

## CASE SERIES

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# Severe Combined Immunodeficiency: A Case Series and Review from a Tertiary Pediatric Hospital

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## ABSTRACT

Severe combined immunodeficiency syndrome (SCID) is a life-threatening condition leading to early infant death as a result of severe infection, due to impaired cellular and humoral immune systems. Various forms of SCID are classified based on the presence or absence of T cells, B cells and natural killer cells. Patients usually present with recurrent infections and failure to thrive. Definitive treatment is hematopoietic stem cell transplantation. To achieve the best outcome, it should be performed prior to the development of severe infection.

In This study, we described 10 patients (6 male and 4 female) with SCID who were admitted to Mofid Children Hospital, Tehran, Iran, from 2006 to 2013. We reviewed patients' clinical manifestation, laboratory data, family history and outcome.

The mean age at the time of diagnosis was 131.8 days. One patient had non-consanguineous parents. Seven patients received BCG vaccine before the diagnosis of SCID, three of them showed disseminated BCG infection. One patient presented with invasive pulmonary aspergillosis. Flow cytometric analysis showed T<sup>+</sup>B<sup>+</sup>NK<sup>-</sup> in three patients, T<sup>+</sup>B<sup>+</sup>NK<sup>+</sup> in five patients, T<sup>+</sup>B<sup>-</sup>NK<sup>-</sup> in one patient, and T<sup>+</sup>B<sup>+</sup>NK<sup>+</sup> in one patient.

This study highlights the importance of early diagnosis and patient referral before the occurrence of serious infection.

**Keywords:** Neonatal screening; Primary immunodeficiency disorder; Severe combined immunodeficiency

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## INTRODUCTION

Severe combined immunodeficiency (SCID) is a life threatening syndrome and prototype of the primary immunodeficiency disease (PID). It consists of a heterogeneous group of inherited defects and is characterized by severe impairment of humoral and cellular immune systems due to deficiency in T-cells development.<sup>1</sup>

Neonates with SCID are normal at birth and become symptomatic in the first few months of their life with recurrent infections caused by various types of bacteria, viruses and fungi.<sup>2</sup>

Patients commonly present with failure to thrive, chronic diarrhea, persistent oral candidiasis, pneumonia, and sepsis. Death usually occurs in infancy due to severe infections.<sup>2,3</sup>

SCID can be inherited as X-linked recessive and autosomal recessive patterns. It is classified by affected lymphocyte subsets (T-cells, B-cells, NK-cells).<sup>4</sup> X-linked SCID is due to interleukin-2 receptor gamma chain (IL-2RG) gene mutation and made up to 50% of all cases.<sup>4-6</sup> The most common cause of autosomal recessive SCID is adenosine deaminase (ADA) gene mutation, which results in ADA deficiency, and is found in 15-20% of all patients.<sup>5,6</sup>

The primary treatment of choice for most types of SCID, is allogeneic hematopoietic stem cell transplantation. To achieve the best outcome, transplantation should be performed prior to the development of severe infection. Hence, early diagnosis is essential as instituting proper treatment is lifesaving.<sup>1-6</sup> Gene therapy has also been successfully used to treat some forms of SCID.<sup>5</sup>

This study describes the clinical presentation of ten cases with SCID who were admitted to our hospital from 2006 to 2013. Some of patients had unique clinical manifestations that must be considered by primary care physicians for the accurate diagnosis.

## MATERIALS AND METHODS

This is a retrospective study of patients who were diagnosed with SCID and had been admitted to Immunology Department of Mofid Children's Hospital (a tertiary referral hospital) in Tehran, Iran from 2006 to 2013. Informed consent was obtained from all parents.

Among 90 patients with clinical presentations of

immunodeficiency, 10 cases were diagnosed with SCID according to the ESID criteria.<sup>7</sup>

We reviewed patients' medical records including clinical presentations, laboratory study, family history, and outcome. Laboratory data included complete blood cell count with differential (manual diff), immunoglobulin levels (IgA, IgE, IgM, and IgG) using Nephelometry, Binding site company, flow cytometric study of lymphocytes subtypes (CD3, CD4, CD8, CD19, CD16, CD56) using FACS calibur, BD biosciences. HIV PCR was negative in all the subjects. Unfortunately, genetic study was not performed in our cases.

## RESULTS

### Patients' Characteristics

Patients' age, sex, parental consanguinity and clinical presentation are summarized in Table 1. Patients were 6 males and 4 females (male to female ratio: 1.5/1). 9 patients were Iranian, and one patient was from Azerbaijan Republic. The average age at the time of diagnosis was 131.8 days. Two patients had third degree consanguineous parents, seven had second degree consanguineous parents and one had non-consanguineous parents. Six patients had a history of early infant death in their siblings, two patients had relatives with SCID, and two patients had no history of immunodeficiency in their family.

Three patients had not received BCG or any other live attenuated vaccine due to suspicious family history, however seven patients had been vaccinated according to national vaccination program prior to the diagnosis of SCID.

### Clinical Manifestations

The clinical presentations of the patients are summarized in Table 1. Pneumonia was the most common presentation in our patients (7 patients), followed by failure to thrive (6 patients). One patient presented with invasive pulmonary aspergillosis, in whom, diagnosis was made based on the positive serum galactomannan and Computerized Tomography (CT) scan findings (Figure 1).

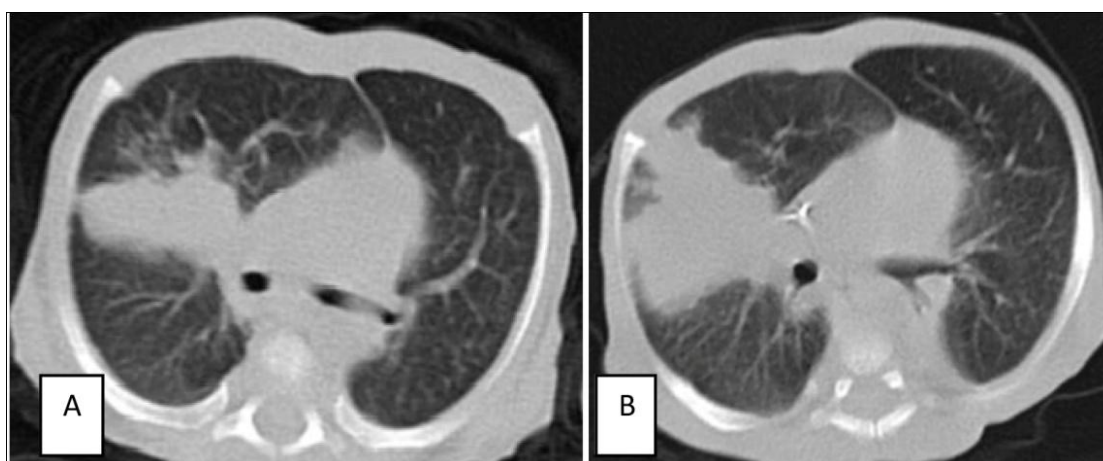
Three patients showed signs and symptoms of disseminated BCG infection (BCGosis). The first patient presented with axillary and inguinal lymphadenopathy and eczematous skin rashes.

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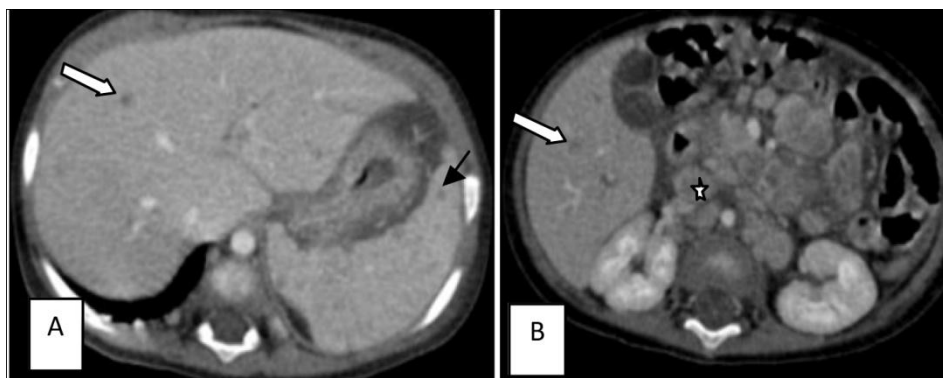
**Table 1. Demographic data and clinical presentation of ten patients with severe combined immunodeficiency**

No	Sex	Age at time of diagnosis (Days)	Parental consanguinity	First clinical presentations	Other clinical presentations
1	Female	83	Positive	Chronic cough FTT	Oral candidiasis, genitalia ulcer, weight loss, invasive pulmonary aspergillosis
2	Male	30	Positive	Evaluated due to positive family history	Sepsis
3	Female	150	Positive	Pneumonia, oral ulcer, skin Rash	Diarrhea, membranous colitis
4	Male	160	Positive	Oral candidiasis, cough, noisy breathing, FTT	Diarrhea
5	Female	175	Positive	Pneumonia, diarrhea	Encephalitis
6	Male	120	Positive	Prolonged fever, FTT, skin rash, BCGosis	Pneumonia
7	Male	180	Positive	Fever, lymphadenopathy, BCGosis	
8	Female	1	Positive	Evaluated due to positive family history	Gastroenteritis, fever
9	Male	210	Negative	Recurrent pneumonia, oral candidiasis, skin nodules, BCGosis	Sepsis
10	Male	210	Positive	Fever, pneumonia	

FTT: Failure to thrive



**Figure 1. Chest CT-scan showing invasive pulmonary aspergillosis in a patient with severe combined immunodeficiency**



**Figure 2. Abdominal CT-scan showing disseminated BCG infection in a patient with severe combined immunodeficiency: splenomegaly, hypodense lesions in the spleen and liver, and multiple lymphadenopathies**

CT scan revealed splenomegaly, several hypodense lesions in the spleen and liver, and multiple lymphadenopathies (Figure 2). Polymerase Chain Reaction (PCR) was performed on lymph node discharge and bone marrow specimen that identified *Mycobacterium bovis*. The second patient presented with prolonged fever and eczematous rashes on his trunk. Abdominal CT scan revealed multiple hypoechoic lesions in the liver and spleen. Mycobacterial infection was not detected in this patient, but the clinical diagnosis of BCGosis was made due to history of BCG vaccination in addition to his clinical symptoms. The third patient was an 8 month-old male infant who was presented with recurrent pneumonia, cutaneous lesions and normal growth parameters. Physical examination showed some purple skin nodules measuring 1×1cm (Figure 3). Skin biopsy revealed acid fast bacilli.

### Laboratory Findings

The Laboratory data including complete blood cell count with differential and immunological studies are summarized in Table 2. Nine patients had lymphopenia and eight patients had low IgG levels.

Flow cytometry results revealed T<sup>-</sup>B<sup>-</sup>NK<sup>+</sup> SCID in 5 patients, T<sup>-</sup>B<sup>-</sup>NK<sup>-</sup>SCID in 1 patient, T<sup>-</sup>B<sup>+</sup>NK<sup>-</sup>SCID in 3 patients, and T<sup>-</sup>B<sup>+</sup>NK<sup>+</sup>SCID in 1 patient.

### Outcome

All Patients were followed in the outpatient clinic. Two of them received bone marrow transplantation (BMT) and have been followed up. They are both in good health condition several years after BMT. Flow

cytometry result is available for one of them: CD3 - 76%, CD4- 38%, CD- 3 7%, CD19- 0/2%. Matched donors were not found for the other 8 patients, and they died before the age of one despite receiving IVIG and prophylactic antibiotics.



**Figure 3. Cutaneous Lesions due to disseminated BCG infection in an 8 month-old male infant with severe combined immunodeficiency**

**Table 2. Laboratory data of the ten patients with severe combined immunodeficiency**

Patients number	White blood cell count (/ $\mu$ L)	Lymphocyte count (/ $\mu$ L)	IgA (mg/dL)	IgM (mg/dL)	IgG (mg/dL)	IgE (IU/mL)	Lymphocyte Profile
1	14400	3312	10	7	70	1	T <sup>-</sup> B <sup>-</sup> NK <sup>+</sup>
2	7000	560	<3	5	50	3	T <sup>-</sup> B <sup>+</sup> NK <sup>-</sup>
3	1600	656	75	56	900	0.5	T <sup>-</sup> B <sup>-</sup> NK <sup>+</sup>
4	15600	1092	10	7	<18	0.1	T <sup>-</sup> B <sup>-</sup> NK <sup>-</sup>
5	4900	1078	<3	45	46	1	T <sup>-</sup> B <sup>-</sup> NK <sup>+</sup>
6	10900	981	15	39	1661	2	T <sup>-</sup> B <sup>+</sup> NK <sup>-</sup>
7	11900	595	3.3	4.5	<18	0.2	T <sup>-</sup> B <sup>-</sup> NK <sup>+</sup>
8	6000	2220	13	58	139	4	T <sup>-</sup> B <sup>+</sup> NK <sup>+</sup>
9	8900	356	4	15	50	2	T <sup>-</sup> B <sup>+</sup> NK <sup>-</sup>
10	12000	1440	15	20	153	7	T <sup>-</sup> B <sup>-</sup> NK <sup>+</sup>

IgA: Immunoglobulin A, IgM: Immunoglobulin M, IgG: Immunoglobulin G, IgE: Immunoglobulin E, T: T lymphocyte, B: B lymphocyte, NK: Natural killer cell

## DISCUSSION

SCID is a group of genetically inherited diseases resulting from different gene mutations that affects humoral and cellular immunity. Prevalence of SCID is estimated to be 1 in 100000 live births<sup>5</sup>. It is more prevalent in regions with high rates of consanguineous marriages.<sup>6</sup>

T-lymphocytes numbers and functions are greatly decreased in SCID. B-lymphocytes absence or dysfunction may also be present. Different molecular defects are responsible for the disease: Interleukin-2 receptor common gamma chain (IL-2RG), Janus kinase 3 (Jak3), Interleukin-7 receptor alpha chain (IL-7R $\alpha$ ), Recombinase-activating genes 1 and 2 (RAG1, RAG2), Artemis, CD3 $\delta$ , CD45 and adenosine deaminase (ADA) are known as responsible genes.<sup>2,5</sup>

In our study, flow cytometry results of 3 patients were suggestive of T<sup>-</sup>B<sup>+</sup>NK<sup>-</sup>SCID. Mutations in IL2RG or JAK3 can be responsible for the genetic defects in these patients<sup>2</sup>. Five patients categorized into T<sup>-</sup>B<sup>-</sup>NK<sup>+</sup> group. Mutations in RAG1, RAG2, Artemis, DNA protein kinase catalytic subunit (DNA-PKcs), DNA ligase IV, Cernunnos/XRCC4-like factor (XLF) can be the underlying genetic defects in these patients<sup>2</sup>. One patient categorized into T<sup>-</sup>B<sup>-</sup>NK<sup>-</sup> group, in whom, the mutation in ADA or reticular dysgenesis could be the responsible genetic defect<sup>2</sup>. One patient categorized into T<sup>-</sup>B<sup>+</sup>NK<sup>+</sup> group. Possible gene mutations in this patient are IL-7R $\alpha$  (CD127), Actin-regulating protein coronin 1A (CORO1A), CD3 chain components and CD45.<sup>2</sup>

In a study conducted by Aghamohammadi et al (2002), 14 cases of SCID were reported among 440 patients with primary immunodeficiency (PID) (3.1% of patients with PID).<sup>8</sup> However, a recent report of the National Registry of Iran showed higher prevalence SCID among PID cases (21.1%).<sup>9</sup> Matamoros Flori et al study on PIDs in Spain showed 5.7% of the patients had SCID.<sup>10</sup> In our study, 10 out of 90 patients with PID were diagnosed as SCID (11%). The higher rates that are shown in the recent studies can be attributed to the increased awareness of primary care physicians in diagnosis and referral of suspicious cases to the tertiary hospitals.

Prevalence of SCID is not clear in Iran as many of patients die before the diagnosis is made. In a survey by Boyle et al, the number of patients who were diagnosed with PID (1 in 1200 persons) was higher than previous studies. They reported that 9% of patients with PID have been recognized as SCID.<sup>11</sup>

The mean age at diagnosis was 131.8 days in our patients, which is lower than the mean age reported by previous studies.<sup>1,6,12,13</sup> Male predominance in our study is likely due to X-linked transmission of some forms of SCID. It is similar to Yeganeh et al's study, but lower than the other studies.<sup>1,6,13</sup> Additionally, consanguinity rates were higher in our patients compared to the other studies.<sup>1,6,13</sup>

One of our patients had a suspicious history of early infant death of his sibling. Parents reported hydrocephalus in their deceased child, however there was no documented report. Flow cytometric analysis in this patient was compatible with T<sup>-</sup>B<sup>-</sup>NK<sup>-</sup> group. We

assumed that this patient had ADA deficiency.

Different neurologic abnormalities have been reported in some patients with ADA deficiency. Nofech-Mozes et al have reported three ADA deficient patients with neurologic symptoms including: head lag, truncal hypotonia, rotary nystagmus, developmental delay, convulsive disorder and sensorineural deafness.<sup>14</sup>

All types of SCID are susceptible to BCG vaccine complications. Disseminated BCG infection is the most common complication following BCG vaccination in these patients and it is associated with high mortality rates in immunodeficient patients.<sup>15,16</sup>

In this study, 7 patients had received BCG vaccine at birth and 3 of them showed complications related to BCG vaccination. In the study by Yeganeh et al, 45% of patients showed BCGosis.<sup>1</sup> Stephan et al have reported that 35.7% of patients with SCID who were vaccinated with BCG had shown complications.<sup>12</sup> Afsharpeyma et al reported a case series of 17 patients with disseminated BCG infection, of which, 8 patients were diagnosed with SCID.<sup>17</sup> Sadeghi et al studied 8 patients with BCGosis and all of them were diagnosed as SCID.<sup>18</sup> Given these reports, some authors have suggested neonatal PID screening before BCG vaccination<sup>16,18</sup>.

Cutaneous involvement is common in PID. Patients with SCID may show different cutaneous manifestations including: bacterial, fungal, and viral skin infection, erythroderma, or eczematous rash.<sup>19,20</sup> Localized reaction and systemic infection with cutaneous eruptions had been described following BCG inoculation. In Shah mohammadi et al case series, 3 out of 17 patients with BCGosis showed skin rashes. Their literature review, reported that 88.2% of BCGosis patients had shown skin eruptions<sup>21</sup>. In the Talbot et al study, 6 out of 28 patients with disseminated BCG infection showed disseminated cutaneous lesions. Most of the patients were diagnosed with immunodeficiency.<sup>22</sup> Antaya R J et al, reported two cases with different presentations of cutaneous BCG infection following BCG vaccination. Both infants had immunodeficiency, one patient had T-cell signaling defect and the other one had SCID.<sup>22</sup> Gantzer et al, also reported 4 cases of SCID with disseminated BCG infection, who had skin involvements.<sup>23</sup> In our study, one of the patients with BCGosis showed skin manifestations.

Invasive pulmonary aspergillosis is a fungal infection with a poor prognosis. This condition is

frequently seen in HIV and immunocompromised patients. There are also some reports of this condition in patients with chronic granulomatosis disease.<sup>24,25</sup> This infection is not commonly seen in SCID, but it was present in one of our patients.

In some countries neonatal screening for SCID is performed using T cell receptor excision circles (TREC) assay.<sup>3,5,6</sup> In countries in which TREC assay is not available, complete blood count with differential can be alternatively used as neonatal screening for SCID.<sup>6,5</sup> Although it is less expensive, it has less sensitivity and specificity for the diagnosis of SCID.<sup>5</sup> Screening allows the physicians to diagnose SCID before the development of severe infection. Early diagnosis and referral is essential since instituting proper treatment at the appropriate time is lifesaving.<sup>12</sup> Despite of early diagnosis our patients had very poor outcomes. Most of them died before receiving bone marrow transplantation. Limited access to bone marrow transplantation and availability of suitable donors were the major causes of death in our patients.

Our study has limitations that are noteworthy. Our patients did not have genetic study. SCID is an emergency disease and BMT needs to be performed as soon as possible. Genetic study takes few months and is expensive, therefore, we were not able to perform genetic study in our case series.

In conclusion, SCID is a pediatric emergency which should be considered in patients with history of recurrent infections, family history of early childhood death, and consanguineous marriage. Immunization with live vaccines, BCG vaccine and transfusion of non-irradiated blood products should be avoided in suspected patients. Early diagnosis is essential for the definitive treatment, because survival depends on expeditious stem cell transplantation which must be performed before the onset of severe infection.

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