

Bacille Calmette-Guérin Lymphadenitis and Recurrent Oral Candidiasis in an Infant With a New Mutation Leading to Interleukin-12 Receptor β -1 Deficiency

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■ Abstract

Mendelian susceptibility to mycobacterial diseases (MSMD) is a rare syndrome characterized by predisposition to infections caused by weakly virulent mycobacteria, such as those in bacille Calmette-Guérin (BCG) vaccine and environmental mycobacteria. Salmonellosis has been reported in almost half of affected patients. Patients are also vulnerable to *Mycobacterium tuberculosis* infection. Several other infectious diseases may occur, albeit rarely. Mucocutaneous candidiasis is more common. Interleukin-12 receptor β 1 (IL-12R β 1) deficiency is the most frequent genetic cause of MSMD. Here, we describe an infant with a single episode of BCG lymphadenitis who also suffered from recurrent oral candidiasis. Genetic analysis revealed a new homozygous mutation (64+1G>T) in the *IL12RB1* gene that caused complete IL-12R β 1 deficiency. IL-12R β 1 deficiency should be considered in patients with BCG infection, even in those who experience a single episode of BCG lymphadenitis or recurrent mucocutaneous candidiasis. Every attempt should be made to heighten awareness in countries where BCG vaccination is performed.

Key words: BCG lymphadenitis. IL-12R β 1 deficiency. Mendelian susceptibility to mycobacterial diseases. Mucocutaneous candidiasis.

■ Resumen

La susceptibilidad mendeliana a enfermedades micobacterianas (MSMD) es un síndrome poco frecuente caracterizado por la predisposición a infecciones causadas por micobacterias con baja virulencia, como las presentes en la vacuna del bacilo de Calmette-Guérin (BCG) y micobacterias ambientales. En casi la mitad de los pacientes afectados se ha notificado salmonelosis. Los pacientes también son susceptibles a infecciones por *Mycobacterium tuberculosis*. Pueden producirse otras muchas enfermedades infecciosas, aunque con poca frecuencia. La candidiasis mucocutánea es la más frecuente. La deficiencia de receptor de interleucina-12 β 1 (IL-12R β 1) es la causa genética más frecuente de MSMD. En este artículo se describe el caso de un lactante con un único episodio de linfadenitis por BCG que también sufrió candidiasis oral recurrente. Los análisis genéticos revelaron una nueva mutación homocigota (64+1G>T) en el gen *IL12RB1* que causaba una deficiencia de IL-12R β 1. Debe considerarse la deficiencia de IL-12R β 1 en pacientes con infección por BCG, incluso en aquellos que experimentan un único episodio de linfadenitis por BCG o candidiasis mucocutánea recurrente. Deben destinarse todos los esfuerzos posibles para que los países donde se practica la vacunación con BCG estén más concienciados al respecto.

Palabras clave: Linfadenitis por BCG. Deficiencia de IL-12R β 1. Susceptibilidad mendeliana a enfermedades micobacterianas. Candidiasis mucocutánea.

Introduction

Mendelian susceptibility to mycobacterial disease (MSMD) (OMIM 209,950) is a rare congenital syndrome conferring predisposition to infections caused by weakly virulent mycobacteria (eg, bacille Calmette-Guérin [BCG] vaccines and nontuberculous environmental mycobacteria) in otherwise healthy individuals [1]. Patients are also susceptible to *Mycobacterium tuberculosis* infection [2]. Severe disease caused by nontyphoidal *Salmonella* serovars is also observed in nearly half of cases [3]. Study of patients with MSMD has revealed the key role of the interleukin (IL) 12/interferon (IFN) γ axis in immunity to mycobacteria in humans [4]. Disease is caused by 5 autosomal genes—*IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, and *IL12RB1*—and an X-linked gene—*NEMO*—and allelic heterogeneity accounts for the existence of 13 defined disorders, all of which result in impaired IFN- γ -mediated immunity [2,3]. IL-12R β 1 deficiency is the most frequent known genetic etiology of MSMD and is found in about 40% of patients with a known genetic defect [3]. We present the case of an infant with BCG lymphadenitis and recurrent oral candidiasis due to complete IL-12R β 1 deficiency caused by a new homozygous mutation (64+1G>T) in the *IL12RB1* gene.

Case Description

A 7-month-old boy presented with a 2 to 3-week history of left axillary lymphadenopathy. His past medical history was unremarkable with the exception of recurrent oral candidiasis. His parents were first-degree relatives. His family history was negative for genetic disorders and tuberculosis. He was vaccinated with BCG at the age of 3 months. On admission, routine physical examination was unremarkable, with the exception of enlarged lymph nodes (5 cm in diameter) in the left axillary region. A BCG vaccine scar was visible on his left shoulder.

The tuberculin skin test was positive (15 \times 15 mm). Thoracic computed tomography and abdominal ultrasonography were normal. Histopathology of the lymph node biopsy specimen revealed a widespread lymphohistiocytic infiltration and a few small granulomas with no caseous necrosis. Ziehl-Neelsen staining for acid-fast bacilli revealed the presence of multibacillary histiocytes. *M tuberculosis* complex polymerase

chain reaction and culture were negative. The results of routine immunological evaluation including serum immunoglobulin (Ig) G, IgA, IgM, IgE, peripheral blood lymphocyte subsets, and phagocyte respiratory burst assay were normal. Whole blood samples were activated in vitro with BCG, BCG plus IL-12, and BCG plus IFN- γ , as described previously [4]. IL12p40 production was increased after stimulation with BCG plus IFN- γ (Figure, A). In contrast, IFN- γ production to BCG plus IL-12 was blunted (Figure, B). Flow cytometry revealed IL-12R β 1 expression on activated T cells to be negative (data not shown). DNA sequencing of the *IL12RB1* gene revealed a new homozygous mutation (64+1G>T). The patient's parents and brother were heterozygous for this mutation and healthy. Therefore, following the genetic analysis, the healthy brother was vaccinated with BCG at the age of 3 months.

The patient was treated with isoniazid, rifampicin, and ethambutol for the first 2 months and with isoniazid and rifampicin for a further 6 months. Drainage of purulent material from the surgical wound was discontinued at the fourth month of treatment. Eight months after the end of treatment, the patient was doing well, with the exception of oral candidiasis.

Discussion

We report the case of an infant with BCG lymphadenitis and recurrent oral candidiasis due to complete IL-12R β 1 deficiency caused by a new homozygous mutation (64+1G>T) in the *IL12RB1* gene.

IL-12-dependent IFN- γ secretion is essential for the control of intracellular pathogens, especially mycobacteria. *IL12RB1* encodes the first chain of the IL-12 (IL-12R β 1) and IL-23 receptors [3]. IL-12 binds to its receptors (IL-12R β 1 and IL-12R β 2) on T lymphocytes and natural killer cells and is a potent inducer of IFN- γ . Conversely, binding of IL-23 to its receptors (IL-12R β 1 and IL-23R) induces IL-17 [1]. IFN- γ binds to the IFN- γ receptor on macrophages and dendritic cells and leads to phosphorylation of signal transducer and activator of transcription type 1 (STAT-1). Defects in any pathway of the IL-12/IFN- γ axis cause susceptibility to mycobacteria or other infectious pathogens in humans [5-7]. IL-12R β 1 deficiency is the most common form of MSMD: it has been demonstrated in 141 affected patients from 30 countries, and 54 mutant alleles have been identified [7]. IL-12R β 1 deficiency, which

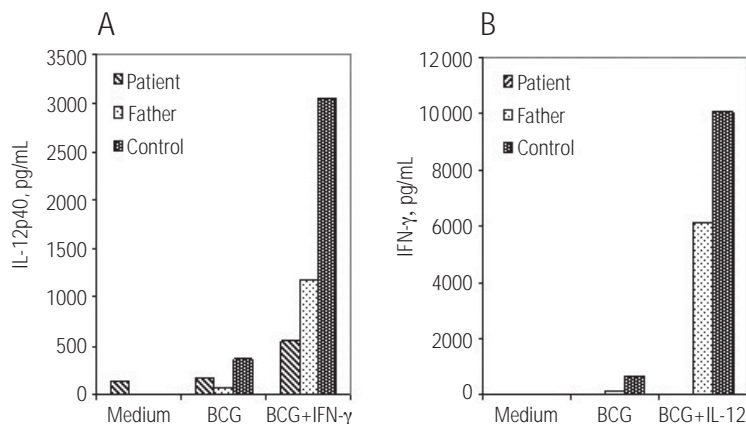


Figure. Impaired IFN- γ production. A, Whole blood samples were stimulated with BCG and BCG plus IFN- γ . Secreted IL12p40 was measured by enzyme-linked immunosorbent assay. B, Whole blood samples were stimulated with BCG and BCG plus IL-12. Secreted IFN- γ was measured by enzyme-linked immunosorbent assay. BCG indicates bacille Calmette-Guérin; IFN, interferon; IL, interleukin.

is a relatively common disease in Turkey, is not due to a single mutation [6,8-11].

The clinical features of patients with MSMD are not restricted to predisposition to mycobacterial disease. Salmonellosis has been reported in almost half of affected patients, and a significant number present with isolated salmonellosis [1,7,11]. de Beaucoudrey et al [7] found that 84 out of the 108 patients with IL-12R β 1 deficiency vaccinated with BCG developed BCG disease, which presented as a localized infection in 17 patients. Disseminated tuberculosis has been reported in several patients [7,10]. Recurrent oral candidiasis was also observed in our patient. de Beaucoudrey et al observed mucocutaneous candidiasis in 32 (24%) of 132 symptomatic patients. The importance of *Candida* infections in IL-12R β 1 deficient patients is now being analyzed by Rodríguez-Gallego et al (manuscript in preparation) [12]. Despite the high frequency of mucocutaneous candidiasis, disseminated fungal infections such as histoplasmosis and paracoccidioidomycosis have been diagnosed in a single patient [7,13]. Other infectious diseases (toxoplasmosis, nocardiosis, and leishmaniasis) have occurred in a single patient, but *Klebsiella* infection was also reported in 5 patients [7,14]. In addition, IL-12R β 1 deficiency, and other disorders of the IL-12/IFN- γ axis might even predispose to cancer [15,16]. Therefore, MSMD, and particularly IL-12R β 1 deficiency, may be more heterogeneous than previously thought.

In most cases, patients are treated conservatively with a prolonged course of antibiotics, and additional recombinant IFN- γ treatment has been shown to be effective in those who do not respond well [1,9]. Our patient responded well to antituberculosis treatment and did not require IFN- γ therapy. Abdominal surgery has often been required to remove splenic and mesenteric lesions, which respond poorly to antibiotics and IFN- γ [3]. Mycobacterial recurrence was observed in 15% of patients with mutations in *IL12B* and *IL12RB1*, and this was probably due to reactivation of the initial mycobacterial agent upon premature treatment cessation in most cases [17].

The mortality rate among symptomatic patients was 32%, which is somewhat higher than previously reported (15%) and with a less favorable outcome than previously thought [2,7].

In conclusion, IL-12R β 1 deficiency should be considered in patients with BCG infection, even those who experience a single episode of BCG lymphadenitis. In addition, patients with recurrent mucocutaneous candidiasis should also be evaluated for IL-12R β 1 deficiency. Every attempt should be made to heighten awareness in countries where BCG vaccination is performed.

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