Primary Immunodeficiency Disorders including Severe Combined Immunodeficiency Syndrome

Background

Primary immunodeficiency disorders (PID) are rare disorders of the immune system. Affected children have increased susceptibility to infection and many are at greater risk of autoimmune and malignant disease in adult life. The incidence of PID in the Australian population is unknown. The Australian Society of Clinical Immunology and Allergy (ASCIA) formed a Primary Immunodeficiency Disorder study group in 1990 to develop a register of current PID cases. Attempts to determine prevalence were hampered by under-reporting so a study was commenced through the APSU to prospectively identify and classify incident cases in children.

Objectives

- To estimate the incidence of PID in Australian children
- To describe clinical features of PID in children
- To establish requirements for immunoglobulin therapy and bone marrow transplantation in Australian children with PID

Case definition

Any child or adolescent under 15 years of age who has been diagnosed with a primary immunodeficiency disorder in the last month, based on clinical and laboratory findings, which fits into one of the following categories:

- *Predominantly antibody defects, eg; X-linked agammaglobulinaemia, common variable immunodeficiency, IgA deficiency, IgG subclass deficiency* ***or***
- *T-cell and combined immunodeficiencies, eg; severe combined immunodeficiency* ***or***
- *Immunodeficiencies with other major defects, eg; Wiskott-Aldrich syndrome, DiGeorge anomaly, Ataxia Telangiectasia* ***or***
- *Complement deficiencies, eg; C1-esterase inhibitor deficiency (hereditary angioneurotic oedema)* ***or***
- *Defects of phagocyte function, eg; chronic granulomatous disease, leucocyte adhesion deficiency, Schwachman's syndrome* ***or***
- *Other, as yet unclassified disorder, eg; Chronic mucocutaneous candidiasis.*

The immunodeficiency must not be secondary to any infection such as HIV/AIDS, or to any other disease process such as malignancy or trauma.The above categories are based on the current World Health Organisation classification of PID.

Results and discussion

There were 245 notifications of PID to the APSU between January 1997 and December 1999. Questionnaires were returned for 233 (95%) cases, of which 126 were incident cases, 37 were duplicate reports, and 70 were reporting errors that did not fulfil the case definition criteria mainly because of diagnosis outside the study period.

Incident cases of Primary Immunodeficiency Disorders

On the basis of 126 cases newly diagnosed in 1997-9, the incidence of PID was 1.1/100 000 children under 15 years. The incidence in children under five years was 1.5/100 000, which was significantly greater than the incidence (0.8/100 000) in children aged 5-15 years (p=0.04). The cumulative incidence of PID for the first three years of life for the 1997 birth cohort was 4/ 100 000 live births. Cases were reported from NSW (60), Victoria (30), Queensland (14), Western Australia (12), South Australia (8), and Tasmania (2). No cases were reported from the Northern Territory or the ACT (Figure 10). Queensland had an annual incidence of PID that was significantly less than that of NSW but similar to the other states.

Clinical features:

Eighty-four (67%) of the 126 children were boys. The median age at presentation (with interquartile range) was 24.0 (7.4-75.0) months and the median age at diagnosis was 60.0 (18.8-108.0) months. The median time from presentation with clinical symptoms to diagnosis of PID was 5 (0.4-22.5) months and most children were diagnosed within six months of presentation.

Consanguinity was reported in four (4%) of the108 children in whom these details were available. Details about a family history of PID were available in 105 children, of whom 29 (28%) had a definite history, predominantly in siblings. Twenty (69%) of the 29 children with a family history of PID were male and most of their affected family members were also male.

Categorisation of PID

The major diagnostic categories of children with PID are shown in Figure 11 and the sub-categories in Table 8.

Predominantly antibody defects were diagnosed in 92 (73%) children. Common variable immunodeficiency (CVI) and immunoglobulin (Ig) class deficiency were the most frequent diagnoses in this category. IgA deficiency occurred in 27 (90%) of the 30 children with Ig class deficiency, six (22%) of whom had associated IgG2 deficiency.

A range of diagnoses accounted for the 21 (17%) incident cases which were classified as T-cell and/or combined immunodeficiencies. Severe combined immunodeficiency (SCID) was diagnosed during infancy in five (4%) children: two boys with the classical X-linked form; a boy with B-cell SCID; a girl with presumed autosomal recessive SCID; and another boy with as yet unclassified SCID. Three children were diagnosed in early childhood with combined immunodeficiency (CID): a girl with Nezelof syndrome; a boy with possibly a milder form of classical X-linked SCID; and another boy with CID clinically but uncertain aetiology.

Complement deficiencies occurred in only 2% of children and defects of phagocyte function in 8%. Eight of the ten children with phagocyte defects had chronic granulomatous disease (CGD).

Therapy

Therapy was required in 75 (60%) children as shown in Table 9. Fifteen (12%) children had two treatment modalities. Immunoglobulin (Ig) therapy was used in 54 (43%) children, most commonly for CVI as shown in Table 10. Ig therapy was required in all children with X-linked agammaglobulinaemia and Hyper-IgM syndrome and 13 (67%) of the 21 children with T-cell and/or combined immunodeficiencies.

The median age of commencing Ig therapy was 49.0 (11.3-104.5) months. Ig therapy was predominantly given monthly and intravenously but two children received weekly Ig subcutaneously and one child received second weekly intramuscular Ig. The median amount of Ig used per child per year, using the doses and treatment frequency documented at the time of notification, was 108.0 (58.5-153.5) grams. Adverse effects of Ig therapy were reported in seven children and included serum sickness (3), fever (2), aseptic meningitis (1), headache (1) and cough, wheeze and leg pain (1).

Bone marrow transplantation (BMT) had been performed for six children and was planned for another two children at the time of notification. BMT services were thus required for 6% of children over the three-year study period. Apart from the boy with Chediak-Higashi Syndrome, all other bone marrow transplants were indicated for PID of T-cell and/or combined immunodeficiency category. One boy with CID died of severe graft versus host disease and multi-organ failure in the month after receiving his mismatched allogeneic bone marrow transplant.

Other therapy included interferon-gamma in four children with CGD, C1 esterase inhibitor for a child with C1 esterase inhibitor deficiency and PEG-ADA for a child with ADA deficiency who was awaiting BMT.

Outcome

At the time of notification, ongoing symptoms were reported in 69 (61%) of the 114 children for whom details were available. Twenty-one (45%) of 47 children remained symptomatic despite the commencement of Ig therapy. Seven children died in the period between notification and questionnaire return. Five of these children had T-cell and combined immunodeficiencies. Two children, one with Hyper-IgM syndrome and another with veno-occlusive disease of the liver, died from respiratory failure due to *Pneumocystis carinii* pneumonia. One girl with IgA deficiency and ANA positivity but no other demonstrable immune abnormality had a fatal cardiorespiratory arrest due to idiopathic anaphylaxis.

Conclusion

This study has provided new information about the minimum incidence of PID in Australian children. It is the only study conducted worldwide where the incidence of PID has been determined in children younger than 15 years so international comparisons are not possible. Our study confirms that most PID is due to antibody defects, with 25% of cases due to CVI and 21% due to IgA deficiency. The true incidence of IgA deficiency is likely to be higher than that reported for two reasons: most cases of IgA deficiency are asymptomatic and hence diagnosed incidentally; and mildly symptomatic IgA deficiency is often not considered part of the PID spectrum by clinicians. A delay between onset of symptoms and diagnosis of PID is not uncommon.

Most children in this study required at least one form of therapy. Regular Ig therapy was required by 43% of children with PID and complications were infrequent. High rates of morbidity (61%) and mortality (6%) after therapeutic intervention were reported. One of six children died post-BMT but the procedure was

successful in all other recipients.

Service planning for Australian children with PID will be facilitated by the data obtained through this study regarding the requirement for replacement Ig therapy and BMT. This information is important in the current era of critical Ig shortage and resource limitation. Although rare in children, PID presents diagnostic and management challenges for clinicians. The active surveillance system provided by the APSU has enabled the collection of unique data for use by paediatricians.

Investigators

Dr Miriam Codarini (Principal Investigator),
Dr Alyson Kakakios **,**
Clinical Professor David Isaacs,
Department Immunology & Infectious Diseases,
New Children's Hospital, PO Box 3515, Parramatta NSW 2124
Tel: 02 9845 3412 Fax: 02 9845 3421
Dr Karl Baumgart, Immunologist, North Shore Medical Centre, 66 Pacific Highway, St Leonards NSW 2065
Associate Professor Warwick Britton, Department of Clinical Immunology, Royal Prince Alfred Hospital Sydney NSW 2006
Associate Professor Martyn French, Department of Clinical Immunology, Royal Perth Hospital, Wellington Street, Perth WA 6000
Dr Michael Gold,
Professor Don Roberton,
University Department of Paediatrics, Women's and Children's Hospital, 72 King William Road, Adelaide SA 5006
Dr Pat Hogan, Department of Immunology, 3rd Floor, Lions Building, Princess Alexandra Hospital, Ipswich Road, Woolloongabba QLD 4102
Professor Kevin Forsyth, Department of Paediatrics & Child Health, Flinders Medical Centre, Flinders Drive, Bedford Park SA 5042
Dr Elizabeth Benson, Department of Immunopathology, ICP & MR, Westmead Hospital, Westmead NSW 2145
Dr Andrew Kemp, Director of Immunology, Royal Children's Hospital, Flemington Road, Parkville VIC 3052
Dr Richard Loh, Director of Clinical Immunology, Princess Margaret Hospital for Children, PO Box S1400 Perth WA 6001
Associate Professor John B Ziegler, Head, Department Immunology/Allergy, Sydney Children's Hospital, High Street, Randwick NSW 2031

Figure 10 Incidence figures of PID by state

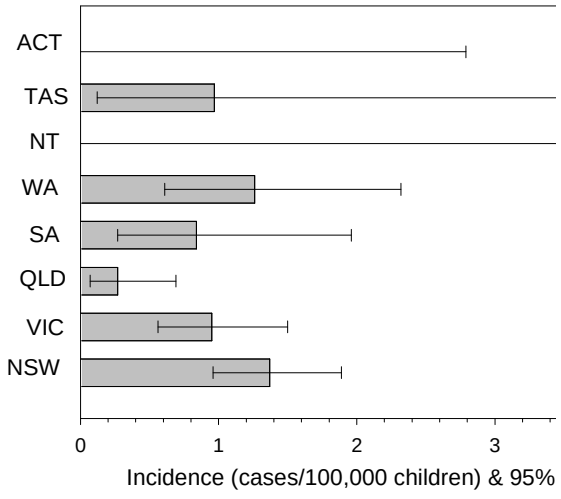

Figure 11 Diagnostic categories of new cases of PID by type, Jan 1997 - Dec 1999

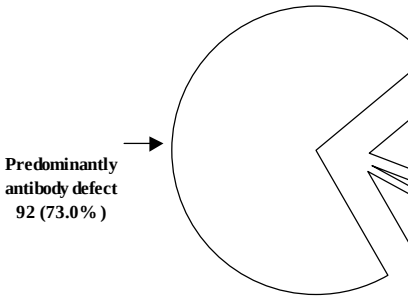

Table 8 Diagnostic categories of new cases of PID

Diagnostic Category
Predominantly antibody defects
Common variable immunodeficiency
Ig class deficiency (IgA or IgM or IgG)
X-linked agammaglobulinaemia
Ig subclass deficiency (IgG_2)
Transient hypogammaglobulinaemia of infanc
Hyper-IgM syndrome
T-cell and combined immunodeficiencies
Other severe combined immunodeficiency
Combined immunodeficiency
Chronic mucocutaneous candidiasis
X-linked severe combined immunodeficiency
Veno-occlusive disease of liver
DiGeorge anomaly
Wiskott-Aldrich syndrome
T-cell immunodeficiency
ADA deficiency
Omenn's syndrome
Short limbed dwarfism
Complement deficiencies
C1-esterase inhibitor deficiency
Properdin deficiency
C9 deficiency
Defects of phagocyte function

Table 9 Therapy in PID

Therapy	No. of cases*
Immunoglobulin	52
Bone marrow transplant	6
Interferon-gamma	4
Prophylactic antibiotics	16
Asthma therapy	4
Prednisone	2
Hormone therapy	2
C1-esterase inhibitor	1
PEG-ADA	1
Nil	51

*Some cases had more than one therapy

Table 10 Diagnostic indications for the use of IG therapy

Diagnosis	No. of cases (% of IG recipients)
Predominantly antibody defects	
Common variable immunodeficiency	17 (31)
X-linked agammaglobulinaemia	11 (20)
Hyper-IgM syndrome	4 (7)
Ig class deficiency	4 (7)
Ig subclass deficiency	3 (6)
Transient hypogammaglobulinaemia of infancy	1 (2)
T-cell and combined immunodeficiencies	
SCID	5 (9)
CID	3 (6)
Veno-occlusive disease of liver	1 (2)
Wiskott-Aldrich syndrome	1 (2)
ADA deficiency	1 (2)
Omenn's syndrome	1 (2)
Short limbed dwarfism	1 (2)
Complement deficiencies	
C9 deficiency	1 (2)
Total	**54 (100)**