Evaluation of Clinical and Laboratory Data in Patients with Recurrent Infections and Suspected Immunodeficiency

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Abstract

Introduction:
Frequent infections is among the most frequent clinical dilemmas for primary care physicians. Immunodeficiency disorders are a heterogeneous group of illnesses that predispose patients to the recurrent infections, autoimmunity and malignancies. The aim of this study is to evaluate the clinical and laboratory data collected for the final diagnosis of patients referred with recurrent infections and suspected immunodeficiency to a local immunodeficiency clinic.

Materials and Methods:
This epidemiological study was carried out between April 2010 to September 2012 at the Immunodeficiency Clinic of Mashhad-Iran. All patients with clinical manifestations of immunodeficiency who were referred to our clinic during this period of time were included in this study.

Results:
Forty one patients, aged between 10 months and 51 years, were evaluated. Eleven patients had a primary immunodeficiency, four cases had a secondary immunodeficiency, in three patients an underlying structural disease were found, eight patients were predisposed to recurrent infections as a result of allergies and finally, fifteen cases were found to be normal individuals.

Discussion:
Most patients with recurrent infection have a normal immune system. Allergic disorders are the most common predisposing factor to recurrent infection. However, as immunodeficiency disorders are potentially serious, early diagnosis can improve the quality of life and outcome and prevent severe sequels in future.

Key words: Allergy, Primary immunodeficiency, Recurrent infection, Secondary immunodeficiency.

Introduction

Recurrent infections are common presentations, a challenge for clinicians to identify the relatively rare primary immunodeficiency (PID) disorders among many cases with normal immune function. Young children have an increased susceptibility to infections, with an average of six respiratory infections per year (1). However, these infections will usually be short-lived and not invasive in children with normal immune function (2, 3). Risk factors for recurrent infections in children include: frequent contact with other people, allergic diseases, active or passive smoking and anatomic abnormalities of the upper and lower airways (4).

There are more than 200 PIDs which can be associated with an inherited deficiency of any components of the immune system. In order to provide the correct treatment for PID, making an accurate diagnosis is vital (5). There is a lack of awareness of PIDs amongst physicians; however the understanding of these disorders and diagnostic techniques has improved in recent years (2,6,7). An increased awareness of PIDs can lead to early diagnosis, initiation of appropriate lifesaving treatments and follow up visits which can significantly improve their long-term quality of life and reduce their morbidity and mortality (7,8).

The key elements of taking a history include: age at the onset of infections, sex, anatomic site of infection, particular infectious agents involved and family history of immunodeficiency (9). Collection of a detailed history, physical examination, and screening laboratory tests are often enough informations for the clinician to ascertain whether a patient's immune system is normal or not (10) . Advanced laboratory tests might be required for selected patient to rule out an immunodeficiency.

The aim of this study is to evaluate the clinical and laboratory data in patients with recurrent infections and suspected immunodeficiency referred to a local immunodeficiency clinic in Mashhad-Iran.

Materials and Methods

This was a prospective study of patients referred to the Immunodeficiency Clinic of Mashhad, Northeast of Iran between April 2010 to September 2012. Participants were individuals of any age with recurrent infection referred mostly by pediatricians, infectious disease specialists and respiratory physicians. This study was approved by the Mashhad University of Medical Sciences ethics committee. Written informed consent was obtained from all participants prior to their inclusion in the study. Recurrent infections were defined as four or more new ear infections in one year, two or more serious sinus infections or pneumonia in one year, recurrent deep skin or organ abscesses, persistent thrush in mouth and deep-seated infections including septicaemia. These recurrent infections, as well a family history of primary immunodeficiency (PID), unexplained failure of infants to gain weight, requirement of intravenous therapy (IV) treatment to clear infections or more than two months on antibiotics with little effect.

A detailed medical history, physical examination and screening laboratory tests were performed. If the results of screening tests were abnormal or the patient history strongly suggested an immunodeficiency, a second more advanced panel of laboratory tests were used (Table.1).

Table 1: Schedule of assessments for patients referred for suspected immunodeficiency disorders

Schedule	Assessments
Screening laboratory tests	Complete blood count (CBC), erythrocyte sedimentation rate (ESR), serum immunoglobulin levels, isohemagglutinins; specific antibody responses (diphtheria, tetanus, pneumococcus); nitro blue tetrazolium test (NBT), CH5O, delayed skin test with Candida albicans intradermal skin test, allergy skin prick test; sweat test; The human immunodeficiency virus (HIV) test (high risk patients)
Advanced laboratory tests	flowcytometric evaluation of lymphocyte subsets; lymphocyte transforming test (LTT); phagocytosis; opsonization; chemotaxis; Mutation analysis

The study population was classified into five distinct categories: normal individuals, presence of an allergic disorder, an underlying structural disorder, secondary immunodeficiency and primary immuno-deficiency.

Results

Forty one patients, aged between 10 months to 51 years, were evaluated. The majority (59%) of patients referred to the clinic were aged between six months and five years. The final results of the study population were as follows: primary immunodeficiency (26.8%), secondary immunodeficiency (10%), allergy as predisposing factor (19%), an underlying structural diseases (7.3%), and normal individuals (36.5%).

The most common presenting manifestation in patients referred to our clinic was pneumonia (46%), followed by skin infection/ulcer (29%) and otitis media (Table.2).

Table2: Comparing clinical manifestations and laboratory data between five groups

	Normal immune function	Allergic disorders	Underlying structural disorders	Secondary immunodeficiency	Primary immunodeficiency	Total
Demographics						
Number of cases	15	8	3	4	11	41
Age [median (range)]:Years	10.5(1.5-51)	3.8(2-7)	4.2(2-7)	18.5(2.5-41)	10.3(0.2-26)	
Sex (M:F)	9:6	5:3	1:2	1:3	6:5	22:19
Presenting Manifestations*						
Pneumonia	4	3	2	3	7	19
Otitis media	4	3	0	1	2	10
Sinusitis	2	1	0	0	3	6
Thrush	1	0	0	2	2	5
Skin infection or ulcer	5	3	0	1	3	12
Bronchiectasis	0	1	1	0	2	4
Osteomyelitis	0	0	1	1	1	3
Abscess formation	0	0	1	1	5	7
Fever without local sign	2	2	0	1	1	6
Medical history						
Abnormal growth	0	0	1	2	3	6
Positive consanguinity	3	4	1	2	8	18
Atopy	0	6	1	1	4	12
Hospital admissions (mean)[§]	0.7	0.6	2	3	2.8	
Screening laboratory tests						
Abnormal Neutrophil counts	0	0	0	0	2(Neutrophilia)	2
Lymphopenia	0	0	0	0	0	0
Low serum immunoglobulins	0	0	0	0	4	4
Abnormal antibody function	0	0	0	0	4	4
High IgE levels(>2000IU/ML)	0	0	0	0	2	5
Abnormal Candida skin tests	0	0	0	2	2	4
Abnormal phagocyte function	0	0	0	2	3	5
Abnormal sweat test	0	0	0	0	0	0
Positive allergy skin test	0	6	1	0	3	10
Abnormal ciliary function	0	0	1	0	0	1

Patient medical history demonstrated that those diagnosed with a PID had positive consanguinity in 73% of cases, compared to less than 50% in other cases. Those diagnosed with PID, secondary immuno-deficiency and underlying structural disorders, and had a longer mean hospital stay compared to other groups. This is likely a reflection of the severity of their condition.

All screening laboratory tests revealed normal results in cases diagnosed as normal individuals. Those diagnosed with allergic disorders had positive allergy skin tests, high

immunoglobulin E (IgE) levels and normal immune system in screening tests. The most common infectious microorganism detected was bacteria (25 cases), virus (5 cases), fungus (4 cases), parasite (1 case) and vaccine-associated (2 cases). No micro-organism was found in seven patients. In three cases, underlying structural abnormalities (cystic fibrosis, ciliary dyskinesia and neonatal onset multisystem inflammatory disease) were detected. Four patients had secondary immunodeficiency due to malnutrition (3cases) and Eosinophilic granuloma. The remaining patients (11 cases) were diagnosed as PID by screening and advanced panel of testing (Table.3).

Table3: Details of 11 patients with primary immunodeficiency and their diagnostic tests

Primary Immunodeficiency	Number	Diagnostic tests
Antibody defect	4	Serum antibody titters, antibody function, flowcytometric assay of B lymphocytes, mutation analysis
Leukocyte Adhesion Defect1(LAD1)	2	Flow cytomertic evaluation of CD18 and CD11 markers on leukocytes
Chronic Granulomatosis disease(CGD)	1	NBT(Nitroblutetrazolium) test, DHR(Dihydrohodamine) test
severe combined immunodeficiency(SCID)	1	Flow cytomertic assay(CD3, CD4, CD8, CD19, CD56), Mutation analysis(RAG1, RAG2)
Hyper IgE syndrome	2	Total IgE, Scoring table
Interferon gamma deficiency	1	Interferon gamma assay(ELISA)
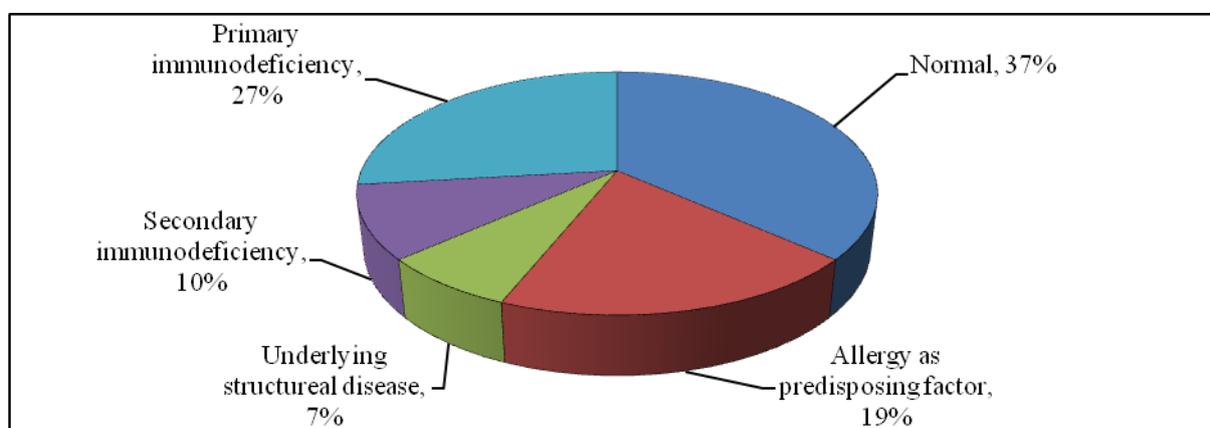
Fig1: Final diagnosis in the study population

Discussion

In this study the most common final diagnosis in patients with recurrent infection were normal individuals followed by primary immunodeficiency, allergy as predisposing factor, secondary immunodeficiency and an underlying structural disease. This highlights the usefulness of a stepwise plan to easily and accurately identify those with PIDs.

The majority of patients (59%) were aged between six months and five years. Characteristics of this age group, including an immature and naïve immune system, hand-to-mouth habit, higher prevalence of allergic diseases and exposure to

other individuals, are suggested causes for an increased risk of infections during this specific period of time (11).

The most common type of infection was pneumonia, which was seen 46% of cases. In those with a final diagnosis of PID this rate was 64%. In the Iranian PID registry and other registries, the most common presenting features of PID patients were sinopulmonary infections and pneumonia (12,13). During evaluation of any patient with recurrent pneumonia or sinusitis, immune defects should be considered as a possible etiology. Early diagnosis can prevent occurrence of the permanent sequelae like bronchiectasis or repeated sinus surgery (7).

In this study, skin problems including skin abscess or skin ulcer were also common presentations. The percentage of children with primary and secondary immunodeficiencies presenting with these manifestations were 73% and 50%, respectively. In approach to any patient with recurrent or permanent skin lesions, immune defects particularly phagocytic disorders should be considered. One of our patients had a persistent ulcer on her left leg for over two years with a persistent neutrophilia in complete blood counts. A plain radiography of the left leg revealed osteomyelitis. Further tests using flowcytometry showed abnormally low CD18 levels. Leukocyte adhesion defect type1 (LAD1) was diagnosed and she successfully undergone stem cell transplantation to prohibit subsequent life-threatening complications (14).

In the present study, 20% of cases had allergy as a predisposing factor for recurrent infection. In fact, allergy is the most common predisposing factor in patients with recurrent infection visiting primary care physicians. Even in our selected referral patients, allergy was very common. This confirms that most patients with recurrent infection are normal individuals or have simple risk factors, such as allergy, instead of a having a defect in their immune system (6).

In three cases, underlying structural abnormalities (cystic fibrosis, ciliary dyskinesia and neonatal onset multisystem inflammatory disease) were detected. This area is one of the most important pitfalls for clinicians who evaluate patients with recurrent infection, as any misdiagnosis may lead to delayed diagnosis and higher morbidity and mortality.

Secondary immunodeficiencies are far more common than PIDs and can arise from a number of conditions, such as malnutrition, treatment with glucocorticoids and immunomodulatory drugs, malignant and infiltrative disease, and chronic infections such as those caused by human immunodeficiency virus (HIV) (15). Malnutrition is the most common causes of immunodeficiency worldwide (9). In our study, 4 cases of immunodeficiency were diagnosed secondary to malnutrition (3 cases), and lymphoproliferative diseases.

Primary immunodeficiency was the final diagnosis in 11cases (26.8%) which is higher than other studies. This may be explained by our patient selection method as our patients were mostly referred by infectious disease specialists, respiratory physicians or pediatricians. The prevalence of PIDs varies in different countries. Studies in Singapore, Taiwan and Australia have highlighted that the most frequently diagnosed type of PID was antibody deficiency (16, 17). Most of the 11 cases were identified following medical history, physical examination and a screening laboratory test panel. An advanced panel of laboratory testing were required for the final diagnosis of some patients with highly suspected clinical manifestations. Two patients in the study had persistent neutrophilia and were given a final diagnosis of LAD1. Although normal levels of IgE indicate a normal antibody function, very high levels of IgE (more than 2000 IU/ml), can be seen in hyperimmunoglobulin E syndrome (HIES). We had two patients with

severe eczema, recurrent skin abscess and recurrent pneumonia who were finally diagnosed as HIES.

Conclusion

The number of patients suspected to have immunodeficiency far exceeds the number of actual cases, as most patients with recurrent infections do not have an identifiable immunodeficiency disorder. However, as PIDs are potentially serious disorders, early diagnosis through a stepwise diagnosis approach and early intervention can improve their quality of life and outcome and prevent severe sequels in future.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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