ASSESSMENT OF PRIMARY IMMUNODEFICIENCY DISORDERS AMONG CHILDREN AT ZAGAZIG UNIVERSITY HOSPITAL

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ABSTRACT

Aim of study: To identify and report various type of primary immunodeficiency disorders in children at Zagazig university hospitals, and their characteristic features, clinical manifestations and laboratory profiles.

Patients and methods; patients with history,clinical findings and laboratory findings matching with any of eight classes of primary immunodeficiency were included in this study, also we used ten warning signs,immunodediciency disease related score in evaluation of patients.

Results: Fifty patients were diagnosed with different primary immunodeficiency disorders in Pediatric department, Zagazig University Hospital during period from July 2011 to July 2013. The spectrum of PIDs in our center was as follow: predominantly antibody deficiency was the most common category (46%) followed by combined immunodeficiency (22%) then well defined syndromes (20%), auto inflammatory disorders (8%), complement disorders (4%). No cases were diagnosed in any category of phagocytic disorders, innate immunity or immune dysregulation. Selective IgA deficiency was the most frequent disease type. Median age of onset of symptoms was 7 months, the median age of diagnosis lag was 24 months.Pneumonia was the most common presentation. Consanguinity rate was 60%. Mortality rate was 20% mostly duo to bronchopneumonia.

Conclusion: primary immunodeficiency disorders are not rare in our center ,but under diagnosed.

Keywords: Primary immunodeficiency disorders,frequency,registry,Egypt

INTRODUCTION

Primary immunodeficiency diseases (PID) are a diverse group of rare genetic disorders that affect the development and/or function of the immune system. Affected individuals are predisposed to increased rate and severity of infections, allergy, autoimmunity, and malignancy[(1)].

During the last decade, expansive increase in the knowledge of basic immunology and human genetics has led to recognition of several distinct immunodeficiency disorders and their underlying genetic causes. There are more than 150 different PID recognized by the World Health Organization[(2)].

According to the International Union of Immunological Societies (IUIS) Primary Immunodeficiency Diseases Classification Committee, PID are classified into eight categories: (1) combinedT- and B-cell immunodeficiencies. (2) predominantly antibody deficiencies.(3) other well-defined immunodeficiency syndromes. (4) diseases of immune dysregulation. (5) congenital defects of phagocyte number, function, or both. (6) defects in innate immunity. (7) autoinflammatory disorders.(8) complement deficiencies[(3)].

Primary immunodeficiency diseases are considered rare; physicians and general practitioners have little knowledge about the clinical presentation, diagnostic approach, and health impact of PID. Consequently, affected persons may either die or remain undiagnosed for several years and eventually suffer from long-term morbidity[(4)].

Epidemiological studies have shown wide geographical and racial variations in terms of prevalence and pattern of immunodeficiency. Many countries worldwide have developed registries to estimate the prevalence and characteristics of different PID phenotypes among their populations.Apart from local registration in some centers there is no national registry of PID in Egypt, and hence, the prevalence of these disorders in our population is still unknown[(5)].

It is important to recognize the child with an underlying PID and investigate and treat appropriately, and yet not over-investigate normal children. Prompt, accurate diagnosis of PID helps to direct the most appropriate treatment, predict prognosis and facilitate genetic counselling for the family[(6)].

An increasing number of PID are recognized, and effective treatments are possible. Early and judicious use of prophylactic antibiotics and replacement immunoglobulin can prevent significant end organ damage and improve long-term outlook and quality of life in these patients[(7)].

PATIENTS AND METHODS

The present study was conducted in Zagazig University Hospital, Pediatric Department, in both the Pediatric Hospital and the Pediatric Outpatient Clinic and Clinical Pathology Department during the period from July 2011 to July 2013.

Inclusion criteria:

Age: patients under 15 years were included in this study,sex:both sexes,patients:all patients that were suspected to be of any type of eight classes of PID were included in this study, Most patients were first diagnosed at pediatric department or pediatric outpatient clinic. Some patients were referred to us from other centers and hospitals in the government for further evaluation and accurate diagnosis.

Patients that were selected to undergo complete workup for PID were chosen according to three main parameters:

1- Family history of PID.
2- Clinical data either by history or clinical examination that match diagnosis of any type of immunodeficiency, most important, severe or recurrent infection or any of the ten warning signs[8]**.** Also we included patients with clinical finding matching with other types of PID such as auto inflammatory or complement disorders in whom the main complaint may not be recurrent infections and need high index of suspicition.
3- Any abnormal laboratory parameters during investigations done for other indications such as severe lymphopenia, neutropenia, eosinophilia

Diagnosis and classification were established according to The International Union of Immunological Societies (IUIS)[3].

Fifty patients were diagnosed with different PID during this period and were included in this study after consent from parents of patients. These patients were subjected to:

1- Full history taking with special emphasis on history of: Positive consanguinity. Positive family history of primary immunodeficiency ,number of attacks of otitis media, sinus infection, tonsillitis, diarrhea per year and the response to antibiotics, previous attacks of pneumonia, recurrent abscesses, previous attacks of life threatening infection as septicemia or meningitis, drug administration for previous diseases.

2- Complete clinical examination with special emphasis on: Anthropometric measurements: weight, height, midarm circumference, presence of oral moniliasis, cutanous candidiasis, eczyma. Presence of lymphadenopathy, splenomegaly or on the other side hypoblastic tonsil, adenoid, lymph nodes, system by system examination.

3- Investigations: Complete blood count with differential (CBC with differential), erythrocyte sedimentation rate (ESR). Measurement of serum immunogl, bulins (IgA, IgG, IgM, IgE), delayed cutanous hypersensitivity test after tuberculin or BCG vaccine, measurement of basic panel of T cell subsets(CD3,CD4,CD8)and if needed B-cell markers(CD19), natural killer cells(CD16, CD56) by flowcytometry. Nitrubluetetrazolium test if needed (NBT test, assessment of expression of CD11, CD18 on neutrophils if needed, assessment of complement system by CH50 assay or assessment of complement components, Genetic testing and enzyme assay were not available in our laboratories.

Exclusion criteria:

Patients under treatment with immunosuppressive drugs or patients infected with HIV or patients with immunodeficiency secondary to any disease such as nephrotic syndrome,protein losing enteropathy or severe malnutrition.

Warning signs

We also employed a list of ten warning signs**(8)** for immunodeficiency, which was developed to guide physicians to suspect immunodeficiency in cases that meet one or more of these signs. Each patient was evaluated and was given a score out of ten representing the number of positive warning signs.

Immunodeficiency disease related score (IDR score)

Also we used the immunodeficiency disease related score[9] which was designed to evaluate severity of disease along course of illness.

A score of 5 or more was chosen as threshold for indicating severity of primary immunodeficiency.

Evaluation sheet

For the purpose of documentation, an evaluation sheet was developed to contain all patients demographic information including: name, sex, date and place of birth, age at onset of symptoms, age at diagnosis of PID, parental consanguinity, family history of PID and/or recurrent infection, number of sibs, order between sibs, previous sib death whether unexplained or due to infection. Number of warning signs, IDR score. Any abnormal clinical finding elicited during clinical examination was recorded, positive investigations, treatment.

Statistical analysis

Data in database were analysed with SPSS 21.The data here are not in homogenous distributions, so the median and range were used to present characters of focused variables.

RESULTS

Frequency and Distribution of Primary Immunodeficiency disorders

Fifty patients were diagnosed with PID in Zagazig university hospital during the studied period from July 2011 to July 2013.

In this study, patients were distributed in 11 diseases of five main categories of PID. None of patients were identified in any category of defects in the innate immunity, Immune dysregulation or phagocytic disorders.

Predominantly antibody deficiency was the most common category and number of patients in this class were 23 patients (46%). Selective IgA deficiency was the most common type in this class: 18 patients (36%) followed by Bruton agammaglobulinemia: 4 patients (8%) and only one case diagnosed with common variable immunodeficiency (2%).

The next type was combined immunodeficiency. The number of patient in this class were 11 patients(22%).Ten patients(20%) were diagnosed with SCID and only one case with CD40 ligand deficiency (2%).

Ten patients (20%) were diagnosed in the category of well defined syndromes .The most common phenotype encountered in this category was Hyper IgE syndrome: 5 patients (10%) followed by Ataxia telengectasia:3 patients (6%) and two patients (4%) were diagnosed with DiGeorge syndrome.

Four patients (8%) were diagnosed in the category of auto inflammatory disorders. They were all familial mediterranian fever.

Two patients (4%) were diagnosed with complement disorders one patient had deficiency in C5. And the other had deficiency of C1 Inhibitor.

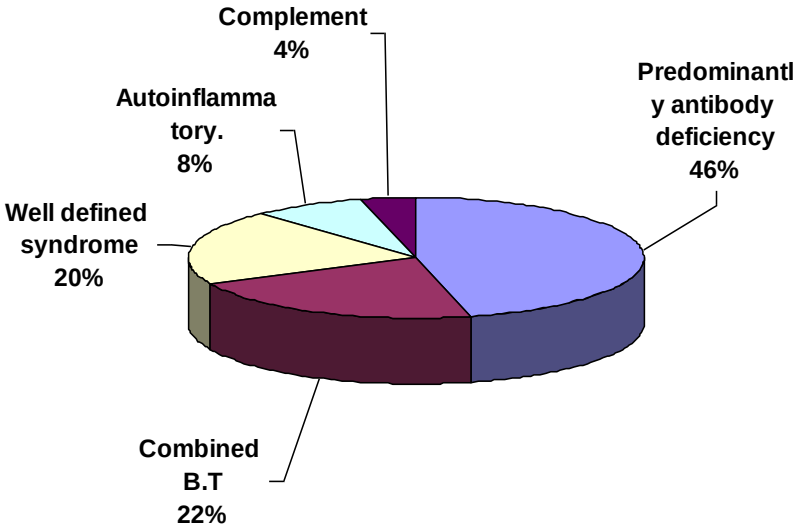

Fig. (1): Distribution of different classes of primary immunodeficiency.

Patient Characteristics

The study population comprised 30 boys and 20 girls with a male-to-female ratio of 3:2. In addition to X-linked disorders, such as X-linked SCID the number of boys has far exceeded that of girls in autosomal disorders.

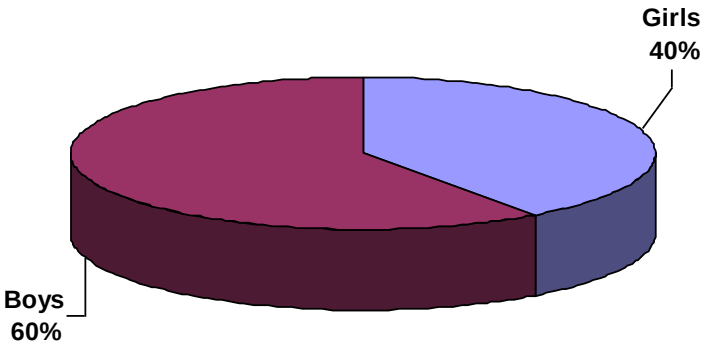

Fig. (2): Sex distribution.

Age Distribution

In all patients, the median onset age of symptoms was 7months (range, 1–84 months), the median age at diagnosis was 24 months (3–120 months), and the median of diagnosis lag,which represents the time elapsed between onset of symptoms and diagnosis, was 18 months (2–68 months).

Patients belonged to antibody deficiency category presented symptoms much later (median 36 months).

Especially, selective IgA deficiency and common variable immunodeficiency disorder (CVID) and auto inflammatory disorders had the latest onset. 16 infants (32%) were below the age of 1 year, 16patients (32%) were between 1 and 3 years, and 18 patients(36%) were above the age 3. The maximum age at diagnosis recorded in this study was 10 years which was recorded in a patient with CVID. No antenatal diagnosis was made. The age at onset of symptoms, age at diagnosis, and then diagnosis lag showed considerable variations between different PID phenotypes .

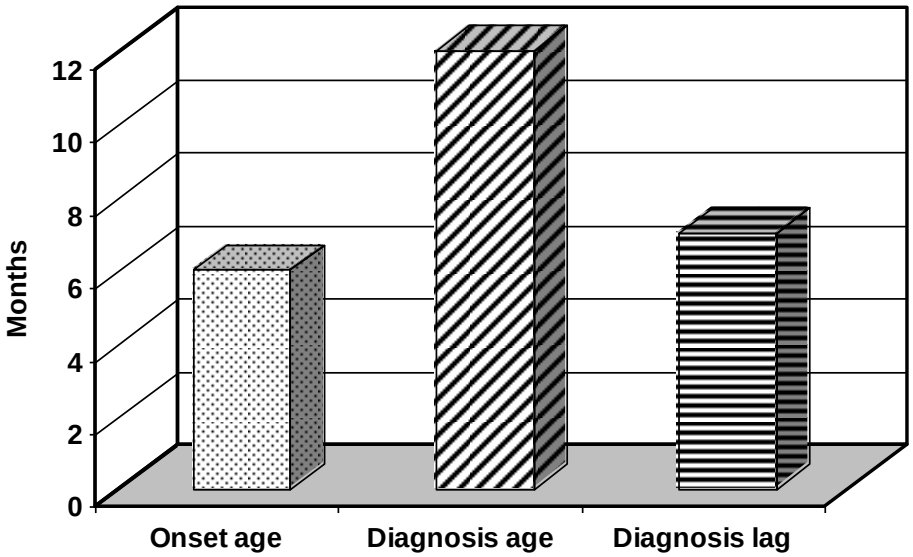

Fig. (3): Age distribution of combined B, T.

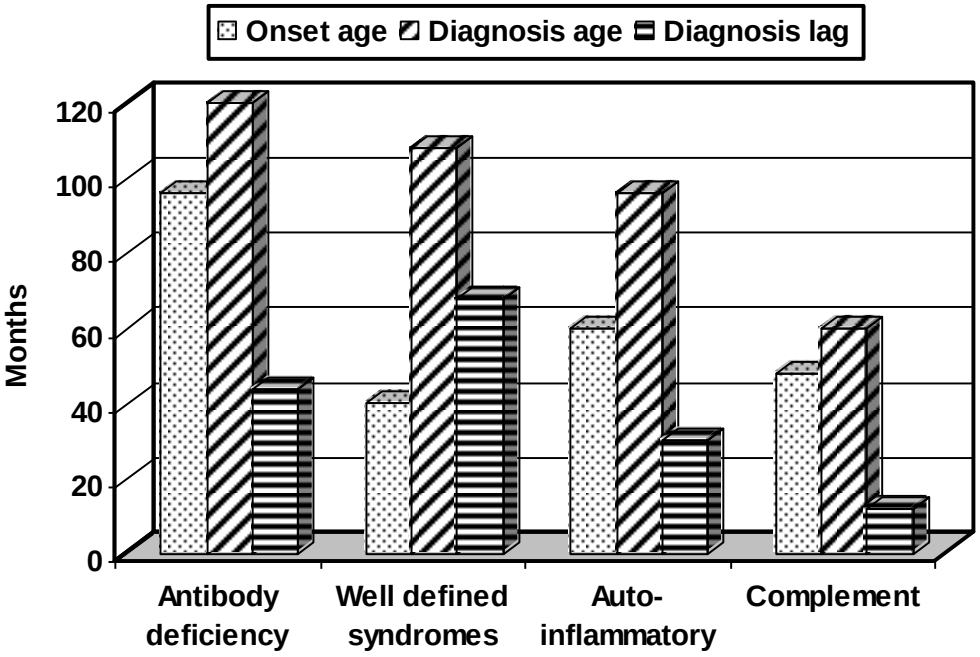

Fig. (4): Age distribution of other classes of immunodeficiency.

Consanguinity and family history:

Thirty patients were products of consanguineous marriages,in most cases first cousins. Familly history of PID in 7 patients(14%).

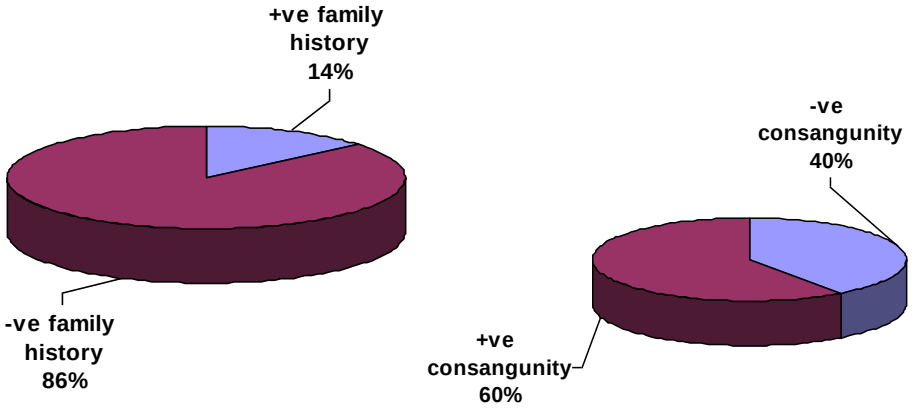

Fig. (5): Consanguinity and family history.

Clinical Features

At time of diagnosis, PID patients showed a wide spectrum of clinical manifestations. Infection in all sites was the main presentation, and pneumonia was the most common infection. The least frequent infections were sinusitis, septic arthritis. A combination of failure to thrive, pneumonia, and/or diarrhea was seen in 15 patients (30%). In 25 patients (50%), multiple sites of infection such as pneumonia, gastroenteritis, skin abceeses were found at time of diagnosis. In the other 50% only one site of infection at time of diagnosis with history of previous and recurrent infection .The most common site is respiratory tract infection. The most common presention is pneumonia then bronchitis then otitis media.

Table (1): Frequency of presentation in children with different PID categories.

	Predominance antibody deficiency	Combined B, T	Well defined syndrome	Auto inflammatory	Complement
Otitis media	12	-	1	-	-
Pneumonia	20	10	8	-	1
Bronchial asthma	6	2	7	-	-
Bronchiectasis	3		6		
Failure to thrive	6	11	7	-	1
Chronic diarrhea	3	7	4		
Septicaemia	1	1	-	-	-
Meningitis	1	1	-	-	1
Ataxia			3		
Eczyma		3	4		
Oral candidia	4	10	4		
Hepatomegal		3			
Splenomegaly		3	2		
Superifical infection	3	2	5		1
Deep abcess					1
Sinusitis			1		
Septic arthritis		1			

Frequency of the Ten Warning Signs

The ten warning signs were all elicited in our patients with variable frequencies. One warning sign was seen in three patients(6%) two warning signs was seen in seven patients (14%), . Twelve patients (24%) had three warning signs. Eight patients (16%) had four warning signs Ten patient (20%) had five warning signs. Five patients(10%) had six warning signs, five patients(10%) had no warning signs at all.

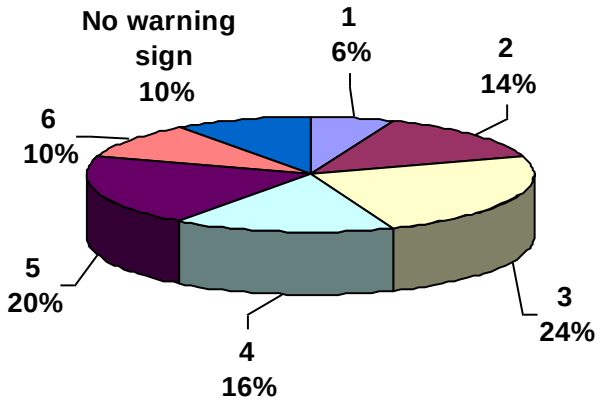

Fig. (6): Frequency of warning signs.

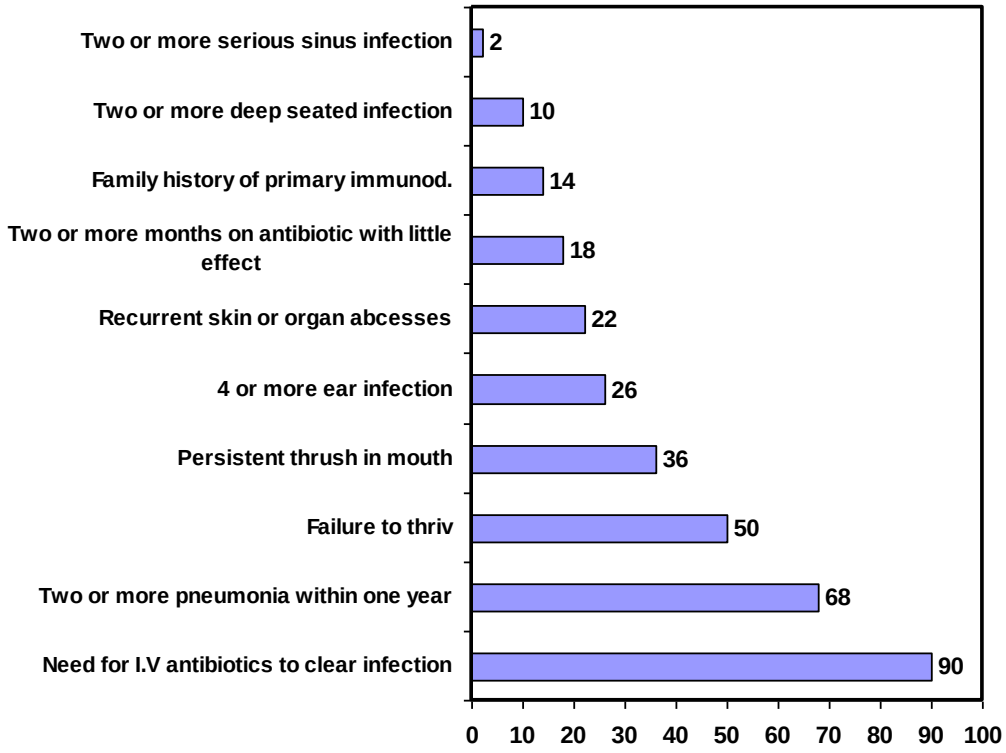

Fig. (7): Frequency of ten warning signs.

Immunodeficiency-Disease-Related Score

22 patients (44%) had scores more than 5, and the highest score was 20, which was achieved by a patient suffering from SCID. The IDR score showedvariation between different PID diseases. 28 patients (56%) could not achieve scores higher than 5.

IDR scores of patients show considerable variation between different categories. IDR scores were high in combined B,T immunodeficiency and were low in auto inflammatory disorders and igA deficiency.IDR score can be taken as indicator of course of illness.

Therapy

Antimicrobial therapy was used in 49 patients (98%) and antifungal therapy in 19 patients (38%).18 patients (36%) received intravenous immunoglobulin (IVIG) replacement therapy. No side effects of IVIG were recorded in these patients.In all PID patients during acute episodes of infections,a combination of two parenteral broad-spectrum antimicrobials, in most cases were used.

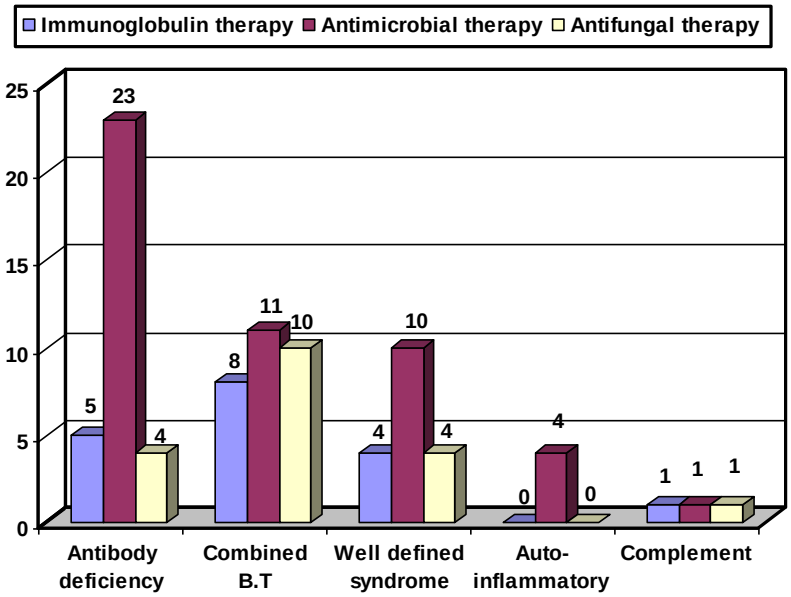

Fig. (8): Different types of therapy in primary immunodeficiency.

Mortality

Ten patients died during the study period. Of these patients, seven died before their first birthday, three were between the ages 1 and 3 year. Fulminant infection, septicemia,respiratory failure due to pneumonia were the most common causes of death.

Table (2): Causes of death in PID cases

No of case	Cause of death	Percentage (%)
6	Brochopneumonia and respiratory failure	60%
2	Septicemia	20%
1	Dehydration	10%
1	Meningitis	10%

Table (3):Characteristic features of patients with primary immunodeficiency

Category	Disorder	No of cases	Sex boys/girl	Diagnosis age median-range	Diagnosis lag median-range	Family history	IDR score	Mortality
Antibody deficiency	Selective IgA ↓	18	10/8	36 (10-84)	24 (4-44)	2	3(1-6)	-
	Bruton's a gamma	4	3/1	11 (8-12)	7(4-12)	1	8 (7-12)	2
	Comm.variable immunodeficiency	1	♀	120	12 months	-	6	-
Combined B, T	SCID	10	8/2	6 (3-12)	3 (2-7)	2	8 (5-20)	5
	Hyper IgM	1	♀	8	3	-	4	-
Well defined syndrome	Hyper IgE	5	3/2	18 (8-36)	10(4-24)_	-	7 (4-10)	1
	Ataxia telengeclensia	3	1/2	96 (72-108)	60 (48-68)	1	8(7-9)	1
	DiGeorge syndrome	2	1/1	5	(2-4)		6	
Auto-inflammatory.	familialmediterranian fever	4	3/1	84 (60-120)	21 (18-30)	-	1(1-3)	-
Complement								
C5 ↓	C5 ↓	1	♂	12	3 months	1	13	1
C1 inhibitor ↓	C1 inhibitor	1	♀	60	12 months		0	

DISCUSSION

The reported number of PID patients in this study represents a single-center study, and it is expected that the prevalence of these disorders in our city is much higher. Definitely, our data underestimated the disease burden, since it did not include patients admitted in other hospitals and those with mild forms of PID , who are usually managed as outpatients at various health centers and private clinics. There is no routine screening test to detect any of PID in Egypt; consequently, asymptomatic PID patients were not included in the study.

We also expect that some severe forms of PID such as SCID usually die during infancy from severe infections before being identified as immunodeficient patients**(5).**

Unfortunately, there is no national registry of PID in Egypt and currently, only 160 Egyptian PID children registered by European Society for Immunodeficiency (ESID).These patients are registered in two centers in the country: one at Ain Shams University (100 cases) and the other at Cairo University (60 cases).These figures don't represent at all the actual burden of PID in Egypt[10]**.**

The distribution of PID in our study shows both similarities and differences with national registries in other countries and other centers. The predominance of the category of predominantly antibody deficiency (46%) was compatible with registries in most centers and countries and also compatible with the global study of PID done by Jeffery Modell Foundation in which predominantly antibody deficiency constitute 51.6%of cases followed by well defined syndromes 15%[11]**.**

Selective IgA deficiency was the most common type in this class similar to registries in Spain[12], Latin America[13]**,** Saudia Arabia[14] and contrary to registries in Ain Shams University[5], Iran[15], USA[16]**,** Europe[17] where CVID was the predominant type. Bruton agammaglobulinemia was the predominant in Chinese children[18]**.**

The low incidence of CVID in this study may be explained that the symptoms in CVID occur with two major peaks of onset at 5–10 and 20–30 years[19,20]**.** For the second peak, patients were not defined as children and excluded from our study, thus it may decrease the percentage of CVID in our results. Combined T- and B-cell immunodeficiencies were the second common PID category comprising nearly 22% of our patients, which is much higher than registries from European countries,[17] Far-East countries like Japan[21] and Singapore[22], Australia [23]**,** and Latin America[13]. However, the high frequency of combined T- and B-cell immunodeficiencies in our series is close to figures reported by some Middle Eastern countries such as Kuwait[24]**,** Saudi Arabia[14], and Iran[15]. This could be due to geographical, ethnic, genetic predisposition of certain PID diseases, and the prevalence of consanguineous marriages in that area of the world.

As this study was conducted in both Zagazig university hospital and Zagazig outpatient clinic both mild disorders like IgA deficiency and severe disorders like SCID were represented in this study.

The incidence of phagocytic disorders and immune dysregulation was lower than Ain Shams university (12%, 3%)[5], china (10%,3%)[18], Europe (12%, 1.3%)[17].

In fact, the rate of consanguinity seen in our study is nearly similar to the high rates reported from other countries in the regions: Iran[15], Kuwait[24]**.**

In our study, almost all of the patients were children. Results from other studies suggested that PIDs were no longer considered pediatric diseases, which was further convinced by surveys conducted in Europe and USA. It was shown that only 67.71% of the patients were below 20 in Europe[17] and about a quarter (26%) was below 18 in USA[16]**.** In different countries, average onset ages were mostly under 15 months .In our study the median age was 7 months and 36% of patients were above 3 years. This explained by high percentage of disorders of later onset like IgA deficiency.

In our study the median age of diagnosis lag was 18 months which was similar to study in Chinese children[15]**.** Although this is considered along time, the diagnosis lag was longer. In Ain Shams university the mean of diagnosis lag was 30 months[5]**,** also time was longer in studies in Kuwait[24], Iran(42-62 months)[15]. In Europe the mean of diagnosis lag was 4 years[17]**.**

The USA survey showed an unusual prolonged delay in diagnosis, which was even 12.4 years in 2007[16]. This may partly associated with the large constitution of adult patients in America. Therefore, adult patients need to be taken into account in further research to gain an accurate description of the disease. The delay in diagnosis reflects the poor knowledge about PID among general practitioners. This delay has definitely led to significant morbidity and mortality.

Male predominance seen in our study is similar to registries of Australia[23]**,** Iran[15] and Kuwait[24]**.**

A variety of clinical manifestations were observed in our patients, which indicates that any body system could be involved in PID. Although oral thrush, frequent respiratory tract infections, and diarrhea were common[25]. Allergic manifestations that would suggest hyper IgE syndrome [26].

20% of patients died during the time of the study, which is higher than other reports in Iran[15], Kuwait[24] and nearly similar to study in Ain Shams university[5]. One half of deaths were patients with combined T- and B-cell immuno-deficiencies.

Although improved supportive care and utilization of IVIG have extended the life span of PID patients, definitive cure is generally only achieved by HSCT[27]. In Egypt, we still have limited experience in stem cell transplantation in immunodeficiency conditions, which may explain the relatively high mortalities among SCID patients in our cohort. This acknowledges the importance of stem cell/bone marrow transplantation for SCID as a curative therapy and highlights the fact that, without early intervention with bone marrow transplantation or gene therapy, these infants will inevitably die[25].

Scoring systems when coupled with clinical indicators may provide a useful guide to the identification of PID patients[9].

Aloi and Colleguesin[28] did not meet a single warning sign in 30% of their patient, indicating that these signs may not be encountered in some patients with detected PID. In our study 10%of patients (five patients)had no warning signs. These patients were four patients with familial Mediterranean fever who were mainly complaining of recurrent fever and abdominal pain which of course not included in the ten warning signs. The fifth patient had C1 inhibitor deficiency in whom was the main complaint recurrent angioedema. However, the sensitivity and predictive value of the ten warning sings for detecting PID cannot be determined in this study since all patients in our cohort were those with proven PID diagnosis.

On the other hand, the IDR score was higher than 5 in 44% of patients, which indicates disease severity of PID. Our cohort was comparable with the pediatric patients seen in the series of **Yarmohammadi and associates**[9] and also similar to study in Ain Shams university**(5)** in terms that both series had comparable IDR score values in many classes of PID patients. It is worth mentioning that the diagnosis of PID could have been missed in one fifth of our patients if the evaluation was primarily based only on the evaluation of the IDR score.

LIMITATIONS OF STUDY

1- This study was conducted in single center in Zagazig city.
2- All the patients recorded in the study were from pediatric inpatients, outpatients in Zagazig University Hospital.
3- Many patients in ZUH were missed duo to attendance in other specialties as dermatology.
4- Many patients were asymptomatic or with very mild disease and so missed duo to nature of disease itself.
5- Lack of awareness of pediatricians in different specialties about PID disorders.
6- There is no routine screening test.

SUMMARY AND CONCLUSION

This study was conducted in pediatrics in Zagazig University Hospital from July 2011 to July 2013 aiming to study the frequency, distribution and characteristic features of PID in this center.

The results of study conclude that PID are not rare in Zagazig but the knowledge and practice of pediatricians concerning PID is unsatisfactory. The prevalence of both mild and severe types of PID was high especially selective IgA deficiency and SCID.

The true incidence and prevalence of these conditions will never be known until there is newborn or population screening for these defects. Usually, the only way one knows that an underlying immunodeficiency exists is that the patient develops recurrent or serious infections and is then tested for these defects. These patients appear outwardly normal in most cases so that their appearances usually do not trigger a suspicion of immunodeficiency. Occasionally, the diagnosis is made before infections set in when there is a family history of such defects and family members are screened.

Since there are no screening tests performed for PID, early diagnosis can only be achieved by increasing the index of suspicion of physicians about these disorders.

The current study suggests that these conditions are sufficiently common that primary care physicians are likely to see patients with underlying primary immunodeficiency disorders in their practice and should test for these disorders in patients with recurring, unusual or serious infection.

RECOMMENDATIONS

It is essential to establish a national registry of PID in Egypt. Such registry will not only help in evaluating the prevalence of primary immunodeficiency diseases but will also increase the awareness of physicians and provide a base for

standardized therapy of these disorders in the country.

A- So implementation of strategies to improve the awareness of pediatricians about PID so early interventions with intravenous immunoglobulins and immune reconstitution can be used to prevent significant tissue damage, morbidity, and mortality, which results into economic savings.

These strategies may include:

1- Comprehensive under- and post-graduated education, organizing courses, and publishing educational materials (posters, booklets, articles) .

2- Wall posters for the ten warning signs in pediatric department, outpatient clinic, other specialties can increase awareness of PID.

3- Not only pediatricians should be aware of PID but also general practioners and family doctors should be aware of ten warning signs and refer to immunologist once suspect PID. The study handout (guidelines, investigations) can take part in this area.

4- Early referral of cases from pediatric outpatient clinics, other primary centers in the government to our immunology clinic.

B- This study can be a start point for registration of our cases to be followed and continued by further annual studies on a large scale

C- We should improve outcome of stem cell transplantation which may be the only life saving therapy for many disorders. Publishing our results may attract the attention of the stem cell transplantation center in Zagazig University which is recently developed to include this category of patients on their list.

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