            |                |             |              |            |
| 9 | M   | 9   | Morocco| yes | yes        | yes            |                |                |             |              |            |
| 10| M   | 11  | Morocco| yes | yes        |                |                |                |             |              |            |
| 11| F   | 3   | Morocco| yes | yes        |                |                | yes            |             |              |            |
| 12| M   | 10  | Morocco| yes | yes        |                |                | yes            |             |              |            |
| 13| F   | 3   | Morocco| yes | yes        |                |                | yes            |             |              |            |
| 14| F   | 12  | Morocco| yes | yes        |                |                | yes            |             |              |            |
| 15| M   | 13  | Morocco| yes | yes        |                |                | yes            |             |              |            |
| 16| M   | 5   | Morocco| yes | yes        |                |                |                |             |              |            |
| 17| F   | 10  | Morocco| yes | yes        |                |                |                |             |              |            |
| 18| F   | 11  | Morocco| yes | yes        |                |                |                |             |              |            |
| 19| M   | 10  | Morocco| yes | yes        |                |                | yes            |             |              |            |
| 20| F   | 4   | Morocco| yes | yes        |                |                | yes            |             |              |            |
| 21| M   | 4   | Morocco| yes | yes        |                |                | yes            |             |              |            |
| 22| M   | 9   | Morocco| yes | yes        |                |                | yes            |             |              |            |
| 23| F   | 8   | Morocco| yes | yes        | yes            |                |                |             |              |            |
| 24| F   | 4   | Morocco| yes | yes        | yes            |                |                |             |              |            |
| 25| F   | 1.1 | Morocco| yes | yes        | yes            |                |                |             |              |            |
| 26| M   | 2   | Morocco| yes | yes        | yes            | yes            |                |             |              |            |
| 27| M   | 0.5 | Morocco| yes | yes        | yes            | yes            |                |             |              |            |
| 28| M   | 10  | Morocco| yes | yes        | yes            | yes            |                |             |              |            |
| 29| M   | 3.5 | Morocco| yes | yes        | yes            |                |                |             |              |            |
| 30| F   | 2   | Morocco| yes | yes        | yes            |                |                |             |              |            |
| 31| M   | 1.2 | Morocco| yes | yes        | yes            |                |                |             |              |            |
| 32| F   | 6   | Morocco| yes | yes        | yes            |                |                |             |              |            |
| 33| M   | 4   | Morocco| yes | yes        | yes            |                |                |             |              |            |
| 34| F   | 5   | Morocco| yes | yes        | yes            |                |                |             |              |            |
| 35| M   | 9   | Morocco| yes | yes        | yes            | yes            |                |             |              |            |
| 36| F   | 1.8 | Turkey | no  | yes        |                |                |                |             |              |            |
| 37| F   | 0.45| Turkey | yes | yes        |                |                |                |             |              |            |
| 38| F   | 15  | Turkey | yes | yes        |                |                |                |             |              |            |
| 39| M   | 4   | Turkey | no  | yes        |                |                |                |             |              |            |
| 40| M   | 3   | Turkey | no  | yes        |                |                |                |             |              |            |
| 41| F   | 15  | Turkey | yes | yes        | yes            |                |                |             |              |            |
| 42| M   | 14  | Turkey | no  | yes        |                |                |                |             |              |            |
| 43| F   | 0.75| Turkey | no  | yes        | yes            |                |                |             |              |            |
| 44| M   | 6   | Turkey | yes | yes        | yes            |                |                |             |              |            |
| 45| F   | 14  | Turkey | yes | yes        | yes            |                |                |             |              |            |
| 46| F   | 10  | Turkey | no  | yes        | yes            |                |                |             |              |            |
| 47| M   | 0.58| Iran   | yes | yes        | yes            |                |                |             |              |            |
| 48| F   | 12  | Iran   | yes | yes        | yes            |                |                |             |              |            |
| 49| F   | 15  | Iran   | yes | yes        | yes            |                |                |             |              |            |
| 50| F   | 14  | Iran   | yes | yes        | yes            |                |                |             |              |            |

The two patients presenting with IL-12Rβ1 deficiency are in bold. N means number and age is indicated in years.

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