PROTOCOLS

Severe combined immunodeficiency

Principal investigators

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Background

Severe combined immunodeficiency (SCID) is a serious, life-threatening condition with high morbidity and mortality. While no Canadian data is available on the incidence of SCID, it would appear that the rate is higher in the aboriginal population. As part of the strategy to reduce the incidence and severity of tuberculosis (TB) in children living on reserves with endemic TB, the First Nations and Inuit Health Branch (FNIHB) of Health Canada recommends the use of the live, attenuated BCG (bacille Calmette-Guerin) vaccine for newborns. Six cases of disseminated BCG infection in First Nations and Inuit children were reported between 1993 and 2002. All six children died, four had SCID, one was HIV positive and one had another immunodeficiency. The observed rate of disseminated BCG in First Nations and Inuit populations in Canada is 205 cases (CI 42-600) per 1,000,000 doses), greatly exceeding global estimates of 0.19–1.56 cases per 1,000,000 doses given. It may well be that this unusual rate of disseminated BCG infection is associated with a high incidence rate of SCID in the Aboriginal population. Hence, data on the incidence of SCID is required to make an evidence-based decision about the risks and benefits of continuing to offer BCG vaccine to First Nations and Inuit children on reserves with endemic tuberculosis, and to guide future decisions regarding discontinuation of BCG vaccination.

SCID, a group of rare genetic disorders characterized by profound abnormalities in the development and function of the T and B lymphocytes and natural killer cells, was first reported more than 50 years ago. In the past two decades, great advances have been made in the understanding and treatment of SCID. A variety of molecular defects have recently been found to cause SCID, including defects in

the gene encoding the common gamma chain (X-linked form), adenosine deaminase deficiency (ADA), interleukin-7 receptor deficiency, janus tyrosine kinase-3 (JAK-3) deficiency and recombinase activating gene (RAG)-1 and RAG-2 deficiency.[1,2] The two most common forms of SCID are the X-linked SCID (about 50% of all cases) and those due to an ADA deficiency (about 15-20%).[2]

Epidemiology

General estimates of the incidence of SCID range from 1 in 75,000–100,000 live births[1] with higher than expected rates in Switzerland at 24.3 in 100,000 live births and in the United States Navajo population at 52 in 100,000 live births. No Canadian incidence data for SCID is available.

Clinical presentation

Infants with SCID usually present in the first few months of life with frequent episodes of diarrhea, pneumonia, otitis, sepsis and cutaneous infections. Growth may appear normal initially, but severe wasting begins soon after infections and diarrhea start.[1–3] The median age at diagnosis is 4.6 months of age (range 0–812 days),[3] which is about two months after the first clinical manifestations. Persistent infections with opportunistic organisms, such as *Candida albicans, Pneumocystis carinii*, varicella, adenovirus, parainfluenza, cytomegalovirus, Epstein-Barr virus (EBV), and bacillus Calmette-Guérin (BCG), may lead to death.[2] Oral and/or genital ulcers have been described as a distinctive finding among Athabascan-speaking American Indian children with SCID, including the Dene of the Northwest Territories. These infants also lack the ability to reject allografts, leaving them at risk for fatal graft-vs-host disease (GVHD).[1]

Diagnosis

A persistent lymphocyte count of less than 3,000 is the most important clue in diagnosis[3] and should alert physicians to the possibility of SCID and the need for such further immunologic investigation as lymphocyte subset enumeration and immunoglobulin levels.

The diagnostic criteria for primary immunodeficiencies (Table 1) put forth in 1999 by PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies), were designed to "establish simple, objective, and clear guidelines to ensure that different physicians and scientists are using the same definitions."[4]

Differential diagnoses

The following differential diagnoses should be considered for SCID:[3]

- HIV infection
- Cystic fibrosis
- Other primary immunodeficiencies

Severe combined immunodeficiency (continued)

Table 1: Diagnostic criteria for primary immunodeficiencies

Severe combined immunodeficiency (SCID)

A. Definitive

Male or female patient less than 2 years of age with either (a) engraftment of transplacentally acquired maternal T cells or (b) less than 20% $CD3^+$ T cells, an absolute lymphocyte count of less than 3000/mm^3, and at least one of the following:

1. Mutation in the cytokine common gamma chain (yc)
2. Mutation in JAK3
3. Mutation in RAG1 or RAG2
4. Mutation in IL-7R*a*
5. ADA activity of less than 2% of control or mutation in both alleles of ADA

B. Probable

Male or female patient less than 2 years of age with (a) less than 20% $CD3^+$ T cells, an absolute lymphocyte count of less than 3000/mm^3, and proliferative responses to mitogens less than 10% of control or (b) the presence of maternal lymphocytes in the circulation

X-linked severe combined immunodeficiency (XSCID)

A. Definitive

Male patient (under 2 years) with either (a) engraftment of transplacentally acquired maternal T cells or (b) less than 10% $CD3^+$ T cells, less than 2% $CD16/56^+$ NK cells, and more than 75% $CD19^+$ B cells and who has one of the following:

1. Mutation in the cytokine common gamma chain (yc)
2. Absent yc m RNA on Northern blot analysis of lymphocytes
3. Absent yc protein on the surface of lymphocytes or lymphocyte cell lines
4. Maternal cousins, uncles, or nephews with severe combined immunodeficiency

B. Probable

Male patient (under 2 years) with less than 10% $CD3^+$ T cells, less than 2% $CD16/56^+$ NK cells, and more than 75% $CD19^+$ B cells who has all of the following:

1. Onset of failure to thrive before 1 year of age
2. Serum IgG and IgA more than 2SD below normal for age
3. Persistent or recurrent diarrhea, URI or thrush

C. Possible

Male patient with greater than 40% $CD19^+$ B cells in the peripheral circulation and one of the following:

1. Engraftment of transplacentally acquired maternal T cells
2. Maternal cousins, uncles, or nephews with a history of severe combined immunodeficiency

Clinical management

The prognosis for infants with SCID is greatly improved if they are diagnosed and treated before overwhelming infection develops. In fact, it should be considered a paediatric emergency, as the expected outcomes for infants with SCID are very poor, unless immune reconstitution can be accomplished.[2] If they

are not treated, most children will die before the age of one or two. Since 1981, the development of bone marrow transplant (BMT) has allowed the successful use of haplo-identical (parental) and unrelated mismatched donors. Related marrow donors, other than HLA identical siblings, can give a 95% success rate if performed within the first 3.5 months of the life of an infant with SCID.[2] Success rates vary depending on the type of SCID, the donor and transplant regimen, the presence of opportunistic and other infections. Adenosine deaminase deficiency may also be treated by weekly intramuscular injections of a substituted enzyme.[1] Finally, gene therapy has been used successfully in infants with X-linked SCID and holds promise as an area of future development.[1]

As part of the patient care strategy is to reduce the incidence of opportunistic infections, prophylaxis and early identification and treatment of infections is crucial. Also, it is important to remember that if SCID is suspected, the child should not receive any live vaccines. Therefore, if an infant is under investigation for this disease and has not yet received BCG, the vaccine should not be given until a definitive diagnosis has been made.

Methods

Through the active participation of nearly 2,400 paediatricians and paediatric subspecialists who respond monthly to the CPSP, it is anticipated that sufficient data will be collected to capture cases of SCID in Canada, since the majority of cases will be referred to a specialist due to the severity of this disease. As well, it is expected that infants in Aboriginal populations residing in remote or Northern communities will be transferred outside their home community for specialized care.

Data collection tool and analysis

The proposed data collection tool will be used to record demographics according to the standard ethnicity breakdown, clinical information including investigations, as well as treatment and outcome information about each case. Obtaining data on Aboriginal demographics is critical, because of the concern about the risk of disseminated BCG infection.

Due to the rarity of the condition, the study will focus on disease incidence and basic descriptive analysis of demographic, clinical and outcome data.

Demographic and clinical data

The variables to be described will include gender, country of birth, Aboriginal ancestry, age at diagnosis, main clinical presentations (including disseminated BCG infection), treatment (particularly BMT status) and outcome. The description will include counts, proportions and means depending on the number of cases captured.

Severe combined immunodeficiency (continued)

Disease Frequency

Disease frequency in the Canadian paediatric population will be calculated as follows:

a. SCID incidence rate in Canadian children:

$$\frac{\text{number of CPSP confirmed cases}}{\text{number of live Canadian births*}} \text{ over the study period}$$

* Derived from provincial vital statistics; expressed as number of cases per 100,000 live births. Source: Statistics Canada

It is possible that no Aboriginal cases of SCID will be identified during the time period, due to the expected small numbers. However, if cases are reported, the following measure of disease frequency is proposed.

b. SCID incidence rate in Aboriginal children:

$$\frac{\text{number of CPSP confirmed cases in Aboriginal children}}{\text{number of live births in the Aboriginal population*}} \text{ over the study period}$$

* For an estimate of the number of births in the Aboriginal population, FNIHB is able to produce (in-house) birth rate data collected through provincial vital statistics. Although this data source has identified weaknesses, it is the only feasible source of birth rate information for this population. This data will be supplemented by Indian and Northern Affairs Canada (INAC) and census data, for the Inuit and off-reserve population.

In addition, the number of cases reported through the CPSP will be compared to the number of SCID cases identified through the hospital discharge database of the Canadian Institute for Health Information (CIHI) to assess completeness of reporting.

Case definition

Report any child less than two years of age with:

- the clinical features of SCID (i.e., chronic diarrhea, recurrent pneumonia, failure to thrive, persistent thrush, opportunistic infections, etc.)

and at least one of the following:

- an absolute lymphocyte count of less than 3000/mm^3 or less than 20% CD3$^+$ T cells
- familial history of primary immunodeficiency.

Exclusion criteria

Infants with HIV infection or cystic fibrosis.

This CPSP case definition for SCID is less specific than the PAGID/ESID diagnostic criteria for primary immunodeficiencies, which require additional diagnostic investigations that are not always readily available to community-based paediatricians. Study investigators will therefore need to review each case report individually to determine if it is a confirmed case of SCID.

Objectives

- To estimate the incidence of SCID in Canada.
- To estimate the incidence of SCID in Aboriginal children in Canada.
- To describe the basic demographics, clinical features and outcomes of SCID in Canada.

Duration

April 2004 to March 2006 (renewable)

Expected number of cases

Based on the existing estimates for the rate of SCID and the annual birth rate in Canada, the expected number of new cases of SCID is three to 17 per year. Due to the rarity of SCID, the study may need to be extended to a period of five years, in order to capture sufficient cases. The project team will review the case numbers and decide whether to seek an extension in September 2005.

Ethical approval

Health Canada Research Ethics Board
Research Ethics Board at IWK Health Centre

Analysis and publication

Data will be analyzed by the investigators, and annual reports will be distributed to all CPSP participants.

Data will be published in a peer-reviewed journal when the two-year study is completed.

References

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4. Conley M, Notarangelo L, Etzioni A (representing PAGID, Pan-American Group for Immunodeficiency, and ESID, European Society for Immunodeficiencies). Diagnostic criteria for primary immunodeficiencies. *Clin Immunol*; 93:3 December 1999: 190-7.