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Profile of the patients who present to immunology outpatient clinics because of frequent infections

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Abstract

Aim: We aimed to determine the rate of primary immune deficiency (PID) among children presenting to our immunology outpatient clinic with a history of frequent infections and with warning signs of primary immune deficiency.

Material and Methods: The files of 232 children aged between 1 and 18 years with warning signs of primary immune deficiency who were referred to our pediatric immunology outpatient clinic with a complaint of frequent infections were selected and evaluated retrospectively.

Results: Thirty-six percent of the subjects were female (n=84) and 64% were male (n=148). PID was found in 72.4% (n=164). The most common diagnosis was selective IgA deficiency (26.3%, n=61). The most common diseases other than primary immune deficiency included reactive airway disease and/or atopy (34.4%, n=22), adenoid vegetation (12.3%, n=8), chronic disease (6.3%, n=4) and periodic fever, aphtous stomatitis and adenopathy (4.6%, n=3). The majortiy of the subjects (90.5%, n=210) presented with a complaint of recurrent upper respiratory tract infection. PID was found in all subjects who had bronchiectasis. The rates of the diagnoses of variable immune deficiency and Bruton agammaglubulinemia (XLA) were found to be significantly higher in the subjects who had lower respiratory tract infection, who were hospitalized because of infection and who had a history of severe infection compared to the subjects who did not have these properties ($p<0.05$ and $p<0.01$, respectively). Growth and developmental failure was found with a significantly higher rate in the patients who had a diagnosis of severe combined immune deficiency or hyper IgM compared to the other subjects ($p<0.01$). No difference was found in the rates of PID between the age groups, but the diagnosis of XLA increased as the age of presentation increased and this was considered an indicator which showed that patients with XLA were being diagnosed in a late period.

Conclusions: It was found that the rate of diagnosis was considerably high (72.4%), when the subjects who had frequent infections were selected by the warning signs of PID. (Türk Ped Arş 2014; 49: 210-6)

Key words: Primary immune deficiency, bronchiectasis, frequent infections

Introduction

In infancy and childhood periods, antigens are introduced to the immune system and frequent infections occur because most pathogens are encountered for the first time. 6-8 upper respiratory tract infecton or 1-2 simple gastroenteritis attacks a year may occur especially in children attending kindergarten or school. This causes parents to feel anxious and refer to physicians and to unnecessary investigations of children, though it is usually a normal condition.

Conditions which lead to predisposition to infection as a result of congenital deficiency or insufficiency of one or more types of cells, cell receptors, cell binders, enzymes, proteins required for cell function, surface proteins which function in the immune system and enzyme and proteins in the complement system are collected under the title of primary immune deficiencies (PID). Better knowledge of diseases and studies conducted at molecular levels with the contribution of new methods developed shed light on the etiology of many primary immune deficiencies.

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Frequent infections are the most important finding leading to a diagnosis of PID. Underlying PID can be sometimes found in upper respiratory infections as well as in atypical and resistant infections. The Jeffrey Model Foundation devoted to diagnosis and treatment of PID defined 10 warning signs of primary immune deficiency conditions which included 8 upper respiratory tract infections a year, more than 2 severe sinus infections a year, inefficient antibiotic usage for longer than 2 months, a history of pneumonia more than two times a year, growth and developmental retardation, recurrent deep tisuue or organ abscesses, chronic fungal infection in the mouth or on the skin after the age of one year, requirement for intravenous antibiotic usage to cure infection, more than two infections localized in deep tissues and a familial history of PID (1).

A physician who examines a child with one of the signs mentioned above should absolutely keep the possibility of PID in mind. In the differential diagnosis, many different possibilities should be kept in mind including crowded family environment which leads to frequent infections, asthma, exposure to smoking, presence of chronic disease, nutritional deficiency, metabolic diseases and anatomical abnormalities. In this study, it was aimed to evaluate the rates of PID in children who had frequent infections and the relation between the severity of infection and the type of PID, to compare the findings of Turkish children and the children of the world and to determine the appropriate diagnostic and treatment flow path in patients presenting with a complaint of having frequent infections in the light of the information obtained.

Material and Methods

In our study, the files of a total of 232 children who were referred to the Division of Pediatric Immunology Outpatient clinic between January 1999 and October 2011 because of recurrent infections and were investigated in terms of primary immune deficiency and followed up were evaluated retrospectively.

The age, gender, age at the time of presentation, clinical properties, familial history, examination findings and laboratory findings of the patients were examined. In this context, consanguinity between the mother and father, familial history of immune deficiency, yearly numbers of upper respiratory tract infections, lower respiratory tract infections, otitis, sinusitis and urinary tract infections, history of other serious infections including meningitis/sepsis, history of hospitalization because of nosocomial infection, examination findings at the time of presentation, growth and developmental retardation, leukocyte and absolute lymphocyte counts, hemoglobin values, immunoglobulin levels, assessment of cellular immunity (CD3, CD4, CD8, CD19, CD20, CD16-56, HLA-DR), presence of gastroesophageal reflux, assessment of lung graphy and/or thoracal tomography, antibody response to vaccines containing protein, throat culture results, "purified protein derivative" (PPD) values and the diagnosis made as a result of all assessments and presence of additional diseases were recorded. The data of the patients were collected by using the records in the files in the pediatric immunology outpatient clinic.

Complete blood count and examination of peripheral smear were performed and absolute neutrophil counts were calculated, IgG, IgA, IgM, IgE and IgG subgroup, CD4, CD8, CD19, CD20, CD16-56 and HLA-DR (+) CD20 (-) levels were recorded. The values below 2 standard deviation (SD) for age were considered low (2).

The diagnoses of PID made as a result of investigations and after at least one year of follow-up were recorded. The diagnosis of primary immune deficiency was made according to the characteristics determined by the International Union of Primary Immunology Societies.

In children in whom primary immune deficiency was not found, the diagnoses other than PID including gastroesophageal reflux (GER), adenoid vegetation, chronic diseases and asthma were recorded. The children in whom no disease could be found were considered healthy.

Statistical analysis

Number Cruncher Statistical System (NCSS) 2007&Power Analysis and Sample Size (PASS) 2008 Statistical Software (Utah, USA) was used for statistical analyses. When assessing the study data, descriptive statistical methods (mean, standard deviation, frequency, percentage) were used and Chi-square test and Fisher's Exact test were used in comparison of the percentages of the groups. A p value of <0.05 was considered significant.

Results

The ages of the subjects included in the study ranged between 5 and 216 months (mean 52.87±42.82 months). 36.2% of the subjects (n=84) were female, 63.8% were (n=148) male. Familial PID was found in 15.5% of the children (n=36) (Table 1).

In the follow-up of the patients who presented to our outpatient clinic with a complaint of recurrent infections, it was found that 90.5% (n=210) had more than 8 upper respiratory tract infection a year, 38.8% (n=90) had 2 or more lower respiratory infection a year, 22.4% (n=52) had 2 or more sinusitis attacks, 29.7% (n=69) had 2 or more otitis attacks, 9.9% (n=23) had 2 or more urinary tract infection attacks (Table 2).

9.5% of the children (n=22) had a history of serious infection including meningitis and sepsis. 29.7% (n=69) had a history of hospitalization because of infection, while 70.3% (n=163) had no history of hospitalization.

Table 1. Descriptive properties of the subjects

	(n)	(%)
Age groups		
0-1 year	20	8.6
1-5 years	142	61.2
5-16 years	68	29.3
16 years and older	2	0.9
Gender		
Female	84	36.2
Male	148	63.8
Consangunity		
Yes	35	15.1
No	197	84.9
Familial history		
Yes	36	15.5
No	196	84.5

Physical examination, laboratory and endoscopic findings at the time of presentation are presented in Table 3.

Lung imaging findings, throat cultures and PPD values of the children are summarized in Table 4.

While 72.4% of the children (n=168) were diagnosed with PID, PID was not found in 27.6% (n=64) (Table 5).

No statistically significant difference was found in the rates of lower respiratory tract infection according to the diagnoses of selective IgA deficiency, transient hypogammaglobulinemia of infancy (THI), IgG subgroup deficiency, unclassified hypogammaglobulinemia, XLA, hyper IgM, severe combined immune deficiency (SCID), disorder of neutrophil number and function, hyper IgE and non-PID disease ($p>0.05$), whereas the rate lower respiratory tract infection was found to be significantly high in children diagnosed with common variable immune deficiency ($p<0.05$) (Table 6).

When the rates of upper respiratory tract infections alone were compared with the rates of upper respiratory tract infection associated with other infections in patients with primary immune deficiency, no statistically significant difference was found between the rates of upper respiratory tract infections according to the diagnoses of selective IgA deficiency, transient hypogammaglobulinemia of infancy (THI), IgG subgroup deficiency, unclassified hypogammaglobulinemia, hyper IgM, severe combined immune deficiency (SCID), disorder of neutrophil number and function, hyper IgE and non-PID disease ($p>0.05$). The rate of upper respiratory tract infection was found to be 26.9% in children with selective IgA deficiency, 23.1% in children with THI, 11.5% in children with IgG subgroup deficiency, 3.8% in children with unclassified hypogammaglobulinemia, 1.3% in children with disorder of neutrophil number and function and 33.3% in children in whom PID was not found. No case of upper respi-

Table 2. Frequency of complaints of the patients at presentation

	(n)	(%)
URTI	210	90.5
Sinusitis	52	22.4
Otitis	69	29.7
LRTI	90	38.8
UTI	23	9.9
Severe infection	22	9.5
Hospitalization	69	29.7

URTI: upper respiratory tract infection; LRTI: lower respiratory tract infection; UTI: urinary tract infection

Table 3. Physical examination, laboratory and endoscopic findings of the patients at presentation and their frequencies

		(n)	(%)
Growth and developmental retardation		26	11.2
Tonsillary hypertrophy		74	31.9
Postnasal drip		55	23.7
Hepatosplenomegaly		6	2.6
Lymphadenopathy		11	4.7
Gastroesophageal reflux (grade 2 and more)		24	12.2
Anemia	No	146	63.2
	Yes	85	36.8

Table 4. Results of lung graphies, throat cultures and PPD measurements of the subjects

	(n)	(%)
Lung graphy		
Normal	193	84.3
Infiltration	19	8.3
Bronchiectasis	8	3.5
Increased aeration	9	3.9
Growth in throat culture		
No growth	160	84.2
Bacterial growth	24	12.6
Fungal growth	6	3.2
PPD		
0 mm	62	41.6
5-15 mm	76	51
>15 mm	11	7.4

PPD: purified protein derivative

Table 5. Diagnoses of primary immune deficiency in the patients who presented with the complaint of frequent infections

	(n)	(%)
Selective IgA deficiency	61	26.3
THI	43	18.5
IgG subgroup deficiency	19	8.2
Unclassified hypogammaglobulinemia	13	5.6
X-linked agammaglubulinemia	9	3.9
Hyper IgM	4	1.7
CVID	10	4.3
SCID	1	0.4
Neutrophil count and function disorder*	6	2.6
Hyper IgE	2	0.9
Patients with no PID	64	27.6

CVID: common variable immune deficiency; SCID: severe combined immune deficiency; PID: primary immune deficiency; THI: transient hypogammaglobulinemia of infancy; *neutrophil count and function disorders include (Kostman) PIDs which progress with cyclic neutropenia and congenital neutropenia

Table 6. Frequency of lower respiratory infections by diagnoses

	Frequency of LRTI		
	LRTI + n (%)	LRTI – n (%)	p value
Selective Ig A deficiency	20 (22.2%)	41 (28.9%)	0.262
THI	15 (16.7%)	28 (19.7%)	0.560
IgA subgroup deficiency	7 (7.8%)	12 (8.5%)	0.855
Unclassified hypogammaglobulinemia	6 (6.7%)	7 (4.9%)	0.575
XLA	4 (4.4%)	5 (3.5%)	0.723
Hyper IgM	3 (3.3%)	1 (0.7%)	0.302
CVID	7 (7.8%)	3 (2.1%)	0.038*
SCID	1 (1.1%)	0 (0.0%)	0.388
Neutrophil count and function disorder*	3 (3.3%)	3 (2.1%)	0.680
Hyper IgE	0 (60.0%)	2 (1.4%)	0.523
Diagnoses other than PID	24 (26.7%)	40 (28.2%)	0.803

LRTI: lower respiratory tract infection; THI: transient hypogammaglubulinemia of infancy; XLA: Bruton agammaglobulinemia; CVID: common variable immune defiency; SCID: severe combined immune deficiency; PID: primary immune deficency

ratory tract infection alone was found in children who were diagnosed with hyper IgM, SCID and hyper IgE.

Upper respiratory tract infection alone was not found in children diagnosed with Bruton agammaglobulinemia; XLA was found with a rate of 5.3% in children who were diagnosed with URTI and other diagnoses in association and this rate was found to be statistically significantly higher compared to the children with a diagnosis of PID and in children in whom PID was not found ($p<0.05$).

Upper respiratory tract infection alone was not found in children diagnosed with common variable immune deficiency; the rate of CVID was found with a rate of 6.8% in children who were diagnosed with URTI and other diagnoses in association and this rate was found to be statistically significantly higher compared to the children with other PID diagnoses and in children in whom PID was not found ($p<0.05$).

Discussion

Primary immune deficiencies are a group of diseases which are characterized with disorders in the function of the immune system, increased sensitivity against infection and a predisposition to autoimmune diseases and malignancy (3).

The prevalence of primary immune deficiencies in the community ranges between 1/10 000 and 1/100 000 in developed countries. When all PIDs are considered, the prevalence is ½ 000 and 1/ 10 000 (3-6). Since consanguineous marriage occurs with a high rate of 25-35% in our country, it is reported that especially autosomal recessive PIDs are observed more frequently (3, 7).

While it has been estimated that the prevalence of PID excluding asymptomatic IgA deficiency is 1/10 000 worldwide, it ranges between 1/1 200 and 1/ 2 000 in recent publications (3-5). Yorulmaz et al. (8) reported the prevalence of SCID to be 1 in 10 000 live births in the region of Konya.

In our study, 61.2% of the patient presented at the age of 1-5 years. It is not surprising that patients with recurrent infections present most commonly at the age of 1-5 years considering attandence to kindergartens and nursery schools and the preschool period when play is the leading activity. 57.7% of the patients presenting with primary immune deficiency were the ones who presented at the age of 1-5 years. It has been predicted that 40 of these patients are diagnosed below the age of one, 40% are diagnosed at the age of 1-5 years, 15% are diagnosed at the age of 5-16 years and 5% are diagnosed in the adulthood (2). Since children who had frequent infections were included in our study, the rates of having a diagnosis of PID by age were found to be considerably different. In our clinic, most patients below the age of one are diagnosed by hospitalization in the infection ward because of sepsis, meningitis, pneumonia, organ abscess, chronic diarrhea or by suspicion because of abnormal phenotype (including DiGeorge syndrome, CHARGE syndrome) (9). Since healthy children also have frequent infections during the period of 1-5 years, this is a period during which the diagnosis of PID should not be missed.

In our study, the rate of the diagnosis of selective IgA deficiency increased as the age at presentation increased. Selective IgA deficiency is observed with a rate of 85-90% in the community and asymptomatic IgA deficiency is observed with a rate of 1/142-1/15 000 (10). The most commonly observed infections include recurrent sinopulmonary infections and gastrointestinal infections (11, 12). Transient hypogammaglobulinemia of infancy is defined as a IgG value below 2 SD of normal after 6 months, normal B cell count and reversal to normal up to the age of 2-3 years (13). Most patients are diagnosed at the age of 6-12 months (14). In our study, 60% of the patients presented at the age of 0-1 years. As the age at presentation increased, the rates of THI decreased. In our study, the rates of XLA increased, as the age at presentation increased. Bruton agammaglobulinemia is frequently manifested with recurrent lung infections, otitis media, sinusitis and gastrointestinal infections after the age of one year (15, 16).

The most common infection in the patients was upper respiratory tract infection with a rate of 90.5%. The most common type of infection has generally been reported to be pneumonia in patients with primary immune deficiency (17, 18). When a patient has a complicated infection including recurrent pneumonia, sepsis, meningitis or arthritis, he/she is usually referred by the physician to a further center with a suspicion of PID without presenting to a hospital with the complaint of recurrent infections. When the patients who had frequent URTI alone and the patients who had URTI and/or other system infections including URTI and/or LRTI, otitis, sinusitis, urinary tract infection, meningitis and sepsis were compared, no statistically significant difference was found in terms of having a diagnosis of selective IgA deficiency, THI, IgG subgroup deficiency, unclassified hypogammaglobulinemia, hyper IgM, SCID, disorder of neutrophil number and function and hyper IgE. However, no patient with URTI alone was found among XLA and CVID patients and the diagnosis was made with a history of serious infection including pneumonia, sepsis, osteomyelitis accompanying the history of URTI in these patients. PIDs found rarely in the community were found with a higher rate than expected; SCID which has a prevalence of 1/50 000 was found in 0.4 of 234 patients (n=1), hyper IgM which has a prevalence of 1/500 000 was found in 1.7% (n=4), congenital disorder of neutrophil number and function which has a prevalence of 1/1 000 000 was found in 2.6% (n=6), CVID which has a prevalence of 1/10 000-50 000 was found in 4.3% (n=10), XLA which has a prevalence of 1/100 000 was found in 3.9% (n=9), hyper IgE which is found very rarely was found in 0.9% (n=2). Although these are selected cases, these results are considerably frightful and an important clue in terms of the frequency of PID in our community. In patients who had a history of more than 2 lower respiratory tract infection attacks a year, the rate of having a diagnosis of CVID was found to be significantly higher compared to the other PID groups.

A history of consanguinity and familial history should be warning especially in terms of autosomal recessive, autosomal dominant and X-linked PIDs. In our study, history of consangunity was found with a rate fof 15.1% in all subjects. This rate was found to be 16% in the patients with primary immune deficiency and 12.5% in the patients who had no primary immune deficiency. No significant relation was found between a history of consanguinity and a familial history of PID in first degree relatives and the rates of PID. In some single-center studies conducted in Turkey, the rates of consanguineous marriage was found to be 37.5-40% in patients diagnosed with PID (19, 20).

In our study, PID was found in 72.4% of the patients (n=232). In similar studies, PID has been found with a rate of 8-48% (21, 22). In this study, the most common PIDs included selective IgA deficiency (26.3%), THI (18.5%), IgG subgroup deficiency (8.2%) and unclassified hypogammaglobulinemia (5.6%). Antibody deficiencies constitute approximately 60-70% of PID patients in the community (23). Most clinical immunology centers have published tha date related only with selected patients followed up with a diagnosis of PID and CVID constitues the great majority of antibody deficiencies in contrast to our study (21, 23, 24). The European Society for Immune Deficiencies (ESID) reported that the most common PID was CVID with a rate of 21% among 13 708 recorded PID patients in the data belonging to 2011 published recently (23). This was followed by selective IgA deficiency with a rate of 10.4%.

Serious infections including meningitis, sepsis or organ abscess are important findings of PIDs. The rates of serious infections were found to be high in the patients diagnosed with XLA, CVID and disorder of neutrophil number/function compared to the other groups. Considering that the numbers of patients wiht other PIDs with a severe course including hyper IgM, SCID and hyper IgE are limited in terms of statistical significance, it is not surprising that PIDs with a more severe course are found in severe infections.

In our patients, the rate of hospitalization because of infection was found to be 29.7%. The rate of hospitalization was found to be significantly lower in the patients diagnosed with selective IgA deficiency compared to the patients diagnosed with other PIDs. Selective IgA deficiency is asymptomatic with a rate of 85-90%, sinopulmonary infections occur frequently and severe infections requiring hospitalization is generally not expected (11).

11.2% of our patients had growth and developmental delay. Reda et al. (24) found the rate of growth and developmental delay to be 28% in patients with PID. In our study, the rates of having a diagnosis of hyper IgM and congenital disorder of neutrophil number and function were found to be higher in the patients with growth and developmental delay com-

pared to the other groups. Growth and developmental delay is observed in subjects with SCID, hyper IgM, enteropathy and frequent infections with delayed treatment. Although the number of patients was limited, growth and developmental delay was also found in patients with hyper IgM and disorder of neutrophil number/function. The fact that growth and developmental delay was also found in patients who had no PID shows that frequent infections can be observed in situations where socioeconomical conditions are inadequate in addition to presence of nutritional disorder.

Cystic fibrosis, asthma, nutritional deficiencies, anatomical disorders, passive smoking, drugs which supress the immune system and periodical fever syndromes including familial mediteranean fever and PFAPA (periodical fever, adenitis, pharyngitis and aphtous ulcer) should be included in the differential diagnosis. Atopy, asthma and reactive airway disease were found in 34.4% of the children in whom PID was not found. The other conditions found included adenoid vegetation with a rate of 12.3%, chronic diseases with a rate of 4% and PFAPA in three patients. Yamohammadi et al. (21) investigated 213 patients who were referred with suspected PID and did not found PID in 52% of them. Asthma, allergy, autoimmune diseases, systemic lupus erythematosus, inflammatory bowel diseases and familial mediteranean fever constituted the cases in which PID was not found. No morbidity was found in 11.6% of the children with a complaint of frequent infections.

Association of selective IgA deficiency and atopy has been reported with a variable rate ranging between 13% and 58% (11, 25, 26). Increased aeration on lung graphy was found with a markedly higher rate in the patients with selective IgA deficiency compared to the other PIDs (44.4%). In our study, the rates of XLA, hyper IgM, CVID and hyper IgE were found to be higher in the subjects who were found to have bronchiectasia on lung graphy compared to the other PIDs and the patients in whom no PID was found. Though bronchiectasia is found more frequently in CVID and XLA (35-65%), it is a complication which has long been known to be related with PIDs (27, 28). The diagnosis of hyper IgE was found with a higher rate in the patients who had infiltration on lung graphy. In hyper IgE syndrome, recurrent cutaneous infections caused especially by S. aureus, S. pneumoniae and H. influenzae and lung infections and pneumatocel are obsered frequently (29, 30).

Gastroesophageal reflux also leads to recurrent upper and lower respiratory tract infections and should be absolutely investigated (31, 32). In our study, the frequency of GER was found to be 12.2% in all patients.

Throat culture remained negative in 84.2% of our patients. Pathogenic bacteriae were grown with a rate of 12.6% and candida was grown with a rate of 3.2%. The rate of having a diagnosis of CVID was found to be high in the patients in whom candida was grown in throat culture.

In our study, the rate of patients with hepato-splenomegaly did not reach statistical significance in terms of the diagnosis of PID.

When all data were considered, it was found that the rates of PID were as high as 72%, the diagnosis of PID was delayed, 90% of the subjects presented with a complaint of frequent upper respiratory tract infection and a diagnosis of severe PID could be made even in these subjects, especially patients with bronchiectasia should be evaluated with a high level of suspicion and physicians ignored immune deficiencies. Our study demonstrated the necessity of raising awareness of PID in the community and among physicians.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University Cerrahpaşa Faculty of Medicine.

Informed Consent: Because the study was conducted retrospectively and the patients' records were disclosed, the informed consent was not taken.

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