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Severe combined immunodeficiency: A national surveillance study

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National immunodeficiency registers in several countries have reported prevalence but not incidence rates for severe combined immunodeficiency (SCID). The objective of this study was to document the incidence and type of SCID in Australia, the age and clinical features at presentation and short-term management. The Australian Paediatric Surveillance Unit conducts active, monthly, national surveillance of rare disorders with reporting by child-health specialists. Between May 1995 and December 2001, clinicians provided clinical and laboratory data on children newly diagnosed with SCID. Thirty-three incident cases of SCID were identified [incidence $1.8/10^5$ live births per annum; 95% confidence interval (CI) 1.2–2.5]. Twenty-six children had classical SCID ($1.45/10^5$ live births; 95% CI, 0.9–2.0) and 20 (77%) of these were boys. Classical SCID was X-linked in 13 children, autosomal recessive (AR), not further classified in four, and attributed to adenosine deaminase deficiency (ADA) in four, interleukin-7 receptor alpha chain deficiency in one, Ommen syndrome in two, and Di George syndrome in two. Twenty-one (81%) received bone marrow/stem cell transplantation, three of whom died between 1 and 4 months after transplantation (two ADA deficient, one AR). Seven children had atypical SCID, five of whom died within 1–4 yr of diagnosis. Most children with SCID presented with failure to thrive and recurrent infections and there was no significant delay between presentation and diagnosis. The reported national incidence of classical SCID in Australia ($1.45/10^5$ or ~4 cases per year or 1/69,000 live births) is consistent with the rate ($1.4/10^5$) previously reported in Victoria. Diagnosis is rarely delayed, and transplantation is associated with good short-term survival.

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Severe combined immunodeficiency (SCID) is a group of rare primary immunodeficiencies (PID) (1, 2), in which, affected children have lymphopenia and low immunoglobulin levels in addition to absent B- and T-lymphocyte function from birth. Children in infancy present with recurrent, severe or opportunistic infections, failure to thrive, rash and hepatosplenomegaly. Left untreated, most children die before the age of 2 yr. The inheritance is X-linked or autosomal recessive (AR). Standard treatment includes immunoglobulin replacement, antimicrobial prophylaxis, enzyme replacement therapy, stem cell transplantation and gene therapy.

National immunodeficiency registers, established in several countries, were not designed to assess disease incidence (3–10). The annual SCID incidence has been estimated in one Australian state (11) to be approximately 1:71,000 live births. The Australian Paediatric Surveillance Unit (APSU) study is the first prospective national incidence study on SCID conducted since improved and more sensitive diagnostic methods, including lymphocyte subset analysis by flow cytometry, have become readily available.

The aims of the study on SCID were to determine: (i) the incidence of SCID in Australia;

(ii) the age, clinical features and duration of symptoms at diagnosis; (iii) the proportion of children referred for and receiving stem cell transplantation; and (iv) the short-term survival of SCID with or without transplantation.

Methods

The APSU surveillance method has been previously described (12). In brief, all pediatricians known to be in clinical practice in Australia receive a monthly card or e-mail message asking them to indicate the number of children newly diagnosed with a selection of uncommon conditions and seen by them in the preceding month. For the duration of the study on SCID, all members of the Australian Society of Clinical Immunology and Allergy, including immunologists practicing adult medicine, also received monthly report cards.

Severe combined immunodeficiency was reportable to the APSU between May 1995 and December 2001 (inclusive). Pediatricians were asked to report any child newly diagnosed with classical, atypical or suspected SCID that was seen in their practice. The case definitions used are shown in Table 1. Pediatricians reporting for May 1995 were also asked to include any cases seen in the period between January and May 1995. During the period 1997–99 (inclusive), APSU reporting was expanded to include all PID.

Clinicians who notified a case of SCID were sent a brief, reply-paid questionnaire requesting de-identified clinical and laboratory details. Information collected included the child's age at diagnosis, clinical features at presentation, family history, initial management including bone marrow transplantation (BMT) and short-term outcome. Laboratory data, including immunoglobulin levels, full blood count, lymphocyte subset analysis and results of genetic studies were also collected. Confidence intervals were calculated using the method of Silva (13).

Table 1. Case definition for severe combined immunodeficiency (SCID)

Classic SCID
Any infant with absent T- and B-lymphocyte function as characterized by:
Low numbers of circulation CD3-, CD4- and CD8-positive lymphocytes and/or
Markedly reduced lymphocyte proliferation following mitogen stimulation and
Defective IgG, IgA and IgM production
Atypical SCID
Clinical features of SCID (i.e., failure to thrive, chronic diarrhea, opportunistic infections, persistent thrush, persistent bronchiolitic disease) and
Combined immunodeficiency but with some evidence of immunoglobulin production.
Suspected SCID
Any infant dying from infection, who at post-mortem has the characteristic features of SCID (i.e., severely hypoplastic, dysplastic lymph nodes and thymus) or
Any child with some of the features of classic or atypical SCID, who is not yet fully investigated

Results

Epidemiology of SCID

During the study period, the return rate of over 1000 monthly report cards was 96%. Between May 1995 and December 2001, there were 67 notifications of SCID to the APSU. The subsequent questionnaire response rate was 100%. Of the 67 notifications, nine were erroneous reports and 25 were duplicated reports from more than one clinician caring for the child. The remaining 33 notifications were confirmed as cases and included 26 children with classic SCID and seven with atypical SCID. No 'suspected' cases were reported. The categorization of notifications to the APSU is shown in Fig. 1. Based on 33 new cases identified during a 7-yr period, the reported incidence of SCID cases was 1.8 per 10^5 live births per annum (95% CI, 1.2–2.5). Based on 26 cases of classical SCID, the reported incidence was 1.45 per 10^5 live births (95% CI, 0.9–2.0). SCID was reported from all states and territories apart from Tasmania, and the geographic distribution

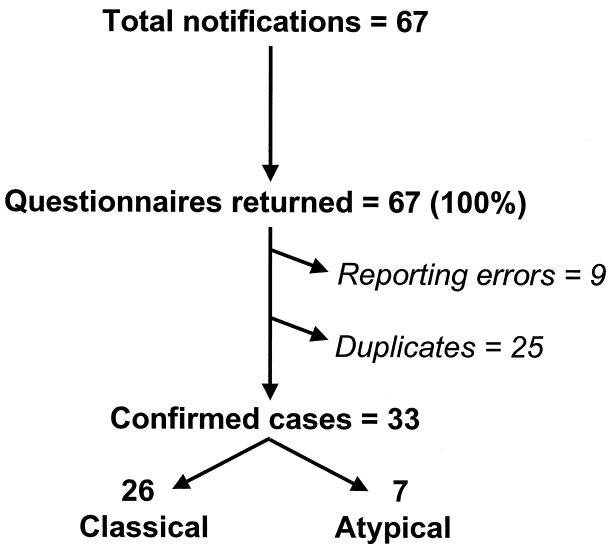

Fig. 1. Severe combined immunodeficiency notifications, January 1995 to December 2001.

Table 2. Geographic distribution of classical severe combined immunodeficiency in Australia

State or territory	Number	Population (in millions as in 2000)
New South Wales	10	6.0
Victoria	5	4.8
Queensland	5	3.6
South Australia	2	1.5
Northern Territory	2	0.2
Western Australia	1	1.9
Australian Capital Territory	1	0.3
Tasmania	0	0.5

Table 3. Characteristics of severe combined immunodeficiency (SCID) patients

Characteristic	Classical	Atypical
Numbers	26	7
Clinical features		
Sex (M:F)	20:6	3:4
Median age at presentation in months (range)	4 (0–10)	4.5 (0–13)
Median age at diagnosis in months (range)	6 (0–20)	16 (1–58)
Positive family history	8	2
Consanguinity	5	2
PCP on presentation	20	4
FTT on presentation	14	3
Type of SCID		
X-linked SCID	13	0
ADA deficiency	4	0
Interleukin-7 receptor alpha chain deficiency	1	0
CHH	0	2
VODI	0	2
Other	8*	3
Outcomes		
BMT	21	3
Survival post-BMT	18	1
Thymic transplant	1	N/A
Survival post-thymic transplant	1	N/A
Non-BMT-related death	1	3
Total survival	22	2

PCP, *Pneumocystis carinii* pneumonia; FTT, failure to thrive; ADA, adenosine deaminase; BMT, bone-marrow transplantation; N/A, not applicable; CHH, cartilage hair hypoplasia; VODI, veno-occlusive disease associated with immunodeficiency.
*Includes Omenn syndrome, two cases; Di George syndrome, two cases; autosomal recessive SCID, four cases.

of cases reflects the population distribution in Australia (Table 2).

Classification of SCID

In 13 cases (50%) of classic SCID, the disease was X-linked. Other causes included ADA deficiency, interleukin-7 receptor alpha chain deficiency, Omenn and Di George syndromes and AR SCID (Table 3). Of the seven atypical SCID cases, two were diagnosed with cartilage-hair hypoplasia (CHH) and two with immunodeficiency associated with veno-occlusive disease (VOD) (14).

Clinical characteristics of children with SCID

The characteristics of children with confirmed SCID cases are shown in Table 3. Overall, 77% were males, including most of the children with classical SCID, which was predominantly X-linked. The median age at diagnosis was 6 months (range birth-20 months). In most cases, there was no significant delay between presentation with clinical symptoms and diagnosis. However, the time between presentation and diagnosis exceeded 6 months in six children (three cases of classical SCID and three cases of atypical SCID) with a delay in diagnosis of 51 months in one child with atypical SCID. There was consanguinity in 7/32 (22%) families and a family history of SCID in 10/32 (31%) families. Eight children with classical SCID and two with atypical SCID were investigated at birth and were diagnosed before the onset of symptoms because of positive family history. Most children with SCID had failure to thrive (54%) and opportunistic infection (77%) at diagnosis. Infants without these symptoms were usually those diagnosed in the neonatal period. One female child presented at 10 months of age and was diagnosed with classic SCID despite normal immunoglobulin levels. She had marked T-cell lymphopenia. Other information regarding B-cell functions was not available. Two children with atypical SCID had familial hypogammaglobulinemia and presented with *Pneumocystis carinii* pneumonitis and hepatic VOD (14). Laboratory features in children with classical SCID were low or absent CD3, CD4 and CD8. The IgA and IgM levels were sometimes normal in boys with X-linked SCID. In very young infants, the IgG levels reflected the maternal IgG level.

Management and short-term outcome

Of the 26 children with classic SCID, 21 (81%) received a hematopoietic stem cell transplant/BMT and one child received two BMT/stem cell transplant. The median age at BMT was 9.8 months (range 1–36 months). Three of the children (two with ADA deficiency and one with another AR form of SCID) died soon after transplantation. One child with SCID, presumed to be AR because of parental consanguinity, died from overwhelming sepsis while awaiting BMT. One child with Di George-related SCID had a thymic transplant at 9 months of age and remained well 18 months post-transplant. Two children with X-linked SCID were alive and thriving on monthly immunoglobulin replacement while waiting for BMT transplant at ages of

Table 4. Immunodeficiency surveys

Reference	Country	Time period	Cases identified (no. SCID/no. PID)	Incidence SCID per 100,000	Prevalence SCID per 100,000
(11)	Australia (Royal Children's Hospital, Melbourne)	1970–82	18/38	1.4	N/A
(3)	Sweden	1974–79	8/174	1.4*	0.38
Present study	Australia (APSU)	1995–2001	26/	1.8	
(4)	Switzerland	1975–85			2.4
(5)	Japan	1960–75	46/497		†
(7)	Italy	1972–82	45/797		†
(10)	Spain	1980–95	61/849		0.08
(9)	Brazil	1981–96	8/166		†
(15)	Australia	1990–94	26/500		0.14
(6)	Latin America	1993–97	65/1428		†
(8)	Norway	1999	12/372	0.89*	0.45

SCID, severe combined immunodeficiency; PID, primary immunodeficiency; APSU, Australian Paediatric Surveillance Unit.
*Extrapolated from prevalence data.
†At-risk population size not presented.

12 and 24 months. One child with ADA deficiency is alive and well while receiving enzyme replacement. Three children with atypical SCID received BMT (one child received two transplants), and two of these children died in the early post-transplantation period from overwhelming sepsis. The median age of BMT for atypical SCID was 41.8 months (range of 17–75 months). Two children with atypical SCID died from sepsis before transplantation was performed. Another child with atypical SCID died after developing non-Hodgkin's lymphoma 4 yr after diagnosis. One child with atypical SCID remained alive and well 10 yr after diagnosis with monthly immunoglobulin replacement.

Discussion

Over time, estimates of incidence of SCID have varied around one to three per 100,000 live births (3, 11). In one previous Australian study in 1982 in a single Australian state, the estimated incidence of SCID was 1.4 cases per 100,000 live births (11).

Immunodeficiency registers have been established in several counties, including Sweden (3), Switzerland (4), Spain (10), Italy (7), Norway (8), Japan (5) and Brazil (9). However, these registers generally report prevalence rather than incidence rates (Table 4). Prevalence rates range from 0.08 per 100,000 of population in Spain (10) to 2.4 per 100,000 in Switzerland (4). The Australasian Society of Clinical Immunology and Allergy (ASCIA) group (15) identified 26 prevalent cases of SCID over 3 yr from 1990 to 1993 with ages ranging from <5 to >31 yr. The prevalence was estimated as 0.14/100,000 population. Three incidence studies have been published. Hosking and Roberton studied a defined pediatric population in Melbourne, Australia, and reported an incidence rate of 1.4 per 100,000 live births (11). Fasth reported a similar incidence rate in Sweden over a 5-yr period from 1974 to 1979 (3). In this retrospective study, data were collected by sending questionnaires to specialist centers. From the prevalence rate of 8.4 cases of PID per 100,000 live births, Fasth estimated an incidence rate of 1.4 cases of SCID per 100,000 live births. In Norway, a much lower incidence rate was reported at 0.89 per 100,000 live births in 1999. In this 20-yr prevalence study, extrapolation was used to derive an incidence estimate for SCID (8). To our knowledge, the present study is the first prospective national study designed to estimate the incidence of SCID.

As the Australian population is relatively small, the study was conducted for 7 yr, thus representing a birth cohort of about 1.75 million. Because there is no other source of data on SCID, we were unable to verify the completeness of reporting. However, there was no time period when the number of reported cases was markedly divergent from the average of four confirmed cases annually. In Australia, children with SCID would be expected to be referred to one of the country's seven tertiary referral centers. Regular contact with colleagues during the study did not reveal missed cases. Under-reporting could have resulted from death prior to the establishment of the diagnosis of SCID, although we are not aware of any such cases. Furthermore, during the study period, all adult and pediatric physician members of the ASCIA reported to the APSU each month.

Many cases were reported to the APSU more than once, resulting in 25 duplicate reports. Confirmed cases were reported by one to four

clinicians, with a mean of three clinicians notifying each case (e.g., general pediatrician, immunologist and gastroenterologist). This over-reporting increases our confidence that cases were not missed. Once cases were notified to the APSU, we obtained detailed clinical and laboratory information in every case. We confirmed the previously reported predominance of X-linked SCID in the type of SCID reported (50% of cases) (2, 16). We showed that the diagnosis is usually made soon after presentation and that BMT/stem cell transplantation is undertaken early and is associated with excellent survival rates. Nevertheless, our estimate of 1.45 cases of classical SCID per 100,000 populations should be considered a minimum estimate because of the possibility of missed cases.

It appears likely that in populations in which significantly fewer than 1.7 classic SCID cases per 100,000 populations per year are diagnosed, cases of SCID are being missed. The number may be higher in populations with high frequency of genes for AR forms of SCID. Newborn screening for SCID is now technically feasible (17, 18) and potentially can offer significant clinical benefit from early intervention following early diagnosis (19). A study, which assumed an incidence rate similar to that found in our study, suggests that newborn screening may be cost-effective (20).

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