Mendelian Susceptibility to Mycobacterial Disease: Retrospective Clinical and Genetic Study in Mexico

ANA KAREN PEÑAFIEL VICUÑA
MARCO Yamazaki-Nakashimada
Ximena León-Lara
ELIZABETH MENDIETA FLORES
MARÍA ENRIQUETA NUÑEZ NUÑEZ
JUAN CARLOS LONA-REYES
LETICIA HERNADEZ NIETO
MARÍA GUADALUPE RAMÍREZ VÀZQUEZ
JOEL BARROSO SANTOS
ALVARO LÓPEZ IÑIGUEZ
YOLANDA GONZÁLEZ
MARTHA TORRES
JOSÉ LUIS LEZANA FERNANDEZ
CARLA M Román-Montes
EDGAR ALEJANDRO MEDINA-TORRES
EDITH GONZÁLEZ SERRANO
JUAN CARLOS BUSTAMANTE OGANDO
SAUL LUGO REYES
OSCAR ZAVALETA MARTÍNEZ
AIDÉ TAMARA SATINES BOONE
EDNA VENEGAS MONTOYA
NANCY EVELYN AGUILAR GOMEZ
CAMILLE SOUDEÉ
EMMANUELLE JOUANGUY
ANNE PUEL
Stéphanie Boisson-Dupuis
SIFREDO PEDRAZA SÁNCHEZ
JEAN LAURENT CASANOVA
FRANCISCO ESPINOSA ROSALES
SARA Espinosa- Padilla
Jacinta Bustamante
Lizbeth Blancas-Galicia (blancas.lizbeth@gmail.com)
National Institute of Pediatrics https://orcid.org/0000-0002-3861-8864

Research Article

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Abstract

BACKGROUND. Mendelian susceptibility to mycobacterial disease (MSMD) is a rare genetic disorder with impaired immunity against intracellular pathogens, such as mycobacteria, attenuated *Mycobacterium bovis*-Bacillus Calmette-Guérin (BCG) vaccine strains, and environmental mycobacteria, in otherwise healthy individuals. In Mexico, the estimated incidence of tuberculosis in 2019 was 23 cases/100,000 people. BCG vaccination is mandatory in Mexico.

PURPOSE. To review the clinical, immunological, and genetic characteristics of MSMD patients followed in ten hospitals across Mexico.

METHODS. This retrospective study describes the clinical, immunological, and genetic characteristics of patients in Mexico diagnosed with MSMD from 2006 to 2021.

RESULTS. Twenty-two patients from 17 kindreds were diagnosed with MSMD. Fourteen were male (64%) and eight were female. After BCG vaccination, 12 patients (70%) developed BCG infections. Six (22%) developed infections caused by *Salmonella*, and 11 (50%) developed infections caused by fungi, particularly *Histoplasma*. Thirteen different pathogenic variants were identified in *IL12RB1* (*n* = 13), *IFNGR1* (*n* = 3), and *IFNGR2* (*n* = 1). Seven of the 22 patients died; the main cause was disseminated BCG infection.

CONCLUSION. Interleukin-12Rβ1 deficiency was the main cause of MSMD in the Mexican cohort. The main etiologic agent responsible for morbidity and mortality was BCG.

Introduction

Tuberculosis (TB) is a public health problem in Mexico, with an estimated 23 cases/100,000 people in 2019 [1]. Vaccination with attenuated *Mycobacterium bovis*-Bacillus Calmette-Guérin (BCG) is universally administered to all Mexican babies soon after birth to protect them against severe forms of TB. Two different strains of this vaccine have been used in Mexico. The Danish-1331 strain was administered until 2005, and the Tokyo-172 strain has been administered since 2005 [1]. Adverse events following BCG immunization include manifestation of Mendelian susceptibility to mycobacterial disease (MSMD). MSMD is a rare group of inborn errors of immunity (IEI) characterized by selective susceptibility to clinical diseases caused by BCG vaccines and environmental mycobacteria in otherwise healthy patients, and the absence of overt immunological abnormalities in routine evaluations [2]. Disorders of 19 genes (*IFNG*, *IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, *IL12RB1*, *IL12RB2*, *IL23R*, *RORC*, *TBX21*, *IRF8*, *SPPL2A*, *ISG15*, *USP18*, *TYK2*, *JAK1*, *ZNFX1*, *NEMO*, and *CYBB*) have been identified. These define up to 34 genetic disorders reflecting their high levels of allelic heterogeneity [2]. The pathogenesis of MSMD mostly depends on gene mutations that lead to either insufficient production or inadequate response to interferon-gamma (IFN-γ), which is mandatory for an efficient immune response to mycobacterial species in humans [3]. The severity and penetrance of MSMD are inversely correlated with residual levels of IFN-γ activity [4]. Biallelic mutations of *IL12RB1* are the most frequent genetic cause; the mutations are present in approximately 60% of patients diagnosed with MSMD [4]. Although MSMD patients in Mexico have been reported frequently in case reports [5–15], the situation of this IEI in different states is unknown [16].This paper reports the genetic, immunological, and clinical features of the first cohort of patients from ten hospitals in four states in Mexico.

Materials And Methods

Patients

Medical records of patients from ten hospitals in Mexico with a confirmed genetic diagnosis of MSMD due to recurrent and severe infections by intracellular bacteria and fungi from 2006 to 2021 were retrospectively reviewed. This study was approved by the ethics committee of the National Institute of Pediatrics, Mexico. All centers were contacted via e-mail and requested to provide patient details using a questionnaire. Demographic characteristics, family history, clinical manifestations, radiological imaging information, treatment, and follow-up data were obtained. Other information collected included routine immunological and microbiological records, laboratory functional evaluation of IFN-γ immunity, and genetic results. Clinical criteria for localized or regional (BCG-itis) and disseminated (BCG-osis) infections have been defined previously [17, 18]. The diagnosis of mycobacterial infection was confirmed by culture in addition to PCR, histopathology, and acid-fast bacilli (AFB) findings.

Immunological analyses

Routine immunological laboratory tests, including lymphocyte subsets, NADPH oxidase activity in neutrophils by dihydrorhodamine (DHR) flow cytometric assay, nitroblue tetrazolium (NBT) assay, and detection of serum immunoglobulins (Ig) G, A, and M, were performed as previously published in a Mexican cohort of patients with chronic granulomatous disease (CGD) [17]. The expression of CD212, IFN-γR1, and IFN-γR2 was assessed using flow cytometry. The production of IFN-γ and IL-12 in whole blood after stimulation with medium alone, BCG, BCG plus IFN-γ, or BCG plus IL-12 was assessed in some patients using ELISA as previously described [7].

Genetic analyses

Genetic diagnosis was made by Sanger sequencing (P1-P2, P5-P7, P12-P14, P17-22), next-generation sequencing panel (P10-P11, P16), or whole-exome sequencing (WES; P8-P9, P15) [5–15]. Deleterious variants identified by WES were confirmed using Sanger sequencing. Familial segregation was performed when genomic DNA was obtained from relatives. PolyPhen-2, sorting intolerant from tolerant, and combined annotation-dependent depletion scores were used to predict the pathogenic effects of unreported variants. The Statistical Package for Social Science version 25.0 (SPSS Inc., Chicago, IL,

USA) was used for data analyses. The results are presented as medians for continuous variables and percentages for nominal variables. Survival was analyzed using the Kaplan–Meier method.

Results

Demographic findings in 17 kindreds of MSMD

Between 2006 and 2021, 22 patients (including 17 probands) from 17 unrelated kindreds (identified with capital letters A to P) were referred from ten different health service institutions located in four states of Mexico. The country has eight different regions [19]and the distribution of MSMD patients according to the regions of Mexico was as follows: East, $n = 6$; West, $n = 1$; North Center, $n = 3$; South Center, $n = 10$; and Southwest, $n = 2$ (Tables 1 and 2). Of the 22 patients, 14 (64%) were males and eight (36%) were females (Tables 1and 2). Consanguinity was positive in two kindreds. The median age of the first manifestation was 6 months (range: 4 months to 22 years), and the median age of the clinical MSMD diagnosis was 4.5 years (range: 3 months to 33 years). The median age of definitive MSMD genetic diagnosis was 8.3 years (range 5 months to 34 years), except for two patients, in whom the genetic diagnosis was made 4 months posthumously. The median age of the living patients at the time of the study was 14 years (range, 4–51 years).

Table 1
Genetic, demographic, and infectious phenotypes in patients with impaired production of IFN-g (IL-12Rb1 deficiency)

	P1 (Kindred A)	P2 (Kindred B)	P5 (Kindred B)	P6 (Kindred C)	P7 (Kindred D)	P8 (Kindred E)	P9 (Kindred F)	P10 (Kindred G)
General Data								
Gender	M	F	F	M	M	M	F	F
Place of origin	Oaxaca	State of Mexico	State of Mexico	State of Mexico	Veracruz	Jalisco	State of Mexico	Mexico City
Region of Mexico	Southwest	South Center	South Center	South Center	East	West	South Center	South Center
First manifestation of infection disease	Right axillary adenitis post-BCG vaccine	Right axillary adenitis post-BCG vaccine	Oral candidiasis	Right axillary adenitis post-BCG vaccine	Right axillary adenitis post-BCG vaccine	Right axillary adenitis post-BCG vaccine	Right axillary adenitis post-BCG vaccine	Right axillary adenitis post-BCG vaccine
Mutated gene	*IL12RB1*							
Pathogenic variant coding DNA level / protein level	p.S220C/ p.S220C	c.1791 + 2T > G/ c.1791 + 2 T > G	c.1791 + 2T > G/ c.1791 + 2T > G	c.1791 + 2T > G/ c.1791 + 2T > G	p.R486* /p.R486*	p.R173W/ p.Y134*	c.1791 + 2T > G/ c.1791 + 2T > G	R212Q/ p.S584P*
Detection Methods	Sanger sequencing	Sanger sequencing	Sanger sequencing	Sanger sequencing	Sanger sequencing	whole exome-sequencing	whole exome-sequencing	Gen panel sequencing
Inheritance pattern	AR	AR	AR	AR	AR	AR	AR	AR
BCG vaccine & infection								
Age of BCG vaccine administration	5 days	1 day	–	6 months	1 day	6 days	5 days	5 days
Age of first BCG infection event	4 months	6 months	–	6 months	6 months	13 months	6 months	6 months
BCG infection	BCG-osis	BCG-osis	–	BCG-osis	BCG-osis	BCG-osis	BCG-osis	BCG-osis
Localization of BCG infection	Lung, liver, spleen, skin, soft tissue and, cervical, inguinal, mediastinal, and mesenteric lymph nodes	Lung, liver, spleen, and, cervical, axillary, mediastinal, and mesenteric lymph nodes	–	Lung, skin and, cervical, axillary, and mesenteric lymph nodes	Liver, spleen, spinal cord, skin, soft tissue and, cervical, axillary, mediastinal and mesenteric lymph nodes	Lung, skin, soft tissue, cervical and axillary lymph nodes	Lung, skin, soft tissue, cervical, mediastinal, mesenteric and inguinal lymph nodes	Axillary and mesenteric lymph nodes
BCG method detection	Culture	PCR	–	Culture	Culture	Culture	Culture	Culture
Number of mycobacterial regimens (Treatment)	3	5	–	2	4	3	3	2 and completing the third
Other bacterial infections								
Etiology	–	–	– –	–	Non typhoidal salmonellosis *K. pneumoniae*	*M. abscessus*	–	–
Isolation site	–	–	– –	–	Bone marrow Blood	Cutaneous abscess	–	–
Event number	–	–	–	–	1	1	–	–

	P1 (Kindred A)	P2 (Kindred B)	P5 (Kindred B)	P6 (Kindred C)	P7 (Kindred D)	P8 (Kindred E)	P9 (Kindred F)	P10 (Kindred G)
Henoch-Schonlein purpura	–	–	–	–	–	–	Yes, one event	–
Viral infections								
Etiology	–	–	–	–	–	–	Varicella virus syncytial virus influenza A (H1N1)pdm09 SARS-CoV-2	–
Manifestations	–	–	–	–	–	–	Mucocutaneous lesions and pneumonia	–
Fungal infections								
Histoplasma infection	No	No	–	No	No	No	No	No
Age and localization of first event	–	–	–	–	–	–	–	–
Candida infection	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Localization	Oral mucosa	Oral mucosa, gastric juice, and urinary tract	Oral mucosa	Oral mucosa	Urinary tract, cerebrospinal fluid	–	Oral mucosa	Oral mucosa
Treatment								
Recombinant human IFN-g	Yes	Yes	–	Yes	Yes	–	–	Yes
Surgical procedure	Cholecystectomy (bile duct obstruction), cervical Lymph node biopsy	Cervical lymph node biopsy	–	Exploratory laparotomy (abdominal pain) and cervical lymph node biopsy	Lymph node biopsy and dorsolumbar drainage abscesses	Multiple lymph node resections	Arthrotomy (Septic arthritis), Lymph node axillary abscess and thoracic fistula drainages	Intestinal anastomosis (Intestinal perforation)
Follow-up								
Death	Yes	Yes	No	Yes	Yes	Yes	No	No
Age of death	4 years 9 months	3 years 5 months	–	16 years 7 months	4 years 6 months	3 years 11 months	–	–
Cause of death	Multiorgan failure secondary to refractory BCG infection	Multiorgan failure secondary to refractory BCG infection	–	Multiorgan failure secondary to refractory BCG infection	Multiorgan failure secondary to refractory BCG infection	Multiorgan failure secondary to refractory BCG infection	–	–

Table 2. Genetic, demographic, and infectious phenotypes in patients with impaired response to IFN-g (IFN-gR1 or IFN-gR2 deficiency).

	P17 (Kindred N)	P20 (Kindred O)	P21 (Kindred P)	P22 (Kindred Q)
General data				
Gender	F	M	M	M
Place of origin	Guanajuato	Veracruz	Veracruz	Estado de México
Region of Mexico	North Center	East	East	South Center
First manifestation of infectious disease	Right axillary adenitis post-BCG vaccine	Right axillary adenitis post-BCG vaccine	Right axillary adenitis post-BCG vaccine	Right axillary adenitis post-BCG vaccine
Age of onset disease	2 months	1 year	2 years	6 months
Gen	*IFNGR1*	*IFNGR1*	*IFNGR1*	*IFNGR2*
Pathogenic variant coding DNA level / protein level	c.201-2A>G/ c.201-2A>G	c.819_822del/WT	c.805delT/WT	c.371C>T/c.371C>T
Detection Methods	Sanger	Sanger	Sanger	Sanger
Inheritance pattern	AR	AD	AD	AD
BCG vaccine & infection				
Age of BCG vaccine administration	1 month	1 month	2 years	1 month
Age of first BCG infection event	2 months	–	2 years 15 days	6 months
BCG infection	BCG-osis	–	BCG-osis	BCG-osis
Localization of BCG infection	Multifocal osteomyelitis, skin, lungs and axillary, inguinal and popliteal lymph nodes	–	Lungs, liver, multifocal osteomyelitis and axillary, cervical, mediastinal, and inguinal lymph nodes.	Supraclavicular lymph nodes
BCG method detection	Culture	–	Culture	ND
Other bacterial infections				
Etiology	*Salmonella* spp.	Mycobacterial infection	*M. colombiense* *M. avium* *P. aeruginosa*	M. *avium*
Isolation site	Septic shock	Multifocal osteomyelitis, spleen, liver, lymph nodes	Lung, spleen, lymph nodes, bones (vertebrae) intestine, lung Blood	Skin, lung
Viral infections				
Etiology	–	Epstein-Baar virus	Herpes Zoster	–
Localization	–	Systemic	Right upper extremity	–
Fungal infections				
Etiology	*Candida albicans*	–	*Candida parapsilosis*	–
Localization	Urinary tract	–	Blood & urine	–
Treatment				

Recombinant human IFN-g	No	No	No	Yes
Surgical procedure	Lymph node biopsy	bone biopsy	Exploratory laparotomy, tracheostomy, liver, and bone biopsy	ventriculo-peritoneal shunt (tuberculoma)
Follow-up				
Death	Yes	Yes	Non	Non
Age of death (years)	4 years	7 years	–	–
Cause of death	Multiorgan failure secondary to refractory mycobacteria infection	Multiorgan failure secondary to refractory disseminated mycobacteria infection	–	–

(P) proband; (M) male; (F) Female; (NAR) no adverse reaction; (PCR); Polymerase chain reaction; (AR) autosomic recessive; (AD) autosomic dominant.

Genetic findings in 17 MSMD kindreds

The pathogenic variants of MSMD genes were detected in the 17 kindreds using Sanger sequencing ($n = 10$), copy number variants $n = 1$ target gene sequencing panel ($n = 3$), and WES ($n = 3$) [5–15]. The affected genes were *IL12RB1* in 13 kindreds (76%), *IFNGR1* in three (18%), and *IFNGR2* in one (6%). The pathogenic variants identified in the *IL12RB1* gene are described as coding DNA sequences and protein levels: c.655A > T (p.S220C), c.402C > A (p.Y134*), c.517C > T (p.R173W), c.635G > A (p.R212Q), c.635A > T (p.R212Q), c.1456C > T (p.R486*), c.1561C > T (p.R521*), c.1750C > T (p.S584P*), c.1791 + 2 T > G (p.A573Lfs*22), and deletion of exon 8 (designated △8). All variants have been previously reported [20, 21] except for c.1750T > C. Ten kindreds had homozygous pathogenic variants and three heterozygous compound states (Table 1). Three pathogenic variants were identified in the *IFNGR1* gene: c.201-1G > T, c.819_822del (p.N274Hfs*2), and c.805delT (p.Y269Ifs*8). The hereditary patterns were autosomal recessive (AR) in kindred N, conferring a complete deficiency. Dominant inheritance was observed in kindreds O and P. Finally, a homozygous pathogenic variant in *IFNGR2* was found; c.371C > T (p.S124F) in kindred Q was responsible for an AR partial (RP) disease (Table 2). Familial segregation was performed when biological material was available. Parents of B, C, E, G, H, J, I, L, and M AR-kindreds could be studied. All were detected as heterozygous. In this cohort, mutations were identified in three genes (*IL12RB1*, *IFNGR1*, and *IFNGR2*).

Biological findings in MSMD patients

In patients with mycobacterial infection, it is necessary to rule out other IEI before conducting studies for MSMD [2]. Accordingly, we assessed the samples of 14 patients using the DHR or nitroblue tetrazolium (NBT) assays to measure the oxidative burst. All results were in normal range (Supplementary Table 1). IgG, IgM, or IgA were quantified in 13 patients. The values were higher than those of the reference. IgG was measured in 11 patients (50%), IgM in six (27%), and IgA in 10 (45%) (Supplementary Table 1). Global lymphopenia was detected by flow cytometry in five patients, but this information was obtained during uncontrolled acute infections other three patients had normal values (Supplementary Table 1). In 11 (50%) IL-12Rβ1 deficiency probands (P1, P2, P5, P6, P9-P14, P16), the expression of IL-12Rβ1 in phytohemagglutinin (PHA)-activated T cells was measured. The expression was abolished in comparison to healthy controls, including P10, who had a novel mutation [5, 6, 10, 13, 15]. Sixteen patients from 13 kindreds had an impaired production of IFN-γ due to AR IL-12Rβ1 deficiency. The AR IFN-γR1 deficient patient (P17) had no expression of IFNγR1 in monocytes compared to that in the healthy controls. In AD IFN-γR1 deficient P21, IFN-γR1 expression on monocytes was higher than that in healthy controls. In the AR IFN-γR2 deficient P22 cells, the expression of IFN-γR2 on Epstein-Barr transformed B lymphocytes (EBV-B cells) was diminished compared to that in healthy controls [11].

Mycobacterial infections in patients with impaired IFN-γ production Fourteen (87%) patients with IL-12Rβ1 deficiency were symptomatic, while the rest were asymptomatic (P3 and P4). All patients were vaccinated with BCG, except for P3-P5. Administration was intradermal, and the site was the upper right arm. Eleven (85%) cases (P1, P2, P6-P9, P11-P13, P15, and P16) received the Tokyo-172 strain and the two remaining (P10, P14) received the Danish-1331 strain. Nine vaccinated patients developed BCG infection. The median age of the first BCG event was 6 months (range: 4–13 months). The median time between vaccine administration and appearance of BCG infection was 5 months. BCG infection was present on one side for P12 (11%), with a regional infection (BCG-itis) that remitted spontaneously. Infection on the other side was observed in eight patients. In six patients (P1, P2, P7-P9, P11) the infection evolved from BCG-itis to BCG-osis. In the remaining two patients (P6, P10), regional BCG-itis resolved in the first year of life. P6 and P10 had recurrent BCG-osis at 10 and 15 years of age, respectively (Table 1). The first clinical manifestation of the disease was adenitis in 12 patients (86%). This was consistent with the description of adenitis as the most frequent initial manifestation of IL-12Rβ1 deficiency [22]. The localization of adenitis was axillary adenitis ($n = 9$; 56%), bilateral cervical adenitis ($n = 1$; 6%), bilateral cervical purulent adenitis ($n = 1$; 6%), bilateral cervical, axillary, and supraclavicular adenitis ($n = 1$;6%) (Fig. 3). BCG-osis was present in eight patients; the most frequently affected organs were the lung ($n = 6$), skin soft tissue ($n = 4$), liver ($n = 3$), spleen ($n = 3$), intestine ($n = 1$), kidney ($n = 1$), brain ($n = 1$), and spinal cord ($n = 1$) (Fig. 4-A). The affected lymph nodes in patients with BCG-osis were cervical ($n = 7$), axillary ($n = 6$), mesenteric ($n = 6$), mediastinal ($n = 4$), and inguinal ($n = 2$) lymph nodes (Fig. 4-B). P1 developed portal hypertension and chronic obstructive hepatopathy due to mesenteric adenomegaly compressing the portal vein (Fig. 2-C). The culture of *M. bovis-BCG* was positive in all patients with BCG-osis. Five patients with BCG-osis (P1, P2, and P6-P8) were refractory to antimycobacterial treatment and died. P9 relapsed after completing the first anti-tuberculous regimen; she is currently completing the second regimen as an outpatient, which has

been administered for one year with the plan to complete 2 years. P10 received two antimycobacterial regimens, with relapse occurring after completing each. The patient received a third regimen for 2 years with successful recovery. Finally, P11 was the last patient diagnosed in the cohort. He remains hospitalized and has undergone anti-TB treatment (Table 1). P8 also had *M. abscessus* isolated from the purulent secretion of an abscess, which was a coinfection with BCG (Table 1 and Fig. 2).

BCG infections in patients with impaired response to IFN-γ

Of the 22 MSMD patients, six had diseases with an impaired response to IFN-γ. An AR complete IFNγR1 deficiency [8] was identified in P17, P18, and P19, AD IFNγR1 deficiency in P20 and P21, and AR partial IFN-γR2 deficiency in P22 [11]. P17 had two cousins (P18 and P19) with identical AR complete IFNγR1 deficiency. The cousins were born and treated in the United States, where BCG vaccination is not mandatory. Among the four probands (P17-P22), the first clinical manifestations were adenitis in three (75%) and multiple osteomyelitis in one (25%). All these patients received intradermal BCG vaccine in the upper right arm, P17 received the Danish-1331 strain, and the rest received the Tokyo-172 strain. The vaccination age was prior to 2 months of age P17, P20, and P22, and at 2 years of age for P21. P17, P21, and P22 showed adverse reactions to BCG vaccine. P17 and P21 developed BCG-osis one and three months after vaccination, respectively. P21 experienced two BCG-osis episodes at one and 17 years after vaccination. P22 had BCG-itis 2 months after vaccination. According to the method of diagnosis, in P17 *M. bovis*-BCG was isolated from a bronchioalveolar lavage. For P21 the diagnosis for the first event was based on clinical and radiological findings, and the second was based on positive culture for *M. bovis*-BCG. For P22, diagnosis of BCG-itis was based on clinical findings and resolved following a 6-month isoniazid treatment. In terms of localization and evolution, P17 was affected in the bones, skin, and lungs. This patient was not cured because of inadequate adherence to the TB treatment. For P21, the first infection affected multiple lymph nodes. Improvement was observed upon completing a 9-month regimen of isoniazid, pyrazinamide, and rifampicin. This patient's second event involved the lungs, liver, spleen, lymph nodes, and bones. For P22, BCG-itis was resolved by a 6-month isoniazid treatment.

Other mycobacterial infections in patients with impaired response to IFN-γ

Patients with an impaired response to IFN-γ are more severely affected and can develop other mycobacterial infections distinct from BCG [23]. P20 had two different episodes of mycobacterial infection documented with histopathological findings. At 4 years of age, he developed a disseminated infection affecting the liver, spleen, multiple bones, and lymph nodes. An intensive anti-TB regimen was administered successfully for 3 years. The patient's second episode was at 7 years of age, affecting multiple bones and lungs, chest wall, and soft tissue. The infection resulted in multiorgan dysfunction and death [14].

At 9 years of age, P21 had *M. tuberculosis* complex disseminated infection (vertebrae, lymph nodes, and liver) detected by PCR. The infection was ameliorated with an anti-mycobacterial regime. However, at 26 years of age, he developed disseminated *M. colombiense* infectious disease (lung, spleen, multiple lymph nodes, vertebrae), with a poor response to the anti-TB regimen was poor. At 28 years of age, he developed a disseminated *M. avium* infection (intestine, spleen, lung, vertebrae, and lymph nodes). He is currently being treated using clarithromycin, rifampicin, and ethambutol.

At 2 years of age, P22 had clinical, histological, and radiological lymphatic and pulmonary TB. He improved upon treatment with isoniazid, rifampicin, and pyrazinamide for 18 months. At nine years of age, he developed a peritoneal and dermal mycobacterial infection (erythema nodosum). A skin biopsy revealed AFB. These bacteria were ameliorated with a 9-month treatment with isoniazid, rifampicin, and pyrazinamide. One year later, he had cerebral TB confirmed by a positive *M. tuberculosis* complex PCR. Treatment involved isoniazid, rifampicin, pyrazinamide, and ethambutol. At 18 years of age, he had lung and skin disseminated mycobacterial infection. The culture was positive for *M. avium*. The treatment was a one year regimen of isoniazid, rifampicin, ethambutol, and clarithromycin. Relapse at 23 years of age may have been due to poor adherence to treatment (Table 1).

Salmonella **and other bacterial infections in 22 MSMD patients**

Approximately half of the MSMD patients, particularly those with IL-12Rβ1 or IL-12p40 deficiency, are also particularly susceptible to non-typhoidal *Salmonella* with a broad spectrum of clinical diseases, ranging from gastroenteritis to septicemia and disseminated infection [4, 7, 24]. In this cohort, six patients (22%) had *Salmonella* infection, including five with complete AR IL-12Rβ1[25] deficiency (P7, P9, P12, P13, P14) and one with complete AR IFNγR1 deficiency (P17) (Tables 1 and 2).

P7 had one isolate of non-typhoidal *Salmonella* in bone marrow culture. P9 had Henoch-Schönlein purpura diagnosed at 3 years of age and arthralgias and reddish-purple spots in the abdomen and lower extremities. Microorganism isolation was negative, but the patient responded well to antibiotic treatment.

P12 had 30 episodes of septicemia caused by *Salmonella* group B, *S. enterica* serotype *Typhi*, *S. choleraesius*, or *S. enteritidis* (blood culture isolations), including recurrent Henoch-Schönlein purpura, arthritis, and renal biopsy showing IgA nephritis [12]. Considering that the gallbladder was the bacterial reservoir in IL-12Rβ1 deficiency, cholecystectomy was performed. This did not improve the patient's condition. However, relapse has ceased with monthly subcutaneous gammaglobulin.

P13 had five *Salmonella enterica* group D infections from 18 months to 5 years of age. The infections were diagnosed using blood, stool, and brain abscess secretion cultures (Fig. 2-D). At 2 years of age, the patient developed Henoch-Schönlein purpura.

Infection developed in P14 at one year of age. The infection featured gigantic, fistulized, and purulent cervical adenitis secondary to *Salmonella* (Fig. 2-A). Recurrence occurred despite treatment with antibiotics. He was ultimately treated successfully with specific dialyzable leukocyte extract at 6 months of age.

P17 experienced septic shock due to *Salmonella* spp. and required intensive care therapy. P7, P11, and P16 first had a mycobacterial infection. For each of these patients, a second bacterium was isolated at the same site of infection (*K. pneumoniae* for P7, *Acinetobacter ursingii* and *Stenotrophomonas maltophilia* for P11, and *Pseudomonas aeruginosa* for P16).

Fungal infectious disease in Mexican patients with MSMD

MSMD patients are also susceptible to fungal infections, such as *Candida*, *Paracoccidioidomyces*, and *Histoplasma* [7, 23–25]. Eleven (50%) of 22 MSMD patients had at least one fungal infection. Twelve had IL-12Rβ1 deficiency, and one had IFNγR1 deficiency patients (Tables 1 and 2). Candidiasis was present in eight patients (31%; P1, P2, P5, P6, P7, P9, P10, and P11). According to the site of infection, mucocutaneous candidiasis was present in nine (40%) patients, urinary tract in three (14%), gastric juice in three (14%), and central nervous system in one (4.5%). Furthermore, three (14%) patients with complete AR IL-12Rβ1 deficiency (P12, P15, and P16) from regions with a humid subtropical climate developed disseminated infections caused by *Histoplasma* spp., affecting lymph nodes in particular. P12 had two events of histoplasmosis. The first was identified in a lymph node biopsy at 3 years of age. The second was in the bone marrow at 4 years of age. Both infections remitted with antifungal treatment.

Infection first occurred in P15 at 20 years of age. The *H. capsulatum* infection involved the lung, liver, spleen, and multiple lymph nodes. Remission was achieved with amphotericin. The patients continued with itraconazole antifungal prophylaxis to the present day without fungal relapse or other mycobacterial infection.

At 6 years of age, P16 experienced his first disseminated histoplasmosis infection in the lymph nodes, liver, and spleen. The fungal infection remitted with amphotericin treatment. Four years later, the patient developed a second disseminated histoplasmosis affecting the meninges, lymph nodes, liver, spleen, and bone marrow. A splenectomy was necessary due to multiple fungal abscesses. The infection remitted with amphotericin along with histoplasmosis. The patient developed hemophagocytic syndrome and demyelinating axonal neuropathy of the left limb. Current treatment is prophylaxis with itraconazole.

Viral infectious disease in MSMD patients

Patients with MSMD do not have a selective predisposition to severe viral infections [23, 25–27]. In this cohort, five (23%) patients had a viral infection (P9, P11, P20, P21, and P22) (Tables 1 and 2). Interestingly, P9 had non-complicated varicella and three viral pneumonia events. The patient was first hospitalized at 3 years of age and required oxygen because of respiratory syncytial virus pneumonia. Her condition improved without complications. At 5 years of age, she developed influenza A (H1N1)pdm09 pneumonia, which required only mechanical ventilation. Months later, she was readmitted because of severe acute respiratory syndrome–related coronavirus-2 (SARS-CoV-2) pneumonia and was treated with supplemental oxygen, with satisfactory resolution.

P11 had SARS-CoV-2 pneumonia at 4 years of age. She required supplementary oxygen and had satisfactory resolution. P20 developed a systemic Epstein-Barr virus (EBV) infection associated with hemophagocytic syndrome, which improved with the HLH-04 chemo-immunotherapy protocol [28] that included etoposide, dexamethasone, and cyclosporine A. At 15 years of age, P21 suffered a herpes zoster virus infection in the right upper limb without relapse. Finally, P22 was infected with SARS-CoV-2, which resolved with ambulatory treatment. Although viral infections were present in some of the described MSMD cases, all resolved successfully. The data from this cohort confirm previous viral features in MSMD.

Mortality and survival in MSMD patients

Mortality of MSMD patients varies depending on genetic defects as well as other parameters, such as the clinical outcome, infectious agent, and therapeutic approach used [7, 23]. Among the 22 patients, 20 were followed-up at the hospital until publication or death. After clinical and genetic MSMD diagnosis, the median follow-up time was 4 years (range, 6 months to 17 years). Seven of the 22 patients died (P1, P2, P6, P7, P8, P17, and P20). The global survival rate of patients with MSMD was 92% and 83% at 5 and 10 years of age, respectively. The global mortality rate was 31.8%. Of the seven deceased probands with MSMD, five were male and two were female. According to the genetic etiology of the deceased MSMD patients, five had IL-12Rβ1 deficiency (P1, P2, P6, P7, and P8), which represented 38% of patients with this IEI, one had AR complete IFNγR1 deficiency (P17), and the other had AD IFNγR1 deficiency (P20). The median age of death in the seven deceased MSMD patients was 4.5 years (range, 3 years to 16 years, 7 months). The unique cause of death in the seven deceased MSMD patients was multiorgan failure secondary to refractory disseminated mycobacterial infection. The cause was BCG infection in six probands (P1, P2, P6, P7, P8, and P17) and non-identified mycobacteria species in one (P20). P2 and P7 had a coinfection in the lethal mycobacterial episodes, involving disseminated *Candida* spp. and *K. pneumoniae* sepsis.

Discussion

To the best of our knowledge, this is the first report of a Mexican MSMD cohort including 22 patients. In 2019, the number of registered births in Mexico reached two million, and the crude birth rate was 16.8 births per 1,000 inhabitants nationwide in 2020 [29]. Considering that MSMD affects approximately 1/50,000 individuals worldwide [2], the number of reported cases (confirmed at the genetic level, such as the group of patients reported here) in Mexico suggests that MSMD is under-diagnosed. Other IEI, such as CGD or dysgammaglobulinemia, are more commonly diagnosed in Mexico because of significant suspicion among physicians and the central accessibility to screening tests [16, 17]. Among the 19 causal genes of MSMD, which define up to 34 genetic disorders [4], this study describes mutations in three genes (*IL12RB1, IFNGR1*, and *IFNGR2*), which define four genetic disorders (AR IL-12Rβ1 deficiency, AR complete IFNγR1 deficiency, AD partial IFN-γR1 deficiency, and AR partial IFN-γR2 deficiency). One of the most frequent mutations found in *IL12RB1* Mexican kindreds was c.1791 + 2T > G; this variant is the most frequently reported worldwide [20, 30]. P10 had a compound heterozygous variant in *IL12RB1*, c.635G > A, which was recently reported (21), and c.1750C > T, which has not been previously reported. The patient did not express IL-

12Rβ1 in phytohemagglutinin-activated T cells (PHA-blasts); her parents were heterozygous carriers of each variant. In contrast, in *IFNGR1*, the most significant number of mutated alleles were found in exon 6 due to a deletion hotspot (c.819_822del), which often arises *de novo* [31]. One of the three described patients in this series harbored this mutation.

BCG vaccination is mandatory in Mexico, similar to other countries [3, 22, 32–34]. MSMD patients have M. *bovis* BCG as the main infectious agent. Therefore, BCG infection was the principal cause of morbidity and mortality in the patients described here. Health policies in countries where BCG is mandatory must include warning signs of MSMD and/or screening for MSMD patients in children with an adverse reaction to the BCG vaccine. Patients deficient in IL-12Rβ1 are also susceptible to *Salmonella*; the infection has been associated with recurrent leukocytoclastic vasculitis [12]. One of the patients in this study also developed nephritis in parallel with recurrent leukocytoclastic vasculitis. However, the link between the autoimmune manifestations of IL-12Rβ1 deficiency and Salmonella infection is not clear [12, 35]. Interestingly, subcutaneous gammaglobulin ceased the refractory relapses of *Salmonella* sepsis in P12, suggesting that subcutaneous gammaglobulin might be a therapeutic option in cases of recurrent *Salmonella* infection. P13 presented with *Salmonella* brain abscess. Salmonella brain abscesses have been described in CGD patients [36, 37]. However, to our knowledge, this clinical manifestation has not been described in patients with MSMD. Histoplasmosis is an endemic infection in Mexico [38], and it is present in patients with IL-12Rβ1 deficiency. MSMD may be considered in cases with histoplasmosis without other infections, even in adulthood. Leishmaniasis has been associated with IL-12Rβ1 deficiency [33, 39–41] and this parasitic infection is endemic in the southern region of Mexico [42]. However, no patients were detected in the cases described here, but we do not exclude its presence. The mortality rate in the present study was 31.8%, which raises the question of whether these patients should undergo hematopoietic stem cell transplantation.

In conclusion, the clinical, immunological, and molecular characterization of this patient series with MSMD in Mexico confirmed the previous data reported in other studies. As BCG vaccination is mandatory in Mexico, cases of adverse reactions to BCG must be investigated for MSMD diagnosis. To prevent life-threatening complications of BCG infection, BCG vaccination should be formally contraindicated in newborns with siblings and relatives with a history of MSMD. Patients with unexplained infections caused by endemic intracellular pathogens, such as Histoplasma or other deep mycoses, should be suspected of having MSMD and studied for genetic defects in IFN-g-mediated immunity.

Declarations

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Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest.

Availability of data and material

All data are either included in the manuscript or available upon request.

Authors' contributions

A.K.P.V., K.X.L., S.P.S., A.L.I., Y.G., M.T., E.M.T., and C.S. performed the experiments. M.A.Y.N., E.M.F., M.E.N.N., J.C.L.R., L.H.N., M.G.R.M., J.B.S., J.L.L.H., C.M.R.M., J.C.B.O, O.Z.M., T.S.B., E.V.M, N.E.A.G., S.L.R., A.P., and E.G.S. diagnosed and treated the patients, E.J., and S.B.D. performed the genetic analysis. L. B. G., and K.X.L.L. drafted the manuscript. S.P.S., J.L.C., F.E.R., S.E.P., and J.B. supervised this study. All the authors have discussed, revised, and approved the manuscript.

Ethics approval

Informed consent for participation in this study was obtained in accordance with local regulations, with approval from the relevant Institutional Review Boards. The experiments described here were performed in Mexico and France in accordance with local regulations and with the approval of the Institutional Review Board of Necker Hospital for Sick Children, France.

Consent to participate

Written informed consent to participate was obtained from the parents of the patient.

Consent for publication

Consent for publication was obtained from the patient's parents. All authors approved the final version of the manuscript.

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Figures

Figure 1

Family segregation of 17 kindreds with MSMD. Each kindred (K) is designated by a capital letter (A-P). Each generation is designated by a Roman numeral (I-III). The double lines connecting the parents indicate known or presumed consanguinity. An arrow indicates the probands (P); the proband number is indicated inside of the symbol. Individuals whose genetic status could not be evaluated are indicated by the symbol "?". IL-12Rβ1 Deficiency was diagnosed in kindreds A-L, AR complete IFNgR1 deficiency was diagnosed in kindred M, PD IFNgR1 deficiency was diagnosed in kindreds N and O, and AR partial IFN-gR2 was diagnosed in deficiency kindred P.

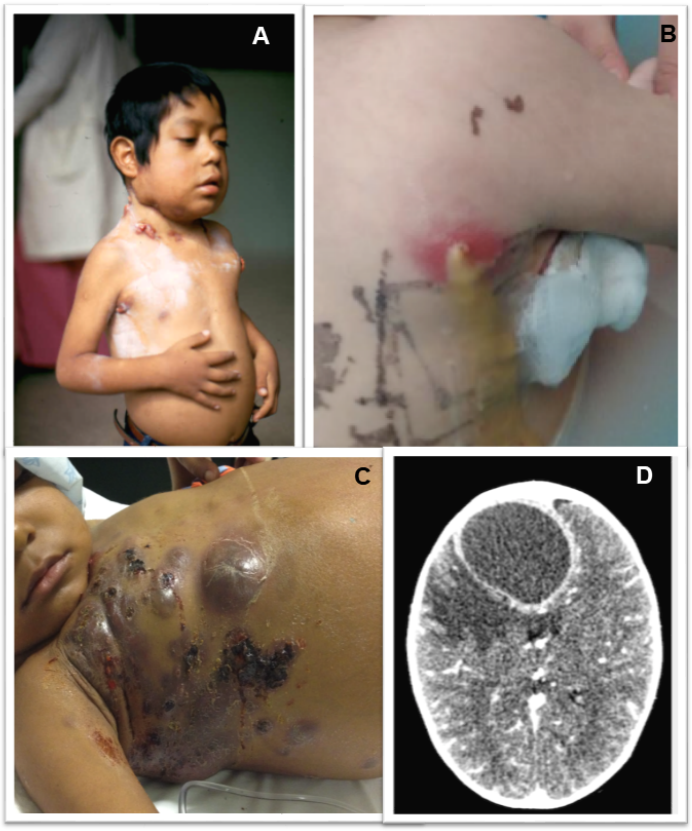

Figure 2

Clinical and radiological findings in IL12Rβ1 deficient patients. **A.** Fistulized and purulent cervical adenitis developed in P14 due to *Salmonella* infection. **B**. Purulent right axillary adenitis in an IL-12Rβ1 deficient patient P8; *M. abscess* and *M. bovis*-BCG was isolated from purulent secretion. **C.** Multiple serohematic blisters in thoracic region in P1 secondary to BCG-osis; distended abdomen due to hepatomegaly was also observed. **D.** A cerebral abscess image in computed tomography scan. The abscess in the left frontal lobe shifts the midline in P13. *Salmonella enterica* group D was isolated in the purulent secretion.

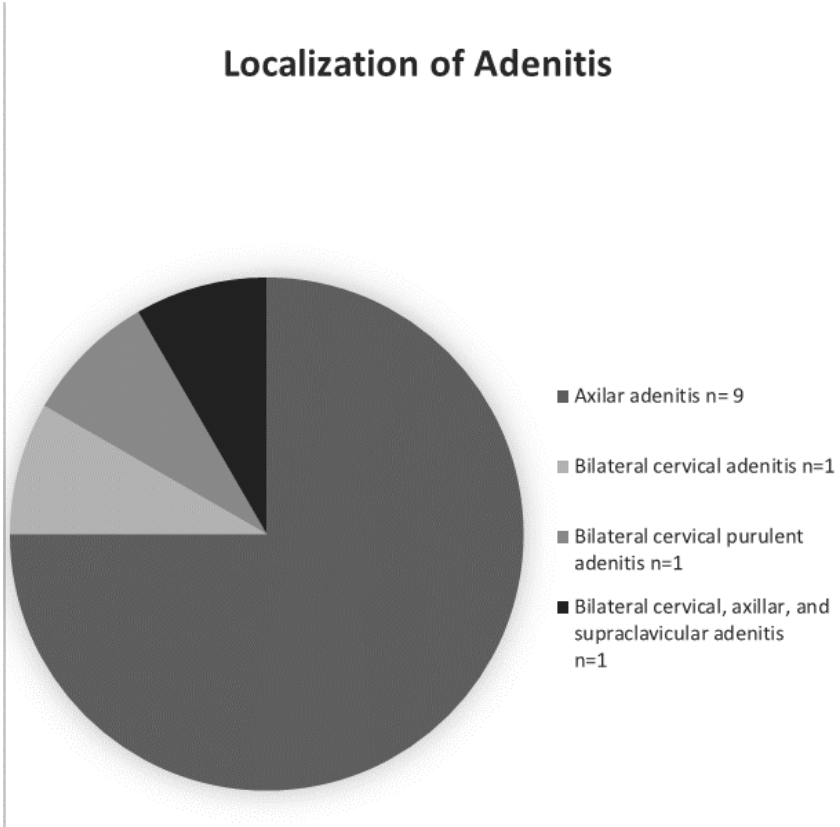

Figure 3

Adenitis in IL12Rβ1 deficient patients. The graphic shows the distribution of all adenitis events in patients with IL12Rβ1 deficiency.

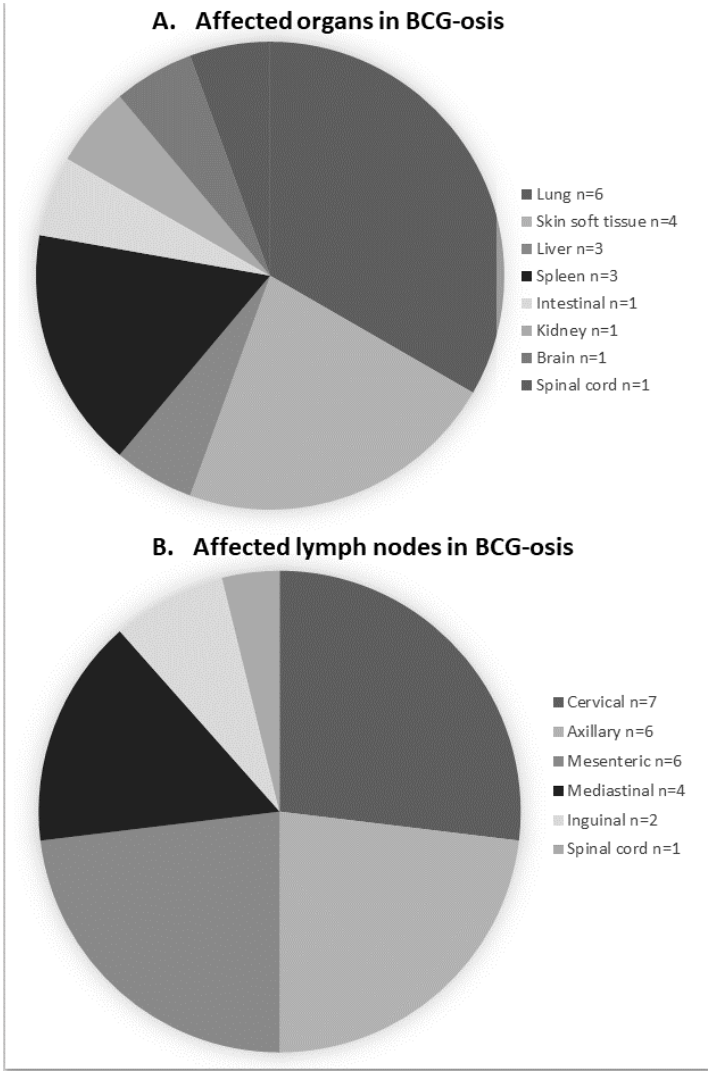

Figure 4

BCG infection in IL12Rβ1 deficient patients. **A.** The graphic shows the distribution of affected organs by BCG infection. **B.** The graphic shows the distribution of affected lymph nodes by BCG infection.

Supplementary Files

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