

Primary immunodeficiency diseases at Red Cross War Memorial Children's Hospital

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Objective. To describe the spectrum of primary immunodeficiency diseases (PIDs) diagnosed at Red Cross War Memorial Children's Hospital.

Design. Retrospective, descriptive study.

Setting. Tertiary, referral hospital.

Patients. All patients investigated by the immunology service because of suspected PIDs, between January 1983 and December 1996.

Methods. Review of immunology service database and hospital case records.

Results. During the 14-year review period, 515 patients were investigated, a mean of 36.8 new patients per annum. Ninety-three patients with PIDs were diagnosed, a mean of 6.6 new patients per annum. The spectrum of PIDs was similar to that reported in developed countries. As in other series, antibody deficiencies predominated, accounting for 56% (52/93) of diagnoses. The male/female ratio was 1.5:1; 73% (62/85) came from the Western Cape, the remaining 27% (23/85) resided in five other provinces. Eighty per cent (70/87) presented with recurrent or atypical infection, with or without failure to thrive. Sinopulmonary infections (80%), diarrhoeal disease (19%) and candidiasis (18%) were the most common preceding infections. By the age of 5 years, only 60% had been diagnosed, compared with about 80% in developed countries. During the study period, 20% (19/93) were known to have died.

Conclusions. The results show a pattern of PIDs incidence similar to that in developed countries. Diagnosis was delayed in many patients, which probably contributed to morbidity and mortality. To facilitate earlier diagnosis and to improve outcome, children should be considered for an immunological assessment if they exhibit increased susceptibility to infection.

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The incidence of primary immunodeficiency diseases (PIDs), excluding IgA deficiency, is approximately 1 in 10 000.¹ While PIDs are readily diagnosed in developed countries and reported to national registries, their occurrence in developing countries is less clearly documented. In these countries secondary immunodeficiencies caused by nutritional disorders such as protein-energy malnutrition, vitamin A deficiency or iron deficiency, and infectious diseases such as HIV infection and measles, account for a significant proportion of children who present with increased susceptibility to infection. Therefore, children who present with recurrent or atypical infection caused by underlying PIDs, with or without failure to thrive, may be overlooked or misdiagnosed.

The paediatric immunology service at Red Cross War Memorial Children's Hospital (RXH) commenced in 1983. It has developed both diagnostic and therapeutic capacities. Since its inception a database of all patients investigated for PIDs has been maintained. We therefore had the opportunity to establish the spectrum of PIDs in our setting, and to compare it with published series from developed countries. Furthermore, we set out to determine whether diagnosis had been delayed significantly, and to compile the clinical and demographic profile of our patients.

Methods

A retrospective case study of all patients referred to the immunology service at RXH because of suspected PIDs was completed. The study period was from January 1983 to December 1996. The details of immunological investigations and results, and diagnoses were obtained from the immunology service database. Clinical data were extracted from the hospital case records of patients with PIDs. Some of the hospital case records were unavailable or incomplete. PIDs were classified according to the latest World Health Organisation classification of PIDs.²

Data on the immunological service were evaluated according to the number of patients investigated and the number of different investigations performed per annum. Data on the patients with PIDs were analysed according to the following criteria: number of patients with various PIDs, age and sex distribution, geographical origin, indication for investigation, spectrum of infections preceding diagnosis, treatment and follow-up arrangements and deaths.

Results

Immunology service

Between 1983 and 1996 515 patients were investigated for suspected PIDs, a mean of 36.8 patients per annum (range 27 - 53). During this period 93 (18%) were diagnosed with PIDs, a mean of 6.6 new patients per annum (range 1 - 11). The spectrum and frequency of diagnoses is shown in Table I. The median (range) number of investigations undertaken per annum were: lymphocyte transformation to one or more mitogens, or recall antigens 34.5 (22 - 54), lymphocyte subset quantitation 35.5 (22 - 52), nitro-blue tetrazolium test

29 (17 - 38), complement screen 27 (16 - 43), immunoglobulin quantitation 42 (15 - 57), and IgG subclass quantitation 30 (27 - 38). IgG subclass quantitation was first performed in 1993, functional antibody responses to tetanus toxoid and *H. influenzae* capsular polysaccharide in 1994, and lymphocyte subset quantitation by flow cytometry in 1994. Specific phagocytic functions other than the nitro-blue tetrazolium test and functional antibody responses were done infrequently during the study period.

Table I. PIDs diagnosed at RXH between January 1983 and December 1996

Disease/category	Total (%)	Females	Males
I. Primary specific immunodeficiency	78 (84)	32	46
Combined immunodeficiencies	7 (8)	3	4
T-B ⁻ SCID	4 (4)	3	1
T-B ⁺ SCID	3 (3)	0	3
Predominantly antibody deficiencies	52 (56)	18	34
X-linked agammaglobulinaemia	10 (11)	0	10
Autosomal hyper-IgM syndrome	1 (1)	1	0
Selective IgG deficiency ± IgA deficiency	5 (5)	4	1
Common variable immunodeficiency	19 (20)	9	10
IgA deficiency	10 (11)	3	7
Transient hypogammaglobulinaemia of infancy	7 (8)	1	6
Predominantly T-cell defects	2 (2)	1	1
Primary CD4 ⁺ T-cell deficiency	2 (2)	1	1
Immunodeficiency associated with other major defects	17 (18)	10	7
Wiskott-Aldrich syndrome	2 (2)	1	1
Ataxia-telangiectasia	11 (12)	6	5
DiGeorge anomaly	4 (4)	3	1
II. Immunodeficiencies associated with or secondary to other diseases	7 (8)	4	3
Hyper-IgE syndrome	6 (6)	3	3
Chronic mucocutaneous candidiasis	1 (1)	1	0
III. Complement deficiencies	4 (4)	1	3
C1-esterase deficiency	1 (1)	0	1
C6 deficiency	3 (3)	1	2
IV. Defects of phagocytic function	4 (4)	0	4
Chronic granulomatous disease	2 (2)	0	2
Myeloperoxidase deficiency	1 (1)	0	1
Myelokathexis [†]	1 (1)	0	1
Total number of deficiencies (%)	93 (100)	37 (40)	56 (60)

SCID = severe combined immunodeficiency.

Patients with PIDs

Age and sex distribution. Sixteen per cent (15/93) were diagnosed in the first year of life, 44% (41/93) between 1 and 5 years of age, 37% (34/93) between 5 and 16 years of age and 3% (3/93) after the age of 16 years. The male/female ratio was 1.5:1, largely because males predominated in the antibody deficiency conditions (Table I).

Health sector. Sixty per cent (50/83) of patients originated from the public sector and 40% (33/83) from the private sector.

Geographical location. Seventy-three per cent (62/85) were from the Western Cape. The remaining 27% (23/85) resided in 5 other provinces of South Africa. Of the 62 patients from the Western Cape, 21% (13/62) lived outside the Cape metropolitan region at the time of diagnosis.

Indication for investigation. Seventy per cent (61/87) presented with recurrent or atypical infection, 9% (8/87) with recurrent infection and failure to thrive, 2% (2/87) with a family history of PID, 1% (1/87) with a family history of PID and recurrent infection, and 17% (15/87) with a recognisable syndrome (DiGeorge (4), ataxia-telangiectasia (9), Wiskott-Aldrich (1), congenital angio-oedema (1)).

Infections preceding diagnosis. Table II shows the infectious spectrum before diagnosis in those with PIDs presenting clinically with recurrent or atypical infection, with or without failure to thrive. Sinopulmonary infections (80%), diarrhoeal disease (19%) and candidiasis (18%) were the most common infections.

Table II. Spectrum of infections before diagnosis (N = 70)

Infection	No.	(%)
Sinopulmonary	56	(80)
Lower respiratory	48	(69)
Otitis media	29	(43)
Diarrhoea	13	(19)
Candidiasis	12	(18)
Dermatological	9	(13)
Septicaemia	7	(10)
Meningitis	6	(9)
Urinary tract	5	(7)
Abscess formation	4	(6)
Laryngo-tracheobronchitis	4	(6)
<i>P. carinii</i> pneumonitis	3	(4)
Osteitis/arthritis	1	(1)

Treatment. Thirty-three per cent (27/81) received intravenous immunoglobulin, 3% (2/81) received intramuscular immunoglobulin, 4% (3/81) were initially managed with intramuscular immunoglobulin but later changed to intravenous immunoglobulin, 1% (1/81) received intravenous immunoglobulin and prophylactic antibiotics, 6% (5/81) received prophylactic antibiotics, 1% (1/81) received tranexamic acid, 1% (1/81) required intermittent platelet infusions and 1% (1/81) underwent bone marrow transplantation (BMT). Forty-eight per cent (39/81) did not receive specific therapy.

Follow-up arrangements. Twenty per cent (17/84) were managed by the immunology clinic at RXH or Groote Schuur Hospital, 26% (22/84) at other clinics at RXH, 14% (12/84) at other state hospitals in South Africa, and 29% (24/84) in the private sector in South Africa; 6% (5/84) died before any follow-up arrangements could be made and 5% (4/84) were discharged without any follow-up arrangements.

Deaths. Twenty per cent (19/93) were known to have died during the study period. The cause of death of 13 patients was established (Table III).

Malignancies. One patient developed Hodgkin's lymphoma, diagnosed at autopsy.

Table III. Cause of death of patients with PIDs

Patient	Diagnosis	Age at diagnosis (mo.)	Age at death (mo.)	Cause of death
1	SCID	4.5	5.0	Septicaemia
2	SCID	14.0	15.0	Pneumonia/respiratory failure
3	SCID	4.5	5.0	Presumed septicaemia
4	SCID	5.0	9.0	Unknown
5	SCID	18.0	Unknown	Unknown
6	SCID	6.0	Unknown	Unknown
7	XLA	32.0	32.5	Respiratory failure
8	XLA	22.0	48.5	Pneumonia
9	XLA	161.5	162	Bronchiectasis/respiratory failure
10	CVID	10.0	17.5	Pneumonia
11	CVID	37.0	130.5	Cardiomyopathy/cardiac failure
12	CVID	64.5	74.5	Septicaemia/Hodgkin's lymphoma
13	Hyper-IgM	93.5	172.5	Presumed septicaemia
14	AT	40.0	97.5	Disseminated candidiasis
15	AT	126.0	190.5	Neurological progression
16	AT	55.5	105.5	Unknown
17	DiGeorge	2.5	3.0	Surgical death (truncus repair)
18.	Hyper-IgE	114.0	120.0	Unknown
19.	CGD	16.0	Unknown	Unknown

SCID = severe combined immunodeficiency; XLA = X-linked agammaglobulinaemia; CVID = common variable immunodeficiency; AT = ataxia-telangiectasia; CGD = chronic granulomatous disease.

Specific conditions

Severe combined immunodeficiency (SCID). Seven patients were diagnosed during the study period, 4 with absent (or near absent) T and B lymphocyte function (T-B⁻ SCID), and 3 with absent (or near absent) T lymphocytes (T-B⁺ SCID). The median age at diagnosis was 6.0 months (range 4.5 - 18.0 months) for all patients with SCID, 4.8 months for those with T-B⁻ SCID, and 7 months for those with T-B⁺ SCID. The median total lymphocyte count at diagnosis was $2.050 \times 10^9/l$ ($N = 6$; range 1.275 - 4.760) for the whole group, $1.965 \times 10^9/l$ ($N = 4$, range 1.275 - 2.576) for those with T-B⁻ SCID, and $3.380 \times 10^9/l$ ($N = 2$, range 2.000 - 4.760) for those with T-B⁺ SCID. Adenosine deaminase and purine nucleoside phosphorylase function were normal in 4 patients tested. Six patients died, 3 within 1 month of diagnosis and 1 within 6 months of diagnosis. Details of the deaths of the other 2 patients are not known (Table III). One patient had an HLA-identical BMT in 1996. He is currently well.

X-linked agammaglobulinaemia (XLA). Ten patients were identified, including 4 from a single family in the Western Cape. Median age at diagnosis was 28.5 months (range 14 - 161.5).

Common variable immunodeficiency (CVID). Nineteen patients were identified. The median age at diagnosis was 61 months (range 3.5 - 202). All patients had significantly reduced IgG levels with or without reductions of other immunoglobulin concentrations. Three patients had depressed cell-mediated immunity (CMI).

Autosomal hyper-IgM syndrome. This patient developed persistent lymphadenopathy from the age of 3 years, associated with failure to thrive and recurrent infection, mainly otitis media, impetigo and pneumonia. Despite intravenous immunoglobulin therapy she continued to experience recurrent infections and her IgM concentration increased progressively. She died of presumed septicaemia at the age of 14.5 years. Immediately prior to death the IgM concentration was 12.5 g/l.³

Ataxia-telangiectasia. Ataxia-telangiectasia (with associated immunodeficiencies) was diagnosed in 11 patients. Results of immunological investigations showed that 2 patients had IgA deficiency, 3 had depressed CMI, and 6 had depressed CMI and IgA deficiency. The concentration of α -fetoprotein was significantly elevated in 8/8 patients.

Myelokathexis. This patient had persistent neutropenia and neutrophil maturational arrest on bone marrow biopsy, as well as hypogammaglobulinaemia; and experienced recurrent viral wart and sinopulmonary infections.⁴

Discussion

The spectrum of PIDs in Cape Town (Table I) is similar to that documented in developed countries. As in other studies, antibody deficiency conditions predominate.⁵⁻⁷ Patients with IgA deficiency are not usually referred to our immunology service, hence the low number. Although the average number of patients we investigated per annum was small, 18% of the total had PIDs. In developed countries about 10% of all patients investigated have either primary or secondary immunodeficiencies.¹ Our analysis included patients referred because of suspected PIDs. HIV infection was excluded before patients were considered for investigation. These factors probably contributed to the apparently higher proportion of positive results.

In developed countries 40% of patients with PIDs are diagnosed by 1 year of age, 80% by 5 years and 95% by 16 years.¹ Accordingly, diagnosis was delayed in many of our patients, and probably contributed to morbidity. Furthermore, the majority of infections preceding diagnosis were common childhood infections. Atypical infections were less frequent (Table I). To facilitate diagnosis and therefore reduce morbidity and mortality children should be considered for immunological investigation if they exhibit increased susceptibility to infection. Suggestive clinical features include frequent ear infections ($\geq 6-8$ infections per annum), the need for prolonged oral or intravenous antibiotics to clear infection, recurrent proven pneumonia (≥ 2 episodes), failure to thrive, recurrent deep skin or organ abscesses, recalcitrant thrush, especially beyond 1 year of age, two or more deep-seated infections such as meningitis, osteomyelitis, cellulitis or septicaemia, and a family history of PID.^{1,8}

The high male/female ratio, previously documented in other series,⁵⁻⁷ was largely due to the preponderance of X-linked disorders such as XLA and X-linked SCID (Table I). Forty per cent of our patients were from the private sector and 27% originated in provinces other than the Western Cape, highlighting the need for specialised immunological

services at all academic institutions in South Africa. Furthermore, PIDs are associated with a high mortality rate (20%). The true mortality rate of our cohort is probably higher, as many patients were not followed up at RXH, or have been lost to the service. Only 1 patient was known to have developed malignancy. With improved management and follow-up one could expect this figure to increase several fold.⁹

The estimated incidence of SCID is 1 in 66 000 live births.¹ Over the past 14 years 7 patients have been diagnosed at RXH. Hague *et al.*¹⁰ recently reported that the vast majority of patients with SCID have total lymphocyte counts persistently below $2.8 \times 10^9/l$. This could be used as an early criterion to facilitate diagnosis, as those diagnosed after 6 months of age tend to have a poorer prognosis.¹⁰ Six of our patients had total lymphocyte counts prior to diagnosis. All 4 with T-B⁻ SCID, and 1 of 2 with T-B⁺ SCID, had total lymphocyte counts below $2.8 \times 10^9/l$. Without definitive therapy, patients with SCID usually die before the age of 2 years. In August 1996 the first BMT for T-B⁻ SCID was performed at Groote Schuur Hospital. In future BMT will help to improve the outcome of SCID and other PIDs such as Wiskott-Aldrich syndrome and leucocyte adhesion deficiency in Cape Town.¹¹

The median age at diagnosis of patients with XLA and CVID was significantly higher than for those with SCID. Three of the 10 patients with XLA were diagnosed after the age of 5 years, 1 at the age of 13.5 years. This patient had already developed advanced bronchiectasis with chronic respiratory failure following repeated lower respiratory tract infections. He died shortly after diagnosis (Table III). His clinical course illustrates how delayed diagnosis and resultant suboptimal treatment lead to significant morbidity, and shorten the lifespan of patients with PIDs. CVID, a heterogeneous group of conditions characterised by defective antibody production, may manifest itself at any age. The wide age range of our patients at diagnosis confirms this.

Hyper-IgM syndrome is inherited in an X-linked or autosomal manner. X-linked hyper-IgM syndrome is due to mutations in the CD40 ligand gene, which impairs immunoglobulin isotype switching.¹¹ Autosomal hyper-IgM syndrome, by contrast, has been reported infrequently,^{3,12,13} and the underlying mechanism has not yet been elucidated. Ataxia-telangiectasia is caused by mutations in a single gene on chromosome 11q22.23, which encodes a protein similar to mammalian phosphatidylinositol-3-kinases. Mutations of this gene may result in a recombination defect which interferes with the arrangement of T-cell and B-cell genes, resulting in cellular and/or humoral deficiencies in about 70% of patients.¹⁴ The immunological manifestations documented in our patients are typical of ataxia-telangiectasia. Myelokathexis is a form of congenital neutropenia with defective release of neutrophils from the bone marrow cavity caused by neutrophil maturational arrest.⁴ Mentzer *et al.* and Wetzler *et al.* have previously reported patients with myelokathexis in association with hypogammaglobulinaemia, recurrent respiratory infection and viral warts.^{15,16} The cause of this syndrome may relate to a regulatory mechanism involving both myeloid and lymphoid systems.¹

Conclusion

Results of this study show a pattern of PIDs similar to that in developed countries. However, diagnosis was delayed in many patients. By the age of 5 years, only 60% had been diagnosed, compared with about 80% in developed countries. To ensure earlier diagnosis, children should be referred for an immunological assessment if they exhibit increased susceptibility to infection, i.e. increased frequency or severity of infection, prolonged duration of infection, increased dependence on antibiotics, unexplained or severe complications, develop infection caused by uncommon micro-organisms or have a suggestive family history.

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