Incidence and Temporal Trends of Primary Immunodeficiency: A Population-Based Cohort Study

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OBJECTIVE: To determine the incidence and temporal trends of primary immunodeficiency diseases (PIDs) and examine whether an association exists between delayed diagnosis and increased morbidity.

PATIENTS AND METHODS: We performed a historical cohort study to describe the epidemiology of PIDs in Olmsted County, Minnesota, during a 31-year period from January 1, 1976, through December 31, 2006, using the Rochester Epidemiology Project. Incidence and trends over time, presence of comorbid conditions, and trends in management were determined.

RESULTS: During the 31-year study period, 158 new cases of PIDs were diagnosed, with an overall incidence rate of 4.6 per 100,000 person-years. The rate of PIDs from 2001 through 2006 (10.3 per 100,000 person-years) was nearly 5 times higher than that from 1976 through 1980 (2.4 per 100,000 person-years). The associations between continuous variable(s) and categorical outcome(s) were assessed by using the Wilcoxon rank sum test. Longer delay in diagnosis was significantly associated with recurrent sinusitis ($P<.001$), recurrent pneumonia ($P=.03$), and subsequent treatment with immunoglobulins ($P<.001$). On the basis of Kaplan-Meier survival estimates, the proportion of patients surviving at 10 years after diagnosis was 93.5% (95% confidence interval, 85.9%-97.1%). However, older age at diagnosis was significantly associated with mortality ($P=.01$).

CONCLUSION: This is one of the first population-based studies to examine the temporal trends of PIDs. The incidence of PIDs increased markedly between 1976 and 2006. In this cohort, a delay in diagnosis was common and was associated with increased morbidity. Despite substantial morbidity, most patients with PIDs can expect a normal life span.

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CI = confidence interval; PID = primary immunodeficiency disease

Primary immunodeficiency diseases (PIDs) are a class of disorders in which there is an intrinsic defect in the human immune system. Although PIDs are often described as rare disorders, the true incidence and prevalence of these diseases, either individually or in aggregate, are unknown.¹

As the field of PID research continues to expand and newer molecular defects are recognized,²⁻⁴ the impetus is

growing for a newborn screen for PIDs, especially severe combined immunodeficiency.⁵⁻⁷ We need estimates of the incidence and prevalence of the disease in the population to determine the cost-effectiveness of routine screening. Some estimates have been made of the incidence and prevalence of PIDs based on PID registries in various countries⁸⁻¹³; however, the incidence of PIDs in the United States is unknown. Boyle and Buckley¹ conducted a telephone interview study by random-digit dialing to evaluate the prevalence of PIDs in 2006-2007, but the numbers are approximate and may not correspond to the true incidence and prevalence of PIDs in the population. Our objectives in this study were to (1) describe the epidemiology of PIDs in a defined population in Olmsted County, Minnesota, during a 31-year period using the Rochester Epidemiology Project and (2) evaluate factors associated with morbidity and mortality in the long-term care of patients with PIDs.

PATIENTS AND METHODS

Epidemiological research in Olmsted County, Minnesota (2000 US Census population, 124,277), is optimized by the county's relative isolation from other urban centers and the delivery of nearly all medical care to county residents by a small number of health care provider groups. With the exception of a higher proportion of the working population employed in the health care industry, the characteristics of the population of Olmsted County are similar to those of US whites (Figure 1).¹⁴

Since 1907, every patient at Mayo Clinic has been assigned a unique identifier; all information from every contact (including hospital inpatient and outpatient, office, emergency department, and nursing home visits, as well as death certificate and autopsy information) is contained within a unit medical record. Under the auspices of the Rochester Epidemiology Project, this records-linkage system was expanded to include non-Mayo Clinic providers of care to county residents. A single medical dossier exists for each patient, into which medical diagnoses, surgical interventions, and other key information from medical records are regularly abstracted and coded into computerized indices using the *International Classification of Diseases, Ninth Revision (ICD-9)*, adapted codes for hospitals.¹⁴ The computerized indices allow the linkage of medical records

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FIGURE 1. Characteristics of the population of Olmsted County, Minnesota, according to the Olmsted County records-linkage system.

from all sources of care used by the population (both Mayo Clinic and Olmsted Medical Center), providing an infrastructure to analyze disease determinants and outcomes.^{14,15} This records-linkage system therefore constitutes an opportunity to ascertain the incidence and prevalence of PIDs in a defined, nonreferred population. This study was approved by the institutional review boards of Mayo Clinic and the Olmsted Medical Center.

INCLUSION AND EXCLUSION CRITERIA

Cases were initially identified using *ICD-9* diagnostic codes for PIDs (Table 1). For all medical records of patients treated from January 1, 1976, through December 31, 2006, that contained at least 1 of these codes, the primary investigator (A.Y.J.) reviewed the clinical profile, laboratory parameters, other comorbid conditions, and the risk and prognostic factors for survival. Potential cases were screened for secondary immunodeficiency (eg, corticosteroid use, chemotherapy, human immunodeficiency virus) and were excluded from the cohort if any of these conditions was present. Patients were included as incident cases if they were first diagnosed as having a PID while residing in Olmsted County and as prevalent cases if the diagnosis was first made at an institution outside of Olmsted County. Outcomes of the study were death from any cause or death due to PIDs.

Complete blood cell count, immunoglobulin levels, and vaccine responses were frequently used to establish the diagnosis of PIDs in the 1970s and 1980s; since the 1990s, T- and B-lymphocyte assays have also been routinely included in the evaluation.

STATISTICAL ANALYSES

For the calculation of incidence rates, the entire population of Olmsted County was considered to be at risk, and the denominator age- and sex-specific person-years were estimated from decennial census data. Incidence rates were first calculated using first-ever diagnosis of PIDs per patient-years during the study period. Rates were then adjusted for sex and age to the population structure of the 2000 US Census, and 95% confidence intervals (CIs) were calculated as the adjusted rate plus or minus 1.96 times its standard error. The effects of sex, age, and calendar year on the rates were assessed by using Poisson regression models¹⁶ fit with the GENMOD procedure (SAS statistical software; SAS Institute, Cary, NC). Long-term survival rates were estimated with the Kaplan-Meier method.¹⁷ The associations between continuous variable(s) and categorical outcome(s) were assessed by using nonparametric tests, such as the Wilcoxon rank sum test. The χ^2 test of independence was used to assess the associations among categori-

TABLE 1. *ICD-9 Diagnostic Codes for Primary Immunodeficiency Diseases^a*

Code description	Code
Ataxia, telangiectasia	334.8
Telangiectasia, ataxia	334.8
Syndrome, Madam Louis-Bar	334.8
Lymphopenia, familial combined immunity deficiency	279.2
Syndrome, Nezelof's	279.13
Agammaglobulinemia, Bruton's X-linked congenital hypogammaglobulinemia	279.04
Agammaglobulinemia, not otherwise specified	279.00
Absence, gamma globulin (blood), hypogammaglobulinemia, unspecified	279.00
Disease, Bruton's congenital hypogammaglobulinemia	279.04
Dysplasia, thymic combined immunity deficiency	279.2
Hypogammaglobulinemia, unspecified	279.00
Deficiency, immunoglobulin not otherwise specified, other selective immunoglobulin deficiencies	279.03
Deficiency, C esterase inhibitor, other deficiencies of circulating enzymes	277.6
Syndrome, Wiskott-Aldrich	279.12
Deficiency, immunoglobulin A (IgA)	279.01
Syndrome, hyper IgE	273.8
Deficiency, immune	279.3
Disease, granulomatous, childhood	288.1
Syndrome, Job's	288.1
Deficiency, leukocyte adhesion	288.8
Defect, chemotaxis, neutrophil	288.2
Deficiency, myeloperoxidase	288.2
Common variable immunodeficiency	279.06

^a ICD-9 = *International Classification of Diseases, Ninth Revision*.

cal data. The effects of potential trends in management on survival were estimated using Cox proportional hazards models; JMP software (version 6.0.0; SAS Institute) was used for analyses. All *P* values were 2-sided, and *P* < .05 was considered statistically significant.

The sample size was essentially fixed because this was an Olmsted County study and all available cases were used. With 158 incident cases (using Poisson regression), an average annual increase of approximately 1% per year was identified during the 31-year period using a 2-sided test with an α of .05 and 80% power.

RESULTS

Review of the 513 records with diagnostic codes related to PIDs revealed 158 incident (31%) and 14 prevalent (3%) cases of PIDs.

The study population was predominantly white (166; 97%), with 4 cases seen among African Americans (3%) and 1 case each from patients of Asian and Hispanic heritage. The median age of the population was 25 years (interquartile range, 4-51 years), and 93 (54%) of the patients were female.

Accurate information on the principal provider of longitudinal care for PIDs was available for 150 (87%) of the patients with PIDs. Primary care physicians (internal medi-

cine, pediatrics, and family medicine) were the primary care provider in 102 patients (68%), followed by allergist/immunologist in 43 patients (29%). Specialists in infectious diseases were caring for 4 patients (3%), whereas a hematologist/oncologist was providing care for 1 patient. Patients who were receiving supplemental IgG were more likely to be followed up by an allergist/immunologist (40% of the patients, Pearson χ^2 test, *P* = .02).

TRENDS IN INCIDENCE

During the 31-year study period, the overall PID incidence rate was 4.6 per 100,000 person-years. The age-specific incidence rates of PIDs are shown in Figure 2. The rate of PIDs from 2001 to 2006 (10.3 per 100,000 person-years) was nearly 5 times higher than that from 1976 to 1980 (2.4 per 100,000 person-years) and nearly twice as high as that from 1996 to 2000 (5.5 per 100,000 person-years).

DISTRIBUTION OF PIDs BY TYPE OF IMMUNE DEFECT

Frequencies of various types of PIDs are shown in Figure 3. Among all PIDs, the B-cell defect predominated with 122 cases, accounting for 78% of all cases of PIDs. As shown in Figure 4, the overall incidence of B-cell defects closely paralleled the overall incidence of all types of PIDs (4.6 per 100,000 person years).

Among the B-cell defects, IgA deficiency was the most common, accounting for 30% of cases, followed by IgG subclass (IgG2, IgG3, and IgG4) deficiency (26%), and hypogammaglobulinemia (including IgG1 subclass deficiency) (23%). Common variable immunodeficiency was diagnosed in 15% of the cases, whereas transient hypogammaglobulinemia of infancy and selective antibody deficiency with normal immunoglobulins were each found in 3% of the cases. The age distribution of incidence of B-cell defects in the 2000-2006 period is shown in Figure 5. Combined B- and T-cell defects, phagocytic defects, and complement defects accounted for 11%, 8%, and 3% of the cases, respectively. A positive family history was more commonly noted in patients with complement defects (25%), followed by those with combined B- and T-cell defects (20%).

DELAY IN DIAGNOSIS

The median interval between the onset of symptoms and the diagnosis of a PID was 4.7 years. As shown in eFigure 1 (available at www.mayoclinicproceedings.com, linked to this article), for patients whose onset of symptoms was before 1986, the median delay in diagnosis was 17.5 years, whereas for patients whose symptoms started from 1986 through 1996, the median delay in diagnosis was 6.7 years. The shortest delay in diagnosis was for patients whose symptom onset was after 1996 (median interval, 2.7 years). Longer delay in diagnosis was significantly associated with recurrent sinusitis

FIGURE 2. Age-specific incidence of primary immunodeficiency diseases (PIDs) in the Olmsted County, Minnesota, cohort from 1976 through 2006.

(Wilcoxon rank sum test, $P < .001$), recurrent pneumonia (Wilcoxon rank sum test, $P = .03$), and subsequent treatment with immunoglobulin (Wilcoxon rank sum test, $P < .001$).

PID-ASSOCIATED MORBIDITY

Recurrent Infections. Recurrent pneumonia (defined as 2 or more lifetime episodes) was the most common initial presentation, occurring in 74 patients (43%), followed by recurrent ear infections and recurrent or chronic sinusitis in 70 (41%) and 69 (40%) patients, respectively.

Gastrointestinal disturbances were reported in 47 patients (27%), 45 (26%) of whom had a documented history of recurrent gastrointestinal infections, especially giardiasis. Such recurrent gastrointestinal infections were significantly correlated with IgG supplementation (odds ratio, 3.5; 95% CI, 1.6-7.9; $P = .002$).

Deep-seated abscesses were the presenting manifestation in 21 patients (12%), whereas recurrent meningitis was reported in 8 patients (5%). Recurrent ear infection was more common in younger ages (Wilcoxon rank sum test, $P = .001$).

Autoimmunity and Atopic Diseases. Autoimmune cytopenias were reported in 61 patients (35%); 59% of these patients were female. Of the patients with PIDs, 95 (55%) also had coexistent atopic disease. No association was found between the type of PID and atopic disease.

Pulmonary Manifestations. Of the 172 patients with PIDs, 73 (42%) had 1 or more pulmonary conditions, including 53 (31%) with bronchiectasis, 11 (6%) with chronic obstructive pulmonary disease, 6 (3%) with asthma, and 3 (2%) with interstitial lung disease. Lower serum im-

munoglobulin levels were correlated with the presence of lung disease, but only lower IgG2 subclass levels were correlated with the presence of bronchiectasis (Wilcoxon rank sum test, $P = .008$). Bronchiectasis was a significant predictor

FIGURE 3. Overall percentage distribution of various types of primary immunodeficiency diseases (PIDs) in an Olmsted County, Minnesota, cohort from 1976 through 2006.

FIGURE 4. The study period-specific incidence rates of primary immunodeficiency diseases (PIDs). The overall incidence rate was 4.6 per 100,000 person-years.

of prophylactic antibiotic use (odds ratio, 2.40; 95% CI, 1.02-6.06; $P=.04$) and was also associated with mortality (odds ratio, 3.60; 95% CI, 0.98-13.40; $P=.05$).

TRENDS IN MANAGEMENT

Preventive Strategies. The incidence and severity of infections such as pneumonia and influenza are higher in persons with PIDs because of their compromised immunity. For that reason, the Advisory Committee on Immunization Practices recommends age-appropriate pneumococcal vaccination¹⁸ and a yearly influenza vaccination¹⁹ for patients with PIDs. We sought to determine the adherence to these recommendations in our population.

A vaccination history was available for 143 patients (83%) in our cohort. Evidence of a complete primary immunization series was available for 51 patients (35%).

We found that 87 patients (51%) had received either a pneumococcal conjugate or a polysaccharide-based vaccine. Of these patients, 14 (16%) had been vaccinated within 1 year and 19 (22%) within 3 years of the diagnosis of a PID. We also evaluated the adherence to current American Academy of Pediatrics recommendations on booster vaccination and found that only 19 (22%) of 86 patients eligible for booster vaccination received the recommended booster. Age at diagnosis was not a predictor of pneumococcal vaccination status. The median age of re-

FIGURE 5. The age distribution of incidence of B-cell defects in the 2000-2006 study period.

TABLE 2. Distribution of B-Cell Defects and IgG Replacement Therapy in the Primary Immunodeficiency Disease Cohort in Olmsted County, Minnesota, 1976-2006

B-cell defect	No. (%) of patients (n=134)	No. (%) of patients receiving supplemental IgG therapy	No. (%) of patients with IgG trough level available	IgG trough level (mg/dL), median
IgA deficiency	39 (29)	0 (0)		
IgG (IgG2, IgG3, IgG4) subclass deficiency	35 (26)	6 (17)	3 (50)	889
Hypogammaglobulinemia (including IgG1 deficiency)	33 (25)	9 (27)	4 (44)	796
Common variable immunodeficiency	19 (14)	11 (58)	8 (73)	860
Transient hypogammaglobulinemia of infancy	4 (3)	0 (0)		
Selective antibody deficiency with normal immunoglobulins	4 (3)	2 (50)	2 (100)	971

cipients of the conjugated pneumococcal vaccine was 2 years, whereas the median age of recipients of the polysaccharide-based vaccine was 40 years. We evaluated the influenza vaccination status in the last year of follow-up and found that 81 patients (57%) received the influenza vaccine.

Therapeutic Strategies. IgG Replacement Therapy.

IgG was replaced in 32 patients (19%); 28 of these patients had a B-cell defect, whereas 4 had a combined B- and T-cell defect (Table 2). No correlation was found between the IgG trough levels and presence of bronchiectasis (Wilcoxon rank sum test, $P=.50$). Longer delay in diagnosis was associated significantly with subsequent IgG replacement therapy (Wilcoxon sign rank sum test, $P<.001$; eFigure 2 [available at www.mayoclinicproceedings.com, linked to this article]).

Prophylactic Antibiotics. Medication data were available for 142 (83%) of all patients with PIDs. Prophylactic antibiotics were prescribed for 24 patients (17%), 15 (63%) of whom had a B-cell defect, 4 (17%) of whom had a phagocytic defect, 3 (13%) of whom had a combined B- and T-cell defect, and 2 (8%) of whom had a complement

defect. In B-cell defects, IgG subclass (2, 3, 4) deficiency was more commonly associated with prophylactic antibiotic use (Pearson χ^2 test, $P=.02$). The presence of bronchiectasis was a significant predictor of prophylactic antibiotic use (χ^2 of independence, $P=.04$).

10-YEAR SURVIVAL RATES

As shown in Figure 6, the proportion of persons surviving at 10 years after diagnosis was 93.5% (95% CI, 85.9%-97.1%). We compared the survival of patients with PIDs to age-, sex-, and race-matched controls from Minnesota and found that PIDs were not significantly associated with decreased survival ($P=.13$). However, older age at diagnosis was significantly associated with mortality (Wilcoxon rank sum test, $P=.01$).

DISCUSSION

Although some data are available regarding the prevalence of PIDs, the current study is the first, to our knowledge, to study their incidence.

We found an overall incidence of 4.6 cases of PIDs per 100,000 person-years, and these incidence rates did not differ by sex. We also found an increasing temporal trend in incidence rates during the past 31 years, with a rate of 10.3 per 100,000 person-years rate in 2000-2006 compared with 2.4 per 100,000 person-years in 1976-1980. Incidence rates were substantially higher in the youngest age group (0-5 years), but we did not find any associations between incidence of PIDs and decreased 10-year survival rates.

Our overall results are consistent with previously reported PID prevalence estimates in other countries,^{9,20,21} which ranged from 1 to 10 per 100,000 person-years. Unlike registry-based studies, in which women tend to be overrepresented, our study had a nearly equal sex distribution. This may be attributable to the population-based nature of our study; we were able to report all cases of PIDs instead of relying only on cases that were eventually reported to PID registries. We also had a greater proportion of IgA deficiency, which has an autosomal dominant inheritance with

FIGURE 6. Percentage of surviving patients with primary immunodeficiency diseases (PIDs) according to time of follow-up.

incomplete penetrance.²² Our results also suggest that male patients may have been underdiagnosed as having PIDs in previous studies.

We noticed an overall increase in incidence over time. This increased incidence could be due to better diagnostic tools and increased physician awareness. B-cell defects comprised the largest proportion of cases, which is consistent with the findings of other studies based on data from registries.^{8,10,20,21} Our percentage of B-cell defects was slightly higher than that reported in a European Society for Immunodeficiency report published in 2000 (78% vs 67%). The percentage of complement deficiency was 3.5%, which is in the range of 2% to 7% as reported from other countries.^{8,11,20,21}

No reports on survival patterns of patients with PIDs have been published. Our finding that the survival of patients with PIDs is unaffected is reassuring. We had insufficient power to evaluate survival in different subcategories of PIDs; such an evaluation by subcategory would be an area for future research.

Our population-based study is unique because it was not based on registry data. Registry data may not include milder forms of PIDs, which would be less likely to be reported to a registry, and thus may underestimate the true incidence and prevalence of this condition. In addition, the availability of more than 31 years of data made it possible for us to examine changes in diagnosis of PIDs over time.

Potential limitations of our study include its reliance on diagnosed cases. The number of undiagnosed cases is not known because no population-based screen is available. Milder forms of PIDs may be diagnosed later in life or never at all. In addition, our case-finding strategy was based on diagnostic codes. Cases in which the clinical symptoms were consistent with PIDs but were not included in the codes representing PIDs could have been missed. Therefore, our findings may have underestimated the true incidence of PIDs in the population.

In addition, the generalizability of the study findings is limited largely to white people because the Olmsted County population is mainly white (~90%-95% during the study period). However, studies comparing various chronic diseases in Olmsted County with those in other communities in the United States indicate that data from this population can be extrapolated to a large part of the population of the country.¹⁴

Finally, the use of a retrospective study design is subject to several biases, including reviewer bias. A reliability study was conducted in a smaller sample (25 patients) of the study patients by an independent physician (V.N.I.). There was complete agreement between the 2 investigators.

CONCLUSION

With the first-ever population-based study on the incidence of PIDs, we have found that the diagnosis of PID increased

during the past 3 decades. We also found that a delay in diagnosis was associated with increased morbidity. Such epidemiological data are crucial if we are to raise the awareness of the medical community about PIDs. With the newborn screen for some types of PIDs (eg, severe combined immunodeficiency) on the horizon, we need epidemiological data to support the public health benefits of early diagnosis and treatment.

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