Recognizing Primary Immune Deficiency in Clinical Practice

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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, autoimmune, 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 proliferative, neutrophil reduction of dihydrorhodamine, and complement testing were performed in a clinical record.

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

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 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 autoimmunity or inflammatory diseases, including rheumatoid arthritis (n = 4), unspecified autoimmunity (n = 3), systemic lupus erythematosus (n = 1), or...
TABLE 2. Characteristics of patient groups

| Characteristic        | 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                                              |

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

**Lymphopenia**

| Diagnosis                        | Percent |
|----------------------------------|---------|
| Selective IgA deficiency         | 12      |
| Lymphopenia                      | 9       |
| Mucocutaneous candidiasis        | 6       |
| Neutropenia (autoimmune, cyclic and idiopathic) | 6 |
| Transient hypogamma globulinemia of infancy | 3 |
| Chronic granulomatous disease    | 3       |
| T and B combined defect          | 2       |
| IgA deficiency and IgG subclass deficiency | 2 |
| IgA and IgG deficiency           | 2       |
| IgA deficiency and lymphopenia    | 2       |
| DiGeorge anomaly                 | 2       |
| Antibody deficiency, normal immune globulins | 2 |
| Hyper IgM syndrome               | 2       |
| Complement deficiency            | 2       |
| Lymphopenia and IgG2 deficiency  | 1       |
| Leukocyte adhesion deficiency type 2 | 1 |
| Common variable immune deficiency and neutropenia | 1 |
| Combined immune defect with multiple intestinal atresias (17) | 1 |
| Hyper IgM syndrome               | 1       |
| Familial lymphohistiocytosis     | 1       |

**Neutropenia**

- Includes a 5-year-old girl and an 8-year-old boy with unexplained combined lymphoproliferative immune deficiency with autoimmunity, not autoimmune lymphoproliferative syndrome.
- 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 3. Diagnoses for patients with identified immune deficiency**

| 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                      | 9               | 59              | 3–85                   | 2–30        |
| Mucocutaneous candidiasis        | 6               | 15.5            | 1–39                   | 4–15        |
| Neutropenia (autoimmune, cyclic and idiopathic) | 6 |
| Transient hypogamma globulinemia of infancy | 3 |
| Chronic granulomatous disease    | 3               | 2               | 1–20                   | 5–9         |
| T and B combined defect          | 2               | 6.5             | 5–8                    | 4–30        |
| IgA deficiency and IgG2 subclass deficiency | 2 |
| 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 |
| Hyper IgM syndrome               | 2               | 4.5             | 4–5                    | 4–9         |
| Complement deficiency            | 2               | 22              | 2–42                   | 12–19       |
| Lymphopenia and IgG2 deficiency  | 1               | 30              | 11                     |
| Leukocyte adhesion deficiency type 2 | 1 |
| Common variable immune deficiency and neutropenia | 1 |
| Combined immune defect with multiple intestinal atresias (17) | 1 |
| Hyper IgM syndrome               | 1               | 4               | 14                     |
| Familial lymphohistiocytosis     | 1               | 2               | 6                      |

* A total of 113 patients were evaluated.

**DISCUSSION**

Primary immunodeficiency diseases are relatively rare disorders, but patients with such diseases may appear in general order, alopecia areata, Hirschsprung’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).
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 scoring system corresponding to the identification of patients with common variable immunodeficiency. J. Allergy Clin. Immunol. 109:1001–1004.

TABLE 4. Comparison of diagnoses and conditions for patient groups

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

* Counted only once in a year's time.

b Significant differences between both groups of patients by categorization of each condition as person years.

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REFERENCES

1. Ballow, M. 2002. Primary immunodeficiency disorders: antibody deficiency. J. Allergy Clin. Immunol. 109:581–591.

2. Buckley, R. H. 2002. Immunoglobulin G subclass deficiency: fact or fancy? Curr. Allergy Asthma Rep. 2:356–360.

3. Buckley, R. H. 2004. The multiple causes of human SCID. J. Clin. Investig. 114:1409–1411.

4. Buckley, R. H., R. I. Schiff, S. E. Schiff, M. L. Markert, L. W. Williams, T. O. Harville, J. L. Roberts, and J. M. Puck. 1997. Human severe combined immunodeficiency: genetic, phenotypic, and functional diversity in one hundred eight infants. J. Pediatr. 130:378–387.

5. P. S. Razi, and C. Cunningham-Rundles. 2002. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. J. Allergy Clin. Immunol. 109:1001–1004.

6. Chapel, H., R. Geha, and F. Rosen. 2003. Primary immunodeficiency diseases: an update. Clin. Exp. Immunol. 132:9–15.

7. Chee, L., S. M. Graham, D. G. Carothers, and Z. K. Ballas. 2001. Immune dysfunction in refractory sinusitis in a tertiary care setting. Laryngoscope 111:2315–2319.

8. Coleman, L. T., S. S. Kramer, R. I. Markowitz, and R. M. Kravitz. 1995. Bronchiectasis in children. J. Thorac. Imaging 10:268–279.

9. Conley, M. E., L. D. Notarangelo, and A. Etzioni. 1999. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiencies) and ESID (European Society for Immunodeficiencies). Clin. Immunol. 93:190–197.

10. Cooper, M. D., L. L. Lanier, M. E. Conley, and J. M. Puck. 2003. Immunodeficiency diseases. Hematol. (Am. Soc. Hematol. Educ. Program)314–330.

11. Cunningham-Rundles, C. 2001. Common variable immunodeficiency. Curr. Allergy Asthma Rep. 1:142–149.

12. Cunningham-Rundles, C. 2003. Immune deficiency: office evaluation and treatment. Allergy Asthma Proc. 24:409–415.

13. Cunningham-Rundles, C., and P. P. Ponda. 2005. Molecular defects in T- and B-cell primary immunodeficiency diseases. Nat. Rev. Immunol. 5:880–892.

14. Cunningham-Rundles, C., P. Sidd, L. Estrella, and J. Doucette. 2004. Identifying undiagnosed primary immunodeficiency diseases in minority subjects by using computer sorting of diagnosis codes. J. Allergy Clin. Immunol. 113:747–755.

15. Folds, J. D., and J. L. Schmitz. 2003. 24. Clinical and laboratory assessment of immunity. J. Allergy Clin. Immunol. 111:S702–S711.

16. Gilroy, R. K., P. F. Coccia, J. E. Talmadge, L. I. Hatcher, S. J. Pirruccello, C. Cunningham-Rundles, C., P. Sidi, L. Estrella, and J. Doucette. 2003. Primary immunodeficiency disorders: antibody deficiency. Nat. Rev. Immunol. 3:747–755.

17. Harville, J. L. Roberts, and J. M. Puck. 1998. Screening for primary immunodeficiencies in the clinical immunology laboratory. Clin. Immunol. 190–197.

18. Koncz, G. 1999. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiencies) and ESID (European Society for Immunodeficiencies). Clin. Immunol. 93:190–197.

19. Kozyrsky, L. M., and W. T. Shearer. 1999. Transient hypogammaglobulinemia of infancy: need to reconsider name and definition. J. Pediatr. 110:47–50.

20. Mead, A. F., D. M. Campbell, and E. E. Wang. 2000. Underlying causes of recurrent infections in children. Arch. Pediatr. Adolesc. Med. 154:190–194.

21. Pasteur, M. C., S. M. Hellwell, S. J. Houghton, S. C. Webb, J. E. Foweraker, R. A. Coulten, C. D. Flower, D. Bilton, and M. T. Keogan. 2004. Donor reconstitution after liver-small bowel transplantation for multiple intestinal atresia with immunodeficiency. Blood 103:1171–1174.

22. Rasmussen, S. M., H. Gallin, F. Greenberg, S. C. Hill, H. L. Malek, J. A. Miller, A. C. O’Connell, and J. M. Puck. 1999. Hyper-IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder. N. Engl. J. Med. 340:92–702.

23. Hermaszewski, R. A., and A. D. Webster. 1993. Primary hypogammaglobulinemia: a survey of clinical manifestations and complications. Q. J. Med. 86:31–42.

24. Hong, R. 1998. The DiGeorge anomaly (CATCH 22, DiGeorge/velo-cardiofacial syndrome). Semin. Hematol. 35:292–290.

25. Kainulainen, L., J. Niskokelainen, and O. Ruuskanen. 2001. Diagnosing findings in 95 Finnish patients with common variable immunodeficiency. J. Clin. Immunol. 21:145–149.

26. Meadey, J. S. 1987. Transient hypogammaglobulinemia of infancy: need to reconsider name and definition. J. Pediatr. 110:47–50.

27. Noroski, L. M., and W. T. Shearer. 1998. Screening for primary immunodeficiencies in the clinical immunology laboratory. Clin. Immunol. 100:237–245.

28. Osma, A. F., D. M. Campbell, and E. E. Wang. 2000. Underlying causes of recurrent infections in children. Arch. Pediatr. Adolesc. Med. 154:190–194.

29. Pasteur, M. C., S. M. Hellwell, S. J. Houghton, S. C. Webb, J. E. Foweraker, R. A. Coulten, C. D. Flower, D. Bilton, and M. T. Keogan. 2004. An investigation into causative factors in patients with bronchiectasis. Am. J. Respir. Crit. Care Med. 162:1277–1284.

30. Spira, T. J., B. M. Jones, J. K. Nicholson, R. B. Lal, T. Rowe, A. C. Mawle, C. B. Lauter, J. A. Shulman, and R. A. Monson. 1993. Idiopathic CD4+ T-lymphocytopenia—an analysis of five patients with unexplained opportunistic infections. N. Engl. J. Med. 328:386–392.

31. Stehle, E. R. 1996. Immunologic disorders in infants & children, 4th ed. The W. B. Saunders Co., Philadelphia, Pa.

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28. Stiehm, E. R., T. W. Chin, A. Haas, and A. G. Peerless. 1986. Infectious complications of the primary immunodeficiencies. Clin. Immunol. Immunopathol. 40:69–86.

29. Umetsu, D. T., D. M. Ambrosino, I. Quinti, G. R. Siber, and R. S. Geha. 1985. Recurrent sinopulmonary infection and impaired antibody response to bacterial capsular polysaccharide antigen in children with selective IgG subclass deficiency. N. Engl. J. Med. 313:1247–1251.

30. Vowells, S. J., S. Sekhsaria, H. L. Malech, M. Shalit, and T. A. Fleisher. 1995. Flow cytometric analysis of the granulocyte respiratory burst: a comparison study of fluorescent probes. J. Immunol. Methods 178:89–97.

31. Whaley, K., and W. Schwaeble. 1997. Complement and complement deficiencies. Semin. Liver Dis. 17:297–310.

32. Winkelstein, J. A., M. C. Marino, R. B. Johnston, Jr., J. Boyle, J. Curnutte, J. I. Gallin, H. L. Malech, S. M. Holland, H. Ochs, P. Quie, R. H. Buckley, C. B. Foster, S. J. Chanock, and H. Dickler. 2000. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore) 79:155–169.

33. Winkelstein, J. A., M. C. Marino, H. Ochs, R. Fuleihan, P. R. Scholl, R. Geha, E. R. Stiehm, and M. E. Conley. 2003. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine (Baltimore) 82:373–384.

34. World Health Organization. 1998. International classification of diseases, 9th revision, clinical modification, 5th edition. World Health Organization, Geneva, Switzerland.