Primary immune deficiency disease awareness among a group of Turkish physicians

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Primary immunodeficiencies (PIDs) are a relatively common occurrence in countries where consanguineous marriages are widespread. A principal factor leading to misdiagnosis and ensuing complications can be the lack of knowledge and proper evaluation. The aim of this study was to assess PID awareness and the identification of diagnostic criteria leading to correct diagnosis. Seven hundred eighty-six questionnaires with 71 items were distributed to physicians attending the 41st National Congress of Pediatrics (2005) and to pediatric residents of two university hospitals from different cities in Turkey. The 217 completed questionnaires revealed that family history (91.2%), consanguineous marriages (87.1%), infant deaths (70.0%), persistent thrush (90.3%), hospitalization for recurrent cellulitis (70.5%), chronic diarrhea due to giardiasis (62.2%), recurrent oral aphthous lesions (58.5%), telangiectasia (82.0%), failure to thrive (78.8%), absence of tonsil tissue (74.7%), oculocutaneous albinism (73.7%), and resistant sinusitis (71.0%) were cited among important indicators of PID. However, neonatal tetany (77.9%), liver abscess (61.3%) and poliomyelitis following oral polio vaccination (51.2%) were not considered as related to PID. Although white blood cell (WBC) and differential were chosen as the preferred initial tests, leukocytosis and lymphopenia were also not judged as related to PID. More comprehensive pre/postgraduate education in PID appears to be necessary for physicians in Turkey.

Key words: primary immunodeficiency, awareness, questionnaire.

Primary immunodeficiencies (PIDs) are a group of diseases that cause susceptibility to infections, autoimmunity and malignancy. PIDs consist of more than 130 inherited conditions. They are estimated to occur from 1 in 10,000 to 1 in 2,000 live births[1]. The clinical spectrum of PID is highly variable[2]. The incidence of PIDs in Turkey is uncertain because of a lack of a national registry system. However, the high ratio of consanguineous marriages makes PID a relatively frequent condition. Pediatricians or residents of pediatric clinics are faced with patients with different complaints and signs. Simple laboratory tests are helpful in the screening and diagnosis of a large number of PID cases[3,4]. If initial laboratory tests are inconclusive, in the case of a suspected PID, further sophisticated tests are warranted.

Early diagnosis and treatment, before severe complications and tissue damage develop, have shown to improve both morbidity and mortality[5]. However, lack of awareness about immunodeficiency can cause misdiagnosis and severe complications.

The objective of this study was to assess PID awareness and the identification of diagnostic criteria leading to correct diagnosis.

Material and Methods

Seven hundred eighty-six questionnaires with 71 items were distributed to physicians attending

the 41st National Congress of Pediatrics (2005) and to pediatric residents of two university hospitals from different cities in Turkey. Two hundred seventeen completed questionnaires were evaluated.

Statistical Analysis

SPSS for Windows 11.5 was used for statistical analysis. Wilcoxon signed ranks test was used to test differences in terms of scores obtained before and after education. A p value <0.05 was considered significant.

Results

Fifty percent of the respondents were pediatricians and the rest were residents. Of total respondents, 81.8% believed that diagnosis of many of the PIDs can be confirmed by a few simple laboratory tests beginning with complete blood count (CBC) and differential, although 50.2% had never diagnosed a PID and 58.8% had never followed up a patient with PID.

Items of the questionnaire and responses are given in Table I.

Discussion

Primary immunodeficiency disorders are inherited disorders of the immune system. Many of them are single gene defects. Common PIDs include predominantly antibody deficiencies (PAD), combined T- and B-cell immunodeficiencies, other well-defined immunodeficiency syndromes, immune dysregulation diseases, phagocyte system defects, and complement deficiencies[2]. Seventy-eight of 118 PIDs classified by Notarangelo et al.[2] have autosomal recessive inheritance. In developing countries where the rate of consanguineous marriages is very high (up to 21% in some areas of Turkey)[6], PID frequently exhibits as an autosomal recessive disease. Therefore, pediatricians working in such countries should have a high awareness of PID.

The largest group of disorders for which the molecular defects have been well defined is combined immunodeficiencies. The most common clinical manifestations of these disorders are chronic diarrhea, failure to thrive, absence of secondary lymphoid tissues, persistent or recurrent respiratory infections, and persistent thrush, as well as opportunistic infections. Laboratory findings typically demonstrate severe lymphopenia ($<3000/mm^3$ in infancy, <1500 in older children) and depressed lymphoproliferative response to mitogens and anergy to candida skin test or PPD[7-9].

While many of the respondents thought that oral moniliasis (90.3%), failure to thrive (78.8%), and absence of tonsils (74.7%) are part of PID, 58% believed that a lymphocyte count of $2500/mm^3$ and a positive PPD test (90.3%) are not related to immunodeficiency. Thus, taken together, it is possible to assume that respondents have some information about severe combined immunodeficiency (SCID). However, while representing easily assessed laboratory data, the lower limit of the lymphocyte count according to age is not well known.

Predominantly antibody deficiencies (PAD) are the most common forms of PIDs, and they are caused by defects in B-cell differentiation and antibody production. Patients with antibody deficiencies often develop bacterial respiratory infections more than eight times a year[10]. Bronchiectasis can follow these frequent infections. They also suffer from chronic diarrhea due to Giardia and disseminated poliomyelitis after oral polio vaccination (OPV)[11]. Laboratory evaluation of antibody deficiencies can be done through the quantitative measurement of serum immunoglobulins, IgG subclasses (in selected patients), and the determination of specific antibodies to ABO blood group antigens, tetanus toxoid, and pneumococcal polysaccharide antigen. B-cell enumeration is also necessary for diagnosis[10]. Hypogammaglobulinemia (98.3%), sinusitis that is resistant to treatment (71.0%), bronchiectasis (63.1%), and chronic diarrhea due to Giardia (62.2%) were considered as part of an immunodeficiency while upper respiratory tract infections occurring six times a year (82.5%) and positive isohemagglutinin titers (80.2%) were not. However, about half of the respondents believed that disseminated poliomyelitis followed by OPV was not related to PIDs. The physicians have relatively sufficient knowledge about antibody deficiencies compared to combined immunodeficiencies.

Table I. Questionnaire Items and Responses

Which of the following medical histories can be a part of an immunodeficiency?		
	Yes (%)	No (%)
Persistent thrush	90.3	9.7
Hospitalization due to sepsis	18	82
Six upper respiratory tract infections (URIs)/year after day care attendance	17.5	82.5
Frequent urinary tract infection	21.2	78.8
Paralytic poliomyelitis after oral polio vaccine	48.8	51.2
Hospitalization for recurrent cellulitis	70.5	29.5
Lymphadenopathy on left supraclavicular region after BCG vaccination	21.7	78.3
Umbilical separation on 10th day of life	18.4	81.6
Recurrent aphthous stomatitis	58.5	41.5
Premature separation of primary teeth	12	88
Liver abscess	38.7	61.3
Delayed wound healing	68.7	31.3
Suppurative discharge of BCG vaccination site	44.7	55.3
Chronic diarrhea due to giardiasis	62.2	37.8
Neonatal tetany	22.1	77.9
Snoring	2.3	97.7
Which of the following family histories can be a part of an immunodeficiency?		
Consanguineous marriage	87.1	12.9
Death of a sibling in infancy	70	30
Family history of recent active pulmonary tuberculosis	10.1	89.9
Presence of a family member with congenital anomaly	27.2	72.8
Family history of connective tissue disease	15.7	84.3
Family history of autoimmune disease	48.8	51.2
Maternal asthma	13.4	86.6
Family history of immunodeficiency	91.2	8.8
Which of the laboratory tests should be chosen first in suspected PID?		
Biochemistry	11.5	88.5
Complete blood count, differential count	84.3	15.7
Serum immunoglobulin level	48.8	51.2
Isohemagglutinin titer	18.9	81.1
PPD	24	76
In vitro lymphocyte function tests	11.5	88.5
Nitroblue tetrazolium (NBT)	8.3	91.7
Which of the clinical signs could be a part of immunodeficiency		
Telangiectasia	82.0	18.0
Petechia	41,9	58.1
Hepatosplenomegaly	67.3	32.7
Gingivitis	46.5	53.5

Dermal scarring lesions	40.6	59.4
Generalized molluscum contagiosum	40.6	59.4
Failure to thrive	78.8	21.2
Short limb dwarfism	32.3	67.7
Suppurative adenitis	42.9	57.1
Oculocutaneous albinism	73.7	26.3
Absence of tonsils	74.7	25.3
Cervical lymphadenomegaly	24.4	75.6
Arthritis	20.3	79.7
Malar rash	19.4	80.6
Tetralogy of Fallot	11.1	88.9
Caput quadratum	8.3	91.7
Low-set ears, hypertelorism, hypoplastic mandible, fish mouth	69.6	30.4
Microcephaly	33.6	66.4
Hypertrophy of tonsil tissue	12.9	87.1
Diplopia	12.9	87.1
Abdominal distension	18.4	81.6
Syndactyly	13.8	86.2
Enlargement of thyroid gland	8.8	91.2
Dextrocardia	32.7	67.3
Resistant sinusitis	71.0	29.0
Which of the laboratory findings could be a part of PID?		
Total 2500/mm^3 lymphocyte count at 3 months of age	42.4	57.6
Thrombocytopenia	62.7	37.3
Total 1200/mm^3 neutrophil count at 8 months of age	66.2	31.8
Leukocytosis	17.1	82.9
Bronchiectasia	63.1	36.9
Positive isohemagglutinin titers	19.8	80.2
Positive NBT test	55.3	44.7
Positive PPD test	9.7	90.3
Giant granules in neutrophils	77.4	22.6
Aspergillus grown in pus culture	63.6	36.4
Positive total hemolytic complement (CH50)	85	15
Hypogammaglobulinemia	98.3	1.7

Questions were asked about some relatively common diseases in the group of "other well-defined immunodeficiency syndromes" like Wiskott-Aldrich syndrome (WAS), ataxia telangiectasia (AT) and Nijmegan breakage syndrome (NBS). Major clinical manifestations of WAS are eczema and petechia due to thrombocytopenia associated with small platelets[12]. AT, characterized by ataxia, often begins with the beginning of walking, followed by bulbar telangiectasia. Laboratory evaluation of AT reveals low serum IgA, IgE and IgG subclasses and elevated serum α fetoprotein level[3]. Microcephaly, facial dysmorphism and mental retardation are characteristics of an AT variant disease, NBS, which differs from AT with the absence of ataxia and normal α fetoprotein levels. Eighty-two percent of respondents believed telangiectasia is related to PID. Thrombocytopenia was considered a part

of PID, although petechia was not (58.1%). Similarly confusing results were also obtained for Di-George syndrome, which is clinically characterized by absent or small thymus, cardiac malformations, hypoparathyroidism – hypocalcemia, and facial dysmorphism. Neonatal tetany (77.9%) and defined facial dysmorphic signs (low-set ears, small mouth, hypertelorism) were accepted as a part of PID but tetralogy of Fallot was not (88.9%). It is possible to assume that respondents know some but not all components of the related syndromes.

Questions about Chediak-Higashi syndrome, one of the "diseases of the immune dysregulation" group, were answered correctly.

Typical clinical features of phagocyte defects are impetigo, cellulitis, suppurative adenitis, periodontitis, abscesses, and osteomyelitis caused by either bacteria (*Staphylococcus, Pseudomonas*) or fungi (*Candida, Aspergillus)* or parasites. Delayed separation of the umbilical cord and poor wound healing are its other distinctive characteristics. Disseminated nontuberculous mycobacterial infection in the absence of immune suppression is seen predominantly in patients with defects of the interferon (IFN)γ / interleukin (IL)-12 axis[4]. Laboratory findings include neutropenia and neutrophilia, negative nitroblue tetrazolium (NBT) and dihydro rhodamine (DHR) tests. Hospitalization for recurrent cellulitis (70.5%), poor wound healing (68.7%), neutropenia (66.2%), aspergillus grown in pus culture (63.6%), and positive NBT test (55.3%) were accepted as phagocyte immunodeficiency. But lymphadenomegaly after BCG vaccination on the left supraclavicular region (78.3%), liver abscess (61.3%), scarring esions of skin (59.4%), suppurative adenitis (57.1%), gingivitis (53.5%), and leukocytosis (82.9%) were not considered as a part of immunodeficiencies. Respondents showed confusion about the evaluation of phagocyte immunodeficiencies because of lack of proper information concerning major clinical features of these diseases together with some problems in the evaluation of laboratory tests such as NBT. 55.3% of the respondents thought the "positive NBT" test as a laboratory finding could be a part of PID. However, 91.7% of all the physicians did not choose NBT as a first-line test to conduct in the setting of a suspected PID. Thus, it is obvious that there is confusion in interpreting the NBT test. In fact, a positive test should be taken as normal while "negative NBT" should be evaluated as a sign of PID.

Complement component deficiencies (CCDs) are rare in the general population. CCDs often exhibit pyogenic infections particularly with encapsulated bacteria. Those with a deficiency of early components (C1, C4, C2) might also have similar infections but more commonly they develop autoimmune diseases like systemic lupus erythematosus (SLE). In the setting of membrane attack complex (MAC) components deficiency (C5, C6, C7, C8), the spectrum of infectious agents changes towards *Neisseria gonorrhoeae* or *N. meningitidis*[13]. A complement abnormality is screened by measuring the total hemolytic complement (CH50) activity. In our study, positive result for CH50 was considered as a part of PID.

Fortunately, before this article was written, a one-day intensive course regarding PIDs was arranged as a part of the 42nd National Congress of Pediatrics in Turkey. These very questionnaires were given to all attending doctors before and after the course. All the correct answers were accepted as 1 point. A significant increase in total points of the attendants was achieved afterwards compared to the initial evaluation done at the beginning of the course ($p<0.05$).

In conclusion, pediatricians living in countries where consanguineous marriages are widespread need to have a much greater awareness about PID. A more comprehensive pre/postgraduate education in PID appears to be necessary for physicians in Turkey.

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