

The spectrum of primary immunodeficiency disorders in Australia

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Background: Primary immunodeficiency disorders (PIDs) are uncommon conditions that require specialized immunologic services for diagnosis and management. It is difficult to estimate the prevalence of these disorders from routinely collected health statistics.

Objective: We attempted to describe the prevalence of PID in Australia and the requirements for specific therapies, such as intravenous immunoglobulin, ascertained from a national register of PID.

Methods: A national longitudinal cross-sectional survey of patients with PID under the care of clinical immunologists was established by the Australasian Society of Allergy and Clinical Immunology in 1990. Details of diagnosis and therapy were provided for patients with major PIDs including symptomatic IgA, IgG subclass, and complement deficiencies. Subjects with asymptomatic IgA deficiency were not included. The clinical features of the first 500 cases enrolled in the register were analyzed.

Results: The most frequent type of PID was predominant antibody deficiency (71%). Common variable immunodeficiency, usually first seen as an antibody deficiency, was the single most common disorder with an estimated prevalence of 0.77/100,000 in the general population. Other types of PID were infrequent, and of these, severe combined immunodeficiency accounted for 5.2% of cases. The estimated prevalence of all forms of chronic granulomatous disease was 0.08/100,000. The national prevalence of all PID cases ascertained from the register was 2.1/100,000, with variation between the larger states ranging from 1.18 to 4.57/100,000. Half (247) of the patients were receiving intravenous immunoglobulin therapy with a median duration of care of 5 to 9 years for the different antibody deficiencies. There was also variation in the patterns of intravenous immunoglobulin use across the country. No new forms of PID were encountered.

Conclusion: This study highlights the requirement for the continuing provision of immunoglobulin as replacement therapy for these patients. In addition, the register documents a cohort of patients with PID whose long-term response to current therapy can be evaluated prospectively. (*J Allergy Clin Immunol* 1997;100:415-23.)

Abbreviations used

ASCIA:	Australasian Society of Clinical Immunology and Allergy
CGD:	Chronic granulomatous disease
CVID:	Common variable immunodeficiency
IVIG:	Intravenous immunoglobulin
PID:	Primary immunodeficiency disorders
SCID:	Severe combined immunodeficiency
WHO:	World Health Organization

Key words: Primary, immunodeficiency, register, Australia, gammaglobulin

Primary immunodeficiency disorders (PIDs) predispose individuals to recurrent or unusual infections and have strong associations with other immune disorders including autoimmune disease and lymphomas.¹⁻⁴ Recognition of these disorders by the clinician is important because appropriate therapy will not only prevent death, but also reduce the long-term morbidity from recurrent infections.⁵ There is often underdiagnosis of these conditions or delay in the diagnosis of treatable conditions. In the past decade, the development of gammaglobulin preparations suitable for intravenous infusion has allowed adequate replacement of standard repertoire with maintenance of immunoglobulin in the physiologic range for patients with hypogammaglobulinemia. This has resulted in clinical benefit with reduced frequency of infections and delayed progression to bronchiectasis and other organ damage.⁵ Recent advances in molecular biology have led to the identification of the molecular defects for a number of PIDs, which has led to the development of new diagnostic tools with the prospect of new therapies for these disorders.^{3, 6-8} Because PIDs occur infrequently and are highly heterogeneous in nature, relatively few centers gain extensive experience in the diagnosis, management, and applied research of these disorders.^{3, 9-11} For these reasons, the Australasian Society of Allergy and Clinical Immunology (ASCIA) established a national register of PID in 1990. The register has several purposes, namely:

- To determine the prevalence of types of PID in Australia
- to collect information on clinical experience with these disorders

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- to determine the requirements for intravenous immunoglobulin (IVIG) and other therapies on a national basis
- to coordinate clinical research into these disorders
- to provide opportunity for patient advocacy

We describe the first 500 cases enrolled in this register, one of the larger international registers of these disorders, and compare the findings with other national registers previously reported.

METHODS

Case ascertainment and data collection

A longitudinal cross-sectional survey of patients with PIDs who were currently receiving care was conducted from January 1990 to March 1994. A questionnaire was mailed on three occasions at 18-month intervals to clinical immunologists who are members of ASCIA and also to tertiary referral departments of clinical immunology in pediatric and general hospitals. The second and third mailings contained information about cases ascertained from the first and second mailings and sought clarification and confirmation of previous responses. The data collection form sought nonidentifying information (the first two letters of the first and last names, postal code, date of birth) about patients whom the clinicians had seen in 1990 with any form of PID listed in the current World Health Organization (WHO) classification¹² or with features consistent with immunodeficiency for which a secondary cause was not apparent. Details on patients with symptomatic IgA, IgG subclass, and complement deficiencies were actively sought. Because the majority of patients with asymptomatic IgA, IgG subclass, or complement deficiency are not in contact with clinical services, it was considered that ascertainment bias would preclude reliable estimates for those with asymptomatic disorders. The questionnaire sought information on patients that were recently deceased, although only 15 such patients, who died between January 1990 and March 1994, are included in this report. Cumulative prevalence rates of PID were determined for these disorders between January 1990 and March 1994. Information collected included diagnostic details, current therapy, duration of treatment, and, in particular, the use of IVIG therapy. No details on ethnic or racial characteristics were collected. The data were analyzed with EPI-INFO Version 5.1, available from the Centers for Disease Control, Atlanta, Georgia.

Response rates

Of the cases ascertained, 60% were reported within 3 months of receipt of the first questionnaire, and the other cases were reported after subsequent questionnaires were received. Responses were obtained from clinicians attached to 23 of the 27 centers known to provide care to patients with PID in Australia and from six independent clinicians. Clinicians who did not respond were telephoned by one of the authors. The calculated cumulative prevalence rates are therefore probably an underestimate of true rates.

RESULTS

Case ascertainment

During a 3-year period, 534 patients were enrolled in the register. Thirty-four were excluded from analysis when 26 were found to be duplicate entries, and eight were patients receiving IVIG for defined secondary immunodeficiency disorders, including pediatric acquired immune deficiency

syndrome and chronic lymphatic leukemia. Details of cases ascertained after March 1994 were not included in this analysis. Fifteen patients have died since enrollment (between January 1990 and March 1994) and their data are included in this report.

Spectrum and distribution of PID cases

The spectrum of patients with PID enrolled in this Register and classified according to a modified WHO classification is shown in Fig. 1. The majority of these patients (70.8%) have predominant antibody deficiency. The major clinical problems in patients with common variable immunodeficiency (CVID) are due to antibody deficiency, even though these patients may have associated T-cell abnormalities. Therefore patients with CVID have been included in the antibody deficiency category. This practice is common with reports from other immunodeficiency registers and is the only major modification of the WHO classification.^{3,9} Patients with asymptomatic IgA deficiency were not included because no true estimate of this or other asymptomatic conditions could be made because of the method of ascertainment.

The estimated national cumulative prevalence rate for all forms of PID was 2.82/100,000 in the general population (Table I). Health services are organized on a federal basis in Australia, and we compared the reported cases from different states and territories. There were substantial differences in the cumulative prevalence rates of immunodeficiency between the different states (Table I). When the smaller population centers (population <0.5 million) are excluded, the prevalence rates range from 1.18/100,000 in Queensland to 4.57/100,000 in Western Australia. The major cause of this variation is most likely ascertainment bias because a small number of centers did not respond. Moreover, fewer PID cases would have been ascertained from those regions where patients with PID are not usually cared for by clinical immunologists. In addition, there may be differences in the criteria used in different centers for the diagnosis of some less severe forms of PID, such as CVID and IgG subclass deficiency. It was believed, however, that the majority of patients with antibody deficiency receiving IVIG and patients with SCID were reported to the register.

Types of primary immunodeficiency

Among the antibody defects reported (Table II), X-linked agammaglobulinemia, autosomal recessive agammaglobulinemia, and hyper-IgM with IgG deficiency generally appear in early childhood. Patients with these conditions, who comprise 11% of those in the register, were in the younger age group with 30 of 55 of these patients less than 20 years old at the time of enrollment. The national prevalence rate for X-linked agammaglobulinemia was 0.23/100,000, compared with 0.77/100,000 for patients with CVID, who comprised the largest single diagnostic category (27.4% of 500 cases ascertained). This is a heterogeneous condition with delayed onset, which manifests as mild to severe anti-

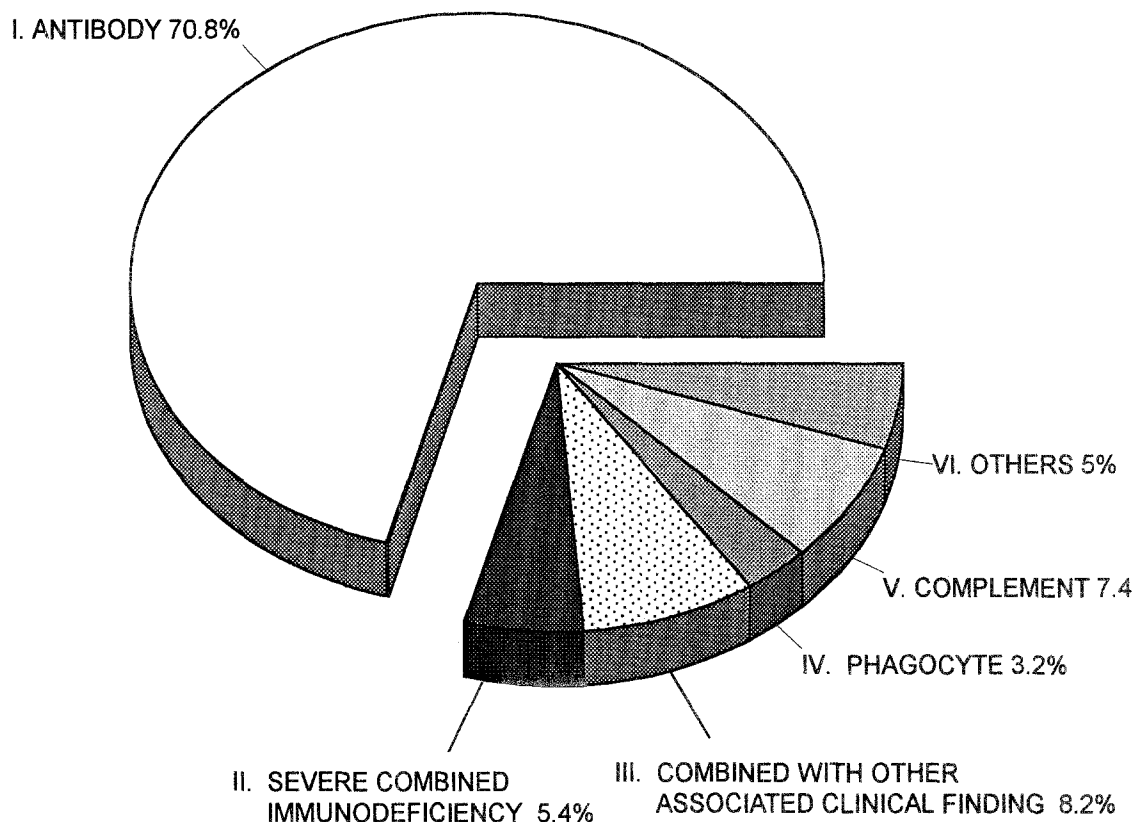


FIG. 1. The spectrum of PID cases ascertained by ASCIA between January 1990 and March 1994 is shown according to a modified WHO classification of PID.

TABLE I. The distribution of subjects with primary immunodeficiency enrolled in the ASCIA PID register and those receiving IVIG therapy in the states and territories of Australia

State	Population* ($\times 10^5$)	Total no. of cases enrolled	Rate (/10 ⁵)	No. of patients receiving IVIG	Rate (/10 ⁵)
New South Wales	60.24	217	3.60	89	1.48
Victoria	44.64	115	2.58	50	1.12
Queensland	31.34	37	1.18	28	0.89
South Australia	14.64	51	3.48	31	2.12
Western Australia	16.84	77	4.57	48	2.85
Tasmania	4.72	2	0.42	1	0.21
Australian Capital Territory	2.99	0	0.00	0	0.00
Northern Territory	1.69	1	0.59	0	0.00
TOTAL	177.10	500	2.82	247	1.39

*Population as recorded in 1993 census.

body deficiency with or without T-cell abnormalities and increased risk of both autoimmune and neoplastic disease. In this register 90 of 137 patients with CVID were older than 20 years. There was a higher proportion of males to females (137 males, 96 females) in the patients with CVID, suggesting that some of the male patients with CVID may have a milder form of X-linked agammaglobulinemia. Patients with symptomatic IgA deficiency or selective deficiencies in IgG subclasses with or

without associated IgA deficiency formed a large mixed group (26.4%) with a higher ratio of older patients (Table II).

Combined immunodeficiencies with impairment of both T- and B-cell function accounted for 5.4% of the total number of PID cases (Table III). Of these patients, 26 of 27 had severe combined immunodeficiency (SCID), which is in itself a heterogeneous collection of defects with both X-linked and autosomal recessive

TABLE II. The frequency and characteristics of subjects with PID with predominantly antibody defects

Category	Male	Female	Median duration of care (yr)	Age range (yr)					Age unknown	No. of cases	Percent of total
				0-5	6-10	11-20	21-30	>31			
X-linked agammaglobulinemia*	41	0	8.5	3	8	11	10	7	2	41	8.2
Autosomal recessive agammaglobulinemia	3	2	6.5	0	2	1	1	0	1	5	1.0
Hyper-IgM syndrome	7	2	9	0	3	2	4	0	0	9	1.8
IgA and IgG subclass deficiency	45	37	8	5	14	14	10	35	4	82	16.4
IgG subclass deficiency	25	25	5	9	6	16	3	16	0	50	10
Selective deficiency (other isotypes)	8	9	7	1	5	8	0	3	0	17	3.4
Antibody deficiency with normal or hypergamma-globulinemia	2	5	ND	1	2	1	0	3	0	7	1.4
Immunodeficiency with thymoma	0	1	8	0	0	0	0	1	0	1	0.2
Transient hypogammaglobulinemia of infancy	4	1	3	1	4	0	0	0	0	5	1
Common variable immunodeficiency†	96	41	6	2	6	13	12	84	20	137	27.4

ND, Not determined.

No patients were ascertained with kappa chain deficiency.

*Including three patients with X-linked agammaglobulinemia and growth hormone deficiency.

†Included in this group rather than as a "Combined Immunodeficiency."

TABLE III. The frequency and characteristics of subjects with PID with combined immunodeficiency with and without other major defects

Category	Male	Female	Median duration of care (yr)	Age range (yr)					Age unknown	Total cases	Percent of total
				0-5	6-10	11-20	21-30	>31			
Without other major defects											
SCID	14	11	3	9	8	6	1	1	0	25	5
SCID with adenosine deaminase deficiency	0	1	4	0	1	0	0	0	0	1	0.2
MHC Class I or II deficiency	1	0	ND	1	0	0	0	0	0	1	0.2
With other major defects											
Wiskott-Aldrich syndrome	12	0	8	2	3	5	1	0	1	12	2.4
Ataxia telangiectasia	6	4	8	0	2	5	0	3	0	10	2
DiGeorge syndrome	6	10	4	9	4	3	0	0	0	16	3.2
X-linked lymphoproliferative disorder†	3	0	23	0	1	0	1	0	1	3	0.6

MHC, Major histocompatibility complex; ND, Not determined.

*Includes patients with reticular dysgenesis, SCID with low B- and T-cell numbers, and SCID with low T-cell, but normal B-cell, numbers.

†Immunodeficiency with defective response to Epstein-Barr virus (Duncan's syndrome).

No patients with purine nucleoside phosphorylase deficiency, transcobalamin II deficiency, or immunodeficiency with partial albinism were ascertained.

patterns of inheritance. There was a slight excess of males among the patients with SCID (M:F = 1.27:1). One patient first seen with SCID was found to have adenosine deaminase deficiency, and another patient had reduced human leukocyte antigen (HLA) surface molecules. No patients with idiopathic CD4 lymphopenia were reported to the register.¹³ Other disorders with impaired T- and/or B-cell function are classified as "immunodeficiency with other major defects" because of associated severe morphologic abnormalities. These accounted for 8.2% of cases in the register. Of these, DiGeorge syndrome, which comprises characteristic fa-

cies, hypoplasia of the thymus and parathyroids with associated hypocalcemia, and congenital heart disease were the most common with an estimated national prevalence of 0.09/100,000 in the general population. Wiskott-Aldrich syndrome, an X-linked condition causing combined progressive T- and B-cell defects with eczema and thrombocytopenia was the next most frequent with a national prevalence of 0.07/100,000 in the general population. Ataxia telangiectasia is an autosomal recessive condition characterized by telangiectasia, combined immunodeficiency, variable endocrine abnormalities, and progressive ataxia in childhood. This af-

TABLE IV. The frequency and characteristics of subjects with PID with, complement deficiencies, defects of phagocyte function, and chronic mucocutaneous candidiasis or "mixed" classifications

Category	Male	Female	Median duration of care (yr)	Age range (yr)					Age unknown	No. of cases	Percent of total
				0-5	6-10	11-20	21-30	>31			
Complement deficiencies*											
C4	0	1	ND	0	0	0	0	1	0	1	0.2
C2	0	4	8.5	0	1	1	1	1	0	4	0.8
C1 inhibitor	18	14	4	0	4	0	3	15	10	32	6.4
Defects of phagocyte function†											
X-linked CGD	10	0	6	0	5	3	1	1	0	10	2
Autosomal recessive CGD	2	3	4.5	0	3	1	0	1	0	5	1
Schwachmann's syndrome	1	0	4	0	0	0	1	0	0	1	0.2
Chronic mucocutaneous candidiasis or "mixed" classifications											
Chronic mucocutaneous candidiasis	5	3	8	0	0	4	2	0	2	8	1.6
Others‡	10	7		2	7	1	3	2	2	17	3.4

ND, not determined.

*No patients with other complement deficiencies were ascertained.

†No patients with adhesive glycoprotein deficiency, Chediak Higashi syndrome, neutrophil G6PDH deficiency, or secondary granule deficiency were ascertained.

‡Others included—disorders not classified elsewhere.

ected 2% of enrolled patients with PID, with a national prevalence rate of 0.06/100,000 in the general population.

Although complement deficiencies accounted for 7.4% of the PID cases, these may be significantly underreported because only cases with symptomatic deficiency were reported (Table IV). Patients with C4 and C2 deficiency are predisposed to immune complex diseases such as systemic lupus erythematosus but do not have the increased frequency of infections typically observed in other forms of PID. The small number of reported cases does not allow for a meaningful estimate of the prevalence of these conditions. The most common form of complement deficiency reported was C1 inhibitor deficiency in 6.4% of PID cases with a national rate of 0.18/100,000 in the general population. In this condition deficient levels or reduced function of C1 inhibitor, inherited as an autosomal dominant condition, may cause recurrent angioedema and abdominal pain without urticaria. Other deficiencies of complement, such as those involving the terminal components (C5 to C9), were infrequently reported to the register. These deficiencies can predispose the patient to recurrent neisserial infection without other evidence of immunodeficiency and so may not be recognized as part of a broader immunodeficiency syndrome.

Patients with defects in phagocyte function were reported infrequently and only accounted for 3.2% of the population (Table IV). The most common form of these defects was chronic granulomatous disease (CGD), which is characterized by impaired generation of oxygen radicals in neutrophils with recurrent bacterial and fungal infections leading to widespread granulomatous lesions in the lungs, lymph nodes, and skin. CGD was described originally as an X-linked condition, but both

X-linked and autosomal recessive forms occur because of a variety of genetic defects in the four components of phagocyte oxidase. Two thirds of 15 patients with CGD were thought to have the X-linked form, and one third were thought to have an autosomal recessive pattern of inheritance. The estimated national prevalence was 0.08/100,000 in the general population. Of the other conditions (Table IV), chronic mucocutaneous candidiasis was infrequently reported to the register, possibly reflecting the effectiveness of new antifungal agents.

Therapy

The median duration of care was determined for each category of patients (Tables II to IV), excluding those for whom insufficient data were recorded. In the case of patients with predominant antibody defects, the register includes a substantial experience of care, encompassing 331 patient-years for X-linked agammaglobulinemia and 702 patient-years for CVID. A significant feature of this register is that this experience has been accrued recently, and consequently, most patients with antibody defects have received at least 5 years of IVIG replacement therapy. There is also a substantial mean duration of care for many of the less common disorders, although for some conditions, such as Wiskott-Aldrich syndrome and X-linked lymphoproliferative disease, these data are skewed by the prolonged survival of a small number of individuals.

Patients with antibody deficiency generally respond well to adequate replacement with IVIG, which replaces the repertoire when physiologic levels are maintained. Of the 247 patients currently receiving IVIG, nearly half had underlying CVID and 20% had IgG subclass deficiency of some form (Table V). Not all registered patients with agammaglobulinemia or CVID were re-

TABLE V. Indications for the use of intravenous immunoglobulin for PIDs

PID	Patients diagnosed	Patients receiving IVIG		
	No.	No.	Percent of diagnosis	Percent of IVIG recipients
X-linked agammaglobulinemia	41	30	73	12
CVID	137	113	83	46
IgG subclass (+/- IgA) deficiency	132	49	38	20
Other predominantly antibody-deficient disorders*	44	39	89	16
SCID	26	9	35	4
X-linked lymphoproliferative disorder	3	2	67	1
Other disorders	117	5	4	2
TOTAL	500	247	389	100

Proportion of patients in each group reported to be receiving IVIG at present. Four additional patients with CVID were receiving intramuscular IG and one patient receiving IVIG had previously received subcutaneous IG.

*Includes other forms of immunoglobulin deficiency described in Table II.

ported to be receiving IVIG because some were treated with subcutaneous or intramuscular immunoglobulin. There were substantial differences in the rate of use of IVIG between the larger states, ranging from 2.85/100,000 in Western Australia to 0.89/100,000 in Queensland with a mean rate of 1.39/100,000 (Table I). This may be due to differences in ascertainment of PID cases in the various states and differences in the clinical use and availability of IVIG supplies between regions.

DISCUSSION

The ASCIA PID register provides the first measure of the national burden of primary immunodeficiency conditions in Australia. Although uncommon, these are chronic conditions with substantial morbidity, as well as death; and, with the advent of effective replacement therapy, they require planned long-term management. Analysis of the first 500 PID cases enrolled in the register reveals a national estimated prevalence of 2.82/100,000 in the general population, with some variation between the states. This did not include subjects with asymptomatic IgA, IgG subclass, or complement deficiency because there was no reliable estimate of the number of such individuals. From previous epidemiologic studies of pediatric immunodeficiency in one Australian state, Victoria,¹⁴ the total case load was expected to be between 1500 to 2500 patients for Australia, excluding cases with asymptomatic IgA deficiency or asymptomatic IgG subclass deficiency. The maximum reported prevalence was 4.57/100,000 in Western Australia (Fig. 2). Comparison of the pattern of cases reported from Western Australia and the pattern in the earlier Victorian study shows a lower frequency of cellular and other nonantibody defects in Western Australia. If the maximum observed prevalence rate is adjusted to include a higher proportion of nonantibody defects, it is estimated that the minimum national case load would be about 1200 persons or 6.8/100,000 in the general population. This estimate assumes that the observed differences between states are due to variations in ascertainment rather than bias in classification or selection for IVIG therapy. Furthermore, it does not

allow for higher levels of ascertainment for other disorders that have been underrepresented in all states, such as deficiencies of complement. Because case ascertainment for this register has been mainly achieved through the return of questionnaires from clinical immunologists, there is a bias towards inclusion of disorders that are seen frequently in referral immunology centers. Further evidence that ascertainment variations may lead to underreporting of milder immune deficiencies is provided by the recently published data that showed that transient hypogammaglobulinemia of infancy had a frequency of 23 per 10⁶ live births in Victoria, which translates into a prevalence rate of 2.3/100,000 in the general population.¹⁵ Patients with other disorders that were first seen with dominant, noninfectious clinical problems, such as ataxia in ataxia telangiectasia, may also be underreported to the register as yet.

The register does provide insight into the present spectrum of PID in Australia (Fig. 1). Antibody deficiencies are the major group of conditions affecting both the pediatric and adult age groups. The molecular basis of the antibody deficiency in Bruton's X-linked agammaglobulinemia has been defined recently as a mutation in the gene encoding a pre-B-cell cytoplasmic tyrosine kinase (*btk*).^{3,6} Index cases typically demonstrate complete absence of antibody. However, some mutations of *btk* are associated with partial antibody deficiency in male offspring of carriers.³ Such patients may have been diagnosed previously with CVID. In fact, the male predominance in subjects with CVID in the register suggests that some patients with partial *btk* deficiency may have been classified erroneously as having CVID. By contrast, the molecular basis for CVID is still unresolved, and the condition is heterogeneous.³ There is a wide range of manifestations in CVID from pure immunoglobulin deficiency to a major T-cell defect complicated by *Pneumocystis carinii* infection or lymphoma.

We have intentionally not sought to recruit subjects with asymptomatic IgA or IgG subclass deficiency to the register to restrict the register to patients with significant consequences of their deficiency. Moreover, because recognition of such deficiency is usually incidental, there

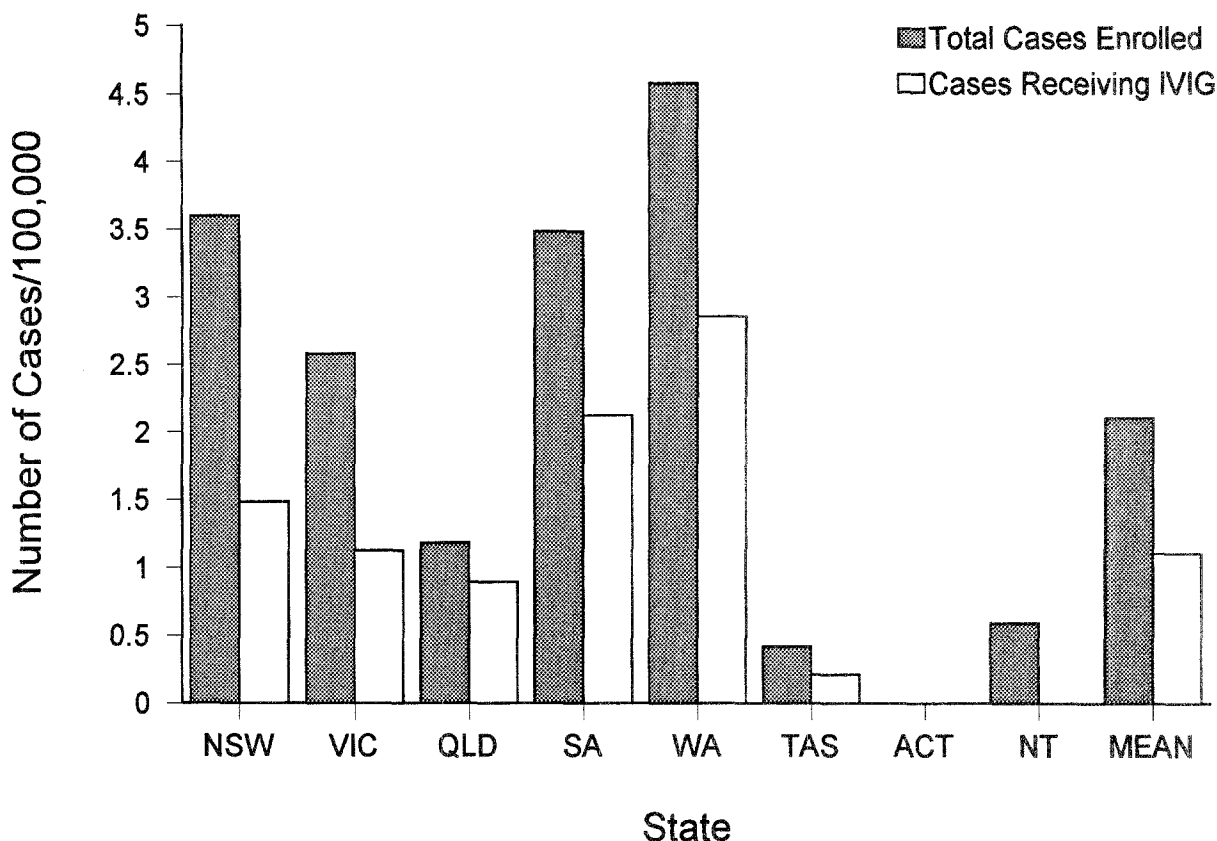


FIG. 2. Cumulative prevalence rates per 100,000 in the general population for PID (shaded columns) and recipients of IVIG for PID (open columns) are shown for each state within Australia. NSW, New South Wales; VIC, Victoria; QLD, Queensland; SA, South Australia; WA, Western Australia; TAS, Tasmania; ACT, Australian Capital Territory; NT, Northern Territory; MEAN, average for all states.

was no reliable way of ascertaining all these individual cases in a community. In addition, the definition of IgG subclass deficiency may still be problematic because of variability in subclass measurements between laboratories and the difficulty in defining the severity and frequency of infections.¹⁶ IgG subclass deficiency alone is not necessarily an indication for IVIG therapy. In Australia, it is recommended that patients should be proven to have a deficient antibody response to protein or carbohydrate antigens.^{17, 18} Patients reported to the register with IgA and/or IgG subclass deficiency had symptoms. Of these patients, 49% and/or 70% were receiving IVIG. The requirements for IVIG therapy in subclass deficiency in Australia¹⁸ include the documentation of two or more infections with relevant bacterial infection per year and impaired antibody response to vaccine antigens.

Patients with SCID are underrepresented in the register compared with an earlier report from Victoria, Australia¹⁴ and the Swedish pediatric register.¹⁹ This is probably because of early death in children with severe immunodeficiency. This syndrome of combined T- and B-cell deficiency can be caused by a wide variety of defects in the development, activation, and function of T cells. The molecular defect has been characterized re-

cently in some forms including X-linked deficiency of the γ chain of the IL-2 receptor,⁷ deficiency of the enzyme adenosine deaminase,³ and the failure to express HLA Class I or II molecules on the surface of antigen-presenting cells.^{3, 20} Definition of the exact molecular defect is of increasing importance because some of these conditions may be amenable to specific therapy such as the potential somatic cell gene therapy for ADA-deficient SCIDs. The molecular defects in the combined immunodeficiencies with other major defects are also being defined. Wiskott-Aldrich syndrome is an X-linked condition caused by a variety of mutations in a novel proline-rich protein, which may play a regulatory role in lymphocyte and platelet function.²² The ataxia telangiectasia gene product is a novel protein with homology to phosphatidylinositol 1-3 kinases.²³

Of the conditions affecting neutrophil function, CGD of both the X-linked and autosomal recessive forms occurred in 1/1.18 million of the general population. Defects that may affect any of the four different components of the enzyme phagocyte oxidase are being increasingly recognized.²⁵ These include some with a milder phenotype, and consequently, the true prevalence of all forms of CGD may be two- to threefold higher than the prevalence recorded in the register.

TABLE VI. Comparison of the cases and features in five national registers for primary immunodeficiency disorders

Register site	Sweden ¹⁹	United States ¹¹	Japan ¹⁰	Italy ⁹	Australia
Years of ascertainment	1974-1979	1975-1977	1974-1979	1977-1987	1990-1994
Source of cases (No. of sources)	Pediatricians (41)	Physicians (178)	Centers*	Centers*	Centers*
Number of cases	174	3356	628	1214	500
Sex ratio (Male:Female)	2:1	ND	1.4:1	ND	1.8:1
Factors analyzed†					
Geographic differences	Yes	No	No	No	Yes
Neoplastic diseases	Yes	Yes	Yes	Yes	No
Allergic diseases	Yes	No	Yes	Yes	No
Autoimmune diseases	Yes	No	Yes	Yes	No
Composition of cases (%)‡					
Predominant antibody deficiency (all)	45	77	64	75	71
Common variable	6	19	5	19	27
Agammaglobulinemia (all forms)	13	8	13	5	8
IgA and/or IgG subclass	25	29	27	51	26
Transient hypogammaglobulinemia of infancy	—	16	19	—	1
SCID (all)	7	6	4	5	5
Combined with other major defects (all)	18	17	16	9	8
Wiskott-Aldrich syndrome	5	4	4	2	2
Ataxia telangiectasia	5	8	7	5	2
DiGeorge syndrome	2	2	4	1	3
X-linked lymphoproliferative disorder	1	0	0	0	1
Complement deficiencies (all)	1	0	0	2	7
C1-esterase inhibitor	0	0	0	0	6
Other components	1	0	0	2	1
Defects of phagocyte function (all)	22	0	9	7	3
Chronic mucocutaneous candidiasis	8	0	2	2	2

ND, Not determined.

*Cases ascertained from major hospital centers with immunology clinics.

†Factors analyzed in the reports of these references included geographic differences in prevalence of types of disorders, the presence of associated disorders (including neoplastic disease, allergic disease, and autoimmune disorders) and whether familial clustering of cases was reported.

‡The proportions of the most common disorders of total number of cases in each register are shown, when this form of PID was analyzed in each register, and expressed as a percentage.

Similar registers containing data on patients with all forms of PID have been established in a number of countries.^{9, 11, 19} In addition, disease-specific registers for conditions such as ataxia telangiectasia, CGD, and X-linked lymphoproliferative disorder are active in Britain and the United States.²⁴⁻²⁶ Four of the national registers are compared with the ASCIA PID register in Table VI. Different forms of ascertainment bias affect the reported distribution of cases. For example, the Swedish register¹⁶ was composed of pediatric PID cases ascertained from practicing pediatricians. Consequently, there is a higher representation of combined immunodeficiency with other defects and phagocyte function abnormalities and a lower proportion of antibody deficiencies, particularly CVID. The largest register from the United States was an immunodeficiency-cancer register¹¹ to which physicians from the United States and elsewhere reported their experience in treating patients with PID with and without malignancy. This was not primarily a register of patients with PID and is not necessarily representative of patients with PID in the United States. A large proportion of patients had mild PID (25% IgA deficiency) or transient hypogammaglobulinemia of infancy (16%). There was also bias

toward reporting patients with tumors, and 267 of the 3356 reported cases had a malignancy, 59% of which were either non-Hodgkin's lymphoma or lymphoid leukemia. Epithelial tumors, especially stomach cancers, were also more frequent. Familial clustering was detected in this larger group of patients and in the Japanese study (Table VI). The rates reported by the Japanese register of immunodeficiency disorders¹⁰ are complicated by some duplication of reporting because of a change in the reporting form between the two surveys. Nevertheless, the study demonstrated an excess of non-infectious complications in patients with PID, including autoimmune disorders in 13% of cases and increased frequency of allergic disorders and malignancy in 1.8% of cases. The latter is a 120-fold increase over that observed in an age-matched population. The highest frequency of ataxia telangiectasia is reported in the U.S. register, probably because this condition is marked by chromosomal sensitivity to radiation and predisposition to development of lymphoma.^{11, 23} This frequency was comparable to a prevalence of 1 in 300,000 in a British study of ataxia telangiectasia.²⁴ Patients heterozygous for the mutation in the ataxia telangiectasia gene have an increased risk for malignancy, in particular breast

cancer, over the general population.^{2,24} Ataxia telangiectasia had a higher proportional representation in the four registers than in the ASCIA register (Table VI).

The Italian register of immunodeficiency disorders⁹ included 1214 patients, of whom 587 (48.3%) had IgA deficiency that was often asymptomatic, and 28 had IgG subclass deficiency. The bias towards including patients with these deficiencies resulted in 83% being classified as having predominant antibody deficiency compared with 71% in the Australian study.

One feature of the ASCIA register is the documentation of the use of IVIG in the management of PID in Australia (Table I). Half of the reported patients were receiving IVIG. Differences in the proportions of patients receiving IVIG between states are linked to differences in ascertainment but may also reflect criteria for use of IVIG in IgG subclass deficiency. A group of IgG subclass-deficient patients with a documented increase in infections clearly respond to IVIG,^{16,27} and it is important to identify this group of patients by careful clinical and microbiologic examination and testing for impaired antibody responses. There is a critical shortage of IVIG in Australia because of a widening of the indications for the use of this product, particularly in autoimmune diseases.²⁷ Data from the register indicate that at the current rate of use, there is a need for 182 kg of IVIG for patients with PID who are dependent on replacement therapy. A consensus statement has been developed in Australia recently to rationalize the use of IVIG in immunodeficiency and autoimmune disorders to conditions in which it has proven value¹⁸ because the immunoglobulin is provided free through the national blood transfusion service. The longitudinal study of a cohort of patients receiving IVIG will permit analysis of the impact of adequate replacement of immunoglobulins on the subsequent development of autoimmune and malignant complications in conditions such as CVID. In addition, the register may facilitate the systematic evaluation of newer therapeutic modalities²⁸ for PID.

Future surveys will record data in a format compatible with the new PID register of the European Group for Immunodeficiency Disorders to facilitate international comparisons. When added to the baseline information currently in the register, these additional studies will provide accurate estimates of the true prevalence and incidence of PID in Australia.

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REFERENCES

- Cooper MD, Butler JL. Primary immunodeficiency diseases. In: Paul WE, editor. *Fundamental immunology*. 3rd ed. New York: Raven Press; 1994. p. 1034-9.
- Stiehm ER. Immunodeficiency disorders: general considerations. In: Stiehm ER, editor. *Immunologic disorders in infants and children*. 3rd ed. Philadelphia: WB Saunders; 1989. p. 157-95.
- Primary immunodeficiency diseases—report of a WHO scientific group. *Clin Exp Immunol* 1995;99(suppl 1):1-24.
- Cunningham-Rundles C, Siegal FP, Cunningham-Rundles S, Lieberman P. Incidence of cancer in 98 patients with common variable immunodeficiency. *J Clin Immunol* 1987;7:294-302.
- Baumgart KW, Cook MC. Therapeutic applications of intravenous immunoglobulin. *Australian Journal of Hospital Pharmacy* 1992;23:148-51.
- Vetrie D, Vorechovsky I, Sideras P, et al. The gene involved in X-linked agammaglobulinemia is a member of the *Scr* family of protein-tyrosine kinases. *Nature* 1993;361:226-3.
- Leonard WJ. The defective gene in X-linked severe combined immunodeficiency encodes a shared interleukin receptor subunit: implications for cytokine pleiotropy and redundancy. *Curr Opin Immunol* 1994;6:631-5.
- Laman JD, Claassen E, Noelle RJ. Immunodeficiency due to a faulty interaction between T cells and B cells. *Curr Opin Immunol* 1994;6:636-41.
- Luzi G, Pesce AM, Rinaldi S. Primary immunodeficiencies in Italy. Data revised from the Italian Register of Immunodeficiencies-IRID (1977-1988). *Immunology Clinics* 1989;8:45-53.
- Hayakawa H, Iwata T, Yata J, Kobayashi N. Primary immunodeficiency syndrome in Japan. I. Overview of a nationwide survey on primary immunodeficiency syndrome. *J Clin Immunol* 1981;1:31-9.
- Spector BD, Perry GS III, Kersey JH. Genetically determined immunodeficiency disease (GDID) and malignancy: report from Immunodeficiency-Cancer Registry. *Clin Immunol Immunopathol* 1978;11:12-29.
- Rosen FS, Wedgewood RJ, Eibl M. Primary immunodeficiency disorders. Report of a WHO scientific group. *Clin Immunol Immunopathol* 1986;40:166-80.
- McNulty AM, Kaldor JM, McDonald AM, Baumgart K, Cooper DA. Acquired immunodeficiency without evidence of HIV infection: a national retrospective survey. *BMJ* 1994;308:825-6.
- Hosking CS, Robertson DM. Epidemiology and treatment of hypogammaglobulinemia. *Birth Defects: Original Article Series* 1983;19:223-7.
- Walker AM, Kemp AS, Hill DJ, Shetton MJ. Features of transient hypogammaglobulinemia in infants screened for immunological abnormalities. *Arch Dis Child* 1994;70:183-6.
- Jefferis R, Kumararatne DS. Selective IgG subclass deficiencies: quantification and clinical relevance. *Clin Exp Immunol* 1990;81:357-67.
- Chapel HM. Consensus on diagnosis and management of primary antibody deficiencies. *Br J Med* 1995;308:581-5.
- Keller T, McGrath K, Newland A, Gatenby P, Cobcroft R, Gibson J. Indications for use of intravenous immunoglobulin. *Med J Aust* 1993;159:204-6.
- Fasth A. Primary immunodeficiency disorders in Sweden: cases among children 1974-1979. *J Clin Immunol* 1982;2:86-92.
- Grisicelli C, Lisowska-Grospierre B, Mach B. Combined immunodeficiency with defective expression in MHC class II genes. In: Rosen FS, Seligman M, editors. *Immunodeficiencies*. Chur: Harwood Academic; 1993. p. 141-54.
- Waldmann TA, Nelson DL. Inherited immunodeficiency. In: Frank MM, Austen KF, Claman HN, Unanue ER, editors. *Immunologic diseases*. 5th ed. Boston: Little Brown; 1995. p. 287-429.
- Derry JM, Ohs HD, Francke U. Isolation of a novel gene mutated in Wiskott Aldrich syndrome. *Cell* 1994;78:635-44.
- Savitsky K, Bar-Shina A, Gilad S, Rotman G, Ziv Y, Vanagaite L, et al. A single ataxia-telangiectasia gene with a product similar to PI-3 kinase. *Science* 1995;268:1749-53.
- Woods CG, Taylor AMR. Ataxia telangiectasia in the British Isles: the clinical and laboratory features of 70 affected individuals. *QJM* 1992;82:169-79.
- Dinauer M, Orkin S. Chronic granulomatous disease. *Annu Rev Med* 1992;3:117-24.
- Sullivan JL, Woden BA. X-linked lymphoproliferative syndrome. *Immunodef Rev* 1992;1:325-38.
- Dwyer JM. Manipulating the immune system with immunoglobulin. *N Engl J Med* 1992;326:107-37.
- Cunningham-Rundles C, Kazbay K, Hassett J, Zhou Z, Mayer L. Enhanced humoral immunity in common variable immunodeficiency after long-term treatment with polyethylene glycol-conjugated interleukin-2. *N Engl J Med* 1994;331:918-21.