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How effective are the 6 European Society of Immunodeficiency warning signs for primary immunodeficiency disease?

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ABSTRACT

Background: The European Society of Immunodeficiency (ESID) developed 6 warning signs to promote the awareness of adult primary immunodeficiency disease (PID).
Objective: To screen adult patients for the presence of PID using these 6 warning signs to determine the effectiveness of this protocol.
Methods: Questions related to the ESID warning signs for adult PID were added to the standard outpatient clinic file system and asked of 3,510 patients who were admitted to our clinic for any reason. Patients with signs and/or suspicion of PID based on their medical history underwent immunologic investigation.
Results: In total, 24 patients were diagnosed as having a PID. The most common reason that patients with PID were admitted was frequent infection (n=18 [75%]), and the most common PID subgroup was common variable immunodeficiency (n=12 [50%]). Twenty patients with PID had at least one positive finding according to the ESID warning signs. Two patients with gastrointestinal concerns and 2 with dermatologic symptoms were also diagnosed as having a PID, although they did not have any of the ESID warning signs.
Conclusion: The ESID warning signs do not specify the need for symptoms to diagnose a PIDs and do not include a comprehensive list of all signs and symptoms of PIDs. As a result, more than infection-centric questions are needed to identify adult patients with immunodeficiencies.
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Introduction

Primary immunodeficiency diseases (PIDs) are rare diseases caused by defects of the immune system, and early diagnosis of PIDs is important for reducing morbidity and mortality. PIDs are characterized by recurrent and/or severe infections, autoimmunity, malignancy, and allergic disorders.[1–3] Diagnostic delays in adult patients with PID are problematic for clinicians worldwide, and most physicians are not familiar with rare disorders. Because of this lack of awareness, immunologic investigations are not commonly used for the diagnosis of PIDs.[1–4] The European Society of Immunodeficiency (ESID) published the common designation for PIDs in 1999. Since then, a working party from the ESID established a European Patient and Research database for continuous long-term documentation of patients with the aim of improving the diagnosis, classification, prognosis, and therapy of PIDs.[5]

The ESID suggested 6 warning signs for the suspicion of PIDs (Table 1),[6] and patients with these signs must undergo further evaluations for an underlying PID. However, the warning signs do not include comprehensive symptoms of PIDs, and the effectiveness

Table 1
The 6 ESID warning signs for adult primary immunodeficiency diseases

1. Four or more infections requiring antibiotics within 1 year (otitis, bronchitis, sinusitis, pneumonia)
2. Recurring infections or infection requiring prolonged antibiotic therapy
3. Two or more severe bacterial infections (osteomyelitis, meningitis, septicemia, cellulitis)
4. Two or more radiologically proven pneumonia within 3 years
5. Infection with unusual localization or unusual pathogen
6. PID in the family

Abbreviations: ESID, European Society of Immunodeficiency; PID, primary immunodeficiency disease.

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Table 2
Demographic data of patients and replies to the 6 ESID warning signs[a]

Patient No./sex/age, y	Diagnosis	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
1/M/36	CVID	Yes	Yes	Yes	Yes	Yes	Yes
2/M/42	CVID	Yes	Yes	Yes	Yes	Yes	Yes
3/F/25	CVID	Yes	Yes	Yes	Yes	No	No
4/F/48	CVID	Yes	Yes	Yes	Yes	No	No
5/F/50	CVID	Yes	Yes	No	No	No	No
6/F/37	CVID	Yes	Yes	Yes	Yes	No	No
7/M/39	CVID	Yes	Yes	Yes	Yes	No	No
8/M/18	CVID	Yes	Yes	Yes	Yes	Yes	No
9/F/36	CVID	Yes	Yes	No	No	No	No
10/M/30	CVID	Yes	Yes	No	No	No	No
11/M/27	CVID	No	No	No	No	No	No
12/F/37	CVID	No	No	No	No	No	No
13/F/45	sIgAD	Yes	Yes	No	No	No	No
14/M/23	sIgAD	Yes	No	No	No	No	No
15/F/56	sIgAD	No	No	No	No	No	No
16/M/57	sIgAD	Yes	No	No	No	No	No
17/M/24	sIgAD	No	No	Yes	Yes	No	Yes
18/M/31	sIgAD	Yes	Yes	No	No	No	No
19/F/33	sIgAD	Yes	No	No	No	No	No
20/F/24	sIgAD	Yes	Yes	No	No	No	No
21/F/34	CD	No	No	No	No	No	No
22/F/24	CD	No	No	No	No	No	No
23/F/28	CGD	Yes	Yes	Yes	No	Yes	Yes
24/M/36	HIES	Yes	Yes	Yes	Yes	Yes	No

Abbreviations: CGD, chronic granulomatous disease; CVID, common variable immunodeficiency, HIES, hyper IgE syndrome, sIgAD, selective immunoglobulin A deficiency.
[a]Question 1: Four or more infections requiring antibiotics within 1 year (otitis, bronchitis, sinusitis, pneumonia)? Question 2: Recurring infections or infection requiring prolonged antibiotic therapy? Question 3: Two or more severe bacterial infections (osteomyelitis, meningitis, septicemia, cellulitis)? Question 4: Two or more radiologically proven pneumonia within 3 years? Question 5: Infection with unusual localization or unusual pathogen? Question 6: Primary immunodeficiency disease in the family?

of this screening protocol in clinical practice remains to be established.[7] The warning signs suggested by the ESID for adult PIDs have been published and are clinically useful; however, this model has not been tested in a clinical trial. Moreover, the infection-based warning signs do not cover the broad clinical spectrum for PIDs.[8] In adults, the clinical presentation of PIDs is usually based on the complications and comorbidities of immunodeficiencies, especially for common variable immunodeficiency (CVID).

This study had 2 major objectives. The first was to determine the prevalence of PIDs among patients who were admitted to our adult clinical immunology and allergy outpatient clinic, independent of their reason for admission. The second objective was to evaluate the effectiveness of the 6 ESID warning signs in the diagnosis of immunodeficiencies.

Methods

This prospective study was approved by the local ethics committee conducted in the Adult Clinical Immunology and Allergy Department, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey. Written informed consent was obtained from the all study participants. Questions regarding the 6 ESID warning signs for adult PIDs were added to the standard outpatient clinic patient file system and asked of 3,510 patients who were admitted to our clinic for any reason from November 2011 to November 2013.

Patients with a suspected immunodeficiency according to the ESID warning signs (with at least 1 positive reply to 6 questions [Table 2]) were initially evaluated for secondary reasons. Laboratory analyses were performed in patients suspected of having an immunodeficiency and included a total blood cell count; a peripheral blood smear; measurement of serum immunoglobulins (IgG, IgA, IgM, and IgE); IgG subclass titers; flow cytometry of peripheral blood lymphocyte subsets, including T cells and B cells (CD3, CD4, CD8, CD19, CD20, CD27, CD81, IgD, CD56/16, CD45RA, CD45RO, HLA-DR, TCR-$\alpha/\beta/\gamma/\delta$, CD11, and CD18); a lymphocyte proliferation test; a neutrophil chemotaxis test; isohemagglutinins; antibody responses (tetanus and pneumococcal); delayed cutaneous hypersensitivity (purified protein derivative); nitroblue tetrazolium dye test; and complement assays (CH_{50}, C3, C4, and C1 inhibitor level and activity), as needed.

PID diagnoses were established according to the ESID criteria[6] and classified according to the criteria of the International Union of Immunological Societies.[9,10] Patients were grouped according to

Table 3
Reasons for patient admission

Reason	No. (%) of total patients (N = 3,510)	No. (%) of patients with PID diagnoses (n = 24)
Frequent infections[a]	137 (3.9)	18 (75.0)
Urticaria or angioedema	1,638 (46.7)	2 (8.3)
Rhinosinusitis	1,105 (31.5)	2 (8.3)
Asthma or BHR	275 (7.8)	0
Drug reactions	264 (7.5)	0
Systemic anaphylaxis	44 (1.3)	0
GIS symptoms	35 (1.0)	2 (8.3)
Family history of PID	12 (0.3)	0

Abbreviations: BHR, bronchial hyperresponsiveness; GIS, gastrointestinal system; PID, primary immunodeficiency disease.
[a]Although frequent infections was the reason for admission in 137 patients (3.9%), 231 patients (6.6%) responded yes to the first European Society of Immunodeficiency question asking whether they had a history of frequent infection (refer to question 1).

Table 4
Frequency and characteristics of patients with PID

PID subgroup	No. (%) of patients (n = 24)
CVID	12 (50.0)
Selective IgA deficiency	8 (33.3)
Complement deficiency	2 (8.3)
CGD	1 (4.2)
Hyper IgE syndrome	1 (4.2)

Abbreviations: CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; PID, primary immunodeficiency.

Table 5
Laboratory findings of patients who were diagnosed as having PID[a]

Parameter	Patient No.										
	1	2	3	4	5	6	7	8	9	10	11
WBC count, $\times 10^3/\mu l$	11.1	14.6	5.9	10.2	6.48	10.7	3.05	6.7	7.06	7.6	6.7
Neutrophil count	6.91	6.1	2.8	6	3.81	7.7	2.25	3.8	3.5	4.8	5.1
Lymphocyte count	2.96	5.2	1.8	3.2	2.12	2.4	0.42	2.5	2.24	2.3	1.4
Serum IgG level	0.333	3.14	2.8	3.66	2.75	1.45	1.96	2.1	3.91	2.29	3.03
Serum IgA level	0.057	0.248	0.240	0.148	0.118	0.238	0.264	0.067	1.580	0.070	0.270
Serum IgM level	0.268	0.182	0.310	0.360	0.442	0.186	0.278	0.265	0.378	0.520	0.300
Serum IgE level	5	14.2	12.6	14.3	5	17.6	10	20	110	10	15
Isohemagglutinin titers	Anti-B 1/1	Anti-A and anti-B 1/32	Anti-A and anti-B 1/64	Anti-A 1/2	Anti-A 1/8	Anti-A 1/8	Anti-A 1/64	Anti-B 1/4	Anti-B 1/64	Anti-B 1/4	Anti-B 1/2
Pneumococcal IgG titers, mU/mL	224	3,200	178	2,400	3,580	2,420	1,800	780	1,686	2,400	1,412
Tetanus IgG titers, IU/mL	0.145	1.12	0.17	1.13	0.45	1.8	2.1	1.82	0.7	1.1	0.25
CD19, %	7	1	10	6	7	5	6	13	6	10	11
CD3, %	85	93	77	74	72	70	69	68	77	80	85
CD4, %	11	26	45	41	24	28	5	29	42	31	15
CD8, %	70	66	8	10	43	62	59	36	26	45	61
CD16/56, %	1	6	6	4	15	12	15	17	3	15	13
Neutrophil function	n	n	n	n	n	n	n	n	n	n	n
C4	0.348	0.303	0.186	0.625	0.280	0.252	0.343	0.361	0.196	0.194	0.304
C1 inhibitor level											
C1 inhibitor activity											
Skin prick test	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Grass	Negative	Negative
Genetic evaluation											

Abbreviations: ARBF, absence of respiratory burst function; PID, primary immunodeficiency; WBC, white blood cell.
[a]References ranges are as follows: IgG, 7.51 to 15.6 g/L; IgA, 0.82 to 4.53 g/L; IgM, 0.46 to 3.04 g/L; IgE, 0 to 165 IU/mL; C4, 0.160 to 0.380 g/L; C1 esterase inhibitor, 0.15 to 0.35 g/L; and C1 inhibitor activity, 70% to 130%.

their reasons for admission, which included rhinosinusitis, asthma or bronchial hyperreactivity, adverse drug reactions, anaphylaxis, dermatologic symptoms, gastrointestinal symptoms, and immunodeficiency screening because of a family history of immunodeficiency. Correlations between a diagnosis of PID and the reasons for admission were also evaluated. The effectiveness of the ESID warning signs was evaluated based on the number of patients with PID who tested positive using the ESID questions compared with patients whose PID remained undetected using the ESID questions.

The analyses performed in this study were primarily descriptive. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and corresponding confidence intervals for each question were calculated. Data analysis was performed using the SPSS statistical software, version 21.0 (SPSS Inc, Chicago, Illinois).

Results

Medical records for 3,510 patients were evaluated in this study. The mean (SD) age of the patients was 39.0 (13.5) years; 2,316 (66%) were female, and 1,194 (34%) were male. Twenty-four patients were diagnosed as having a PID. The most common reason for admission among patients with PID was frequent infection (n=18 [75%]). The number of patients with a final diagnosis of a PID and their reasons for admission are given in Table 3. The most common PID subgroup was CVID (n=12 [50%]) (Table 4). The predictive values for each of the ESID warning signs are given in questions 1 through 6 (eTable 1). The demographic data, laboratory findings, and replies to the 6 ESID warning signs questionnaire are summarized in Table 2 and Table 5.

Twenty patients diagnosed as having a PID had at least one positive ESID warning sign. Two patients with gastrointestinal symptoms (abdominal pain, noninfectious diarrhea, and inflammatory bowel disease–like symptoms) were diagnosed as having a PID (CVID) after an immunologic investigation; however, the results were negative using the ESID warning signs. Two additional patients with dermatologic symptoms (only angioedema) were also diagnosed as having a PID (hereditary angioedema); however, neither had positive ESID warning signs.

Discussion

PIDs are devastating disorders that typically result from monogenic defects of the human immune system. Many PIDs present early in life as an increase in susceptibility to recurrent infections.[11,12] In adults, the largest problem with PIDs is poor awareness because the diseases are generally considered childhood disorders. PIDs are associated with severe morbidity and increased mortality if left untreated.[13] Many PIDs are easily diagnosed, and effective treatment options are available; therefore, careful clinical evaluations are important for patients with potential PIDs.[10,14] In addition, it is important for clinicians to be aware of the symptoms and warning signs of PIDs to determine whether further investigations are required.[15] However, knowledge of PIDs and their management is lacking among physicians, causing many patients to experience diagnostic delays.[16]

The ESID suggested 6 warning signs to indicate PIDs[6] and has called for research groups to evaluate the epidemiology of PIDs in European countries. Moreover, the ESID has composed a survey for the early diagnosis of PIDs. The questions surveyed are relatively simple and can be used to diagnose the diseases in patients in developing countries.[4,5,17]

In this study, 20 of 3,510 adult patients were diagnosed as having a PID using the ESID warning signs. Each of the warning signs has low sensitivity but high specificity and a high negative predictive value. A history of frequent or recurrent infections

Table 5
Continued

Patient No.												
12	13	14	15	16	17	18	19	20	21	22	23	24
5.4	7.14	7.3	6.2	7.9	10.5	8.6	8.4	7.1	7.5	6.8	9.7	7.7
3.7	3.81	3.9	3.4	4.9	5.06	4.9	5.6	4.32	5	4.1	5.9	5.4
1.1	2.62	2.2	2.3	2.2	4.28	3.1	2.2	2.36	1.9	2.1	2.8	1.1
1.43	19.5	14.8	11.5	14.8	13.6	8.51	15.7	11.5	9.2	8.1	18.5	14.4
0.060	0.066	0.052	0.070	0.066	0.076	0.082	0.038	0.042	1.850	0.945	6.58	1.40
0.041	1.18	2.11	0.737	0.714	0.942	0.7	1.77	1.06	1.83	1.03	3.39	0.932
5	45	52	5	24	133	5	5.5	40	11.4	5	60.6	17,600
Anti-B 1/4	Anti-A and anti-B 1/64	Anti-B 1/32	Anti-A and anti-B 1/32	Anti-B 1/64	Anti-A 1/64	Anti-B 1/64	Anti-B 1/128	Anti-B 1/128	Anti-B 1/32	Anti-B 1/64	Anti-A and anti-B 1/32	Anti-A 1/16
1,200	8,700	6,254	2,200	4,580	3,589	7,864	2,587	4,568	8,900	6,478	5,167	1,777
0.12	2.7	4.4	5.4	3.78	2.45	1.80	1.68	1.24	6.7	5.46	1.246	0.115
6	5	10	11	5	23	16	8	6	15	10	12	8
81	79	65	70	80	66	68	69	72	82	78	77	68
41	40	46	43	41	36	38	45	44	50	46	29	68
42	36	18	27	40	32	28	32	34	62	56	26	41
6	5	7	4	6	3	11	2	4	2	2	13	30
n	n	n	n	n	n	n	n	n	n	n	ARBF	n
0.362	0.242	0.350	0.198	0.274	0.320	0.356	0.378	0.260	0.0183	0.0179	0.250	0.202
									<0.03	0.05		
									17	5		
Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative Gp91p	Negative *DOC deficiency*

(questions 1 and 2) were strong indicators for PIDs. Four patients had PIDs that were undetected by the ESID warning sign questions: 2 belonged to the group of 35 patients with gastrointestinal symptom concerns, whereas the other 2 belonged to the group of 1,638 patients with urticaria or angioedema.

Although infections are the hallmark of immunodeficiency, some symptoms, including gastrointestinal symptoms, may be less pronounced on first admission. In contrast, gastrointestinal disease may be the first symptom of an underlying immunodeficiency and should be considered in patients with intractable diarrhea and malabsorption.[18]

Chronic noninfectious diarrhea and/or symptoms of inflammatory bowel disease are not covered by the ESID warning signs for adult PIDs. The gastrointestinal tract is the largest lymphoid organ, and intestinal diseases are common among immunodeficient patients. In fact, approximately half of patients with immunodeficiencies have intestinal diseases.[18] In this study, colonoscopies for the 2 patients with gastrointestinal concerns did not indicate classic inflammatory bowel disease; therefore, biopsies were performed. Follicular lymphoid hyperplasia was observed in the histopathologic examination, which is present in approximately half of biopsy specimens from patients with CVID-associated enteropathy.[19]

Similarly, 2 of 1,618 patients with angioedema were diagnosed as having hereditary angioedema, a subgroup of PID.[20] We could not conclude that dermatologic concerns, such as urticaria or angioedema, need to be considered in the screening of PIDs; however, in some PIDs, including hereditary angioedema, infections are not the main clinical presentation.

Most PID screening protocols are designed for pediatric patients; however, most the pediatric models have been tested, and the results are controversial.[8,21,22] In adults, 6 ESID warning signs are commonly used to screen for PIDs, but to our knowledge, the utility of this screen has not been formally evaluated. Thus, this is the first study, to our knowledge, to evaluate the usefulness of the 6 ESID warning signs.

In conclusion, it is difficult to identify warning signs that are applicable worldwide because of differences in culture, medical systems, and the wealth of different countries. The ESID warning signs do not specify the need for symptoms to diagnose PIDs and do not include a comprehensive list of all signs and symptoms of PIDs.[8,22] As a result, more than infection-centric questions are needed to identify adult patients with immunodeficiencies.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.anai.2015.12.001.

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eTable 1
Responses to the 6 questions

Group	No. (%) of patients	Mean (Range)					
		Sensitivity, %	Specificity, %	PPV, %	NPV, %	PLR, %	NLR, %
Question 1. Four or more infections requiring antibiotics within 1 year (otitis, bronchitis, sinusitis, pneumonia)?							
All patients	3,510	7.79 (4.68–12.04)	99.94 (99.78–99.99)	90.00 (68.30–98.77)	93.90 (93.05–94.67)	127.75 (29.82–547.24)	0.92 (0.89–0.96)
Patients responding yes	231 (6.6)						
PID positive	18						
PID negative	213						
Patients responding no	3,279 (93.4)						
PID positive	2						
PID negative	3,277						
Question 2. Recurring infections or infection requiring prolonged antibiotic therapy?							
All patients	3,510	17.65 (10.23–27.43)	99.85 (99.66–99.95)	75.00 (50.90–91.34)	97.99 (97.47–98.43)	120.88 (44.96–325.00)	0.82 (0.75–0.91)
Patients responding yes	85 (2.4)						
PID positive	15						
PID negative	70						
Patients responding no	3,425 (97.6)						
PID positive	5						
PID negative	3,420						
Question 3. Two or more severe bacterial infections (osteomyelitis, meningitis, septicemia, cellulitis)?							
All patients	3,510	37.04 (19.40–57.63)	99.71 (99.47–99.86)	50.00 (27.20–72.80)	99.51 (99.22–99.72)	129.00 (58.52–284.39)	0.63 (0.47–0.84)
Patients responding yes	27 (0.8)						
PID positive	10						
PID negative	17						
Patients responding no	10						
PID positive	3,473						
Question 4. Two or more radiologically proven pneumonias within 3 years?							
All patients	3,510	36.00 (17.97–57.48)	99.68 (99.44–99.84)	45.00 (23.06–68.47)	99.54 (99.26–99.74)	114.05 (51.85–250.86)	0.64 (0.48–0.86)
Patients responding yes	25 (0.7)						
PID positive	9						
PID negative	16						
Patients responding no	3,485						
PID positive	11						
PID negative	3,474						
Question 5. Infection with unusual localization or unusual pathogen?							
All patients	3,510	13.16 (4.41–28.09)	99.57 (99.29–99.76)	25.00 (8.66–49.10)	99.05 (98.67–99.35)	30.46 (11.66–79.57)	0.87 (0.77–0.99)
Patients responding yes	38 (1.1)						
PID positive	5						
PID negative	33						
Patients responding no	3,472 (98.9)						
PID positive	15						
PID negative	3,457						
Question 6. Primary immunodeficiency disease in the family?							
All patients	3,510	18.18 (5.19–40.28)	99.54 (00.26–99.74)	20.00 (5.73–43.66)	39.64 (99.19–99.69)	39.64 (14.40–109.08)	0.82 (0.67–1.00)
Patients responding yes	22 (0.6)						
PID positive	4						
PID negative	18						
Patients responding no	3,488 (99.4)						
PID positive	16						
PID negative	3,472						

Abbreviations: NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value.