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Primary Immunodeficiency Disorders in the Republic of Ireland: First Report of the National Registry in Children and Adults

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Data collection for the national registry for patients with primary immunodeficiency disorders in the Republic of Ireland commenced in 1996. One hundred and fifteen cases of primary immunodeficiency diseases were registered between December 1996 and February 2003. The most frequent primary immunodeficiency disorders were antibody deficiency ($n = 53$) and complement deficiency ($n = 32$). In addition, patients with T cell deficiency ($n = 11$) and chronic granulomatous disease ($n = 11$) were identified. A small number of patients with Wiskott–Aldrich syndrome, natural killer cell deficiency, DiGeorge syndrome and chronic mucocutaneous candidiasis were also registered. Comparison of our data with that recently reported in the European registry revealed that complement deficiency was more prevalent in the Republic of Ireland compared to other European countries. Results of our registry point to a significant prevalence of primary immunodeficiency disorders in the Republic of Ireland (2.9 cases per 100.000 population). However, it is likely that these figures underestimate the true prevalence of such cases in the country. We hope, with increased awareness of the national registry among primary care physicians, that more patients will be included and we will be able to identify accurately the frequency and the distribution of these disorders.

KEY WORDS: Primary immunodeficiency disorders; registry; Ireland.

INTRODUCTION

Primary immunodeficiency disorders result from intrinsic defects of the immune system. As a consequence, recurrent protozoal, bacterial, fungal, and viral infections of varying severity ensue. Although previously considered a rare pathology, recent reports demonstrate that primary immunodeficiency diseases are increasingly recognized. Advances in our understanding of the immune system and recent developments in diagnostic techniques have contributed significantly to early recognition and more effective therapy of these disorders (1). Deficiencies of various components of the immune system have been identified. The definition of clinical and immunological criteria by the WHO scientific group has allowed a more consistent classification of these disorders and comparison between different series to be made (2).

Reports on registries of primary immunodeficiency disorders are currently available from different countries throughout Europe including the United Kingdom, Italy, Switzerland, and Spain (3–6). Data on primary immunodeficiency disorders in the Republic of Ireland is lacking. The presence of registries for patients with primary immunodeficiency disorders in other countries prompted us to organize a national registry for patients with these diseases in the Republic of Ireland. The main objective of the registry was to determine the prevalence of these diseases in this country and use the registry as a basis to establish a database for patients with primary immunodeficiency in Ireland. This paper provides, for the first time, data on the prevalence of these disorders in the Republic of Ireland.

PATIENTS AND METHODS

The Republic of Ireland is primarily inhabited by a homogeneous Caucasian population. Family size tends to be larger than the European average and this is particularly true of a subgroup in Irish society, the Irish Traveller community. This Traveller community is a nomadic cultural group within the Irish population, with a higher incidence of consanguineous marriage, in particular first cousin marriages.

A simple questionnaire was designed in 1996 and sent to different medical and surgical departments including Internal Medicine, Respiratory Medicine, Gastroenterology, Hematology, Pediatrics, and Ear, Nose and Throat surgeons throughout the Republic of Ireland. The

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information requested included the type of primary immunodeficiency disorder, the patient's date of birth, age at time of diagnosis, family history, immunoglobulin levels and B cell counts, if available. In addition, our centre acted as an important source of information as the majority of patients with primary immunodeficiency disorders were either diagnosed in our laboratory and/or attend our outpatient clinic and day care facility for treatment.

In this report, we ensured that all patients with primary immunodeficiency disorders in the register were diagnosed and classified according to the WHO criteria (2, 7). Data was collected on all patients, both children and adults, living and deceased.

RESULTS

National Registry

Up until 1996, there was no formal register for patients with primary immunodeficiency in the Republic of Ireland. Less than 30 patients with different immunodeficiency states were attending the Clinical Immunology service in St. James's Hospital. The questionnaire concerning the current register was sent to different medical and surgical disciplines in 1996 and after approximately 2 years, meaningful data was available for analysis. By 1998, 90 patients had been identified and immunoglobulin and complement deficiencies were the most frequent disorders registered. The age of patients at diagnosis varied considerably, but in many cases with monogenic disease, the diagnosis was made in early childhood.

It was difficult to accurately estimate the number of new patients identified each year, but based on the available data it was calculated that some five additional patients with primary immunodeficiency are recognized each year. We included in the registry patients with immunoglobulin deficiencies, chronic granulomatous disease, complement deficiencies, and other miscellaneous immunodeficiencies. Information on patients with IgA deficiency and IgG subclass deficiency was not collected.

One hundred and fifteen patients with primary immunodeficiency were identified in the Republic of Ireland between December 1996 and February 2003. Immunoglobulin deficiency cases predominated with 53 cases. Twenty-eight were patients with common variable immunodeficiency (CVID) and 25 had X-linked agammaglobulinemia (XLA). Complement deficiency was the second most frequently established diagnosis with 32 cases. Of these, 16 patients had C1 inhibitor deficiency, 10 had C2 deficiency, 1 had C6 deficiency, and 5 patients had C7 deficiency. In two families, the initial diagnosis of C2 and C7 deficiencies was made following the death of the proband—one patient with meningococcal septicemia and the second with recurrent meningococcal meningitis, respectively. Of the 16 patients with C1 inhibitor deficiency, 4 had type II hereditary angioedema caused by a functional defect of C1 inhibitor: three of these were members of the same family.

Of the 11 patients with T cell defects, 9 had clinical and laboratory evidence of the hyper-IgM syndrome: in two of these patients, CD40 ligand deficiency was confirmed using molecular techniques. Two further patients (both female) were diagnosed with severe combined immunodeficiency. Chronic granulomatous disease was diagnosed in 11 patients: three were members of an Irish Traveller community family. A smaller number of cases with Wiskott–Aldrich syndrome ($n = 2$), natural killer cell deficiency ($n = 2$), DiGeorge Syndrome ($n = 3$), and chronic mucocutaneous candidiasis ($n = 1$) were also identified. The patients with natural killer (NK) cell deficiency were also from Irish Traveller families: both had less than 1% NK cells and severely impaired NK cell function. One of these patients presented with severe failure to thrive and recurrent bacterial and viral infections; the second patient presented with an EBV-related intestinal lymphoma. Details of these cases are reported elsewhere (Dunne, J., *et al*., manuscript in preparation).

The total population of the Republic of Ireland is four million according to the national Census in 2002 with a birth rate of 15/1000 population. Based on these figures and the results of our registry, the prevalence of primary immunodeficiency is estimated to be 2.9 cases per 100.000 population. Many patients with X-linked agammaglobulinemia, complement deficiency, and chronic granulomatous disease had at least one additional affected family member. In a few instances, particularly with respect to XLA and complement deficiency disorders, as many as three to four family members were affected by the same immunodeficiency. Age, sex, and absolute numbers of these patients are summarized in Table I.

Nearly all patients with immunoglobulin deficiency receive regular immunoglobulin infusions on a three- to four-weekly basis and some 44% of these patients attend our Clinical Immunology service. Many receive their infusions on a home therapy basis. All patients with C1 inhibitor deficiency receive long-term prophylaxis with either antifibrinolytic agents or synthetic androgens. C1 inhibitor concentrate is available to treat emergency episodes of angioedema or used as prophylactic measure during pregnancy. Patients with other complement deficiencies and chronic granulomatous disease receive maintenance prophylactic antibiotics. Bone marrow transplant was performed successfully on three

Table I. Age, Sex, and Number of Patients with Primary Immunodeficiency in the Republic of Ireland

Primary immunodeficiency disorders	No. of patients	Age range (years)	Male	Female
Immunoglobulin deficiencies (46%)				
Common variable immunodeficiency	28	12–70	17	11
X-linked agammaglobulinemia	25	9–36	25	0
T cell deficiencies (10%)				
Hyper-IgM syndrome	9	7–20	5	4
Severe combined immunodeficiency	2	15–18	0	2
Complement deficiencies (27%)				
C1 esterase inhibitor deficiency	16	4–49	6	10
C2 deficiency	10	5–24	4	6
C6 deficiency	1	50	0	1
C7 deficiency	5	17–26	2	3
Phagocytic disorders (10%)				
Chronic granulomatous disease	11	3–28	6	5
Other immunodeficiencies (7%)				
DiGeorge syndrome	3	8–10	1	2
Wiskott–Aldrich syndrome	2	25–31	2	0
Natural killer cell deficiency	2	8–13	2	0
Chronic mucocutaneous candidiasis	1	14	0	1

patients—with NK cell deficiency, CD40 ligand deficiency, and SCID, respectively.

Comparison with European Registries

Recent data from the European Society for Immunodeficiency (ESID) show that 9707 patients with primary immunodeficiency are registered in Europe (reference no.8 and Table II). The majority of these patients (66%) suffer from antibody deficiency. Other immunodeficiencies including T cell or combined deficiencies (18%), phagocytic deficiencies (7%), complement deficiencies (6%), and other miscellaneous immunodeficiencies (3%) were less common. In the United Kingdom, a country in close proximity to the Republic of Ireland and with a generally similar ethnic background, 1544 cases with immunodeficiency are listed (reference no.8 and Table II). Antibody (72%) and T cell or combined deficiencies (14%) accounted for the majority of cases reported whereas a smaller number of patients had complement deficiencies and phagocytic disorders.

In agreement with these reports from the UK and the ESID registries, antibody deficiency accounted for the majority of immunodeficiency cases in Ireland. However, complement deficiency was significantly more prevalent in our registry (27%) compared with the ESID and UK registries where only 6% of patients had these disorders. Furthermore, chronic granulomatous disease was relatively more prevalent in Ireland compared with the UK and ESID registries. The data for different primary immunodeficiency disorders in the Republic of Ireland, UK, and all ESID countries is represented in Table II.

DISCUSSION

In this paper, we report for the first time, data on the prevalence of primary immunodeficiency disorders in the Republic of Ireland. One hundred and fifteen patients were identified with immunoglobulin and complement deficiencies being the most common disorders. The inclusion in the last few years of new primary immunodeficiency disorders in the WHO classification, together with

Table II. Patients with Primary Immunodeficiency Disorders in the Republic of Ireland, UK, and all ESID Countries

Primary immunodeficiency disorders	Ireland ($n = 115$)	United Kingdom ($n = 1554$)	All ESID countries ($n = 9707$)
Antibody deficiencies	53 (46%)	1111 (72%)	6433 (66%)
T cell deficiencies and combined deficiencies	11 (10%)	213 (14%)	1707 (18%)
Phagocytic disorders	11 (10%)	87 (6%)	720 (7%)
Complement deficiencies	32 (27%)	97 (6%)	605 (6%)
Other immunodeficiencies	8 (7%)	36 (2%)	242 (3%)

improved and greater access to diagnostic techniques, has made it easier to compare our data with data available in the European Society of Immunodeficiency Diseases (ESID) registry which includes a total of 9707 patients. In order to make such a comparison, primary immunodeficiency disorders were divided into five large groups: antibody deficiencies, T cell deficiencies and combined (T and B) deficiencies, phagocytic disorders, complement deficiencies, and a group of other immunodeficiencies.

In the Republic of Ireland, immunoglobulin deficiency was the most prevalent primary immunodeficiency disorder: this is in agreement with reports from all ESID countries. Of the 53 patients, 27 attend our clinical immunology service on a regular basis for their infusions and follow up. Similar numbers of patients with CVID and XLA were reported in our registry. This finding contrasts with reports in other countries in which CVID was two- to fourfold more prevalent than XLA (9, 10). It is likely that case ascertainment difficulties are responsible for this discrepancy and it is probable that significant numbers of CVID cases remain either to be diagnosed or identified, for enrollment in our registry.

Of interest, in our registry complement deficiencies and chronic granulomatous disease were more prevalent than in the UK and the ESID registries. With respect to complement, a disproportionate number of cases with C1 inhibitor and C2 deficiency were identified. These differences may be explained by the relative ease of case ascertainment of monogenic disorders in Ireland, where large, close-knit families are still common. This is particularly true of a seminomadic group, called the Irish Traveller community, in which there is a higher incidence of consanguineous marriage (11). Several cases of primary immunodeficiency were identified in this community, including two cases of NK cell deficiency.

The finding of clusters of different immunodeficiency states in the Republic of Ireland may be of interest to countries that receive large number of Irish immigrant such as the United Kingdom and the United States of America. Our findings emphasize the importance of considering the ethnic background of a population in the investigation of rare disorders such as primary immunodeficiency. Ireland is largely populated by a homogeneous Caucasian population and currently has small numbers of other ethnic groups, thus, the results of this survey are a true representation of the Irish genetic pool.

The data presented in this paper point to a significant prevalence of primary immunodeficiency disorders (2.9 cases per 100.000 population) in the Republic of Ireland with antibody and complement deficiencies being the most common. However, the overall true prevalence of these immunodeficiency states is probably underestimated: this may be due to a failure to ascertain all affected patients and because some patients remain undiagnosed. We hope, with increased awareness of the national registry among primary care physicians, that more patients will be included and we will be able to identify accurately the frequency and the distribution of these disorders. The role of primary immunodeficiency registries is essential, not only for better understanding of the epidemiology of primary immunodeficiency disorders, but also for the identification of new forms of these conditions and for establishing novel therapeutic approaches. Collecting data for our national registry was an important and beneficial investigation that resulted in valuable information being generated about the prevalence of primary immunodeficiency disorders in this country. Our future plan is to determine the geographical distribution of these disorders in Ireland and to determine the incidence of associated disorders such as autoimmune disease and malignancy in these patients.

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