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Clinical Features, Genetic Background, and Outcomes in Children with Mendelian Susceptibility to Mycobacterial Disease Diagnosed with Mycobacterial Tuberculosis Complex in Saudi Arabia: Case Series

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***Abstract*— *Background*: While live attenuated BCG immunization is generally well tolerated by children, those with certain immunodeficiencies, including Mendelian susceptibility to mycobacterial disease (MSMD) are at high risk for potential adverse reactions. These can range from regional lymphadenitis to fatal disseminated BCG infection (BCGosis). Here, we describe the clinical features, investigations, and underlying primary diseases of MSMD patients in Saudi Arabia.**

***Methods*: This case series reports a retrospective descriptive analysis of patients under 14 years of age who were diagnosed with MSMD and developed disseminated BCGitis after vaccination, between January 2009 and December 2022.**

***Results*: Fourteen patients with disseminated BCG disease were enrolled. The most common symptom was fever, which presented in 9 (64%) of the patients, while GIT symptoms were documented in 5 (35%). The most common signs were localized lymphadenopathy, observed in 8 patients (57.1%), and hepatosplenomegaly in 6 patients (42%). All patients had evidence of *Mycobacterium tuberculosis* complex on culture and the majority were PCR-positive. They were all treated with anti-tuberculosis medications; in addition, 3 patients started rhIFN-γ therapy. There were 2 deaths among the 14 cases (14.3%).**

***Conclusion*: A thorough investigation for immunological defects is crucial in children who develop disseminated BCGitis, and early anti-mycobacterial therapy is highly recommended in MSMD patients with BCG disease.**

***Index terms*— BCG Vaccine; Child; Genetic Predisposition to Disease; Immunologic Deficiency Syndromes; Interferon-gamma; Mycobacterium Infections.**

I. INTRODUCTION

The Bacillus Calmette-Guérin (BCG) vaccine was developed in France, in 1908, by Albert Calmette and Camille Guérin. It was produced by in-vitro attenuation of *Mycobacterium bovis* strains, and first used in 1921 [1]. In 1974, the World Health Organization (WHO) included the vaccine in its Expanded Program of Immunization (EPI) [2].

While the BCG vaccine is well tolerated by most children, it carries the risk of adverse reactions, ranging from regional suppurative lymphadenitis to fatal disseminated BCG infection (BCGosis). The estimated incidence of such reactions is 1 to 3.4 per million, with a high case-fatality ratio reaching 50-71% of cases [3,4]. Patients with Mendelian susceptibility to mycobacterial disease (MSMD) and severe combined immunodeficiency (SCID), respectively, have the highest rates of complications and mortality [5], and early anti-mycobacterial therapy is therefore crucial in this cohort. However, management approaches to BCG

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vaccination complications remain a subject of debate. Here, we present cases of disseminated BCGitis, as well as the associated clinical and diagnostic investigations and underlying primary diseases, in a retrospective cohort of 14 MSMD patients at a single center in Saudi Arabia.

II. MATERIALS AND METHODS

The study included data collected from January 2009 to December 2022, as part of larger study of *Mycobacterial tuberculosis* complex samples submitted to the Microbiology Department of a single tertiary center in Saudi Arabia. All samples were from patients under 14 years of age with confirmed genetic mutations for Mendelian susceptibility to mycobacterial disease. Data were collected from the Patient Electronic Medical Record System and the Microbiology Department's data record using a questionnaire. To ensure anonymity, no patient identifiers were used. Variables included baseline information such as sex, age, nationality, clinical symptoms, underlying primary immunodeficiency conditions, treatment, and prognosis of BCGosis in the studied patients. This case series was approved by the Institutional Review Board (IRB) on 5 May 2020 (IRB log Number 20-271).

III. RESULTS

Demographics:

We evaluated 14 patients with MSMD of whom 7 were male and 7 female (Table 1). Consanguinity was found in the families of 7 patients (50%). Primary immunodeficiency (PID) in child relatives was confirmed in 6 cases (42.8%), and clinically suspected in 2 (14.2%). Majority of patients had received a BCG vaccination at birth, under the previous Saudi national immunization plan. One patient had been vaccinated at 6 months, in accordance with the updated immunization plan, the exact timing of BCG vaccination for one patient is unknown.

Post-vaccination Complications:

Disseminated BCG infection was diagnosed in 12 of the patients (85.7%), while 6 (42.8%) developed generalized lymphadenopathy. The most common symptom was fever, in 9 patients (64.2%). Nine patients (64.2%) were screened for HIV, all were negative.

PCR and Culture:

Samples were collected via fine-needle aspiration or swabs, depending on the site of infection and clinical presentation (Table 2). All patients exhibited evidence of *M. tuberculosis* complex on culture, and PCR testing was positive in 11 (78.5%). As all isolates were resistant to pyrazinamide, the pathogens were most likely *Mycobacterium bovis* BCG strains.

Management and Prognosis:

All patients received anti-tuberculosis medications irrespective of their diagnosis (BCGitis or BCGosis), the duration of treatment ranging from 6 months to 1.5 years or more, depending on clinical response. In addition, 3 patients (21.4%) started rhIFN-γ therapy out of 14 patients, and 5 patient were followed up at our hospital until the time of publication or until their death. Among the remaining 9 patients, 7 were lost to follow-up (some were referred for transplant). It is worth mentioning that 2 of the 14 patients (14.2%) died.

Immunological Screening and Genetic Analysis:

The patients' immunological screening results are detailed in Table 3. A lymphocyte subset count was ordered for 12 patients (85.7%), and was only within normal age-specific range in 5 of the 12. Serum immunoglobulin levels were measured in 11 of the 14 patients (78.5%), elevated IgA levels (above 1.2 g/l) were observed in 6 patients, and elevated IgM levels (above 1.6 g/l) were also found in 6 patients. Additionally, IgG levels exceeded the normal range (10.6 g/l) in 8 patients. Further details are provided in Table 3.

The genetic analysis, conducted for all patients (Table 3), revealed an *IL12B* gene mutation in 6 out of 14 patients (42.8%). Three patients (P1, P12, and P14) had a *STAT1* gene deletion affecting exons 3 and 4. One patient (P1) had a mutation affecting *IL12RB1*, and another (P2) had a homozygous mutation affecting *IFNGR2*. An interesting case (P11) was found to have a dual mutation affecting both interferon receptors *IFNAR1* and *IFNGR2*. Only three patients (P1, P7, and P13) received interferon gamma therapy. The genetic testing reports for four patients (P6, P7, P9, P10) were difficult to retrieve.

IV. DISCUSSION

Mendelian susceptibility to mycobacterial disease (MSMD) is a rare inborn error of immunity that predisposes patients to infection by weakly virulent mycobacterial strains, such as *Mycobacterium bovis* BCG, which is the strain used in the BCG vaccine. These patients also suffer from invasive and

Table 1. Demographic and clinical characteristics of studied patients

No.	Age (Mths)	Sex	Clinical features	Diagnosis	Other infections	Treatment duration (Number of anti-TB drugs)	Follow-up (Prognosis)
P1	5	M	Fever, cough, lymphadenopathy, decrease appetite, weight loss, hepatosplenomegaly	Disseminated BCGosis	None	1 year (Initially 4, later 2)	7 years to date (Alive, good)
P2	3	M	Fever, decreased feeding/activity, localized lymphadenopathy, skin rash	Disseminated BCGosis	Parotitis	1 year (Initially 4, later 2)	lost follow-up - referred for transplant (Alive, good)
P3	11	F	Left axilliary swelling	BCGitis	-	6 months; parents stopped medication (Initially 2, later 2)	lost follow-up (Alive, good)
P4	12	M	Fever, generalized lymphadenopathy, BCG site symptoms	Disseminated BCGosis	Recurrent infection, incl. *Salmonella* lymphadenitis and *Salmonella* isolated from stool	Current (Initially 1, later 3)	3 years to date (Alive, good)
P5	24	F	Generalized lymphadenopathy, BCG site symptoms	Disseminated BCGosis	Recurrent infection, incl. Salmonella Bacteremia and *Salmonella* isolated from stool	Current (Initially 3, later 3)	3 years to date (Alive, good)
P6	1	M	Fever, night sweating, cough, SOB, generalized lymphadenopathy, GIT symptoms, abscess, hepatosplenomegaly	Disseminated BCGosis	Chest infections	(Initially 2, later 4)	(Died)
P7	12	F	Diarrhea, decreased appetite, weight loss, generalized lymphadenopathy, ascites, hepatosplenomegaly	Disseminated BCGosis	-	Unknown (Initially 2, later 4)	Lost follow-up (Alive, good)
P8	2	F	Fever, rash, GIT symptoms, hepatosplenomegaly; patient also had confirmed TB contact.	Disseminated BCGosis	Pneumonia (influenza & PCP), HLH	Unknown (Initially 4, later 4)	Lost follow up - referred for transplant. (Alive, good)

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P9	20	F	Fever, vomiting, diarrhea, GIT symptoms, generalized lymphadenopathy	Disseminated BCGosis	-	Unknown (Initially 2, later 4)	Lost follow-up - family insisted on discharge (Died)
P10	12	F	Fever, decreased feeding & activity, respiratory distress, lymphadenopathy, hepatosplenomegaly	Disseminated BCGosis	Bacteremia (*Klebsilla*)	Unknown (Initially unknown, later 4)	Lost follow-up (Alive, good)
P11	3	M	Localized lymphadenopathy, rash	BCGitis	Recurrent infection - bacterial (*S.viridins*), Viral (CMV, HSV, RSV), and HLH	Unknown (Initially 3, later 3)	Lost follow-up (Alive, good).
P12	24	F	Prolonged fever, rash, diarrhea, localized lymphadenopathy	Disseminated BCGosis	RSV pneumonia	1 year (Initially 4, later 3)	2 years to date (Alive, good)
P13	60	M	Decreased feeding, FTT, night sweating, generalized lymphadenopathy	Disseminated BCGosis	Salmonella isolated from lymph node, *H.pylori*, chronic colitis	Ongoing (Initially 4, later 4)	2 years to date (Alive, good)
P14	3	M	Fever, decreased feeding, abdomen distension, raised liver enzymes, ascites, hepatosplenomegaly, localized lymphadenitis	Disseminated BCGosis	Recurrent infections (viral, bacterial, fungal-Candidemia), NTM co-infection	(Initially 3, later 5)	(Died)

Table 2. Anatomical sites of fine-needle aspiration and swab sample collection

Sample site	**Percentage**
Lymph nodes	(42.8%)
Gastric aspirate	(64.2%)
Peritoneum	(21.4%)
Sputum	(14.2%)
Pleural	(7.1%)
BCG site	(7.1%)
Bone marrow	(7.1%)

Table 3. Summary of immunological screening tests and findings for studied patients

No.	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (mths)*	5	3	11	12	24	11	12
WBC	8.3 (6-17.5)	52 (6-17.5)	13.4 (6-17.5)	20.6 (6-17.5)	11.5 (6-17)	12 (6-17.5)	15.7 (6-17.5)
ALC	4.4 (4-13.5)	15 (4-13.5)	8.1 (4-10.5)	9.5 (4-10.5)	4.4 (3-9.5)	3 (4-10)	5 (4-10.5)
CD3	1.9 (2.5-5.6)	10 (2.5-5.5)	ND	5.4 (1.9-5.9)	4 (2.1-6.2)	0.8 (1.9-5.9)	1.4 (1.9-5.9)
CD4	1.5 (1.8-4)	7.4 (1.6-4)	ND	4.1 (1.4-4.3)	2.5 (1.3-3.4)	0.6 (1.4-4.3)	0.5 (1.4-4.3)
CD8	0.3 (0.59-1.6)	2.56 (0.56-1.7)	ND	1 (0.5-1.7)	1.1 (0.6-2)	0.2 (0.5-1.7)	0.7 (0.5-1.7)
CD19	1.2 (0.43-3)	3.59 (0.3-2)	ND	3.4 (0.6-2.6)	2 (0.72-2.6)	2 (0.6-2.6)	1.3 (0.6-2.6)
IGA g/l	1.1 (0.081-0.84)	1.5 (0.046-0.46)	ND	1.3 (0.16-0.84)	1.1 (0.4-1.23)	1.5 (0.14-0.48)	3.3(0.16-0.84)
IGM g/l	2.4 (0.3-1.08)	0.8 (0.24-0.98)	ND	1.7 (0.41-1.49)	2.3 (0.48-1.68)	2.7 (0.4-1.49)	2.4 (0.41-1.49)
IGG g/l	13.7 (1.72-8.14)	13.6 (1.7-5.8)	ND	20.5 (2.9-10.6)	23 (4.2-10.5)	14.8 (2.9-10.6)	20 (2.9-10.6)
HIV	Negative	ND	ND	Negative	Negative	Negative	Negative
Gene	IL12RB1	STAT1 gene deletion (exon 3&4)	IL12B	IL12B	IL12B	IL12 deficiency details not found	IL12 deficiency details not found
Mutation	c.264C>G	-	c.320dupA	c.320dup	c.320dup	-	-
Protein	p.Tyr88X	-	p.K107FS	p.E108Gfs*8	p.E108Gfs*8	-	-
Mutation Status	-	-	Heterozygous	Homozygous	Homozygous	-	-
IFNγ treatment	Yes	No	No	No	No	No	Yes

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Table 3 continued

No.	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14
Age (mths)*	2	20	12	2	12	36	3
WBC	35 (6-17.5)	10.8 (6-17)	18.2 (6-17.5)	38.3 (6-17.5)	47 (6-17.5)	15.4 (5.5-15.5)	33.1 (6-17.5)
ALC	15.6 (4-13.5)	5.5 (3-9.5)	7.5 (4-10.5)	16.9 (4-13.5)	10.2 (4-10.5)	3.9 (2-8)	5.6 (4-13.5)
CD3	7.5 (2.5-5.5)	ND	1.5 (1.9-5.9)	5.2 (2.5-5.5)	6.4 (1.9-5.9)	1.8 (1.4-3.7)	4.2 (2.5-5.5)
CD4	4.8 (1.6-4)	ND	1.2 (1.4-4.3)	1.1 (1.6-4)	4.5 (1.4-4.3)	1 (0.7-2.2)	2.6 (1.6-4)
CD8	2.9 (0.56-1.7)	ND	0.4 (0.5-1.7)	3.6 (0.56-1.7)	1.8 (0.5-1.7)	0.6 (0.49-1.3)	1.3 (0.56-1.7)
CD19	5.7 (0.3-2)	ND	0.08 (0.6-2.6)	2.3 (0.3-2)	2.2 (0.6-2.6)	1.3 (0.39-1.4)	1.3 (0.7-1.6)
IGA g/l	ND	ND	<0.2 (0.16-0.84)	0.4 (0.028-0.47)	1.1 (0.16-0.84)	4.2 (0.22-1.59)	0.98 (0.046-0.46)
IGM g/l	ND	ND	<0.1 (0.41-1.49)	0.9 (0.17-1.05)	1 (0.41-1.49)	1.9 (0.47-2)	1.56 (0.24-0.98)
IGG g/l	ND	ND	3.1 (2.9-10.6)	6.7 (2.06-6)	20 (2.94-10.6)	22.1 (4.4-11.3)	8.3 (1.7-5.8)
HIV	Negative	Negative	ND	ND	Negative	Negative	ND
Gene	IFNGR2	(IL12B) details not found	(IL12B) details not found	1) IFNAR1 (deletion) 2) IFNGR2 (single nucleotide deletion)	STAT1 gene deletion (exon 3&4)	IL12B	STAT1 gene deletion (exon 3&4)
Mutation	-	-	-	1) c.1671_1821del 2) c.798delT	-	-	-
Protein	p.Y235X	-	-	1) p.*557Glext*46 2) p.C266fs	-	p.(Glu108Glyfs*8)	-
Mutation Status	Homozygous	-	-	Homozygous	Homozygous	Homozygous	Homozygous
IFNγ treatment	No	No	No	No	No	Yes	No

*Age at first immunological screening (in months), P: Patient, ND: not done, NR[A1] : Normal range based on age-related reference range from THE HARRIET LANE HANDBOOK Twenty-first edition - authors: Helen K. Hughes, Lauren K. Kahl.

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recurrent infections by other intracellular organisms such as *Salmonella, Toxoplasma, Listeria,* and *M. Tuberculosis* [5]. Since MSMD was discovered in 1996, it has been linked to multiple gene defect affecting the interferon-γ (IFN-γ). IL12 and IL23 signalling pathways that mediate anti-mycobacterial immunity [6,7].

When a microbe is engulfed by a macrophage, the macrophage produces IL12 and IL23, which bind to their receptors on T lymphocytes and natural killer (NK) cells, stimulating the production of IFN-γ. The IFN-γ, in turn, attaches to its receptor on the infected macrophage, aiding the intracellular killing of the microbe. The most reported type of MSMD is the complete or partial deficiency of IL12 receptor (IL12RB1) expression, which leads to the inability of activated T lymphocytes and NK cells to mount the appropriate immune response to intracellular organisms [8].

With more than 4 billion people worldwide having received the BCG vaccination, and a further 100 million infants receiving it every year, the vaccine ranks as one of the world's most commonly used [9]. Nonetheless, as a live attenuated vaccine, it can cause side effects ranging from localized inflammation to widely distributed infections and even fatalities, especially among immunocompromised hosts [4]. Although disseminated BCG infection is a rare consequence, with an estimated incidence of 0.14 per million vaccinated children, it is fatal in 50–71% of cases [5].

In our study, disseminated BCG infection was documented in 14 patients (seven male and seven female) following routine BCG vaccination. Generalized lymphadenopathy, fever, and hepatosplenomegaly were the initial observed symptoms. In line with prior studies, 86% of our studied patients had lymphadenopathy [10], while hepatosplenomegaly was documented in 42% of our patients, also similar to other reports [3]. The prevalence of fever, rash, and gastrointestinal symptoms was 64%, 28%, and 35%, respectively.

The patients' diagnosis was confirmed by TB culture and sensitivity testing. In nine patients (64%), a gastric aspirate culture was positive for *M.tuberculosis* complex *(*presumed *bovis)*; two of these also had positive cultures from pleural and peritoneal fluid, and two also had positive cultures from respiratory and bone marrow samples. Six patients (43%) were culture-positive from lymph node samples; a higher proportion than reported by Taur et al. (2021), who found lymph node samples culture positive for *M.tuberculosis* complex in 17 out of 55 patients [11]. One patient was culture-positive from intra-abdominal abscess sample, and one from a jejunal mucosal sample. Furthermore, PCR testing was positive for *M.tuberculosis* complex (presumed *bovis)* in 11 patients (78.5%), and ZN staining for acid-fast bacilli was positive in nine (64.2%).

Although no current guidelines exist for the treatment of disseminated BCGitis in paediatric patients, the European Society for Immunodeficiency has established therapeutic guidelines for disseminated BCG infection specific to severe combined immunodeficiency, which recommend treatment with four or more anti-TB agents until clinical improvement is observed, followed by maintenance with two anti-TB drugs as prophylaxis until complete immune reconstitution is achieved post-hematopoietic stem cell transplantation (HSCT) [12]. In cases where early HSCT is planned, a three-drug regimen may be adequate [3]. Most of our patients were treated empirically with three to four anti-mycobacterial drugs, with treatment then modified according to sensitivity. The duration of treatment ranged from 6 months to 1.5 years or longer, depending on clinical response. Anti-mycobacterial drugs may be combined with other antibiotics, including ciprofloxacin and clarithromycin, and recombinant IFN-γ treatment [13]. The choice of empirical agent, and the number and duration of anti-TB drugs, depends on the patient's susceptibility patterns, underlying immunodeficiency, degree of dissemination, and clinical response [14]. In one study, standard anti-mycobacterial therapy was modified based on drug susceptibility patterns, excluding pyrazinamide; more aggressive treatment was then administered over a longer duration according to clinical response [6]. The bacillus Calmette-Guérin (BCG) vaccine contains *Mycobacterium bovis,* which is intrinsically resistant to pyrazinamide. Furthermore, different BCG strains have different susceptibility patterns; for example, the Danish strain (SSI 1331), currently used in Saudi Arabia, has low-level resistance to isoniazid that may not be clinically significant, and is resistant to ethionamide. It is also important to consider these differences when selecting empirical therapy [14].

Most of our patients underwent surgical treatment such as lymph node excision, while two were referred for HSCT. Mortality was reported in 2 of our 14 patients (14.2%); this mortality rate is slightly higher than another study that evaluated 16 patients and reported 2 deaths due to disseminated BCGosis [8]. In contrast, a study evaluating 18 MSMD patients reported 4 deaths from disseminated BCG infection [15]. Another study of 55 MSMD patients reported mortality of 34% [11], and a high mortality of 24% due to BCG infection in MSMD patients was reported in a meta-analysis by Fekrvand et al. [16].

Most of our patients had a good prognosis at the time of their most recent follow-up, with the exception of two patients who died, one of whom was found to have a concomitant NTM infection, while the other, who received a BCG vaccination at birth, presented at the age of one month and was diagnosed with IL-12 deficiency. BCG-related mortality is associated with early BCG vaccination, and most of our patients were vaccinated at birth in line with the previous Saudi national immunization plan. However, the plan was revised according to new recommendations in August 2019, and the BCG vaccination is now administered at 6 months of age. This change aimed to reduce complications associated with BCG vaccination and minimize BCG-related mortality [17].

Our study emphasizes the importance of high clinical suspicion in cases of BGC infection, and early initiation of antimycobacterial drugs to reduce the risk of mortality. Furthermore, there remains a need for established guidelines for the treatment of disseminated BCGitis in the paediatric population.

V. CONCLUSION

MSMD remains challenging to diagnose, particularly because the presenting symptoms are usually delayed. In communities with a high consanguinity rate, it is worth evaluating the family history of PID when administering routine vaccinations. Moreover, in children with disseminated BCGitis after BGC vaccination, a thorough investigation for immunological defects is crucial. Our study provides further insight about MSMD in TB-endemic countries, where BCG vaccination remains necessary despite a high prevalence of inherited diseases, including primary immunodeficiencies. Further studies would add value by investigating the effect of delayed BCG vaccination on the incidence of BCG-related complications.

VI. CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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