

Severe combined immunodeficiency, report of chilean patients diagnosed during the 1999-2020 period

Inmunodeficiencia Combinada Severa, reporte de pacientes chilenos diagnosticados durante el período 1999-2020d

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What do we know about the subject matter of this study?

Severe combined immunodeficiency (SCID) is a lethal disease in all affected individuals. Its prognosis depends on early diagnosis and treatment by hematopoietic stem cell transplantation. To date, only isolated cases reported of SCID have been reported in Chile.

What does this study contribute to what is already known?

This is the first series of Chilean patients with SCID that covers a large period. We identified a delay in the diagnosis of SCID as well as a significant waiting time for transfer to transplantation centers.

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Abstract

Severe combined immunodeficiency (SCID) is the most severe form of primary immunodeficiency. To date, there is little local information about this disease. **Objective:** To describe the epidemiology, complications, prognosis, and use of the BCG vaccine in Chilean patients with SCID. **Patients and Method:** Retrospective review of the clinical records of patients diagnosed with SCID by clinical immunologists between 1999 and 2020 throughout Chile. SCID was diagnosed according to the criteria proposed by Shearer: T lymphocytes (CD3+) < 300 cells/ μ L and proliferation 10% of the limit of normality in response to phytohemagglutinin or presence of T lymphocytes of maternal origin. Data collected from the clinical records were: sex, age at diagnosis, consanguinity, region of origin, lymphocyte subpopulations, genetic diagnosis, infectious and non-infectious complications, BCG vaccination and its complications, age at referral to the bone marrow transplant (BMT) center, and cause of non-BMT-related mortality. **Results:** Between 1999 and 2020, 25 patients were diagnosed with SCID. 78% of them were male, mean age at first manifestation of the disease was 2.3 months (0-7), while the mean age at diagnosis was 3.4 months (0-7). 16% of patients had a family history of SCID. 40% of cases were diagnosed within the Metropolitan Region. The most frequent immunophenotype was T-B-NK+ SCID (48%). Genetic studies were done in 69.5% of cases, mutations in the RAG2 gene were the most common etiology of SCID (39%). 88% of SCID patients received the Bacillus Calmette-Guerin (BCG) vaccine before diagnosis, including 2 cases with a known family history of SCID. 36% of those who received the vaccine had BCG-related complications. The mean age at referral to a bone marrow transplant center was 7.4 months (5-16). 11/25 patients died before being transferred to a transplant center. **Discussion:** There is a clinically significant delay between the first manifestations and the diagnosis of SCID in Chilean patients, as well as an important time gap between the diagnosis of SCID and referral to a center for BMT. Most SCID cases in Chile receive the BCG vaccine, despite a known family history of the disease, and frequently develop vaccine-related complications.

Keywords:

Primary Immunodeficiencies; Severe Combined Immunodeficiency; BCG Vaccine; Stem Cell Transplantation

Introduction

Primary immunodeficiencies (PID) include about 400 genetic diseases that affect the normal function of the immune system¹. The severity of PID varies from generally asymptomatic pathologies, such as selective IgA deficiency, to 100% lethal diseases in patients who are not diagnosed and treated opportunely, such as severe combined immunodeficiency (SCID)². Due to its high mortality, SCID is considered the most serious PID and represents an immunological emergency. Hematopoietic stem cell transplantation (HSCT) is the only curative treatment available in our country for SCID patients and, if performed before 3.5 months of age in patients without infection, it provides a survival rate over 90% at 5 years after transplantation³. In some particular types of SCID, it is possible to offer patients alternative treatments such as enzyme replacement in patients with SCID due to adenosine deaminase (ADA) deficiency^{4,5} and gene therapy in patients with X-linked SCID⁶ and ADA deficiency⁷; however, these treatments are not currently available in our country.

In the United States, before the massive implementation of neonatal screening for SCID, the incidence of SCID was estimated at 1:100,000 newborns (NB), this increased to 1:65,000 NB when this important public health measure started in that country⁸. It is expected

that with the implementation of neonatal screening programs in additional countries, the global incidence of SCID will increase.

To date, 18 genetic defects have been described that can cause SCID⁹. All forms of SCID, regardless of the affected gene, are characterized by an absence of T cells and a variable involvement of B- and NK-cells. The following immunophenotypes are recognized according to whether or not these other cell groups are affected: T-B+NK+, T-B-NK+, T-B+NK-, and T-B-NK-. SCID should be suspected in patients with opportunistic infections, persistent lymphopenia, family history of children who have died without a clear cause or due to infections, and especially in those patients with family history of SCID. The diagnosis can be further confirmed through the study of lymphocyte subpopulations, lymphocyte proliferation and genetic studies.

The treatment of patients with SCID is mainly supportive care and it aims at referring the patient in the best possible conditions to a HSCT center, the only curative treatment currently available in our country. Supportive therapies include nutritional support, use of prophylactic antibiotics, antivirals and antifungals, palivizumab, intravenous or subcutaneous immunoglobulin, absolute contraindication of live-attenuated vaccines, and the use of filtered, irradiated, and CMV-negative transfusions¹⁰. In Chile, the Bacillus Calmet-

te-Guerin (BCG) vaccine is the main live-attenuated vaccine that these patients are exposed. The BCG vaccine is applied to all NBs with birth weight of at least two kilograms at 48 hours of life, when patients with SCID are unrecognizable except for the existence of a family history of the disease.

In Chile, the epidemiology of SCID is unknown and there are no previous reports of national series covering large periods. The objective of this work is to describe the epidemiology, complications, prognosis, and use of the BCG vaccine in Chilean patients with SCID.

Patients and Method

Retrospective review of clinical records of patients diagnosed with SCID between 1999 and 2020 by immunologists or pediatric immunologists throughout Chile, who were presented or referred to centers that had an immunology specialist or were prepared to perform HSCT.

The diagnosis of SCID was made according to the criteria proposed by Shearer et al¹¹ as classic SCID ~~when there is an~~: absence or significantly decreased T cells numbers ($CD3+ < 300$ cells/ μ L) and significantly decreased proliferation ($<10\%$ of the normality limit) in response to phytohemagglutinin (PHA) or presence of maternal T cells.

The diagnosis of Omenn syndrome was defined as the presence of a generalized skin rash with absence of maternal T cells, detectable T cells ($CD3+ > 300$ cells/ μ L), and the absence or less than 30% of normal proliferation to antigens. In cases where there are no proliferation studies, it must present at least four of the following criteria, including at least one of those marked in italics: hepatomegaly, splenomegaly, lymphadenopathies, elevated IgE, eosinophilia, *oligoclonal T cells*, *$> 80\%$ of $CD3+$ or $CD4+$ lymphocytes are $CD45RO+$* , *proliferation to PHA $< 30\%$ of normal*, *proliferation in response to a mixed leukocyte reaction $< 30\%$ of normal*, *or the detection of a mutation in a SCID causing gene*.

From the clinical record, we obtained data corresponding to sex, age at diagnosis, consanguinity, region of origin, lymphocyte subpopulations, genetic diagnosis, infectious and non-infectious complications, BCG vaccination and its complications, age of referral to the HSCT center, and cause of mortality not related to HSCT. The data obtained are expressed as percentages and means with their respective ranges.

The patient's parents were contacted by telephone to obtain informed consent before reviewing the clinical records. In those cases where it was not possible to contact the parents, we ask the director of the respective center not to require informed consent. This study

was evaluated and approved by the pediatric scientific ethics committee of the West Metropolitan Health Service and the ethics committee of Health Sciences of the Pontifical Catholic University of Chile.

Results

Demographic data

During the study period, 25 cases of SCID were diagnosed in 22 families throughout Chile. The mean age at the first manifestation of SCID was 2.3 months (0-7 months), while the mean age at diagnosis was 3.4 months (0-7 months). 16% of patients had a sibling or first cousin affected by SCID. Only one of the 22 families presented consanguinity (4%). The median age at diagnosis of patients with family history of SCID was 3.0 months (0-6 months). Out of 25 patients, 14 (56%) received hematopoietic stem cells transplantation and one patient received gene therapy. The median age at transfer to a center prepared to perform HSCT was 7.4 months (5-16 months). 11/25 patients died before transfer to an HSCT center. 10/25 patients were diagnosed in the Metropolitan Region, the rest of the cases were diagnosed in the Los Lagos Region (4), Valparaíso Region (3), Coquimbo Region (2), La Araucanía Region (2), Libertador Bernardo O'Higgins Region (1), Atacama Region (1), Ñuble Region (1), and Aysen Region (1). Table 1 shows the characteristics of the studied patients.

Clinical manifestations

The most frequent manifestation of SCID was the presence of infections (95.6%), most frequently lower respiratory tract infections (73.9%), sepsis (68%), fungal infections (44%), chronic diarrhea (40%), *Pneumocystis jirovecii* infection (36%), disseminated BCG (32%), and CMV infection (24%). The most frequently observed non-infectious complications of SCID were malnutrition (44%), organomegaly (24%), skin rash (20%), and risk of undernutrition (8%). In two patients of this series, the clinical presentation was Omenn syndrome. Figure 1 shows the clinical manifestations of patients with SCID.

Laboratory studies

At the time of diagnosis, all patients with SCID had lymphopenia. Most patients (87%) had $CD3+$ lymphocyte counts under 300 cells/uL. Lymphocyte proliferation studies were performed in 32% of patients, in those patients in which the test was not performed the causes were the unavailability of the test in their region and T cell counts = 0 cells/uL. In 3 cases the presence of maternal graft in the patient's blood (maternal chimerism) was evaluated by sex chromosome

determination using the FISH technique, while in one case it was carried out using the short tandem repeats (STR) analysis technique. In one patient, a study of T cell receptor excision circles (TRECs) analysis was performed after the diagnosis of SCID (figure 2)¹². One of the patients diagnosed with Omenn syndrome presented increased eosinophil counts (1220 cells/uL) and blood serum IgE levels (112 IU/mL).

More than half of the patients had access to genetic studies (16/25), and all but one of the studied patients presented a genetic etiology. Among the patients who underwent genetic studies, 93% of them did so through research protocols abroad. The most frequently detected genetic defects were mutations in the *RAG2* gene (36%). The two cases of Omenn syndrome in this series were due to mutations in such gene.

Supportive treatments:

All patients received antifungal, *Pneumocystis jirovecii* and herpes prophylaxis. 2/25 of the cases received palivizumab prophylaxis for RSV. All patients received intravenous immunoglobulin before transfer to a transplantation center.

BCG vaccine

88% of the registered patients received the BCG vaccine according to the national immunization program in the first 48 hours of life, including two patients with history of a SCID-affected sibling. Among patients who received the BCG vaccine, 32% experienced pre-HSCT vaccine related complications such as skin nodules, lung involvement, and liver and spleen dissemination. In 36% of the vaccinated cases, the complications associated with the BCG vaccine were the first manifestation of SCID. The mean age at the time of the development of BCG vaccine related complications was 6.4 months (4-9 months). Among patients who received the BCG vaccine before the diagnosis of SCID, 13 patients received isoniazid and 6 patients received isoniazid plus rifampin before the HSCT (table 2).

Discussion

In Chile, the epidemiology of SCID is unknown and there are no previous reports of national series covering large periods of time. Considering the data presented in this work, it is possible to determine that in Chile an average of 3 patients are diagnosed with SCID nation-wide, with an estimated incidence of 1:90,000 live newborns. According to international data, in regions with neonatal screening for SCID, it is likely that this rate may be an underestimation of the actual incidence of the disease since a significant number of cases may die before the diagnosis is suspected.

Nationally, there is a low level of suspicion of PID since they are diseases considered rare and are not regularly included in the undergraduate curriculum of medical schools or graduate programs in pediatrics or family medicine. This could partially explain the difficulties in reaching an early diagnosis even in cases with a family history of the disease. Previous studies in the United States have shown that a family history of SCID significantly reduces the age at diagnosis in affected patients¹³ and this history represents an established warning sign for PID that has been widely disseminated by the Jeffrey Modell Foundation.

The fact that most of the clinical immunologists work in the central area of the country worsens the low diagnostic suspicion, which reflects in that most

Table 1. Clinical characteristics of SCID patients, 1999-2019 (n = 25)

Variable	n (%)
Sex	
Male	20 (80)
Female	5 (20)
Geographical distribution	
North	3 (12)
Center	14 (56)
South	8 (32)
Year	
2000	4 (16)
2005	3 (12)
2007	1 (4)
2008	1 (4)
2010	3 (12)
2011	2 (8)
2012	3 (12)
2015	2 (8)
2017	2 (8)
2018	1 (4)
2019	2 (8)
2020	1 (4)
Consanguinity	
Yes	2 (8)
No	23 (92)
Immunophenotype	
T-B+NK+	4 (16)
T-B+NK-	9 (36)
T-B-NK+	12 (48)
T-B-NK-	0 (0)
Genetic studies	
Yes	16 (64)
No	9 (36)
Mutated gene, n (%)	
<i>IL2RG</i>	7 (28)
<i>RAG2</i>	9 (36)
<i>IL7RA</i>	1 (4)
Desconocido	8 (32)
Deaths before HSCT	11 (44)

of the cases reported in this series lived in this area, mainly the Metropolitan Region, where such professionals are available. Another factor that hinders the timely diagnosis of these patients is the access to diagnostic tests throughout Chile, which is demonstrated by the fact that in 17/25 patients lymphocyte proliferation studies, which allow a functional evaluation of the immune system, were not performed because they were not available. Altogether, these factors would explain the existence of years when no patient has been diagnosed with SCID in Chile, these undiagnosed patients who could have been born in regions without an immunology specialist or without access to diagnostic tests.

SCID is a mortal disease in all affected patients that are not timely treated². HSCT, the only available treatment in Chile, changes the prognosis of SCID from a lethal disease in all cases to a survival rate higher than 90% at five years in those patients transplanted before 3.5 months of age³. Post-transplant survival in patients treated after 3.5 months decreases to 50% at five years, depending on the presence or not of infections at the time of transplantation³. In our case series, 11 patients with SCID died before they could be transferred to a transplant center, 13 patients were treated with HSCT, and one patient received gene therapy as part of an international research protocol. Transplanted patients were transferred to HSCT centers at an average age of 7.4 months. Considering that the average age at diagnosis was 3.4 months, there is evidence of significant

delay in access to curative treatment in this group of patients. This finding is one of the most relevant results of this study, since it identifies a critical point to improve the treatment of patients with SCID in Chile. The delay observed in the referral to transplantation centers, as well as the high frequency of infections in our series, is likely to affect transplantation outcomes.

In our series 64% of the patients had access to genetic studies, most of them through research protocols. In almost all the patients who underwent sequencing studies, we achieved molecular diagnosis, which con-

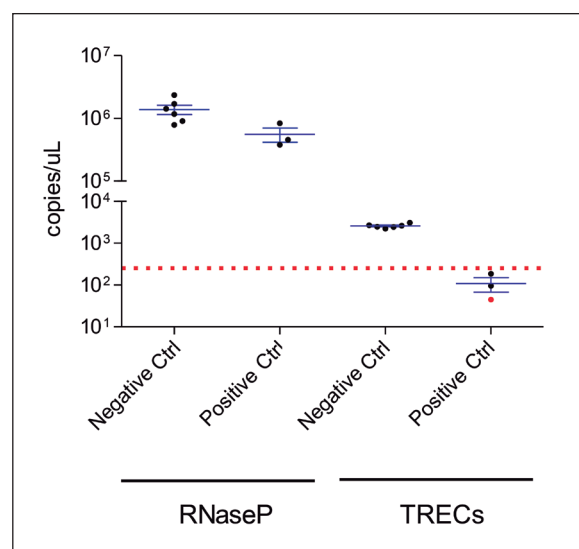


Figure 2. TRECs quantification by multiplex qPCR multiplex on a SCID patient. The dotted red line indicates the cut off value for TRECs quantification by multiplex qPCR (252 copies/mL), results below this cut off are considered abnormal. Data presented as mean and standard error of the mean. RNaseP is quantified as a control to check DNA integrity and its expression must be similar between SCID patients and healthy controls. The red dot indicates a patient with T-B+NK+ SCID. A thymectomized patient and a patient that received thymoglobulin were used as positive controls for severe T cell lymphopenia.

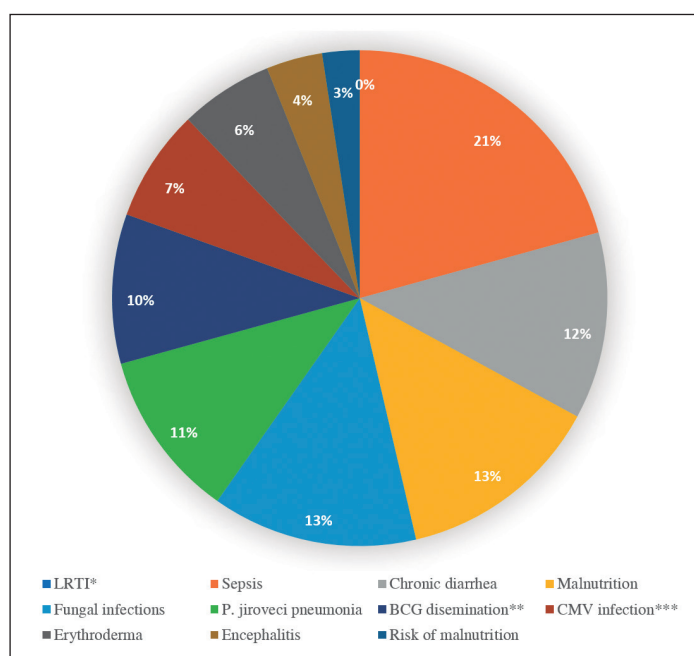


Figure 1. Clinical manifestations of SCID patients, 1999-2019 (n = 25). *LRTI: Lower respiratory tract infection. **BCG: Bacillus Calmette-Guerin. ***CMV: Citomegalovirus.

Table 2. BCG vaccination and related complications in SCID patients, 1999-2019 (n = 25)

Variable	n (%)
BCG vaccination	
Yes	22 (88)
No	3 (12)
BCG related complications	
Yes	8 (36*)
No	17 (64*)
Complication	
Disseminated	7 (87,5)
Local	1 (12,5)

*Percentage of vaccinated patients.

firm the previously reported usefulness of the genetic study techniques currently in use for the study of patients with SCID¹⁴. In this report, the most frequently mutated gene was *RAG2* (36%) followed by *IL2RG* (28%). These findings are different from those reported in the international literature, which reports that in the absence of neonatal screening for SCID, mutations in the *IL2RG* gene explain 46% of cases, while mutations in *RAG2* only affect only 5% of patients with SCID¹⁵. The high frequency of patients with SCID due to defects in *RAG2* stands out, since these defects are inherited in an autosomal recessive manner and the frequency of consanguinity in the country is low. To date, there are no published studies from Latin America that report the breakdown of genetic causes of SCID and the largest proportion of patients with this disease registered in the Latin American Society of Primary Immunodeficiencies (LASID) do not have a genetically confirmed diagnosis. Given these limitations and the low number of patients in this series, it is difficult to clarify whether the high frequency of SCID caused by mutations in *RAG2* is due to a higher proportion of carriers of pathogenic mutations in such gene in our population or whether the distribution of genetic diagnoses in this series is the result of the low number of patients, which would change significantly if all those affected had had access to sequencing studies. Access to genetic studies in patients with SCID not only allows genetic counseling but has also been proven to allow decision-making about the need for transplantation conditioning, as well as to establish both long-term survival and post-transplantation immune reconstitution prognoses¹⁶.

Infectious complications were the most frequent manifestations of SCID in this series, with respiratory and gastrointestinal infections being the most prevalent as in other Latin American series¹⁷. All patients received immunoglobulin and antimicrobial prophylaxis with co-trimoxazole, fluconazole, and acyclovir according to international recommendations¹⁸. In two patients diagnosed during the winter season, palivizumab was used as RSV prophylaxis, which, despite being internationally recommended in SCID patients¹⁸, in Chile is only guaranteed for premature newborns under 32 weeks of gestational age.

A significant percentage of patients experienced infections not preventable by prophylaxis, such as complications associated with BCG vaccination (36%) and CMV infections (24%). CMV infection can be life-threatening in patients with SCID and every precaution should be taken to prevent it, including the use of CMV-negative blood products if necessary, and suspension of breastfeeding in patients whose mothers are CMV-positive¹⁹.

In Chile, the BCG vaccine is administered to all

newborns with birth weight over 2 kg at 48h of life, as established in the national immunization program; however, it is contraindicated in patients with cellular immunodeficiencies. Although it is not a safe vaccine for patients with SCID²⁰, more than 80% of the patients in this series received it at 48h of life, including two patients who had history of an affected sibling with PID.

In patients with SCID who have received the BCG vaccine, vaccine related complications rate are as high as 50-60%, being BCG dissemination the most frequent complication of the vaccine in up to 70% of cases^{17,21}. In our series, 36% of patients experienced BCG related complications, which is a lower percentage than the 51% reported in the largest series of patients with SCID vaccinated with BCG22-; however, the number of patients with a disseminated disease complication in our series is notoriously higher (87.5% v/s 34%). Complications associated with the BCG vaccine in patients with SCID occur in 66% of cases during the first 6 months of life. In line with these international data, the average age at the onset of vaccine complications in our series was 6 months.

Currently, there is no consensus regarding the best antimycobacterial drug regimen in patients with SCID who have received the BCG vaccine; however, it has been reported that in asymptomatic patients there is no significant difference between receiving bi-associated treatment with isoniazid-rifampicin and receiving isoniazid monotherapy²². In our series, 92% of patients received at least isoniazid before referral to HSCT.

The decision to use or not the BCG vaccine and the age of administration established by the immunization programs is complex and must balance the risk of inadvertently vaccinating patients affected by SCID and other mycobacterial-susceptible immunodeficiencies, with the risk of *Mycobacterium tuberculosis* infections in the general population. A study conducted in 2006²³, defined thresholds for tuberculosis infection rate and SCID incidence, to determine when the use of BCG vaccine leads to an increase or decrease in quality-adjusted life years, a measure that combines quality and quantity of life²⁴. Such a study determined that BCG vaccine use is favorable if the annual incidence of tuberculosis is between 0.1 and 1% and the incidence of SCID in the population is between 0 and 5:100,000.

Considering that the current incidence of tuberculosis in Chile is 14:100,000 inhabitants²⁵ and the incidence of SCID is unknown, there are not enough national data to support the suspension of BCG vaccination. However, in the absence of a newborn screening program for SCID and given that even when there is a family history of SCID, affected patients receive the vaccine, major efforts are needed to implement measures to detect patients in whom BCG vaccination should be

postponed until they have been evaluated by an immunology specialist.

Neonatal screening is based on the detection of TRECs from dried blood spots collected on filter paper, which is used for the detection of congenital hypothyroidism and phenylketonuria²⁶. Quantification of TRECs has proven to be a useful tool for diagnosing patients with SCID and other immunodeficiencies characterized by a decrease in the number of circulating T cells, as well as a cost-effective method for early detection of the disease²⁷⁻²⁹. The SCID neonatal screening techniques described internationally and the reported cut-off points apply to our population, as demonstrated by the quantification performed on one of the patients in this series. The massive use of this laboratory test should be promoted by the different scientific societies related to pediatrics, as well as the pertinent authorities, in order to timely identify patients with a lethal pathology whose treatment is available in the country.

This study is the first reports of a multicenter series of Chilean patients with SCID over an extended period of time for the first time. One of the most relevant points in the description of this series of patients is the wide time margin that exists between the diagnosis of SCID and the referral to a transplantation center, a critical point in the treatment of these patients. Facing these data, the implementation of a neonatal SCID screening program in Chile should be considered in order to determine the real incidence of the disease, to increase the safety of BCG vaccine, equalize the diagnostic opportunity of SCID patients throughout Chile,

and reduce the age at which patients receive bone marrow transplantation.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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