ORIGINAL ARTICLE

Severe Combined Immunodeficiency in Brazil: Management, Prognosis, and BCG-Associated Complications

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Abstract

Background: Severe combined immunodeficiency (SCID) is one of the most severe forms of primary immunodeficiency. The objectives of this study were to analyze the diagnosis, treatment, and prognosis of SCID in Brazil and to document the impact of BCG vaccine.
Methods: We actively searched for cases by contacting all Brazilian referral centers.
Results: We contacted 23 centers and 70 patients from 65 families. Patients were born between 1996 and 2011, and 49 (70%) were male. More than half (39) of the diagnoses were made after 2006. Mean age at diagnosis declined from 9.7 to 6.1 months (*P*=.058) before and after 2000, respectively, and mean delay in diagnosis decreased from 7.9 to 4.2 months (*P*=.009). Most patients (60/70) were vaccinated with BCG before the diagnosis, 39 of 60 (65%) had complications related to BCG vaccine, and the complication was disseminated in 29 of 39 (74.3%). Less than half of the patients (30, 42.9%) underwent hematopoietic stem cell transplantation (HSCT). Half of the patients died (35, 50%), and 23 of these patients had not undergone HSCT. Disseminated BCG was the cause of death, either alone or in association with other causes, in 9 of 31 cases (29%, no data for 4 cases).
Conclusions: In Brazil, diagnosis of SCID has improved over the last decade, both in terms of the number of cases and age at diagnosis, although a much higher number of cases had been expected. Mortality is higher than in developed countries. Complications of BCG vaccine are an important warning sign for the presence of SCID and account for significant morbidity during disease progression.

Key words: Primary immunodeficiency. Severe combined immunodeficiency. BCG vaccine. BCG complications. Mycobacterium bovis. Stem cell transplantation.

Resumen

Antecedentes: La inmunodeficiencia severa combinada (IDSC) es una de las formas más graves de la inmunodeficiencia primaria. El objetivo de este estudio fue analizar el estado del diagnóstico, tratamiento y pronóstico de esta enfermedad en Brasil y documentar el impacto de la vacunación con BCG (bacillus Calmette-Guérin).
Métodos: Los casos fueron seleccionados tras contactar con los centros de referencia de Brasil.
Resultados: Se contactaron 23 centros en total, que permitieron recopilar a 70 pacientes entre los años 1996 y 2011 procedentes de 65 familias, 49 de ellos (70%) varones. En más de la mitad de ellos (39), el diagnóstico fue realizado con posteriridad al año 2006. La edad media en el diagnóstico varió entre los 9,7 a los 6,1 meses (p=0.058), antes y después del año 2000, respectivamente, y el tiempo en que se realizó el diagnóstico disminuyó de los 7,9 a los 4,2 meses (p=0.009). La mayoría de ellos (60/70) se habían vacunado con BCG antes del diagnóstico, 39/60 (65%) tuvieron complicaciones con la BCG y en 29/39 (74.3%) la enfermedad se diseminó. En menos de la mitad de los pacientes (30/70, 42,9%) se realizó un trasplate de células madre (HSCT). La mitad de los pacientes (35/70, 50%) murieron; 23/35 de ellos sin HSCT. La diseminación del BCG fue la causa de la muerte, sola o asociada con otras causas, en 9/31 casos (29%, en 4 casos sin datos).
Conclusiones: En conclusión, el diagnóstico de IDSC en Brasil ha mejorado en la última década, tanto en términos numéricos, cómo respecto a la edad de detección de la enfermedad. La mortalidad es alta en comparación con los países desarrollados. La vacuna con BCG provoca complicaciones importantes en estos pacientes, lo cual alerta sobre el posible diagnóstico y progresión de esta enfermedad.

Palabras clave: Inmunodeficiencia primaria. Inmunodeficiencia severa combinada. Vacuna BCG. Complicaciones BCG. Mycobacterium bovis. Transplante de células madre.

Introduction

Severe combined immunodeficiency (SCID) is characterized by the absence or dysfunction of T lymphocytes associated with a defective antibody response. Left untreated, patients will eventually die by their second year of life [1], which means that early diagnosis and good clinical management are critical [2]. SCID defects are classified according to immunological phenotype (SCID with absence of T lymphocytes and presence of B lymphocytes [T–B+ SCID] or SCID with absence of both T and B lymphocytes [T–B– SCID]). Both groups include forms with or without natural killer (NK) cells [2], and clinical presentation is similar [1,3]. There are many genetic causes of SCID, and mutations in more than 13 genes have already been identified [3,4]. In Europe and North America, the incidence of SCID is estimated to be at least 1 case per 100,000 per year [4,5]. In Brazil, laboratory diagnosis is based on variable total and subset lymphocyte counts and absent thymic shadow in the chest radiograph. Laboratory tests such as the lymphocyte proliferation assay, evaluation of chimerism (maternal T-cell engraftment), and molecular diagnosis are rarely available. Supportive treatment includes broad-spectrum antibiotics, antifungals, and intravenous immunoglobulin (IVIG) while waiting for hematopoietic stem cell transplantation (HSCT), the only curative treatment available [2,4].

BCG vaccine, which is contains a live attenuated *Mycobacterium bovis* strain, is part of the nationwide Brazilian vaccination schedule. It is given to all children during the neonatal period. Complications of the vaccine, especially disseminated infection, are known to occur in immunodeficient patients, particularly those with SCID [6], who are asymptomatic when they receive the vaccine.

Epidemiologic data on SCID are scarce in Brazil. The objectives of this study were to analyze the diagnosis, treatment, and prognosis of SCID in Brazil and to document the impact of BCG vaccination on these patients.

Methods

All Brazilian referral centers for diagnosis and treatment of primary immunodeficiencies and pediatric HSCT centers,

which are connected to the network formed by the Brazilian Group for Immunodeficiencies and the Brazilian Association of Allergy and Immunopathology, were contacted by e-mail, by telephone, or in person. Charts were retrospectively reviewed based on a standard data collection form that also included information about BCG vaccination. Data were collected from 2009 to 2011.

SCID was defined according to the diagnostic criteria of the Pan-American Group for Immunodeficiencies and the European Society for Immunodeficiencies (ie, definitive, probable, and possible) [7]. Additionally, purine nucleoside phosphorylase deficiency, Omenn syndrome, and complete DiGeorge syndrome were also considered to be presentations of SCID [2,5,8]. BCG-associated complications were defined based on the classification of the Manual of Postvaccination Adverse Events published by the Brazilian Ministry of Health. The complications included local/regional lesions (ulcer >1 cm in diameter, cold/hot subcutaneous abscess, regional suppurative lymphadenopathy, and lupus-like reaction), disseminated lesions, involvement of >1 organ, and BCG isolated from the skin, osteoarticular tissue, and distant lymph nodes.

The association between categorical variables was evaluated using the chi-square or Fisher exact test, the latter in the case of small samples. The Mann-Whitney test was used to compare groups with a nonnormal distribution.

The Ethics Committee of the Federal University of São Paulo, São Paulo, Brazil approved the study.

Results

Demographics

We contacted 31 physicians from 23 centers (28 responded) and 70 patients from 65 families. Based on the data obtained, the diagnostic criteria, and the fact that no molecular testing had been performed in most cases, patients were classified as having definite SCID (n=7) and probable SCID (n=63). Of these, probable Omenn syndrome was diagnosed in 8 patients (1 B+ and 7 B– phenotype) and complete DiGeorge syndrome in 3. Table 1 shows patient characteristics (totals do not reach 70 owing to missing data in some cases). As of 2011, age ranged from 0 to 15 years (median 5.4, mean 6.2). A suggestive or confirmed positive family history for SCID was observed in 19 families. Twenty siblings were affected, although available data were insufficient to include these cases in the analysis. Eight children were diagnosed at birth or before clinical manifestations because they had a previously affected sibling. Overall, 24 patients were T–B+ and more than half (13/24) were males.

Clinical Manifestations

The most frequent clinical manifestations were pneumonia (unspecified, *Pneumocystis jiroveci*, bacterial, viral) in 41 of 64 patients (64.1%), followed by chronic/acute diarrhea in 30 of 64 (46.9%), candidiasis in 29 of 64 (45.3%), sepsis in 26 of 64 (40.6%), failure to thrive in 23 of 64 (35.9%), skin rash/eczema/erythroderma in 23 of 64 (35.9%), lymphadenopathy and/or hepatosplenomegaly in 22 of 64 (34.4%), and acute otitis media in 13 of 64 (20.3%). These common clinical manifestations were observed equally in T–B+ and T–B– phenotypes.

A pair of siblings (one received BCG, the other did not) were infected by *Mycobacterium kansasii*, which was very difficult to manage. Both patients died.

Table 1. Patient Characteristics

Patients, No.	70
Families, No.	65
Year of birth	From 1996 to 2011
Gender, No. (%)	
Male	49 (70)
Female	21 (30)
Consanguinity in the family, No. (%)	
Yes	16 (23)
No	42 (60)
Unknown	12 (17)
Immune phenotype (retrospective data), No. (%)	
T–	4 (5.7)
T–B–	2 (2.9)
T–B–NK–	17 (24.3)
T–B–NK+	23 (33)
T–B+	1 (1.4)
T–B+NK–	8 (11.4)
T–B+NK+	15 (21.4)
Patients according to the year of diagnosis (n=68), No. (%)	
As of 2000	11 (16.2)
2001-2005	18 (26.5)
2006-2011	39 (57.3)
Age at diagnosis (n=68), mo, mean (SD), median (range)	6.7 (5.7), 8 (0-22)
As of 2000 (n=11)	9.7 (6.9), 8 (0-22)
2001 to 2011 (n=57)[a]	6.1 (5.4), 5 (0-22)
Age at first clinical manifestation (n=58), mo, mean (SD), median (range)	3.3 (4.0), 2 (0-19)
Diagnostic delay (n=49), mo, mean (SD), median (range)	4.8 (4.2), 4 (1-20)
As of 2000 (n=8)	7.9 (4.8), 6.5 (3-17)
2001 to 2011 (n=41)[b]	4.2 (3.8), 3 (1-20)
Time between diagnosis and transplant (n=30), mo, mean (range)	5.8 (0-41)
Deaths, No. (%)	35 (50)
Age at transplant, mo, mean (range)	11.4 (1-41
Transplanted, No. (%)	30 (43.5)
Alive	18 (60)
Dead	12 (40)
Not transplanted	39/69
Alive, waiting for transplant	16 (41)
Dead	23 (59)
Lost to follow-up	1 (1.4)
Number of transplants performed before the age of 3.5 mo, No. (%)	4 (13.3)

[a]Mann-Whitney test (*P*=.058)
[b]Mann-Whitney test (*P*=.009)

Laboratory Tests

At the time of diagnosis, 31 of 42 patients (73.8%) had absolute lymphocyte counts that were inadequate for age-specific reference values. Most patients (52/57, 91.2%) had $CD3^+$ T-cell counts below the tenth percentile (P10) for age (reference values for the Brazilian population). B-cell counts were below P10 in 44 of 61 patients (72.1%), adequate in 9 of 61 patients (14.8%), and above P90 in 8 of 61 patients (13.1%). NK cell counts were below P10 in 28 of 56 patients (50%), adequate in 18 of 56 patients (32.1%), and above P90 in 10 of 56 patients (17.9%).

Low or absent lymphocyte proliferation after stimulation with mitogens was detected in 11 patients. The presence of maternal T-cell engraftment was evaluated in 8 patients and was negative in all cases. Analysis of peripheral blood T-cell subpopulations (6 cases diagnosed after 2010) using flow cytometry revealed a deficiency of naive T cells. The result of the T-cell receptor excision circle assay performed in 2 patients was zero in both cases. Data on adenosine deaminase and uric acid levels (for diagnosis of purine nucleoside phosphorylase deficiency) were available in less than 10% of cases. In 7 patients clinically diagnosed with possible Omenn syndrome, eosinophil counts were markedly increased and varied from 1394/mm^3 to 22 833/mm^3 (mean, 6756/mm^3). In 2 of 7 patients with Omenn syndrome, serum IgE was >2000 IU/mL (data were not available for 1 patient). Thymic shadow was absent in the chest x-ray in 22 of 28 cases where this finding was mentioned. The patient was considered small for age in 2 of 28 cases and doubtful in 4 of 28 cases.

Fluorescence in situ hybridization findings were positive in 2 patients with complete DiGeorge syndrome (data were unavailable for 1 patient). *RAG1* deficiency was identified in 1 case and *IL7RA* deficiency was found in 3 cases. Purine nucleoside phosphorylase deficiency was detected in 1 case.

Supportive Care

Data on 60 of the 70 patients showed that 54 (90%) used trimethoprim/sulfamethoxazole for prophylaxis of *P jiroveci* pneumonia and had received IVIG before transplant. Broad-spectrum antibiotics and antifungal agents were used in 46 of 60 patients (77%) after diagnosis.

BCG Vaccination

Table 2 shows data on BCG vaccination and its complications. In the 9 unvaccinated patients, the newborn was either severely sick or had a previously affected sibling. All patients received the BCG Moreau/Rio de Janeiro strain as an intradermal injection in the right deltoid muscle. Figure 1 shows the clinical manifestations of BCG vaccine complications. Data were available for 38 cases. Some patients had multiple manifestations.

Data on laboratory investigation of *M bovis* were available in 10 of 29 cases of dissemination. Acid-fast bacilli staining was positive in 6 cases (in the pleural effusion, lung, liver, bone marrow, and lymph node), polymerase chain reaction was positive for *Mycobacterium tuberculosis* complex in 2 cases (lungs), and 2 had a positive culture for *M tuberculosis* complex (lymph node and subcutaneous nodule).

Table 2. BCG Vaccination and Associated Complications[a]

Received BCG vaccine (n=70)	Yes	60 (86)
	No	9 (13)
	Unknown	1 (1.4)
Complication (n=60)	Yes	39 (65)
	No	21 (35)
Type of complication (n=60)	Disseminated	29 (48.3)
	Localized	10 (16.6)
Age at vaccination, mo (n=20), mean (range)[b]		0.65 (0-4)
Age at presentation of the complication, mo (n=33), mean (range)[b]		3.7 (0-15)
BCG complication as first clinical manifestation		12 (20)

[a]Data are expressed as No. (%) unless otherwise indicated.
[b]Data available for 20/60 and 33/39.

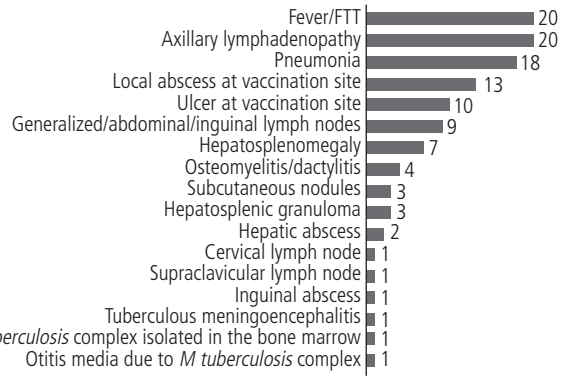

Figure 1. Clinical manifestations of BCG vaccine complications (data available for 38 patients).

For patients who had not undergone transplantation and during the pretransplant period, antituberculosis drugs (isoniazid or isoniazid+rifampicin+ethambutol) were used for prophylaxis in 5 cases (because of BCG vaccination). All other patients were treated after clinical symptoms had started with a variety of drug combinations that included most frequently isoniazid+rifampicin+ethambutol. Other 4-, 5-, and 6-drug combinations used included clarithromycin, azithromycin, streptomycin, ciprofloxacin, ofloxacin, etionamide, amikacin, and terizidone. Pyrazinamide was used in 10 cases. These data were obtained from 45 patients. Out of 25 transplanted patients who had been vaccinated, 14 had BCG complications before, during, and after transplantation. Reactivation of a previously resolved infection was recorded in 2 cases. The remaining 9 patients had no posttransplant BCG complications. Of these, 7 received prophylaxis, and no antituberculosis drugs were used in 2. All the other patients were treated with drug combinations that did not differ from those of the pretransplant period. The mean duration of antituberculosis therapy was 3.8 months (range, 0-9 months) before transplant and 11.9 months (range, 0-48 months) after transplant and also for those who had not yet undergone transplantation (data for 23 patients).

Outcome

Half of the patients died (35/70, 50%). Figure 2 shows the causes of death in patients who had not undergone transplantation (19/31) and those who had (12/31). The cause of death was not available for 3 patients, and 1 case was lost to follow-up. Mean time to death after transplant was 78.9 days (range, 0-460 days). Figure 3 highlights the number of deaths due to disseminated BCG (alone or associated with other causes). For patients who were still alive and had had a BCG vaccine complication (13/39), whether or not they had received a transplant, the complication eventually resolved.

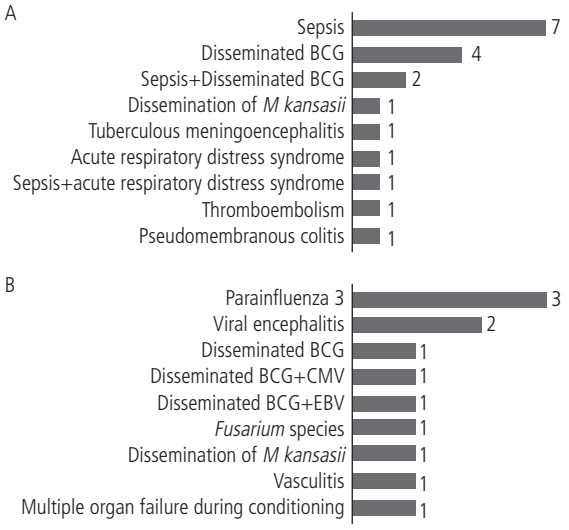

Figure 2. A, Causes of death in nontransplanted patients (data available for 19 patients). B, Causes of death in transplanted patients (data available for 12 patients). EBV indicates Epstein-Barr virus; CMV, cytomegalovirus.

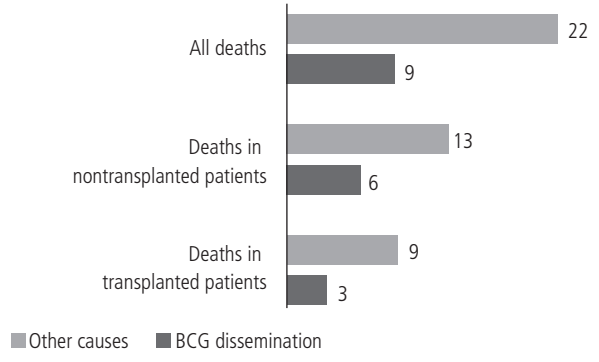

Figure 3. Deaths due to BCG dissemination (alone or in association with other causes) (data available for 31 patients).

Discussion

Few epidemiologic data for SCID have been published in Brazil. Physicians' lack of awareness of SCID highlights an urgent need to improve knowledge of the disease [9]. An active search for cases based on a standard collection form was used in other studies [10,11,12]. We obtained responses from most referral centers in Brazil, although we cannot verify the thoroughness of reporting. All cases had been diagnosed or treated by the doctors we contacted. Owing to the severity of SCID, patients have to be referred to a specialist and thereafter to a transplant center. However, very few transplant centers care for patients with primary immunodeficiency. Furthermore, since lymphocyte subset tests are not routinely performed in the national health system, diagnosis must be made at a referral center. Data from the Latin American Society for Immunodeficiencies (LASID) Registry reveal 31 SCID patients in Brazil and a change in the estimated minimal incidence from 0.04 to 0.12 cases per 100 000 per year before and after 1996, respectively [13]. Therefore, the number of cases we obtained is most likely very close to the real number of current diagnoses. However, analysis of published incidence worldwide indicates that our data may have been underestimated. In 2010, the Brazilian population was approximately 200 million people and there were 3,638,100 live births; consequently, considering an incidence of 1 case per 100 000 per year, we would expect 36 new cases per year. A few cases were diagnosed before symptoms appeared in patients with a positive family history. Comparison with the findings of other authors revealed that median age at diagnosis [5] was similar to the age we recorded, although the mean diagnostic delay was longer [10,14]. It is remarkable that more than half of the diagnoses were made after 2006 and that there were significant decreases in mean age at diagnosis and in diagnostic delay after 2001. These findings most likely reflect an overall improvement in disease recognition. In the last decade, the LASID Registry has been consolidated, and the Brazilian Group for Immunodeficiencies, with the help of the Jeffrey Modell Foundation (which established a center in Brazil in 2007), has developed physician education programs that are changing how SCID is recognized and diagnosed. Nevertheless, much work remains to be done to increase awareness of SCID. Programs should target neonatologists, general pediatricians, intensive care specialists, and family physicians.

Although X-linked is the most common form of SCID in humans, 63.6% of the patients we describe were T–B–, an immunophenotype that is more compatible with autosomal recessive inheritance. In addition, only 54% of T–B+ patients were males. Recent reports from Iran and Greece showed a predominance of autosomal forms and the common γ chain defect in a minority of cases [12,15]. The reasons for our findings could be either an incorrect classification or a true genetic variation in our population; further investigation is necessary. The immunology workup enabled us to classify most cases as probable SCID. Unfortunately, the lack of a genetic diagnosis prevented us from reaching a more accurate definition. There is a clear need to improve the availability of laboratory tests and the quality of diagnosis, especially in cases where lymphopenia is not so evident. Leiva et al [16] showed that this type of testing is generally limited in Latin America by technical and financial restrictions. Consequently, the development of a laboratory network in Brazil and the rest of Latin America is required in order to address these restraints [16].

The most common clinical manifestations were typical and consistent with what was expected for SCID [3,7]. No local

tropical/endemic diseases were recorded, probably because exposure was too short. In most cases, the causative organisms were not identified and patients were treated empirically, as in other centers [1,4]. Supportive care, which was provided mostly by immunologists after diagnosis, seemed unsatisfactory, given that not all patients received trimethoprim-sulfamethoxazole and IVIG before HSCT, as they should have according to standard practice. This observation was also reported in a recent survey of Brazilian allergists and immunologists [17].

In Brazil, the first transplant in a patient with SCID was performed in 1998. Very few data on HSCT in primary immunodeficiencies in Brazil or in Latin America have been published, and no specific data are available for SCID [18]. In comparison with American and European cohorts, overall mortality was very high, especially considering that 23 of 35 patients died before transplant. Mean age at transplant was high, and very few patients underwent transplantation before 3.5 months of life, when prognosis is thought to be better [3,19,20]. Infection (mainly sepsis) accounted for most deaths irrespective of whether the patient had undergone a transplant. Viral infections played a major role, since they were difficult to treat. Viral infections were also problematic in international cohorts, and their absence before transplantation was associated with overall better prognosis [19,20]. The viruses described were similar to those of the transplant recipients in the present study.

BCG Vaccine Complications

Brazil is one of the 22 countries where 82% of all cases of tuberculosis worldwide are concentrated. In this context, the importance of the BCG vaccine is evident, especially for meningeal and miliary forms of tuberculosis. Controversy exists over the protective efficacy of the BCG vaccine against pulmonary tuberculosis, the clinical form that has the greatest impact on tuberculosis control. National public health policies guarantee excellent immunization coverage and make every effort to vaccinate in the neonatal period [21]. In Sweden, Romanus et al [22] suggested that vaccination should be postponed until 6 months of age in countries where there is a low general risk of neonatal tuberculosis. Taking a thorough family history before BCG injection could be a simple and efficacious method of avoiding inappropriate vaccination of an immunodeficient child with previously affected siblings [23]. Once newborn screening for SCID becomes a reality in Brazil, issues concerning timing of BCG vaccination will be discussed [24].

Not all SCID patients experience complications with the BCG vaccine. Some may only experience localized infection, although dissemination is common and can occur without previous local signs [25]. In some cases, BCG disease activity starts only after posttransplant immune reconstitution [26]. In Brazil, an adverse reaction to BCG vaccine is one of the 10 warning signs for primary immunodeficiencies adapted from the Jeffrey Modell Foundation/American Red Cross. In the cases we report, 2 of every 3 patients experienced BCG vaccine complications; almost 1 in 4 had only localized disease, and 3 in 4 had disseminated BCG infection. It is significant that complications of BCG were the first clinical manifestation in 20% of vaccinated patients. These figures are higher than in other case reports [12,14]. The most frequent clinical manifestations of BCG complications were as expected and comparable to those reported recently in 2 studies from Iran [27,28]. Overall, the age at onset of BCG vaccine–related complications was consistent with the age at onset of other clinical manifestations. Given that all patients received the BCG Moreau/Rio de Janeiro strain and that various strains have been associated with different frequencies of adverse events [29], a strain-related factor might be involved in these complications.

The classification of disseminated BCG infection is unresolved [30,31]. Recently, Bernatowska et al [32] proposed criteria for the diagnosis of disseminated BCG infection in patients with primary immunodeficiency. The authors stated that more than 200 cases of disseminated BCG infection had been reported in the literature and pointed out the difficulties in confirming a diagnosis. *M bovis* was not isolated in any of our patients. However, positive acid-fast bacilli smears or *M tuberculosis* complex cultures were found in some cases. Therefore, suspicion of *M bovis* infection should be based on the clinical history and physical examination, and the possibility of disseminated disease should be considered in any diagnosed case of SCID [33].

In most cases, BCG infection was present prior to transplantation, and the decision to administer antituberculosis drugs depended on the clinical symptoms. Several authors have proposed drug combinations and management strategies for BCG infection [31,32,34]. In contrast to other BCG strains, *M bovis* from the Moreau/Rio de Janeiro strain is sensitive to isoniazid [36]. Prophylaxis with isoniazid for all vaccinated patients might prevent complications. Withdrawal of the antituberculosis drugs is a prolonged process, leading to increased toxicity and morbidity. Since there are no clear guidelines on the most suitable treatment for disseminated BCG infection in patients with SCID, possible explanations for poor prognosis include delay in diagnosis or treatment and initial treatment with pyrazinamide, to which BCG is uniformly resistant. Mortality related to disseminated BCG infection, which is difficult to determine because of the presence of concomitant infections, was very high compared to the findings of previous reports [14,30].

Conclusion

In Brazil, diagnosis of SCID has improved over the last decade, both in terms of the number of cases and age at diagnosis, although a much higher number of cases had been expected. The immunology workup should be improved in order to enhance the quality of diagnosis. Supportive care is inadequate, and accessibility to curative treatment is poor; therefore, mortality is higher than in developed countries. BCG vaccine–related complications are an important warning sign for the presence of SCID and account for significant morbidity during disease course.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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