

ORIGINAL ARTICLE

Clinical characteristics of pediatric patients evaluated for primary immunodeficiency

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Abstract

Objective: When to evaluate a child for possible immune deficiency is a challenge, as many children have frequent infections for which they are treated with antibiotics. We aimed to describe the clinical characteristics of children evaluated for possible primary immunodeficiency in a specialist clinic. We specifically aimed to evaluate widely promulgated 'warning signs of primary immunodeficiency' and to evaluate the relationship between primary immunodeficiency and atopy.

Methods: A retrospective analysis of 141 children who underwent testing for possible primary immunodeficiency was undertaken.

Results: Thirty-two (23%) children were diagnosed with an underlying primary immunodeficiency, and published warning signs were neither sensitive nor specific for primary immunodeficiency. Patients with allergy as determined by the presence of antigen-specific IgE were more likely to be diagnosed with immunodeficiency.

Conclusions: Widely promulgated warning signs did not distinguish between patients with and without primary immunodeficiency. Likewise, primary immunodeficiency and allergy may coexist.

The diagnosis of primary immunodeficiency (PID) represents a challenge in that many children have frequent infections requiring treatment with antibiotics, but few of these have a demonstrable PID. Prompt identification of patients with PID is crucial as effective treatment may prevent end-organ damage (1–3) yet diagnosis is often delayed (1–5).

Which children, who present with frequent infection, need evaluation of their immune system is often not evident. The Jeffrey Modell Foundation (JMF) has promulgated warning signs for primary immunodeficiency (6), but these criteria are based on expert opinion and their performance in identifying

patients with PID has not been evaluated. We undertook this study with the goal of examining the characteristics of patients who presented to the allergy/immunology clinic at our center and describing the results of this evaluation. We also evaluated existing criteria for immune work-up of children among these children. We hypothesized we could identify other criteria that might improve our understanding of what pattern of illnesses is predictive of PID.

Given that allergic disease can both mimic and predispose to infections, it can be hard to distinguish PID from atopic illness. Additionally, the ability to produce antigen-specific

IgE may indicate a relatively intact immune axis and mitigate against the diagnosis of PID (7). We therefore evaluated whether the presence of antigen-specific IgE was related to the final determination that a patient did or did not have a primary immunodeficiency.

Patients and methods

Patients

A retrospective chart review of children (birth to age 21) evaluated for primary immunodeficiency in the Allergy and Immunology clinic at Children's Hospital of Pittsburgh over an 18-month period from July 2004 to December 2005. Evaluation for immunodeficiency was undertaken at the discretion of the treating physician, generally because of a pattern of recurrent and/or severe infections; some patients were also referred for immune evaluation by the primary care doctor or another subspecialist (e.g., infectious disease). Patients were identified by ICD-9 codes indicative of either immunodeficiency or frequent infection (8). We excluded patients who had already been diagnosed with PID as our study was designed to evaluate patients presenting for initial investigation. Patients who had any laboratory workup for immunodeficiency were included, and follow-up records were evaluated as available. The Children's Hospital of Pittsburgh institutional review board approved this retrospective chart review. Patient data were entered anonymously into a database with no identifying information retained.

Evaluation

Whether patients met any of the JMF 10 warning signs of primary immunodeficiency was evaluated based on clinic notes. Laboratory testing results were obtained from the paper chart and/or the hospital's electronic medical record. The testing performed was determined by the treating physician based on patient age and medical history and often included repeat studies over time including checking response to vaccinations. There was not a standard panel of testing that all patients underwent. The final diagnosis was determined based on the patient's medical records and laboratory testing. Patients were only classified as having PID if they met criteria for a diagnosis specified in the Primary Immunodeficiency Practice Parameter (1) and were considered to have a significant immunodeficiency by the treating physician. Transient hypogammaglobulinemia of infancy was confirmed by increase in IgG into the normal range over time; common variable deficiency required low IgG levels and impaired antibody response to vaccination. Patients with 22q11.2 deficiency were only included if they had demonstrable immunodeficiency. Patients with significantly low IgG on repeated measurement who were > 5 yr old with normal specific antibody responses were designated as hypogammaglobulinemic. At the time of this study, IgG subclasses were not routinely measured in our clinic, as their importance is controversial (1). Four patients for whom no records of recommended testing being performed could be found were not included.

Differences between groups who met one or more of the warning signs and those who did not were evaluated using chi-square test with one degree of freedom. Fischer's exact test was used to evaluate differences in treatment with IVIG among WS+ and WS- patients, correlation between atopy and WS+, and differences in performance of the warning signs in atopic and non-atopic patients.

Atopy

In patients in whom skin prick or blood testing for allergies was undertaken, the results (positive or negative) were recorded. A patient with positive skin or serologic testing was considered to have evidence of atopy.

Results

A total of 141 patients met criteria for inclusion in the study and had immunologic evaluation. The age and sex distribution of patients are shown in Fig. 1. Boys were overrepresented specifically in the age groups of 3–5 and, to a lesser extent, 6–11 yr. Of the 141 patients, 32 (23%) were diagnosed with a PID. The distribution of diseases identified is shown in Table 1. We detected primarily deficiencies of antibody production, which is consistent with previous series (3, 9). Transient hypogammaglobulinemia of infancy (THI) was the most frequent diagnosis (Table 1). Of the 32 patients diagnosed with PID, 6 were treated with immunoglobulin replacement (IV or subcutaneous), 10 received prophylactic antibiotics, and 16 received no specific therapy.

Performance of warning signs

Of the 141 total patients evaluated, there were 105 (74%) who met one or more of the criteria set out in the '10 Warning Signs of Primary Immunodeficiency' and 35 who did not. Of the 104 warning sign-positive (WS+) patients, 20 (19%) were diagnosed with a primary immunodeficiency (Fig. 2). Of

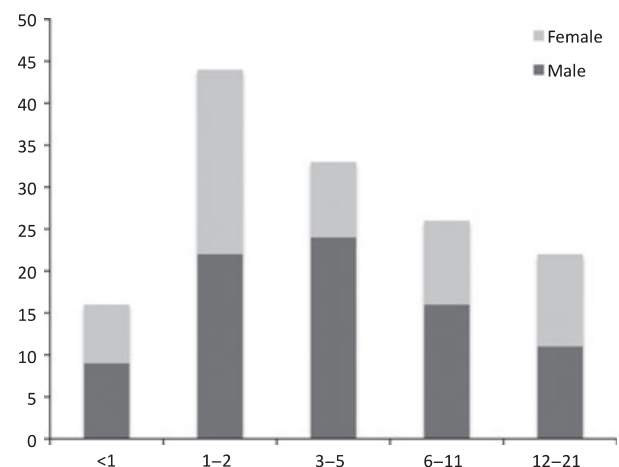


Figure 1 Age and sex distribution of patients investigated for primary immunodeficiency.

Table 1 Classification of patients with primary immunodeficiencies

Diagnosis	Total	WS+	Treatment	WS-	Treatment
THI	13	9	None (7) Prophylactic Antibiotics (2)	4	None (3) Prophylactic Antibiotics (1)
Hypogammaglobulinemia	6	2	None (1) Prophylactic (1) Antibiotics	4	None
SigAD	5	3	Prophylactic Antibiotics (2) None (1)	2	Prophylactic Antibiotics (2)
CVID	4	3	IVIG (3)	1	IVIG (1)
XLA	2	2	IVIG (2)	0	
Congenital neutropenia	1	1	Prophylactic Antibiotics (1)	0	
22q11.2 deletion	1	0		1	Prophylactic Antibiotics (1)

CVID, common variable immunodeficiency; THI, transient hypogammaglobulinemia of infancy; XLA, X-linked agammaglobulinemia; SigAD, selective IgA deficiency.

the 37 patients who were warning sign negative (WS-), 12 (32%) had a primary immunodeficiency. The rate of diagnosis of immunodeficiency was not significantly different between the WS+ and WS- groups ($p = 0.12$ using chi-square test). The sensitivity of the 10 warning signs was 63% and the specificity 23%. Five of 20 patients in the WS+ group vs. 1 of 12 in the WS- group received IVIG ($p =$ non-significant by Fisher's exact test).

Both WS+ and WS- patients had a range of immune deficiencies although for both groups antibody deficiency syndromes were predominant. Table 1 summarizes the diagnosis and treatment observed among the patients diagnosed with immunodeficiency who did and did not meet warning sign criteria. While many patients in both groups had relatively

mild immunodeficiencies (e.g., transient hypogammaglobulinemia of infancy), others showed more profound defects (e.g., common variable immunodeficiency).

The published warning signs of PID encompass a variety of different presentations. We examined the number of patients presenting with each warning sign and the number of these who were subsequently diagnosed with a primary immunodeficiency. Note that many patients met 2 or more warning signs. Numbers are too small in this study to make conclusions about specific warning signs, but the numbers demonstrate that ear and sinus infections along with the need for IV antibiotics were the most often observed warning signs. We did not observe dramatic differences in the performance of specific warning signs in predicting the presence of PID. We had hoped to be able to identify additional warning signs or modify existing ones to improve their performance. However, our study is too small to allow meaningful revision of the current warning signs.

Coexistence of allergic disease and immunodeficiency

As differentiation of infection and allergic disease can be difficult, we hypothesized that some patients evaluated for PID in fact had allergic disease only. It has been proposed that the ability to generate specific IgE demonstrated a relatively intact immune axis and might preclude significant antibody deficiency (7). We therefore evaluated whether the presence of atopy as demonstrated by positive skin prick and/or RAST testing influenced the probability of an immunodeficiency being diagnosed. This analysis was limited to those patients who were evaluated for specific IgE. The results are shown in Fig. 3. Interestingly, patients who had evidence of antigen-specific IgE by skin prick or blood testing were more likely to be diagnosed with an immune deficiency with 9 of 29 patients (31%) with antigen-specific IgE (atopic) being diagnosed with immunodeficiency compared to 6 of 68 (9%)

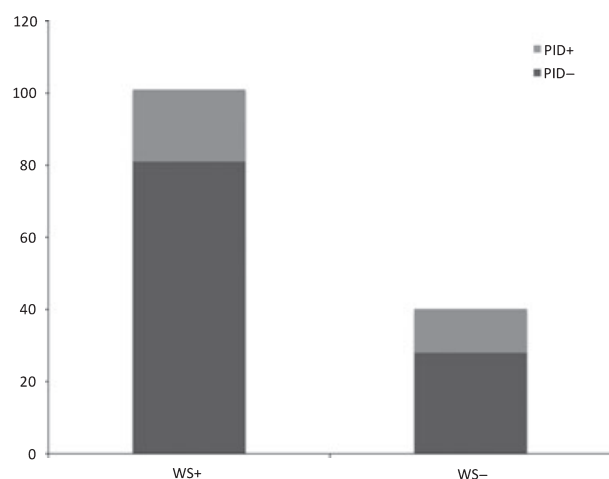


Figure 2 Number of patients who met published warning signs for primary immunodeficiency (PID), and whether PID was confirmed or excluded.

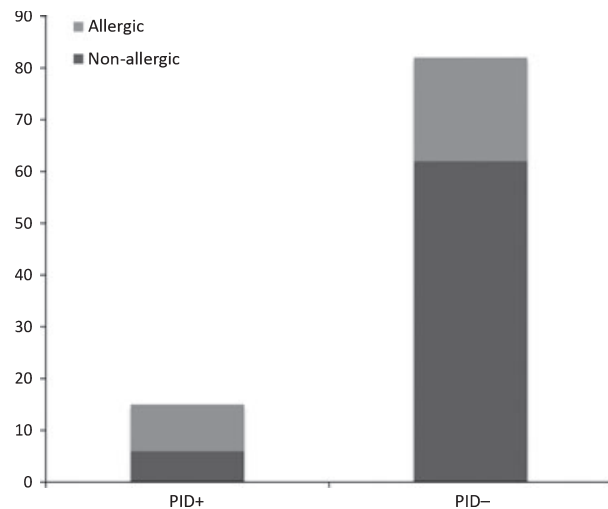


Figure 3 Detection of antigen-specific IgE in patients with and without immunodeficiency.

of those without specific IgE (non-atopic). This difference was significant ($p = 0.011$ by Fisher's exact test). A similar proportion of patients with and without atopy met criteria for one or more warning sign (60% non-atopic and 72% atopic, $p = \text{NS}$). The warning signs correctly identified five of six non-atopic patients with PID as opposed to only five of nine with atopy but this difference was not significant ($p = \text{NS}$) perhaps because of small numbers. The frequent concurrence of atopy and PID may be partially explained by the known high rate of atopy in IgA deficiency (10, 11) as well as the fact that patients with selective IgA deficiency and common variable immunodeficiency (CVID) have an intrinsic dysregulation of the humoral immune system as evidenced by high incidence of autoimmunity (12–14).

Discussion

Frequent infections are a common complaint in pediatrics. Which child merits work-up for primary immunodeficiency is not clear as anatomical issues, environmental exposures such as tobacco smoke, exposure to infections (e.g., daycare attendance), and chance may all play a role. In one study, only 10% of patients with recurrent pneumonia requiring hospitalization had evidence of impaired immune function and only 5 of 238 patients were diagnosed with a primary immunodeficiency (16), although many patients had chronic illnesses. Early identification of patients with PID is crucial to prevent life-threatening infection and irreversible end-organ damage from repeated infection (1–3) and data suggest that recognition of PID is often delayed. Mehra et al. demonstrated that frequently hospitalized patients of all ages at risk of PID were not referred for appropriate subspecialty evaluation (4). This group data also suggested that PID might be under-evaluated and under-diagnosed in minorities (15).

In an attempt to identify children at high risk of PID, the Jeffrey Modell Foundation has promulgated warning signs to

identify individuals at high risk of PID (6). These warning signs were developed in 1994 based on consensus of a group of experts and have been endorsed by the Centers for Disease Control and several NIH institutes. However, they have not been prospectively validated.

Here we show that the '10 Warning Signs of Primary Immunodeficiency' have low specificity and relatively low sensitivity. The low specificity is understandable, as the guidelines act as a screening test and are therefore designed to be inclusive of many children without PID to avoid missing those who do have an immune deficiency. However, our study indicates that some children with significant PID are not caught by the guidelines. Of the 32 children we identified with PID, less than 70% met one of criteria set forth in the 10 warning signs. While the immunodeficiencies we identified were generally mild to moderate, this was true of all our patients. Nonetheless, it is possible we have identified patients with primarily 'mild' immunodeficiencies, particularly in our WS- group, and that some of these patients would do well even without workup or identification. Among patients with identified immune deficiency who met none of the Modell foundation criteria, one required treatment with IgG replacement and four were treated with prophylactic antibiotics. We believe the JMF warning signs have been extremely helpful in increasing the awareness of primary immunodeficiency and decreasing the time between symptom onset and diagnosis. However, some patients with PID do not fulfill any of the criteria; therefore, when clinical suspicion is high, immune evaluation should be undertaken even in patients who not fulfill one or more of these criteria.

Yarmohammadi used an alternative scoring system to identify the likelihood of finding immunodeficiency in patients presenting for immune evaluation (16). They found their system helped discriminate those with and without primary immunodeficiency, but there were significant overlap in the clinical scores obtained from the groups with and without immunodeficiency. Their study also included patients of all ages, while our study is limited to children. As we collected data before publication of that study, we are unable to examine the performance of their scoring system in our patients. Yarmohammadi et al.'s results are consistent with our findings that current criteria may miss a portion of patients with PID.

It is often felt that the presence of allergy as demonstrated by presence of specific IgE precludes PID. Pediatricians and immunologists often decide to pursue testing for one or the other, although the presentations can frequently overlap. Our data suggest that the presence of antigen-specific IgE not only does not rule out immunodeficiency, but that the two are frequently seen together. This is probably because many antibody deficiency syndromes represent dysregulation rather than simple deficiency of humoral immunity, as evidenced by high rates of atopy and autoimmunity in patients with selective IgA deficiency (10–12) and common variable immunodeficiency (13, 14). Autoimmunity and atopy are also seen in non-humoral immunodeficiencies such as chronic granulomatous disease and 22q11.2 deletion (DiGeorge) syndrome (17, 18). Other immunodeficiencies such as the hyper-IgE syn-

drome, Wiskott-Aldrich syndrome, Ommen's syndrome, and IPEX (Immune dysregulation, polyendocrinopathy, enteropathy, X-linked) are characterized by dysregulated immunity leading to elevated IgE production and autoimmunity (19–21).

There are several potential weaknesses to our study. First, we studied only patients seen in the outpatient clinic, which may act to exclude patients with more severe immunodeficiencies. Second, our study is limited to a single site, which may bias which patients were evaluated for immunodeficiency, as different centers and individual immunologists may be more or less likely to pursue evaluation of the immune system. Additionally, as this is a retrospective study of patients seen in clinical practice, there were no standard criteria followed to determine which patients underwent an immune evaluation, nor was a standardized approach to evaluation utilized. The number of patients evaluated may vary in different settings. Because we were limited to a single clinic at a single site, we missed many patients who were evaluated for PID by their primary care physicians, other specialists or outside allergist/immunologists. Finally, our study was retrospective in nature meaning some data were missing from the charts. However, the available data did allow us to determine

the presence or absence of primary immunodeficiency in the vast majority of cases. It is also possible that information in the chart was incomplete and that some patients may have had more infections than they reported or an unrecognized family history of immunodeficiency. However, this corresponds to the situation that is often faced in practice, where full historical information is not always available.

In summary, we found that the Jeffrey Modell Foundation's '10 Warning Signs of Primary Immunodeficiency' did not identify all patients with an underlying primary immunodeficiency. Approximately 35% of patients with PID did not fulfill any of the warning signs. Practitioners should have a low threshold to evaluate immune function in children with severe and/or recurrent infections. Additionally, we found that many patients have both atopy, as indicated by antigen-specific IgE production, and PID. We would also suggest that for some immunodeficient children, identification and treatment of allergies may improve the clinical course. The size of our study and its retrospective nature make it impossible for us to derive better guidelines for which children need evaluation of the immune system. Further research, ideally a multicenter prospective study, will be needed to improve current criteria for the evaluation of immune deficiency.

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