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Orginal Article

Retrospective evaluation of patients with humoral immune deficiency

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Abstract

Aim: Patients, who were being followed up for the last 10 years by Pediatric Immunology unit of the Faculty of Medicine at Erciyes University, were evaluated retrospectively in order to contribute toward the early diagnosis and the treatment of patients with humoral immunodeficiency.

Material and Methods: 412 patients with humoral immunodeficiency were evaluated retrospectively. Patients' age, gender, consanguineous marriages, family history of immune deficiency or similar diseases were studied at the time of complaints and diagnosis.

Results: Humoral immune deficiency was found among 412 out of 536 (76.8%) patients, who were being followed up because of primary immune deficiency. Although the average age of patients at the time of diagnosis was 48.9±4.6 months, the average age was 28.6±33.4 months at the start of complaints. Transient hypogammaglobinemia of infancy was observed the most among patients (50.5%), followed by IgA deficiency (28.4%), hypogammaglobinemia (6.8%), IgA +IgM deficiency (3.6%), IgG subclass deficiency (3.2%), Common variable immunodeficiency (2.4%), Bruton disease (1.2%), and hyper IgM syndrome (0.5%) respectively. IVIG replacements were given regularly to patients who were diagnosed with either hypogammaglobinemia, CVID, Bruton disease and hyper IgM.

Conclusions: In patients with recurrent infections, we need to certainly consider immune deficiency diseases first. Also, we need to be aware of the fact that humoral immune deficiency would relatively be diagnosable and treatable in most of these diseases. Finally,we need to educate the public about the role of marriages among relatives in order to decrease the frequency of these diseases.

Keywords: Humoral Immunodeficiency; Marriage Among Relatives; Recurrent Infections.

INTRODUCTION

Immunodeficiencies are heterogeneous disorders manifesting as a result of abnormalities in one or more components of the immune system, and usually characterized with susceptibility against infections (1). One of the most frequent conditions among primary immunodeficiencies is humoral immunodeficiencies which are characterized with severe decrease in all serum immunoglobulins accompanied by the low number or lack of B cells (2). Immune functions should be assessed in an individual who is showing a sign of a specific immune disorder, or is observed to have unusual, chronic or recurrent infections (3). Other than predisposition to infections, predisposition to autoimmune diseases and malignancies also occurs in immune system diseases (4). Primary immunodeficiency diseases are a group of heterogeneous diseases characterized with hereditary disorders of one or more components of the immune system. To date, more than 150 primary immunodeficiency diseases were identified (5). These diseases or syndromes are grouped based on the immunological mechanisms responsible for key clinical and laboratory findings (6).

According to registries such as ESID and LAGID, the most common immunodeficiency disease is antibody deficiencies. The most frequent one among these with the prevalence of 20% is common variable immunodeficiency (2).

The most frequent primary immunodeficiency group is impaired antibody production. Absence or function abnormalities of B-cells result in decreased immunoglobulin production and antibody deficiency. These deficiencies lead to bacterial infections, particularly otitis, sinusitis, gastroenteritis and pneumonia. As maternal antibodies decrease after the first 6 months of life, recurrent infections start to develop (7-9).

Bruton's disease, also known as X-linked agammaglobulinemia, usually starts 5-6 months after birth and characterized with recurrent pyogenic infections. Blood IgG level is decreased. B-lymphocytes cannot be detected in peripheral blood. X-linked and Autosomal recessive (OR) forms have been identified (10).

Common variable immunodeficiency (CVID) has a heterogeneous clinical presentation can be seen at all ages, and is characterized with recurrent bacterial

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infection, hypogammaglobinemia, impaired antibody responses despite the presence of B-cells, normal or near-normal T-cell immunity (11).

Hyper IgM syndrome has X-linked and autosomal recessive forms. In X-linked forms, CD40 ligand deficiency or impairment is present; and in autosomal forms, CD40-activated cytidine deaminase (AID) or uracil-DNA glycosylase (UNG) defects are present (12).

Isolated IgG subgroup deficiency is defined as the deficiency of one or several subgroups together with the normal or near-normal total IgG levels (2).

Selective immunoglobulin A deficiency is the most frequent primary antibody deficiency. In patients over four years old, if serum IgA level is less than 0.07 g/dL, and Ig G and IgM levels are normal, the diagnosis of selective immunoglobulin A deficiency is made (9).

Transient hypogammaglobinemia of infancy; prolongation of the physiological hypogammaglobinemia period which is normally seen between the first 3 and 6 months of life is defined as transient hypogammaglobinemia (THI) (9).

MATERIAL and METHODS

In this study, upon the approval of ethics committee of Erciyes University, Faculty of Medicine, the records of the patients who were being followed-up and treated with the diagnosis of humoral immunodeficiency between March 2000 and March 2010 in Erciyes University, Faculty of Medicine, Pediatric Immunology Division were retrospectively evaluated. The data for the patients regarding the age of diagnosis and onset of complaints, sex, medical history containing the previous illnesses, and family history including consanguineous marriage, familial history of immunodeficiency, and the history of the loss of a child due to a similar reason were examined. Laboratory test results including blood count, absolute lymphocyte, absolute neutrophil, eosinophil counts, serum immunoglobulin levels, peripheral blood lymphocyte subgroups results were recorded. Treatment and follow-up approaches applied to the patients, complications developed during their follow-up, and if present, the causes of death were recorded.

Following criteria were sought for transient hypogammaglobinemia in patients with the history of recurrent infection.

1- Patients at the age of ≤ 5 years at admittance

2- Serum levels of one or more major Igs (IgG,A,M) being less than 2 SDs than the levels normal for age

3- Cellular immunity being intact, absence of other immunodeficiency syndromes using clinical findings and laboratory workup

Patients who are meeting these criteria were evaluated as hypogammaglobinemia.

Bruton's disease diagnosis was made based on ESID criteria (1). In male patients, the diagnosis was made if CD19+ lymphocytes are less than 2%, at least one of the following criteria is present; recurrent bacterial infections within the first 5 years of life, serum IgG, IgM and IgA levels being less than 2 SDs of the normal levels for that age, absence of isohemagglutinin; impaired antibody response to vaccines, and by ruling out the other causes of hypogammaglobinemia. In case the patient is female, or agammaglobulinemia diagnosis was made. Isolated IgG subgroup diagnosis was made if one or more IgG subgroup levels are less than 2 SDs than the levels normal for that age. IgA deficiency diagnosis was made if IgA level is less than 2 SDs of the reference values identified for that age while serum IgM and IgG levels are normal. Patients with serum IgA level of <7 mg/dL were regarded as selective IgA deficiency. IgM deficiency diagnosis was made if IgM level is less than 2 SDs of the reference values identified for that age while serum IgA and IgG levels are normal. Patients with serum IgM level of <5 mg/dL were regarded as selective IgM deficiency, and CVID diagnosis was made based on ESID criteria (2).

The diagnoses were based on the conditions that at least one or two of the serum immunoglobulin (IgG, A and M) levels being less than 2 SDs than the normal levels for that age, low pneumococcus antibody response and presence of B lymphocytes in peripheral blood, as well as the ruling out of other hypogammaglobinemia causes.

Hyper IgM syndrome diagnosis was made if IgM level is normal or high while IgG A and E levels are low.

Statistical Analysis

Statistical evaluation was performed using "SPSS for Windows, 16.0, SPSS inc, U.S.A" software. For the patients' characteristics and results, descriptive statistical evaluation was performed. Results were expressed as mean ± standard deviation.

RESULTS

Records for a total of 536 patients who were being followed-up and treated with the diagnosis of primary immunodeficiency (PID) for 10-year period between March 2000 and March 2010 by Erciyes University, Faculty of Medicine, Pediatrics Department, Pediatric Immunology Division were obtained. 412 of these patients (76.8%) were detected to be diagnosed with humoral immunodeficiency. 237 of the patients (57.5%) were males, and 175 (42.5%) were females. Male/Female ratio was found to be 1.35. Demographic characteristics of the patients are shown in (Table 1).

The mean age at diagnosis for the patients was 48.9±44.6 months, the diagnosis age ranged from 2 months to 210 months. The mean age at onset of the complaints for the patients was 28.6±33.4 months, the age of onset of the complaints ranged from 1 month to 180 months. The distribution of symptoms to admit the outpatient clinic mostly consisted of recurrent infections (Table 2).

For the patients, recurrent pneumonia was detected in 24.8%, recurrent otitis media in 19.9%, sinusitis in 17%, asthma signs in 13.6%, chronic diarrhea 3.2%, urinary tract infection (UTI) in 2.9%, allergic and infectious skin signs in 2.9%, lymphadenopathy in 2.2%, moniliasis in 2.4%, oral aphthae in 2.2%, bronchiectasis in 1.5%, hepatomegaly in 1%, and other severe infections (meningitis, encephalitis, sepsis, septic arthritis, osteomyelitis sepsis) in 1%. Blood counts and immunoglobulin levels of the patients are shown in (Table 3).

Table 1. Demographic characteristics of the patients

N = 412	
Diagnosis age, month mean ± SD, (min-max)	48.9 ± 44.6 (2-210)
The age of onset of the complaints, month mean ± SD, (min-max)	8.6 ± 33.4 (1-180)
Sex, n (%)	
Male	237 (57.5%)
Female	175 (42.5%)

Table 2. The distribution of patients' complaints at admittance

Complaint at admittance	n	(%)
Pneumonia	102	24.8
Otitis media	82	19.9
Sinusitis	70	17
Asthma/Bronchitis/Bronchiolitis	56	13.6
Chronic diarrhea	13	3.2
Growth retardation	12	2.9
Urinary tract infection	12	2.9
Skin complaints (atopy, eczema, skin infection)	12	2.9
Lymphadenomegaly	11	2.7
Moniliasis	10	2.4
Oral aphthae	9	2.2
Bronchiectasis	6	1.5
Hepatomegaly	4	1
Other (meningitis, encephalitis, sepsis, septic arthritis, osteomye-litis)	5	1
No complaints	8	1.9

Table 3. Blood parameters and Ig values of the patients

Hemoglobin, gr/dL mean ± SD, (min-max)	12.6 ± 1.4 (6.0-16.6)	Ig M, mg/dL mean ± SD, (min-max)	85 ± 58 (3.75-511)
Leukocyte, /mm3 mean ± SD, (min-max)	9847 ± 3972 (2510-34000)	Ig E, IU/ml mean ± SD, (min-max)	47 ± 143 (0-1870)
Absolute lymphocyte count, /mm3 mean ± SD, (min-max)	3897 ± 2778 (300-38550)	Ig G1, mg/L mean ± SD, (min-max)	603 ± 323 (24-1980)
Absolute neutrophil count, /mm3 mean ± SD, (min-max)	5011 ± 3360 (500-22150)	Ig G2, mg/L mean ± SD, (min-max)	162 ± 137 (5.7-767)
Ig G, mg/dL mean ± SD, (min-max)	729 ± 481 (265-3850)	Ig G3, mg/L mean ± SD, (min-max)	62 ± 85 (6.6-951)
Ig A, mg/dL mean ± SD, (min-max)	32 ± 47 (0-716)	Ig G4, mg/L mean ± SD, (min-max)	20 ± 34 (0.1-240)

Consanguineous marriage between parents was detected in 29.9% of the patients (n:123). 4.6% of the spouses (n:19) were first degree relatives, 9.2% (n:38) were second degree relative, and 16% (n:66) were third degree relatives. Twenty-five (6.1%) patients had the history of sibling death. Fourteen (3.4%) patients were detected to have familial history of immunodeficiency. Thirty-four (8.3%) patients were detected to have the body weight of <3 percentile, and 27 (6.6%) patients to have the height of <3 percentile. The distribution of the patients by humoral immune deficiency is shown in (Table 4).

Table 4. Distribution of the patients by humoral immune deficiency

Diagnosis	n	%	Female (n)	Male (n)
Transient hypogammaglobinemia	208	50.5	82	126
Ig A Deficiency	117	28.4	60	57
Hypogammaglobinemia	28	6.8	14	14
Ig A + Ig M Deficiency	15	3.6	8	7
Ig M Deficiency	14	3.4	3	11
Ig G subgroup deficiency	13	3.2	6	7
Common variable immunodeficiency (CVID)	10	2.4	2	8
Bruton's Disease	5	1.2	-	5
Hyper Ig M syndrome	2	0.5	-	2

The characteristics of patients with transient hypogammaglobinemia (Table 5); among patients with transient hypogammaglobulinemia of infancy which is the most common humoral immunodeficiency, 126 (60.6%) were males, 82 (39.4%) were females, and M/F ratio was 1.5. The diagnosis age varied between 6 months and 48 months, and the mean was 25.8 ± 18.0 months. Main complaints at admittance of the patients were recurrent otitis in 27.9% (n:58), pneumonia 26.9% (n:56), asthma findings in 11.5% (n:24) and sinusitis in 9.1% (n:19).

Growth was detected in blood, urine, throat, feces cultures taken under proper conditions from 40 (19.2%) THI patients. Main organisms to grow were E.coli in 10.6% (n:20), Proteus in 2.4% (n:5), S.pneumonia in 1.0% (n:2), H.influenza in 1.0% (n:2), K.pneumonia in 1.0% (n:2), Giardia in 1.0% (n:2), Enterococcus in 1.0% (n:2).

Table 5. Blood parameters and Ig values of the THI patients

Hemoglobin, gr/dL mean ± SD, (min-max)	12.1 ± 1.2 (6.0-16.3)	Ig M, mg/dL mean ± SD, (min-max)	77 ± 42 (4-393)
Leukocyte, /mm3 mean ± SD, (min-max)	10268 ± 3697 (4020-31570)	Ig E, IU/ml mean ± SD, (min-max)	27 ± 59 (0-513)
Absolute lymphocyte count, /mm3 mean ± SD, (min-max)	4305 ± 2414 (500-22150)	Ig G1, mg/L mean ± SD, (min-max)	502 ± 243 (122-1600)
Absolute neutrophil count, /mm3 mean ± SD, (min-max)	54863 ± 3354 (500-22150)	Ig G2, mg/L mean ± SD, (min-max)	135 ± 127 (7-767)
Ig G, mg/dL mean ± SD, (min-max)	506 ± 242 (177-2660)	Ig G3, mg/L mean ± SD, (min-max)	51 ± 22 (10-422)
Ig A, mg/dL mean ± SD, (min-max)	32 ± 22 (4-149)	Ig G4, mg/L mean ± SD, (min-max)	18 ± 11 (0-207)

The characteristics of patients with immunoglobulin A deficiency (Table 6); among patients with immunoglobulin A deficiency which is the second most common humoral immunodeficiency, 126 (60.6%) were males, 82 (39.4%)

were females, and M/F ratio was 1.5. The diagnosis age varied between 6 months and 48 months, and the mean was 25.8 ± 18.0 months. Main complaints at admittance of the patients were recurrent otitis in 27.9% (n:58), pneumonia 26.9% (n:56), asthma in 11.5% (n:24) and sinusitis in 9.1% (n:19). A total of 18 patients had growth in their cultures. Main organisms to grow were E.coli in 3.4% (n:4), and P.aureginosa in 1.7% (n:2).

Table 6. Blood counts and Ig characteristics of the patients with Immunoglobulin A deficiency

Hemoglobin, gr/dL mean ± SD, (min-max)	12.2 ± 1.4 (7.6-16.6)	Ig M, mg/dL mean ± SD, (min-max)	111 ± 56 (22-493)
Leukocyte, /mm3 mean ± SD, (min-max)	9520 ± 3578 (2510-25000)	Ig E, IU/ml mean ± SD, (min-max)	78 ± 205 (0-1870)
Absolute lymphocyte count, /mm3 mean ± SD, (min-max)	3402 ± 1514 (710-8500)	Ig G1, mg/L mean ± SD, (min-max)	829 ± 306 (118-1410)
Absolute neutrophil count, /mm3 mean ± SD, (min-max)	5302 ± 3106 (800-15650)	Ig G2, mg/L mean ± SD, (min-max)	224 ± 149 (10-627)
Ig G, mg/dL mean ± SD, (min-max)	1191 ± 531 (32-3850)	Ig G3, mg/L mean ± SD, (min-max)	74 ± 119 (13-951)
Ig A, mg/dL mean ± SD, (min-max)	14 ± 12 (0-53)	Ig G4, mg/L mean ± SD, (min-max)	21 ± 29 (0-174)

The characteristics of patients with hypogammaglobinemia (Table 7); out of a total of 28 patients with hypogammaglobinemia which is the third most common humoral immunodeficiency, 14 (50%) were females, and 14 (50%) were males. F/M ratio was 1. The diagnosis age varied between 6 months and 210 months, and the mean was 83.4 ± 66.8 months. Main complaints at admittance of the patients were recurrent pneumonia in 39.3% (n:11), otitis in 14.3% (n:4), and sinusitis in 10.7% (n:3). Growth was detected in blood, urine, throat, feces cultures taken under proper conditions from 39.3% of the patients detected to have hypogammaglobinemia. A total of 11 patients had growth in their cultures. Main organisms to grow were E.coli in 7.1% (n:2), S.aureus in 7.1% (n:2), and C. Albicans in 7.1% (n:2). The characteristics of patients with immunoglobulin A and M deficiency (Table 8); immunoglobulin A and M deficiency is ranked as the fourth among all humoral immunodeficiencies, and out of a total 15 patients, 8 (53.3%) were females, and 7 (46.7%) were males. F/M ratio was 1.1.

The age of diagnosis varied from 8 months to 168 months, and the mean age of diagnosis was 66±48.4. The main complaints at admittance of the patients were recurrent pneumonia in 33.3% (n: 5), sinusitis in 20% (n:3) and otitis 13.3% (n:2).

The characteristics of the patients with immunoglobulin M deficiency; out of 14 patients who were detected to have Ig M deficiency which is ranked as the 5th humoral immunodeficiency among patients, 11 (78.6%) were males, 3 (21.4%) were females. M/F ratio was 3.6. The diagnosis age varied between 12 months and 122 months, and the mean was 54.5 ± 30.5 months. Main complaints at admittance of the patients were recurrent pneumonia in 28.6% (n:4), otitis in 28.6% (n:4), and sinusitis in 14.3% (n:2). E.coli growth was detected in the urine culture taken under proper conditions from only one patient detected to have immunoglobulin M deficiency.

Table 7. Blood counts and Ig characteristics of the patients detected to have hypogammaglobinemia

Hemoglobin, gr/dL mean ± SD, (min-max)	11.7 ± 2.1 (7.0-15.9)	Ig M, mg/dL mean ± SD, (min-max)	63 ± 49 (5-183)
Leukocyte, /mm3 mean ± SD, (min-max)	10102 ± 6917 (4240-34000)	Ig E, IU/ml mean ± SD, (min-max)	41 ± 54 (4-213)
Absolute lymphocyte count, /mm3 mean ± SD, (min-max)	3461 ± 2662 (300-10660)	Ig G1, mg/L mean ± SD, (min-max)	368 ± 80 (58-790)
Absolute neutrophil count, /mm3 mean ± SD, (min-max)	5466 ± 4734 (1640-22150)	Ig G2, mg/L mean ± SD, (min-max)	141 ± 107 (30-355)
Ig G, mg/dL mean ± SD, (min-max)	5466 ± 4734 (1640-22150)	Ig G3, mg/L mean ± SD, (min-max)	141 ± 107 (30-355)
Ig A, mg/dL mean ± SD, (min-max)	42 ± 45 (6-222)	Ig G4, mg/L mean ± SD, (min-max)	14 ± 20 (1-85)

Table 8. Blood counts and Ig characteristics of the patients with Immunoglobulin A and M deficiency

Hemoglobin, gr/dL mean ± SD, (min-max)	12.5 ± 1.8 (8.6-14.5)	Ig M, mg/dL mean ± SD, (min-max)	44 ± 15 (22-74)
Leukocyte, /mm3 mean ± SD, (min-max)	7683 ± 3269 (2900-14750)	Ig E, IU/ml mean ± SD, (min-max)	717 ± 205 (356-953)
Absolute lymphocyte count, /mm3 mean ± SD, (min-max)	3490 ± 1928 (1250-8800)	Ig G1, mg/L mean ± SD, (min-max)	717 ± 205 (356-953)
Absolute neutrophil count, /mm3 mean ± SD, (min-max)	3428 ± 1755 (580-8150)	Ig G2, mg/L mean ± SD, (min-max)	123 ± 45 (60-205)
Ig G, mg/dL mean ± SD, (min-max)	861 ± 304 (341-1440)	Ig G3, mg/L mean ± SD, (min-max)	14 ± 10 (7-33)
Ig A, mg/dL mean ± SD, (min-max)	23 ± 22 (6.4-83.5)	Ig G4, mg/L mean ± SD, (min-max)	14 ± 10 (7-33)

The characteristics of the patients with immunoglobulin G subgroup deficiency (Table 9); out of 13 patients who were detected to have Ig G subgroup deficiency which is ranked as the 6th humoral immunodeficiency among patients, 7 (53.8%) were males, 6 (46.2%) were females. M/F ratio was 1.1. The diagnosis age varied between 6 months and 144 months, and the mean was 46.6 ± 40.5 months. Main complaints at admittance of the patients were recurrent pneumonia in 46.2% (n:6), sinusitis in 38.5% (n:5), and bronchiectasis in 15.4% (n:2). S.Pneumonia and H.influenza growth was detected in blood and throat culture, respectively, taken under proper conditions from three patients detected to have Ig G subgroup deficiency.

Table 9. Blood counts and Ig characteristics of the patients detected to have Ig G subgroup deficiency			
Hemoglobin, gr/dL mean ± SD, (min-max)	12 ± 1.4 (8.8-14.4)	Ig M, mg/dL mean ± SD, (min-max)	140 ± 68 (28-267)
Leukocyte, /mm3 mean ± SD, (min-max)	9950 ± 4700 (5800-22900)	Ig E, IU/ml mean ± SD, (min-max)	171 ± 437 (0-1590)
Absolute lymphocyte count, /mm3 mean ± SD, (min-max)	6040 ± 10060 (300-38550)	Ig G1, mg/L mean ± SD, (min-max)	694 ± 470 (213-1980)
Absolute neutrophil count, /mm3 mean ± SD, (min-max)	5370 ± 4560 (1630-18150)	Ig G2, mg/L mean ± SD, (min-max)	103 ± 159 (5-556)
Ig G, mg/dL mean ± SD, (min-max)	1128 ± 488 (561-2070)	Ig G3, mg/L mean ± SD, (min-max)	82 ± 78 (6-290)
Ig A, mg/dL mean ± SD, (min-max)	165 ± 183 (6-716)	Ig G4, mg/L mean ± SD, (min-max)	45 ± 73 (1.4-240)

The characteristics of the patients with common variable immunodeficiency (Table 10); out of 10 CVID patients, 8 (80%) were males, 2 (20%) were females. M/F ratio was 4. The diagnosis age varied between 2 months and 180 months, and the mean was 129 ± 63 months. Main complaints at admittance of the patients were recurrent pneumonia in 40% (n:4), bronchiestasis in 20% (n:2), and sinusitis, otitis and growth retardation in patient each (10%). In the blood, urine, feces and throat cultures taken under proper conditions from three patients who were detected to have common variable immunodeficiency, H.influenza growth was detected in 3 patients (30%), C.albicans in 2 (20%) and S.aureus in 1 (10%).

Table 10. Blood counts and Ig characteristics of the patients with common variable immunodeficiency			
Ig M, mg/dL mean ± SD, (min-max)	11.5 ± 2 (8.4-14.9)	Ig M, mg/dL mean ± SD, (min-max)	24 ± 24 (3-65)
Ig E, IU/ml mean ± SD, (min-max)	10622 ± 3370 (4430-17710)	Ig E, IU/ml mean ± SD, (min-max)	7.6 ± 7.5 (0-24)
Ig G1, mg/L mean ± SD, (min-max)	2100 ± 1590 (750-5900)	Ig G1, mg/L mean ± SD, (min-max)	373 ± 282 (119-890)
Ig G2, mg/L mean ± SD, (min-max)	7380 ± 2890 (2200-10500)	Ig G2, mg/L mean ± SD, (min-max)	161 ± 118 (35-360)
Ig G3, mg/L mean ± SD, (min-max)	246 ± 124 (67-503)	Ig G3, mg/L mean ± SD, (min-max)	83 ± 156 (13-403)
Ig G4, mg/L mean ± SD, (min-max)	13 ± 8 (6-44)	Ig G4, mg/L mean ± SD, (min-max)	20 ± 25 (1.37-71)

The characteristics of Bruton's disease patients were seen (Table 11) in all 5 patients who were detected to have Bruton's disease which is ranked as 8th among patients with humoral immunodeficiency were males. The diagnosis age varied between 21 months and 36 months, and the mean was 26.6 ± 6 months. Main complaints at admittance of the patients were recurrent pneumonia in 40% (n: 2), otitis in 40% (n: 2), and bronchial asthma in 1 patient. In cultures taken under proper conditions from 2 Bruton's disease patients, H.influenza growth was detected in 1 patient (20%), and E.coli in 1 patient (20%).

Table 11. Blood counts and Ig characteristics of the patients with Bruton's disease			
Hemoglobin, gr/dL mean ± SD, (min-max)	11.8 ± 1.3 (9.8-13)	Ig M, mg/dL mean ± SD, (min-max)	14 ± 10 (7-30)
Leukocyte, /mm3 mean ± SD, (min-max)	8270 ± 4110 (3200-12900)	Ig E, IU/ml mean ± SD, (min-max)	11.3 ± 12.7 (0-31)
Absolute lymphocyte count, /mm3 mean ± SD, (min-max)	3340 ± 1800 (950-5800)	Ig G1, mg/L mean ± SD, (min-max)	510 ± 448 (197-1170)
Absolute neutrophil count, /mm3 mean ± SD, (min-max)	4280 ± 2850 (2010-8800)	Ig G2, mg/L mean ± SD, (min-max)	228 ± 115 (127-369)
Ig G, mg/dL mean ± SD, (min-max)	266 ± 210 (60-488)	Ig G3, mg/L mean ± SD, (min-max)	132 ± 222 (12-466)
Ig A, mg/dL mean ± SD, (min-max)	8 ± 4.3 (5.85-16)	Ig G4, mg/L mean ± SD, (min-max)	30 ± 32 (2-71)

The characteristics of hyper immunoglobulin M patients; hyper immunoglobulin M syndrome which is the least frequent among patients with humoral immunodeficiency was detected in 2 patients, and both of them were males. The age at diagnosis ranged from 5 months to 36 months. One patient admitted with the complaint of recurrent pneumonia and the other one with skin infections. Ig M levels of the patients were detected to be 381 and 511 mg/dL, respectively. In the blood cultures taken under proper conditions from three patients with hyper Ig M, H.influenza growth was detected in 1 (50%) patient, and E.coli in 1 (50%) patient.

DISCUSSION

The most common group among primary immunodeficiencies (PIDs) as a result of decrease in maternal antibodies after the first six months of life is antibody deficiencies. Being reported as 56.1% according to the ESID and LAGID registries, this rate was found to be higher in similar studies performed in Turkey (2,13,14).

In our study, out of 536 patients who were being followed up and treated with the diagnosis of PID for a period of 10 years, 412 (76.8%) were detected to have humoral immunodeficiencies. That might be due to the fact that our study is a single-center study and the number of patients is limited. Consanguineous marriage also particularly increase the incidence of OR diseases. In a study performed in Konya province in our country, the consanguineous marriage rate was found to be 37.5% (13). In our study, this rate was detected to be 29.9%. The most common one among our patients with immunodeficiency characterized with antibody deficiency was transient hypogammaglobinemia of infancy (50.5%). The incidence of this disease is not exactly known (15).

However, in two studies performed in our country, THI was reported to be between 12.5% and 37.9% (16,17). The reason for this rate being higher in our study might be the lack of clarity of the criteria regarding the disease.

Studies have reported that the disease is seen two-fold more in males than females (18). In our study, male/

female ratio was detected to be 1.5.

While THI may be asymptomatic, it may also cause recurrent infections. Usually, it is characterized with recurrent URTIs, bronchitis, pneumonia, sinusitis, otitis, gastroenteritis and urinary tract infections. In our patients, the most common recurrent infections were otitis (27.9%), pneumonia (26.9%), asthma (11.5%) and sinusitis (9.1%), and 1.9% of the patients did not show any symptom. Different from our results, Dalal et al. (19) reported meningitis in one patient.

Atopy and allergic problems are known to be higher in patients with THI than normal population. In the study by Yorulmaz A, findings such as asthma, allergic rhinitis and atopic dermatitis were found to be 35.8% of the patients (20). In our patients, asthma and allergic problems were less frequent due to the environmental characteristics of our region (11.5%).

For THI, supportive care and proper antibiotic therapy for the infections is enough. Tunç, A (20) in his placebo-controlled and randomized study, showed that use of Pelargonium sideoides extract in patients with upper respiratory tract infections resulted in considerable reduction in the frequency of nasal congestion and cough, and increased appetite.

IVIG replacement therapy is usually not necessary, but if adequate response to antibiotherapy could not be obtained in severe infections, it may be considered (21). IVIG replacement was not required in any of our patients.

The most common one among PIDs is IgA deficiency. In our study, it was detected to be the second most common among antibody deficiencies (28.4%). While in the literature, the prevalence of IgA deficiency is 1/300-700 when asymptomatic patients were also considered, as our study is not a prevalence study, we cannot speculate the prevalence of IgA deficiency in our region (22,23).

Majority of IgA deficiency patients are asymptomatic, however, studies have shown that respiratory system illnesses such as sinusitis and bronchopneumonia are seen in these patients (24). Main complaints at admittance of our patients were recurrent otitis (27.9%), pneumonia (26.9%), asthma findings (11.5%) and sinusitis (9.1%).

As blocking IgA antibodies are absent in IgA deficiency, increase in allergic reactions and thereby, allergic diseases such as asthma have been reported (25-27). In our series, 11.5% of the patients with IgA deficiency had asthma findings.

It has been reported that there is a close relationship between IgA deficiency and CVID, and patients who were previously being followed up for selective IgA deficiency develop CVID in the advancing years (28). In our study, none of the patients who were being followed up for IgA deficiency developed CVID later, and co-existence of these two diseases in a family was not detected.

CVID is a complex immunological disease with different clinical presentation and variety of immunologic disorders. The incidence of CVID vary between 1/25000 and 66000(13,29-32).

In our patients, the diagnosis age varied between 2 months and 180 months, and the mean was 129 ± 63 months. Cunningham-Rundles (33), in their study, reported this delay as 4 - 6 years in average. The reason for diagnosis delay in our patients is the fact that the physicians believe the hypothesis that immunodeficiencies are rare and do no perform timely workup.

Patients with CVID are predisposed to recurrent infections with encapsulated bacteria. They are the most important cause especially for respiratory tract infections, chronic pulmonary disease and bronchiectasis development. The progression of pulmonary damage may be avoided by regular IVIG replacement, antibiotherapy and respiratory physiotherapy. Also in our patients, the reason for admitting to hospital was usually pneumonia in 40% and bronchiectasis in 20%. CVID patients may also experience recurrent diarrhea attacks. While recurrent or persisting diarrhea and/or malabsorption may be related with infection, they can also be related with inflammatory bowel disease (29-32,34). Also, all of our patients had recurrent diarrhea at admittance, however, this complaint resolved after regular IVIG replacement.

Predisposition to autoimmune diseases and cancer is also known for this disease. To date, autoimmune disease or cancer was not detected in any of our patients. Cunninghan-Rundles et al. (33) reported a mortality rate of 22% in a period of 13 years. None of our patients who were followed-up and treated for CVID died. Early diagnosis and regular IVIG replacement therapy would reduce the mortality and morbidity in these patients.

If Bruton's disease or OR agammaglobulinemia which is seen in females is left untreated, it may cause severe morbidity and mortality. Many patients are exposed to recurrent otitis, sinusitis or pneumonia until the diagnosis is made (34-36). All of our patients with hypogammaglobinemia had the history of recurrent pneumonia, otitis, and recurrent sinusitis infection.

Ledarman et al. (32) reported that 45% of XLA patients develop a pulmonary disease after the age of 10. One of our patient with OR agammaglobulinemia had to be treated in intensive care unit three times due to alveolar proteinosis (37).

Hyper IgM syndrome is a disease which has X-linked and autosomal recessive forms. While IgG and IgA levels are very low, IgM levels may be normal or much more than normal (2,9,12). In our study, hyper IgM syndrome was detected in two patients, and both of them were males. The frequency of infections was reduced by regular IVIG replacement.

CONCLUSION

In conclusion, we can underline the facts that immunodeficiency diseases must be considered definitely in patients with recurrent infections, it should be known that more than half of these diseases are humoral deficiencies which can easily be diagnosed and treated, morbidities as a result of disease-induced recurrent infections can be avoided and the opportunity of early diagnosis and treatment can be given to the patients by promptly performing the necessary investigations when the immunodeficiency is suspected with adequate awareness upon the manifestation of the complaints, and the families and physicians should be informed about

kin marriages by recognizing the role of kin marriages in increase in the incidence of these diseases.

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