Journal of Clinical Immunology (2019) 39:90–98
https://doi.org/10.1007/s10875-018-0582-z

ORIGINAL ARTICLE

Differing Performance of the Warning Signs for Immunodeficiency in the Diagnosis of Pediatric Versus Adult Patients in a Two-Center Tertiary Referral Population

Jaclyn A. Bjelac[1] · Jennifer R. Yonkof[2] · James Fernandez[3]

Received: 9 May 2018 / Accepted: 10 December 2018 / Published online: 4 January 2019

Abstract

Purpose Primary immunodeficiency (PID) represents disorders with a spectrum of clinical presentations. The medical community seeks clinical features to prompt evaluation for immunodeficiency given improved prognosis with early identification. We hoped to identify clinical characteristics that would improve the diagnostic accuracy of the widely disseminated Jeffrey Modell Foundation warning signs for immunodeficiency.

Methods We performed a retrospective chart review in a two-center North American cohort of patients with PID. Charts of 137 pediatric and 400 adult patients with PID were evaluated for the presence of these warning signs and compared to controls with normal preliminary biochemical immune evaluation.

Results Fewer than 45% of adults with PID presented with ≥ 2 warning signs, while diagnostic utility was improved in the pediatric population where the warning signs were found to be 64% sensitive. The warning signs found in a significantly increased proportion compared to controls differed for pediatric PID patients (recurrent pneumonia (OR 2.9, $p < 0.001$), failure to thrive (OR 2.1, $p < 0.001$), need for IV antibiotics (OR 2.1, $p < 0.001$), serious bacterial infection (OR 4.8, $p < 0.001$), recurrent otitis media (OR 1.5, $p = 0.027$)), versus adult PID patients (recurrent otitis media (OR 2.9, $p < 0.001$), recurrent sinusitis (OR 2.1, $p < 0.001$), diarrhea with weight loss (OR 2.2, $p < 0.001$), recurrent viral infection (OR 3.3 $p < 0.001$)). In evaluation for additional criteria to promote identification of immunodeficiency, linear regression models showed slightly improved diagnostic accuracy of the warning signs with the addition of autoimmunity in our pediatric PID cohort (8.7% v 2.8%, $p < 0.001$, ROC 0.58). Adult PID patients demonstrated atopy more frequently than controls (48.0% vs 40.3%, $p = 0.011$), while atopy was found to have a negative association with the presence of PID in the pediatric age group (OR 0.3, $p < 0.01$). No improvement in diagnostic accuracy of the warning signs was found with the addition of allergic disease, autoimmunity, or malignant and benign proliferative disease in the adult cohort.

Conclusions We demonstrate poor diagnostic performance of warning signs for immunodeficiency in patients with PID in a retrospective chart review. Divergent warning signs of statistically significant diagnostic utility were found in pediatric versus adult patients. We suggest education of physicians on differing presentations of possible immunodeficiency between age groups, and expansion of the warning signs to include non-infectious comorbidities such as autoimmunity in pediatric patients.

Keywords Immunodeficiency · warning signs · atopy · autoimmunity

✉ Jaclyn A. Bjelac
bjelacj2@ccf.org

[1] Department of Pediatric Allergy and Clinical Immunology, Cleveland Clinic, 9500 Euclid Avenue, R3, Cleveland, OH 44195, USA

[2] Rainbow Babies and Children's Hospital Case Medical Center, Cleveland, OH, USA

[3] Department of Allergy and Clinical Immunology, Cleveland Clinic, Cleveland, OH, USA

Introduction

Primary immunodeficiency (PID) represents a heterogeneous group of immune disorders with an estimated prevalence of 1 in 10,000 to 1 in 12,000 in the general population [1, 2]. Given the range of immune system derangements that can result in disease, the spectrum of clinical presentations is broad and varied among these illnesses. Despite major recent advances in the characterization of PIDs [3], many patients remain undiagnosed or experience delayed diagnosis, which has been

associated with increased morbidity and mortality in both pediatric and adult populations [4–6].

Given that early diagnosis of PID is also crucial for improving quality of life, the medical community has sought to identify clinical characteristics to prompt evaluation for an immunodeficiency. In the USA, the widely disseminated "Warning signs for immunodeficiency" were developed in 1994 by expert consensus and published by the Jeffrey Modell Foundation (JMF) and remain an important guide for primary physicians to identify patients appropriate for immune evaluation. The warning signs are accompanied by a suggestion that PID be considered for patients with two or more of the warning signs (Table 1). These warning signs for immunodeficiency are focused primarily on increased frequency of, or difficult to treat, infections, which remain a primary clinical manifestation of immunodeficiency. However, more recent literature supports the increased prevalence of autoinflammatory conditions, malignancy, and even allergy in both pediatric and adult patients with PID [7–11]. Furthermore, it has been shown that noninfectious complications in patients with CVID are associated with increased morbidity and mortality [12].

Prior publications have demonstrated that despite widespread use, the JMF warning signs are poorly sensitive and specific in their prediction of immunodeficiency [13, 14]. Most publications in this area represent relatively small, single-center studies and focus primarily on the pediatric population. The sensitivity and specificity of the warning signs are generally calculated based on patients with PID with no control group. Publications outside of the USA have demonstrated that sets of warning signs similar to those from the JMF are also poorly specific, but note the possible utility of additional clinical features [15].

We sought to determine the diagnostic utility of the JMF warning signs for immunodeficiency in a cohort of patients with PID from two large academic medical centers in the USA. We hoped to identify additional clinical characteristics that would improve the diagnostic accuracy of these warning signs.

Table 1 Jeffrey Modell Foundation warning signs for immunodeficiency and EMR search strategy

JMF warning signs	EMR search criteria
For pediatric patients less than 18 years of age	
1. Four or more new ear infections within 1 year	1. Four or more diagnoses of otitis media within 1 year
2. Two or more serious sinus infections within 1 year	2. Two or more diagnoses of sinusitis within 1 year
3. Two or more months on antibiotics with little effect	3. Three or more prescriptions for an antibiotic administered within a 2-month time period
4. Two or more pneumonias within 1 year	4. Two or more diagnoses of pneumonia within 1 year
5. Failure of an infant to gain weight or grow normally	5. Diagnosis of failure to thrive, abnormal weight loss, OR abnormal weight gain in any child older than 1 month of age
6. Recurrent, deep skin, or organ abscesses	6. Two or more diagnoses of abscess
7. Persistent thrush in mouth or fungal infection on skin	7. Two or more diagnoses of thrush OR candida
8. Need for intravenous antibiotics to clear infections	8. Any instance of the receipt of IV antibiotics
9. Two or more deep-seated infections including septicemia	9. Two or more lifetime diagnoses of bacteremia, sepsis, meningitis, or osteomyelitis
10. A family history of PI	10. Family history of immunodeficiency listed
For adult patients 18 years of age and older	
1. Two or more new ear infections within 1 year	1. Two or more diagnoses of otitis media within 1 year
2. Two or more new sinus infections within 1 year, in the absence of allergy	2. Two or more diagnoses of sinusitis within 1 year
3. One pneumonia per year for more than 1 year	3. One or more diagnoses of pneumonia
4. Chronic diarrhea with weight loss	4. Two or more diagnoses of diarrhea AND diagnosis of weight loss, failure to thrive, OR abnormal weight gain
5. Recurrent viral infections (colds, herpes, warts, condyloma)	5. Diagnosis of recurrent infections AND two or more diagnoses of viral infection
6. Recurrent need for IV antibiotics to clear infections	6. Two instances of the receipt of IV antibiotics
7. Recurrent deep abscesses of the skin or internal organs	7. Two or more diagnoses of abscess
8. Persistent thrush or fungal infection on skin or elsewhere	8. Two or more diagnoses of thrush OR candida
9. Infection with normally harmless tuberculosis-like bacteria	9. Diagnosis of mycoplasma infection
10. A family history of PI	10. Family history of immunodeficiency listed

Adapted from http://downloads.info4pi.org/pdfs/10-Warning-Signs%2D%2D-Generic-Text%2D%2D2-.pdf

EMR electronic medical record, Jeffrey Modell Foundation, *PI* primary immunodeficiency

Methods

We performed a retrospective chart review of patients evaluated from January 2006 to December 2016 in outpatient or inpatient sites of Cleveland Clinic locations in the USA, and Rainbow Babies and Children's Hospital Cleveland Medical Center locations. Appropriate Institutional Review Board approval was obtained at each institution. Patients < 18 years old were considered pediatric ("children"). Patients ≥ 18 years-old were deemed adults.

PID patients were identified by International Classification of Diseases Ninth and Tenth Revision codes indicative of primary immunodeficiency. Charts of patients with a diagnosis of PID were reviewed by a physician to confirm that clinical and laboratory evaluation were consistent with a given diagnosis, as specified in the Practice Parameter for the Diagnosis and Management of Primary Immunodeficiency [16]. Patients with 22q11 deletion were only included if they had biochemical evidence of immunodeficiency. Patients with selective IgA deficiency were included if they had recurrent sinopulmonary or gastrointestinal infections. Patients with diagnoses of CVID were eligible for inclusion by fulfilling the ESID/PAGID diagnostic criteria [17]. The electronic medical record (EMR) was examined for the presence of each of the age-appropriate JMF warning signs for immunodeficiency documented at any time in the clinical course (Table 1). Unfortunately, even on manual review, a positive or negative family history of immunodeficiency was inconsistently documented; therefore, these data were not reported. In addition to the published JMF warning signs, the EMR was evaluated for the presence of diagnosis codes for autoimmune disease (arthritis, inflammatory bowel disease, thyroiditis, vitiligo, systemic lupus erythematosis, Sjogrens, mixed connective tissue disease), and atopy (asthma, reactive airway disease, allergic rhinitis, or atopic dermatitis). We also evaluated for benign and malignant lymphoproliferative disorders (diagnoses of lymphoproliferative disorder, myelodysplastic syndrome, autoimmune lymphoproliferative syndrome, lymphocyte variant hypereosinophilic syndrome, lymphocytic interstitial pneumonia) and cancer (including leukemia, lymphoma, neuroblastoma, rhabdoymyosarcoma, osteosarcoma) documented at any point in time (Fig. 1).

To establish a control group, we searched for patients who underwent laboratory immune evaluation and had no subsequent diagnosis of primary or secondary immunodeficiency. Exclusion criteria included HIV/AIDS, history of immunosuppressant or anti-neoplastic therapy, malnutrition, protein losing enteropathy, inflammatory bowel disease, proteinuria, chronic kidney disease, and history of solid organ or stem cell transplant. Laboratory evaluation assessed either the humoral (serum immunoglobulin concentration measured by quantitative techniques with specific antibody production to vaccine responses) or the cellular immune system (flow cytometry of T cell subsets, B cells, and NK cells) [18].

Patients' information collected was described using means and standard deviations for all continuous variables, and counts and percentages for all categorical variables. The study group was divided into two groups (PID/no PID). One-way ANOVA was used to compare continuous variables, and chi-square test was used for categorical variables. Logistic regression models were performed to predict PID/no PID for various JMF warning signs. Receiver operator characteristics (ROC) curves were generated. All analyses were performed by using the SAS 9.4 for Linux (SAS, Cary, North Carolina). The level of statistical significance was set at $p < 0.05$ (two-tailed).

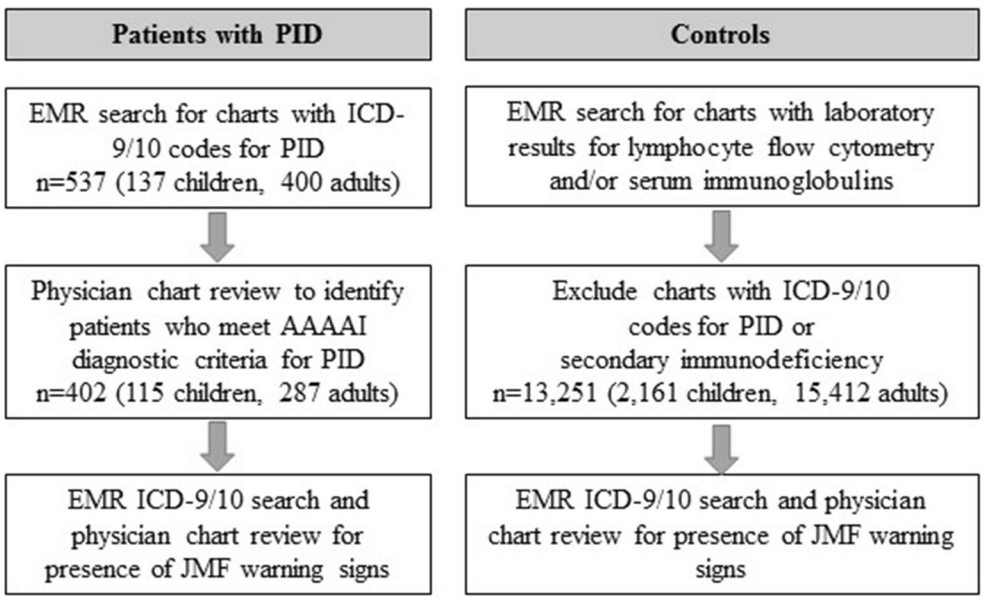

Fig. 1 Methods for identification and evaluation of patients with primary immunodeficiency and controls

Results

Demographics: Patients with Primary Immunodeficiency

Our initial query identified 537 patients with diagnoses of primary immunodeficiency, including 137 children and 400 adults. We eliminated 135 patients (22 children and 113 adults) who did not have sufficient documentation to meet PID diagnostic criteria, or for whom a secondary cause of immunodeficiency was suspected.

Of 115 pediatric patients with primary immunodeficiency, the most common diagnoses were 22q11 deletion syndrome ($n = 62$), specific antibody deficiency (SAD) ($n = 23$), and common variable immunodeficiency (CVID) ($n = 16$, Fig. 2). Only one patient with del22q11 had complete thymic aplasia; the remainder had less severe immunodeficient phenotypes. There were 66 males and 49 females, with mean age 9.0 years (range 3 months–17.5 years).

Of 287 adults with PID, the most frequent diagnoses were CVID ($n = 222$), 22q11 deletion syndrome ($n = 18$,) selective IgA deficiency or SAD ($n = 16$), and hyper IgE syndrome ($n = 10$, Fig. 2). There were 105 males and 182 females, with mean age 48.4 years (range 18.0–93.8 years).

Demographics: Patients with Normal Biochemical Evaluation

We identified 13,251 patients (2161 children and 15,412 adults) who underwent laboratory immunologic evaluation

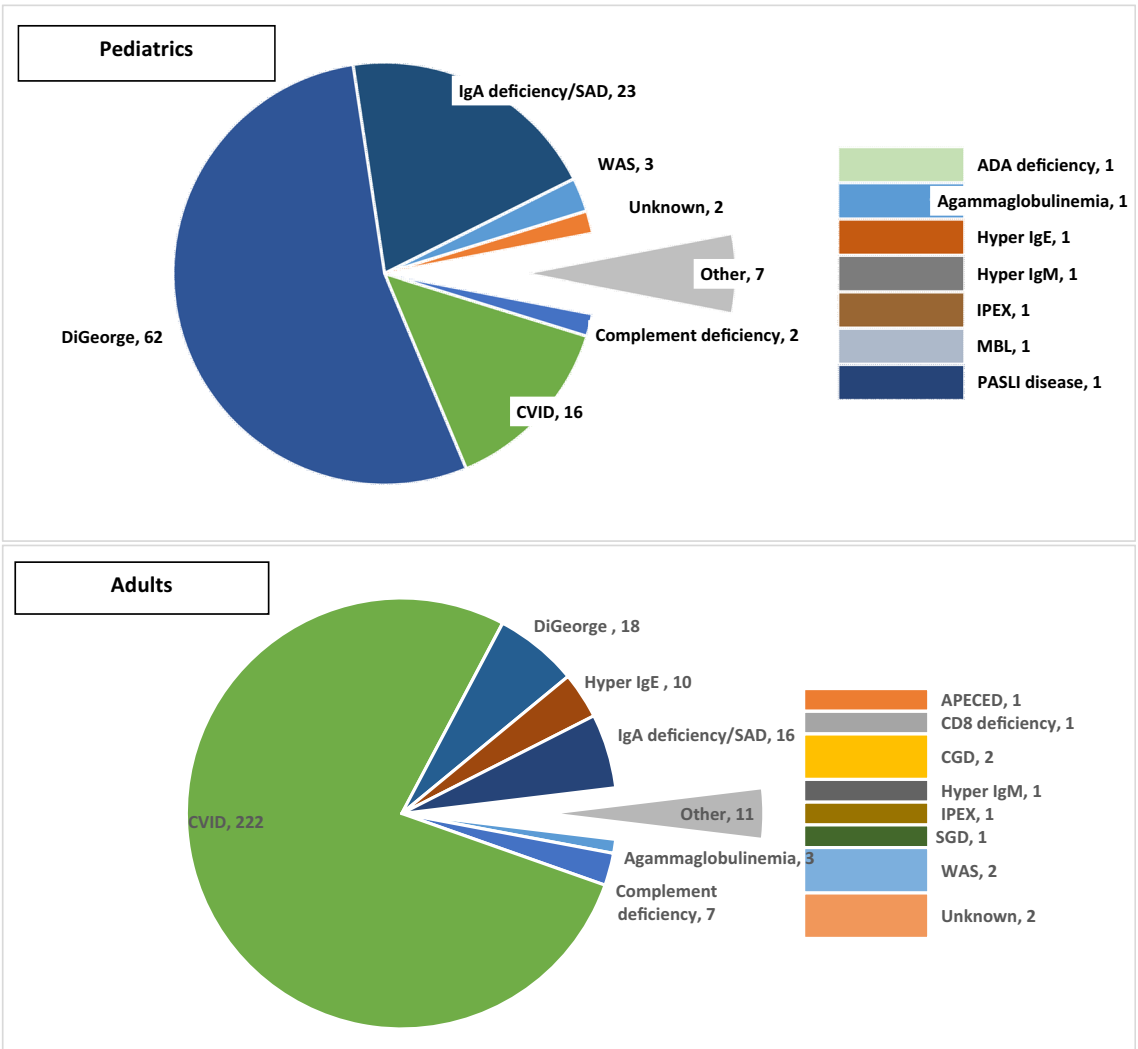

Fig. 2 Frequency of individual primary immunodeficiency diagnoses. *SAD* specific antibody deficiency; *WAS* Wiscott-Aldrich syndrome; *CVID* common variable immunodeficiency; *ADA* Adenosine deaminase deficiency; *IPEX* immune dysregulation, polyendocrinopathy, enteropathy, X-linked; *MBL* mannose binding lectin deficiency; *PASLI* p110 delta activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency; *APECED* autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; *CGD* chronic granulomatous disease; *SGD* neutrophil specific granule deficiency

without subsequent documentation of an ICD-9/10 code for PID, and who were eligible for inclusion. The pediatric group included 947 females and 1214 males, with a mean age of 10.8 years (range 0.4–17.9 years). The adult group included 8336 females and 7076 males, with a mean age of 55.0 years (range 18.0–100.0 years).

In the pediatric group, controls were significantly older than patients with PID (mean age 10.8 ± 4.4 years vs. 9.4 ± 5.1 years, $p = 0.001$), but the groups were matched for gender ($p = 0.80$). In the adult group, controls were significantly older than patients with PID (mean age 55 ± 16.7 years vs. 48.4 ± 18.6 years, $p < 0.001$). There was a significant female predominance in adult patients with PID (63.4%) compared to controls (54.1%, $p = 0.007$).

Warning Sign Evaluation: Pediatric Immunodeficiency

The mean number of JMF warning signs present for a given patient with primary immunodeficiency was 2.3 (range 0–7 warning signs). The highest mean number of JMF warning signs was found in patients with Hyper IgE syndrome (seven warning signs), mannose-binding lectin deficiency (six warning signs), and p110 delta activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency (PASLI) (six warning signs) (Fig. 3). Patients with Wiscott-Aldrich syndrome, hyper IgM syndrome, and immune dysregulation, polyendocrinopathy, and enteropathy X-linked syndrome (IPEX) had the fewest JMF warning signs prior to

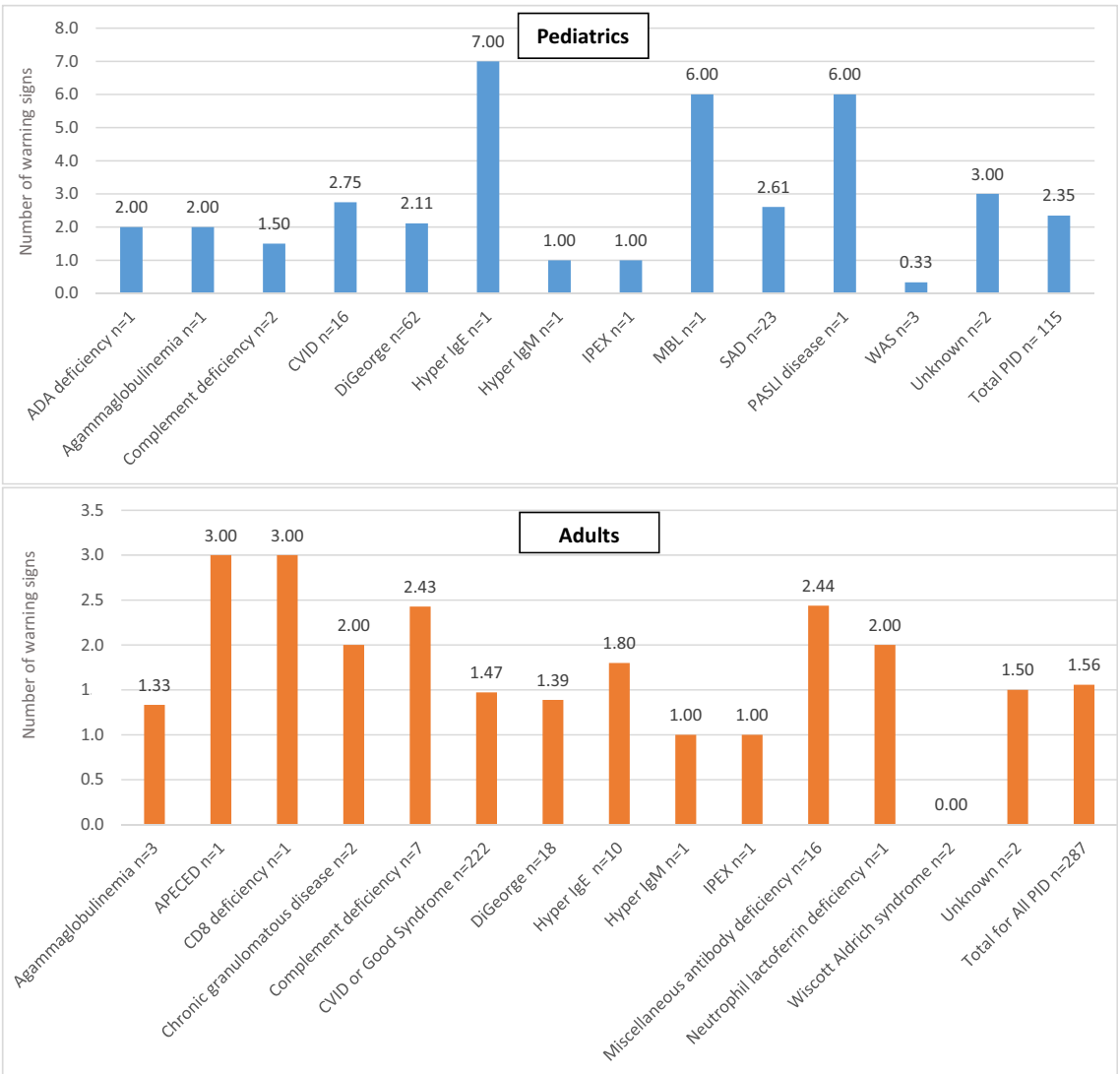

Fig. 3 Number of warning signs in patients with primary immunodeficiencies. Mean reported when $n > 1$. *ADA* adenosine deaminase deficiency; *CVID* common variable immunodeficiency; *IPEX* immune dysregulation, polyendocrinopathy, enteropathy, X-linked; *MBL* mannose binding lectin deficiency; *PASLI* p110 delta activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency; *SAD* specific antibody deficiency; *WAS* Wiscott-Aldrich syndrome; *APECED* autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; *CGD* chronic granulomatous disease; *SGD* neutrophil-specific granule deficiency

laboratory evaluation. Record of > two JMF warning signs was found in 64.3% of pediatric patients with PID.

Compared to controls, pediatric subjects with PID had a significantly elevated frequency of recurrent pneumonia (OR 2.9, $p < 0.001$), failure to thrive (OR 2.1, $p < 0.001$), need for intravenous (IV) antibiotics (OR 2.1, $p < 0.001$), serious bacterial infection ($p < 0.001$), and recurrent otitis media (OR 1.5, $p = 0.027$) (Table 2). The frequency of autoimmune disease was significantly elevated in pediatric patients with PID compared to controls (8.7% vs. 2.8%, $p < 0.001$) (Fig. 4). There was no significant difference in the frequency of proliferative disease in pediatric patients with or without immunodeficiency (7.0% vs. 3.8%, $p = 0.09$). The frequency of atopy was significantly higher in pediatric patients without PID compared to those with PID (75.0% vs. 52.2%, $p < 0.001$) (Fig. 4). Logarithmic regression demonstrated that any combination of two or more JMF warning signs in the pediatric age group was associated with only a 56% chance of identifying presence of immunodeficiency (Table 2). This accuracy was slightly improved with the addition of autoimmunity to the original JMF warning signs (OR 3.2, $p = 0.0012$, ROC 0.58).

Table 2 Warning signs in pediatric and adult patients with PID compared to controls

Warning sign	Odds ratio	95% confidence limits		*p* value*	Area under the curve**
Pediatric patients					
Otitis media	1.5	1	2.3	*0.028*	0.55
Sinusitis	0.9	0.6	1.4	0.79	0.51
Frequent antibiotics	0.7	0.5	1	1.2	0.54
Pneumonia	2.9	1.7	5.1	*0.001*	0.55
Failure to thrive	2.1	1.4	3	*0.0003*	0.58
Abscess	0.7	0.3	1.6	0.41	0.51
Candida	1.3	0.668	2.7	0.4	0.51
IV antibiotics	2.1	1.4	3.1	*0.001*	0.59
Serious bacterial infection	4.8	2.7	8.9	*0.001*	0.56
Two or more warning signs (any)	1.8	1.2	2.6	*0.0047*	0.57
Two or more warning signs + allergic disease	0.3	0.2	0.5	*0.001*	0.66
Two or more warning signs + autoimmunity	3.2	1.6	6.4	*0.0012*	0.58
Two or more warning signs + lymphoproliferative disease	1.6	0.7	3.4	0.228	0.57
Adult patients					
Otitis media	2.9	1.9	4.3	*0.001*	0.53
Sinusitis	2.1	1.6	2.7	*0.001*	0.57
Pneumonia	1.2	0.9	1.5	0.27	0.51
Diarrhea with weight loss	2.2	1.4	3.4	*0.0009*	0.52
Recurrent infection	3.3	2.4	4.4	*0.001*	0.57
IV antibiotics	0.9	0.7	1.2	0.558	0.51
Abscess	1.2	0.8	1.8	0.31	0.51
Candida	1.5	0.9	2.4	0.06	0.51
Mycoplasma	< 0.001	< 0.001	> 99	0.97	0.5
Two or more warning signs (any)	1.7	1.3	2.1	*0.001*	0.56
Two or more warning signs + allergic disease	1.2	0.9	1.6	0.13	0.57
Two or more warning signs + autoimmunity	1.2	0.9	1.5	0.29	0.56
Two or more warning signs + lymphoproliferative disease	0.6	0.5	0.9	*0.01*	0.57

p values less than or equal to 0.05 in italic

*Pearson's chi-square test

**Where sensitivity is graphed over one specificity, and 1 represents a perfect test (accurate in distinguishing the presence or absence of immunodeficiency), and an area of 0.5 indicates no diagnostic utility

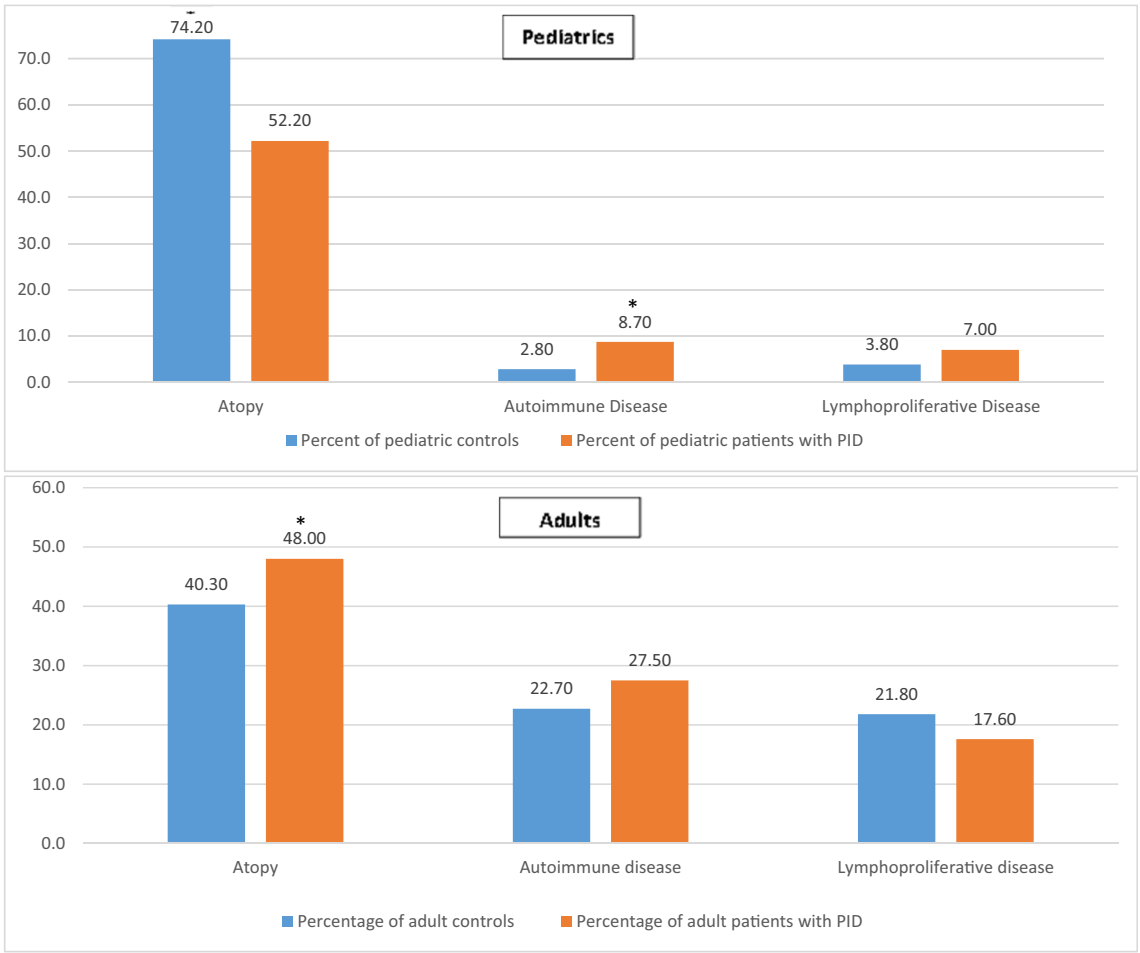

Fig. 4 Percentage of patients with non-infectious comorbities. *Statistically-significant difference (level of statistical significance was set at $p < 0.05$, compared by chi-squared analysis)

Warning Sign Evaluation: Adult Immunodeficiency

The mean number of JMF warning signs per adult with PID was 1.6 (range 0–6 warning signs). The highest mean number of JMF warning signs was recorded in patients with autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) (three warning signs) and CD8 deficiency (three warning signs) (Fig. 3). Diagnoses associated with infrequent documentation of JMF warning signs were Wiscott-Aldrich syndrome (no warning signs recorded for either of two patients), IPEX (one warning sign), and Hyper IgM (one warning sign). Record of > two JMF warning signs was found in just 44.9% of adult PID patients.

Compared to controls, adults with PID had a significantly elevated frequency of recurrent otitis media (OR 2.9, $p < 0.001$), recurrent sinusitis (OR 2.1, $p < 0.001$), diarrhea with weight loss (OR 2.2, $p < 0.001$), and recurrent viral infection (OR 3.3, $p < 0.001$) (Table 2). The frequency of atopy was statistically significantly elevated in adult PID patients compared to controls (48.0% vs 40.3%, $p = 0.011$). There was no difference in the frequency of autoimmune disease or proliferative disease recorded between adults with PID and controls, and the addition of these additional criteria to the original JMF warning signs did not improve diagnostic accuracy (Table 2).

Discussion

This report describes one of the largest North American evaluations of the JMF warning signs of immunodeficiency. Overall, the predictive value of these warning signs was found to be superior in the pediatric PID population compared to adults, and warning signs of immunodeficiency found with statistically significant increased frequency in patients with PID compared to their controls differed in pediatric versus adult patients.

In our search for additional criteria which promote identification of immunodeficiency, we found the frequency of atopy to be higher than the frequency of some individual JMF warning signs in both adult and pediatric PID patients. Atopic disease has previously been identified as a presenting feature of PID [19, 20]. Atopy was found to be negatively associated with a

diagnosis of immunodeficiency in pediatric patients who underwent laboratory evaluation of the immune system, which likely reflects the relatively high prevalence of atopic disease in young children [21]. It is generally accepted that allergic inflammation can predispose patients to infections [22]. It is therefore important that immune evaluation not be dismissed in patients with symptoms consistent with PID on the assumption that their symptoms are due to allergy, as these are not mutually exclusive, and in our adult population, atopy was found in increased numbers in patients with PID compared to controls.

In the pediatric cohort, autoimmune disease was more frequently recorded in patients with PID versus controls, while rates of malignancy were comparable between these groups. In adults, atopy was more frequently recorded in PID subjects compared to controls, with comparable rates of autoimmunity and malignancy (Table 2). These findings may relate to the expected natural history of atopy and autoimmunity in the general population, and to variation in the types of PID represented in our pediatric and adult cohorts. While these features alone may not be beneficial as screening tools to prompt PID evaluation, it is important that subspecialists who manage these conditions be aware of the need for PID evaluation in unusual or difficult-to-treat cases of autoimmune disease or malignancy, particularly when associated with increased rate of infections [23–25].

Our study was limited by its retrospective nature and reliance on documentation in the EMR, which likely results in underestimation of sensitivity. Importantly, family history was not included in our analysis secondary to inconsistent documentation, though it has previously been identified as a relatively specific discriminator for PID [13–15]. The importance of complete documentation of family history is critical when evaluating patients for suspected immunodeficiency. Prospective studies to confirm these findings are needed. This study was not powered to evaluate the predictive value of the JMF warning signs for individual immunodeficiencies. The preponderance of patients with 22q11 deletion syndrome may relate to one site being a tertiary cardiac-referral center.

Controls were selected based on record of laboratory evaluation for immunodeficiency, which may have been motivated by the presence of JMF warning signs. This analysis allowed us to compare patients with the presence of JMF warning signs and a normal biochemical evaluation with patients with a primary immunodeficiency, and pursued that this approach as patients with the presence of JMF warning signs in the general population without laboratory evaluation for an immunodeficiency may have unrecognized immune derangements. We suspect that this may have impacted specificity and resulted in failure to identify JMF warning signs of statistically significant utility. However, our control group represents an invaluable tool for statistical analysis. Furthermore, this is one of the first North American studies of this nature to utilize a control group and to perform analyses beyond descriptive statistics.

Conclusion

Early identification of patients with immunodeficiency remains a challenge given the lack of a single set of warning signs that can identify all patients. Current tools focus primarily on increased and difficult-to-treat infections, which we have determined to be an overall poor indicator of the presence of PID in both pediatric and adult populations. We suggest education of physicians on differing presentations of PID in adult versus pediatric patients, and pending further prospective studies, potential expansion of the JMF warning signs to include non-infectious comorbidities.

Acknowledgements The authors gratefully acknowledge the contributions of Manshi Li, Quantitative Health Sciences, the Cleveland Clinic, and Jennifer Staley, Medical Librarian, Rainbow Babies and Children's Hospital Case Medical Center.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. J Clin Immunol. 2007;27:497–502.
2. Notarangelo LD. Primary immunodeficiencies. J Allergy Clin Immunol. 2010;125(suppl):S182–94.
3. Ballow M, Notarangelo L, Grimbacher B, Cunningham-Rundles C, Stein M, Helbert M, et al. Immunodeficiencies. Clin Exp Immunol. 2009;158(suppl):14–22.
4. Plebani A, Soresina A, Rondelli R, Amato GM, Azzari C, Cardinale F, et al. Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: an Italian multicenter study. Clin Immunol. 2002;104(3):221–30.
5. Seymour B, Miles J, Haeney M. Primary antibody deficiency and diagnostic delay. J Clin Pathol. 2005;58:546–7.
6. Urschel S, Kayikci L, Wintergerst U, Notheis G, Jansson A, Belohradsky BH. Common variable immunodeficiency disorders in children: delayed diagnosis despite typical clinical presentation. J Pediatr. 2009;154(6):888–94.
7. Urm SH, Yun HD, Fenta KH, et al. Asthma and risk of selective IgA deficiency or common variable immunodeficiency: a population-based case-control study. Mayo Clin Proc. 2013;88(8):813–21.
8. Fodil N, Langlais D, Gros P. Primary immunodeficiencies and inflammatory disease: a growing genetic intersection. Trends Immunol. 2016;37(2):126–40.
9. Agarwal M, Jariwala M. Rheumatic manifestations of primary immunodeficiencies in children. Indian J Rheumatol. 2012;7(suppl):52–6.
10. Van der Werff J, Bosh T, Van den Akker M. Genetic predisposition and hematopoietic malignancies in children: primary immunodeficiency. Eur J Med Genet. 2016;59(12):647–53.

11. Salavoura K, Kolialexi A, Tsangaris G, Mavrou A. Development of cancer in patients with primary immunodeficiencies. Anticancer Res. 2008;28(2B):1263–9.
12. Resnick E, Moshier E, Godbold J, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood. 2012;119(7):1650–7.
13. MacGinnitie, Aloi F, Mishra S. Clinical characteristics of pediatric patients evaluated for primary immunodeficiency. Pediatr Allergy Immunol. 2011;22(7):671–5.15.
14. Subbarayan A, Colarusso G, Hughes SM, et al. Clinical features that identify children with primary immunodeficiency diseases. Pediatrics. 2011;127(5):810–6.
15. Arkwright PD, Gennery AR. Ten warning signs of primary immunodeficiency: a new paradigm is needed for the 21st century. Ann N Y Acad Sci. 2011;1238:7–14.
16. Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol. 2005;94(suppl):S1–63.
17. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol. 1999;93:190–7.
18. Oliveira J, Fleisher T. Laboratory evaluation of primary immunodeficiencies. J Allergy Clin Immunol. 2010;125(suppl):S297–305.
19. Tuano KS, Orange JS, Sullivan K, et al. Food allergy in patients with primary immunodeficiency diseases: prevalence within the US Immunodeficiency Network (USIDNET). J Allergy Clin Immunol. 2015;135(4):1092.
20. Aghamohammadi A, Cheraghi T, Gharagozlou M, Movahedi M, Rezaei N, Yeganeh M, et al. IgA deficiency: correlation between clinical and immunological phenotypes. J Clin Immunol. 2009 Jan;29(1):130–6.
21. Thomsen SF. Epidemiology and natural history of atopic diseases. Eur Clin Respir J. 2015;2:10.3402–7.
22. Edwards M, Strong K, Cameron A, et al. Viral infections in allergy and immunology: how allergic inflammation influences viral infections and illness. J Allergy Clin Immunol. 2017;140(4):909–20.
23. Singhi AD, Goyal A, Davison JM, et al. Pediatric autoimmune enteropathy: an entity frequently associated with immunodeficiency disorders. Mod Pathol. 2014;27(4):543–53.
24. Zhu L, Tingting S, Zhong C, et al. IL-10 and IL-10 receptor mutations in very early onset inflammatory bowel disease. Gastroenterol Res. 2017;10(2):65–9.
25. Farmer JR, Ong MS, Barmettler S, Yonker LM, Fuleihan R, Sullivan KE, et al. Common variable immunodeficiency non-infectious disease endotypes redefined using unbiased network clustering in large electronic datasets. Front Immunol. 2018;8:1740.