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Recognizing Primary Immune Deficiency in Clinical Practice

Hale Yarmohammadi,[1]* Lissette Estrella,[1] John Doucette,[2] and Charlotte Cunningham-Rundles[1]

Departments of Medicine and Pediatrics[1] and Department of Community & Preventive Medicine,[2] The Mount Sinai Medical Center, New York, New York

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Primary immunodeficiency results in recurrent infections, organ dysfunction, and autoimmunity. We studied 237 patients referred for suspicion of immunodeficiency, using a scoring system based on clinical information. The 113 patients with immunodeficiency had higher scores and more episodes of chronic illnesses and were more likely to have neutropenia, lymphopenia, or splenomegaly.

Primary immunodeficiency (PI) diseases may be recognized due to sinopulmonary or gastrointestinal tract infections, organ abscesses, autoimmunity, or systemic signs, such as fever or failure to thrive (3, 6, 11, 14, 32). However, because of the diversity of immune defects, range of ages, and different clinical manifestations, distinguishing patients with PI in practice can be challenging. While delays in diagnosis are common (12, 19, 32), studies have shown an 8 to 24% incidence of immunodeficiency in selected patient populations (7, 8, 12, 19, 24, 25, 29).

We previously used a computerized method to identify potentially immunodeficient patients repeatedly hospitalized due to illnesses characteristic of PI (15); 30% of a cohort of these subjects had immune defects (15). In the present study, we evaluated a group of physician-referred patients because of conditions suggestive of immunodeficiency. Our goal was to determine if patients shown to have immune defects had differences from patients who did not.

MATERIALS AND METHODS

Study participants and testing. Adult or pediatric patients who were referred by a physician between 1 January 2001 and 1 July 2003 were asked to participate in the study. Laboratory studies included analyses of immune globulins and antibody responses to vaccines (tetanus, diphtheria, pneumococcus [12 serotypes], *Haemophilus influenzae*) and isohemagglutinin titers (13, 23). Diagnosis of immunoglobulin G1 (IgG1) or IgG2 subclass deficiency was defined as IgG1 or IgG2 levels 2 standard deviations less than the age-related means for individuals with antibody deficiencies (2). Lymphocyte surface markers, lymphocyte proliferation, neutrophil reduction of dihydrorhodamine, and complement testing were done by standard assays (13, 16, 23, 30). A diagnosis of immune deficiency was made by the use of standard criteria (10).

Historical information. The clinical histories for a 5-year period were reviewed. Diagnoses were confirmed by cultures, radiographic procedures, or the review of the records from the referring physicians. As described previously, illnesses suggestive of PI (4, 9, 12, 18, 20, 22, 27, 28, 31, 32) (Table 1) were recorded on a case report form. These illnesses or conditions were arbitrarily assigned a score of "1", "2," or "3" to indicate relative severity (15). Chronic conditions were counted only once in a year's time. An immunodeficiency-related (IDR) score was the sum of the scores acquired over the previous 5 years. To account for the various ages of the patients, the number of years of observation was expressed as the number of "person years" of observation.

Statistical analysis. Chi-square analysis was used to compare the IDR scores for both groups. The numbers of conditions in both groups were compared by using age-adjusted time ("person years") and the Mann-Whitney U test (SPSS statistical software; SPSS, Inc., Cary, NC). A multivariate analysis was performed by evaluating each diagnosis and its association with PI. A P value of less than 0.05 was considered significant.

RESULTS

From 1 January 2001 to 1 July 2003, 237 patients were referred by internists, pediatricians, or allergists for suspected immunodeficiency. Of the patients referred, 52% were females and 72% were Caucasians. The median age was 24.5 years (range, 1 to 85 years); immunodeficiency was diagnosed in 113 patients (48%) (Table 2).

For patients with immunodeficiency, the most common diagnosis was common variable immunodeficiency (32%), followed by IgG subclass deficiency and IgA deficiency (Table 3). For the 124 patients not found to have an immune defect, the reasons for referral included chronic bronchitis, chronic sinusitis, pneumonia, and acute or chronic otitis media. These patients had asthma (n = 11), allergic rhinitis and/or atopic dermatitis (n = 8), or food allergies (n = 2). Twenty-three percent of the patients had autoimmune or inflammatory diseases, including rheumatoid arthritis (n = 4), unspecified autoimmunity (n = 3), systemic lupus erythematosus (n = 1), or

TABLE 1. Scores of diagnoses and conditions assessed from the clinical record

Diagnosis or condition	Score	Diagnosis or condition	Score
Pneumonia, organism unknown	3	Malabsorption	2
		Giardiasis	2
Bacterial pneumonia	3	Autoimmune hemolytic anemia	2
Septicemia	3		
Empyema	3	Chronic sinusitis[a]	1
Bronchiectasis	3	Chronic bronchitis[a]	1
Osteomyelitis	3	Chronic otitis media	1
Other abscess	3	Chronic diarrhea[a]	1
Aseptic meningitis	3	Acute bronchitis	1
Splenic abscess	3	Acute sinusitis	1
Chronic mastoiditis[a]	3	Fever of unknown origin	1
Bacterial meningitis	3	Cutaneous candidiasis[a]	1
Liver abscess	3	Suppurative otitis media	1
Lung abscess	3	Failure to thrive	1
Lymphopenia	2	Thrush	1
Cellulitis	2	Lymphadenitis	1
Neutropenia	2	Gastroenteritis	1
Splenomegaly	2	Mycosis	1
Lymphadenopathy	2	Acute otitis media	1
Immune thrombocytopenia	2	Abnormal weight loss	1

[a] Diagnoses counted as chronic conditions counted only once in a 12-month period.

* Corresponding author. Mailing address: Division of Clinical Immunology, Mount Sinai Medical Center, 1425 Madison Ave., New York, NY 10029. Phone: (212) 659-9261. Fax: (212) 987-5593. E-mail: hale.yar@mssm.edu.

TABLE 2. Characteristics of patient groups[a]

Characteristic	Percent	
	Immune deficient (n = 113)	Patients without known immunodeficiency (n = 124)
Gender		
Male	49.0	47.0
Female	51.0	53.0
Age (yr)		
0–1	6.0	8.1
1–5	20.3	27.4
6–10	3.5	7.3
11–20	10.6	11.1
21–30	9.7	6.5
31–40	9.7	13.7
41–50	17.4	7.3
51–60	12.3	8.1
61–70	9.7	6.5
>70	0.8	4.0
Race or ethnicity		
Hispanic	13.4	16.9
Caucasian	76.9	67.7
African American	3.5	8.1
Asian	3.5	4.9
Other	0.9	2.4

[a] The median age of the immune-deficient group was 31.5 years, and that of patients without a known immunodeficiency was 15 years.

fibromyalgia rheumatica (1). Other subjects had Crohn's disease (n = 3); diabetes mellitus (n = 2); chronic warts (n = 2); or (one each) quadraplegia, swallowing disorder, cleft palate, osteogenesis imperfecta, Gaucher's disease, sarcoidosis, Epstein-Barr virus-related lymphohistiocytosis, obsessive compulsive disorder, alopecia areata, Hirshprung's disease, familial Mediterranean fever, growth hormone deficiency, or ulcerative colitis.

Immune deficiency-related scores and specific medical conditions. Patients with immunodeficiency had a median score of 8 (interquartile range, 5 to 13), which was significantly higher (P = 0.004) than the median score for those who did not (median score, 6; interquartile range, 3 to 10). By the use of age-adjusted comparisons, patients with immune deficiency had a median score of 10 (interquartile range, 5 to 17.5), which was higher (P = 0.025) than the median score of those without immune deficiency (median score, 8; interquartile range, 4 to 14). However, an IDR score of 8 or greater had a positive predictive value of 59%. By consideration of the patients' medical conditions, patients with immunodeficiency had significantly more person years of chronic sinusitis, chronic bronchitis, chronic otitis media, and chronic diarrhea than patients without immune defects (P = 0.001, 0.001, 0.001, and 0.001, respectively) (Table 4). Lymphopenia, thrombocytopenia or neutropenia, and splenomegaly were also more characteristic of immunodeficiency (P = 0.011, 0.027, and 0.011, respectively). In multivariate analyses, splenomegaly was associated with immunodeficiency (odds ratio [OR] = 7.9), followed by neutropenia (OR = 5.0), chronic diarrhea (OR = 2.5), and chronic sinusitis (OR = 1.8). Acute otitis media and suppurative otitis were found more frequently in patients without immune defects (P = 0.001 and 0.012, respectively).

DISCUSSION

Primary immunodeficiency diseases are relatively rare disorders, but patients with such diseases may appear in general

TABLE 3. Diagnoses for patients with identified immune deficiency[a]

Diagnosis	No. of patients	Median age (yr)	Age or age range (yr)	Score range
Common variable immune deficiency	38	40	2–65	0–25
IgG1 or IgG2 subclass deficiency	14	43	3–64	2–21
Selective IgA deficiency	12	46	10–64	1–29
Lymphopenia[b]	9	59	3–85	2–30
Mucocutaneous candidiasis	6	15.5	1–39	4–15
Neutropenia (autoimmune, cyclic and idiopathic)[c]	6	2	1–3	5–12
Transient hypogamma globulinemia of infancy	3	2	1–2	1–7
Chronic granulomatous disease	3	2	1–20	5–9
T and B combined defect[d]	2	6.5	5–8	4–30
IgA deficiency and IgG2 subclass deficiency	2	10	9–11	2–13
IgA and IgG deficiency	2	27.4	20–35	4–6
IgA deficiency and lymphopenia	2	44	28–60	3–8
DiGeorge anomaly	2	7.5	1–14	0–6
Antibody deficiency, normal immune globulins	2	53.5	44–63	5–7
Hyper IgE syndrome	2	4.5	4–5	4–9
Complement deficiency[e]	2	22	2–42	12–19
Lymphopenia and IgG2 deficiency	1		30	11
Leukocyte adhesion deficiency type 2	1		1	13
Common variable immune deficiency and neutropenia	1		41	10
Combined immune defect with multiple intestinal atresias (17)	1		1	3
Hyper IgM syndrome	1		4	14
Familial lymphohistiocytosis	1		2	6

[a] A total of 113 patients were evaluated.
[b] Chronic lymphopenia (total lymphocyte count, less than 600/ mm^3). Four patients had idiopathic CD4 lymphocytopenia (26) one patient had Down syndrome, and one patient had lymphopenia in association with autoimmune liver disease. No clear cause was identified for three patients.
[c] Six patients with neutropenia. Four patients had autoimmune neutropenia, one had cyclic neutropenia, and one is chronically neutropenic after sepsis.
[d] Includes a 5-year-old girl and an 8-year-old boy with unexplained combined lymphoproliferative immune deficiency with autoimmunity, not autoimmune lymphoproliferative syndrome.
[e] Includes two patients with severe complement deficiency: a 42-year-old woman with autoimmune liver disease and with C3, C4, and factor B and absent total hemolytic complement and a 2-year-old with a prolonged absence of total hemolytic complement with bacterial sepsis and fungemia.

TABLE 4. Comparison of diagnoses and conditions for patient groups

Condition	Actual no. of conditions in 5 yr for:		Comparison of person yr (P value)[b]
	Patients with immunodeficiency (n = 113)	Patients without immunodeficiency (n = 124)	
Chronic sinusitis[a]	162	59	0.001[b]
Chronic bronchitis[a]	93	60	0.002[b]
Chronic otitis media[a]	81	39	0.001[b]
Pneumonia	60	89	0.068
Chronic diarrhea[a]	43	16	0.001[b]
Acute sinusitis	22	36	0.157
Bacterial pneumonia	23	40	0.087
Lymphopenia	17	5	0.011[b]
Cutaneous candidiasis	12	6	0.179
Neutropenia	12	3	0.027
Splenomegaly	10	1	0.011[b]
Immune thrombocytopenia	6	1	0.027[b]
Suppurative otitis media	6	21	0.012[b]
Acute otitis media	6	43	0.001[b]
Abnormal weight loss	5	13	0.137

[a] Counted only once in a year's time.
[b] Significant differences between both groups of patients by categorization of each condition as person years.

clinical practice. While severe immune defects are more easily recognized, milder defects may not be diagnosed until illness or hospitalization occurs. However, determination of which patients should be evaluated is not always clear, since conditions that occur in immunodeficient subjects are common in subjects with healthy immune systems.

We previously used a scoring system based on the codes of the *International Classification of Diseases,* version 9 (34), for hospitalized subjects (15) to identify potentially immunodeficient patients. A minimum score of 6 allowed us to identify subjects with immune defects, although most subjects had higher scores (15). In the present study we used a similar method, which we applied to the medical records of patients referred by other physicians. While patients with immunodeficiency had a higher median score than those without immunodeficiency, due to the clinical overlap of conditions, the sensitivity of the IDR scores alone to the identification of PI was low. However, chronic sinusitis, bronchitis, otitis media, and chronic diarrhea were found more often in the immunodeficient group. Note that while pneumonia is characteristic of immunodeficiency (1, 5, 12, 21, 32, 33), this condition was common in both groups.

In a prior report, only 10% of 238 children with recurrent pneumonia had immune defects (24), suggesting that while pneumonia is a useful hallmark of PI, it is a nonspecific indicator.

A scoring system previously proved useful for the identification of immunodeficient subjects in a cohort of patients who had had multiple hospitalizations; a similar scoring system coupled with specific clinical indicators may provide a useful guide to the identification of such patients in the outpatient setting.

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