The Egyptian Journal of Hospital Medicine (October 2022) Vol. 89 (2), Page 7504- 7509

Clinicoepidemiologic Study of Primary Immunodeficiency (PID) Diseases in Children Attending Mansoura University Children's Hospital

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ABSTRACT

Background: Primary immunodeficiency diseases (PIDs) refers to genetic conditions that are typically distinguished by weakened host defense and a higher susceptibility to infection.

Objective: This study aims to spotlights on PIDs syndromes among patients attending Mansoura University Children's Hospital to achieve early detection, proper diagnosis and better outcome.

Patients and methods: A cross-sectional retrospective study was conducted to include all patients diagnosed as PID according to hospital registrations since 2014 till December 2020. Patients with confirmed diagnosis of PIDs based on suggestive clinical diagnosis plus basic immunologic work up were included in our study.

Results: The median age of onset was 9 months, the median age at diagnosis was 24 months, and the median diagnosis lag was 12 months among 158 cases, including 105 (66.5%) men and 53 (33.5%) women. The male-to-female ratio was 1.9:1. Results revealed that PIDs is common between consanguineous parents (58.2%) with positive history of sibling died (15.8%), positive family history of recurrent infections (24.7%) and history of sibling diagnosed as PID (24. 1%). The most common type was primary cellular and combined immunodeficiency (CID) 57 (36.1%) patients with least dominant Disorder of immune dysregulation 1 (0.6%) patient. The most common presentation was recurrent pneumonia (70.6%) of patient and the least sign was family history of PID (8. 2%). Mortality rate was 27.2%.

Conclusions: PID was common among consanguineous parents, more common in male than female. The most common type in our study was primary cellular and CID. The most common presentation was pneumonia.

Keywords: PID, CID, IgA deficiency, HIGM, cross sectional study, Mansoura University.

INTRODUCTION

Conventionally, primary immunodeficiency diseases (PIDs) used to be defined as disorders that are caused by immune system defects, resulting in a raised vulnerability to infections. However, it would now be more accurate to say that PIDs are a collection of varied diseases characterized by abnormalities in the immune system, which are indicated by a variety of combinations of lymphoproliferation, atopy, autoimmunity, recurrent infections, granulomatous processes, and malignancy [(1)].

PID disorders have been classified into eight different groups by the *Primary Immunodeficiency Diseases Classification Committee of the International Union of Immunological Societies* (IUIS): 1-mixed B-cell and T-cell immunodeficiency, 2-mostly antibody deficiency, 3-additional well-defined immunodeficiency disorders, 4-immune dysregulation diseases, 5-congenital deficiencies in phagocyte quantity, function, or both, 6-deficiencies in innate and intrinsic immunity, 7-autoinflammatory disorders, and 8-complement deficiency [(2)].

There are three main ways that PIDs can be inherited, autosomal recessive (AR) which is the most prevalent amongst children of parents who are related; X-linked (XL), which is associated with greater percentages of affected male patients and least commonly, autosomal dominants patients [(3)].

Consanguinity is a common cultural practice in Egypt and its rates are estimated to be between 35.3% and 60%, with greater percentages in more rural areas [(4)].

Those countries where consanguinity is commonplace that have provided reports on PIDs have pointed out a most peculiar pattern, where more severe forms, CID for example, seem to be predominant. This is in direct contrast to other regions, where antibody deficiency is more predominant [(5)].

The National Primary Immunodeficiency Resource Center has made a list of ten potential indications of PID, which essentially focus on frequency, severity, and site of infections. Physicians advised to think of PID if their pediatric patients have any of these signs (**Table 1**) [(6)].

The present study aims to spot lights on primary immunodeficiency syndromes among patients attending Mansoura University Children's Hospital to achieve early detection, proper diagnosis and better outcome.

PATIENTS AND METHODS:

The study was designed as a cross-sectional retrospective study; all patients in this study were diagnosed as primary immune deficiency according to the hospital registrations, since 2014 till December 2020. All patients till the age of 18 years old were recruited. Patients with confirmed diagnosis of PIDs based on suggestive clinical diagnosis plus basic immunologic work up were included in our study. Patients were diagnosed as secondary immune deficiency; insufficient recorded data to meet the required data or refusal of parents to join our study were excluded.

METHODOLOGY

Patients: Detailed personal history, including age, sex, education level, residence (rural versus urban),

Received: 17/07/2022
Accepted: 19/09/2022

consanguinity, number of siblings, order of sibling, history of hospital admissions, history of recurring infection, history of sibling who died either diagnosed with PID or died from severe infection, ask about any sign of 10 dangerous signs (**Table 1**).

Table (1) Clinical Predictors of Primary Immunodeficiency Diseases in Children.

1	Within a year, four or more new ear infections.
2	Within a year, two or more significant sinus infections occur.
3	Antibiotics for two months or more with minimal impact.
4	Within a year, two or more pneumonias.
5	The infant's failure to acquire weight or grow normally.
6	Recurring deep skin or organ abscesses.
7	A cutaneous fungus infection or persistent oral thrush.
8	Intravenous antibiotics are required to treat infections.
9	Septicemia and two or more deep-seated infections.
10	A history of primary immunodeficiency in one's family.

Complete physical examination: Anthropometric measures (body weight, height, BMI) and displaying them on growth curve according to WHO growth curves [(7)], measures for previously diagnosed cases (116) were obtained from recorded data and newly diagnosed cases (42) were taken directly by the author. Physical examination included any associated congenital anomalies (facial in DiGeorge syndrome), skin lesions (Hyper IgE syndrome), organomegaly, and gait examination (ataxia telangiectasia).

Laboratory Work-up: Investigations were relevant to the suspected clinical diagnosis and included the following: CBC, blood film, ESR, and CRP.

Serum immunoglobulins (IgG, IgM, IgA, IgE): The value of immunoglobulin were compared to international standards of immunoglobulin levels [(8)].

***T cell count (CD3, CD4, CD8) B cell count (CD19)*:** CDs were compared to international standards [(9)].
Phagocytic function test Dihydrorhodamine (DHR) test: DHR testing for chronic granulomatous disease (CGD) was interpreted according to its reference [(10)].

Ethical considerations:

Ethical approval was granted by the Mansoura University, Faculty of Medicine's Ethical Committee (Ethics Approval No. MD.19.09.233). A written consent from the guardians/parents of cases was taken. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

Data was collected and analyzed by using SPSS (Statistical Package for Social Sciences, version 26, IBM, and Armonk, New York). Quantitative data with normal distribution were given as mean and standard deviation (SD). Nominal data were given as number (n) and percentage (%). Chi-Square test for comparison of 2 or more groups. Monte Carlo test and Fischer exact test were used as correction for Chi-Square test when more than 25% of cells have count less than 5. P value $\leq$0.05 was considered significant.

RESULTS

As regard classification of PIDs, Primary cellular and combined ID was more prevalent among 57 (36.1%) patients followed by Combined ID with syndromic features 35 (22.2%) patients followed by phagocytic defect 33 (20.9%) patients followed by Predominant antibody deficiency 32 (20.3%) patients with least dominant Disorder of immune dysregulation 1 (0.6%) patient (**Table 2**).

Table (2): Diagnosis among the studied group.

Primary Immunodeficiency Diseases classification	
Primary cellular and combined ID • CID 33 (20.9%) • SCID 23 (14.6%) • Digeorge syndrome 1 (0.6%)	57 (36.1%)
Combined ID with syndromic features • Hyper IGE 27 (17.1%) • Ataxia telangiectasia 6 (3.8%) • Wiskot alderich syndrome 2 (1.3%)	35 (22.2%)
Phagocytic defect • CGD 22 (13.9%) • Congenital neutropenia 4 (2.5%) • LAD 3 (1.9%) • Cyclic neutropenia 2 (1.3%) • Chediak hegashi 2 (1.3%0	33 (20.9%)
Predominant antibody deficiency • CVID 21 (13.3%) • Hyper IGM 6 (3.8%) • X linked agammaglobulenemia 5 (3.2%)	32 (20.3%)
Disorder of immune dysregulation • ALPS 1 (0.6%)	1 (0.6%)

During the study period, we diagnosed 158 patients with PID (53 females and 105 males), with a male-to-female ratio of 1.9:1. PID symptoms typically began to appear at a median age of 9 months, 24 months at diagnosis, and 12 months from symptom beginning to diagnosis. There was a 24.7% family history of PID, while the consanguinity rate overall was 58.2% (**Table 3**).

Table (3): Data about the studied group's socio-demographics.

Socio-demographic data	The studied group (n=158)
Sex Male Female Male: female ratio 1.9:1	 105 (66.5%) 53 (33.5%)
Age of onset (Month) Median (Min-Max)	9.00 (1.0-168)
Age at diagnosis (Month) Median (Min-Max)	24.00 (1.50-172)
Diagnosis lag (Month) Median (Min-Max)	12.00 (0.00-108)
Duration of illness (Month) Median (Min-Max)	48.00 (1.50-160)
Residence Rural **Urban**	 112 (70.9%) 46 (29.1%)

The most common presentation was recurrent pneumonia 70.6% of patient followed by ear infection 41% followed by recurrent abscess 44.3% followed by need for intravenous antibiotics 37%. Failure to thrive represented by 32.9%. The least sign was family history of primary immunodeficiency 8.2% (Table 4).

Table (4): Percentage of Signs suggestive for PID among studied groups.

Signs	The studied group (n=158)
1. Within a year, four or more new ear infections.	65 (41.1%)
2. Within a year, two or more significant sinus infections occur.	30 (19.0%)
3. Antibiotics for two months or more with minimal impact.	38 (24.1%)
4. Two or more pneumonias within one year	112 (70.9%)
5. The infant’s failure to acquire weight or grow normally	52 (32.9%)
6. Recurring deep skin or organ abscesses	70 (44.3%)
7. A cutaneous fungus infection or persistent oral thrush.	18 (11.4%)
8. Intravenous antibiotics are required to treat infections.	59 (37.3%)
9. Septicemia and two or more deep-seated infections.	17 (10.8%)
10. A history of primary immunodeficiency in one's family.	13 (8.2%)

Autoimmunity and malignancy were the predominant comorbidities among PID patients. autoimmune anaemia was found in 6 patients, autoimmune thrombocytopenia was found in 7 patients and autoimmune hepatitis was found in 2 patients. In our study 7 malignant cases were reported (3 lymphoma, 1 leukemia, 1 mylodysplasia, I pituitary carcinoma, 1 HLH) (**Table 5**).

Table (5): Malignancy and autoimmunity among the studied groups.

Malignancy (4 syndromic CID,2 primary cellular and CID, 1 phagocytic) (3 lymphoma ,1 leukemia, 1 mylodysplasia, I pituitary carcinoma, 1 HLH)	 7(4.4%)
Autoimmune AI anemia (4 PAD ,1syndromic CID,1 primary cellular and CID) AI thrombocytopenia (3 PAD,2 primary cellular and CID,1 pahagocytic,1 ALPS) AI hepatitis (syndromic CID)	 6 (3.7%) 7 (4.4%) 2 (1.3%)

There were a total of 23 (27.2%) deaths. The majority of the mortality was caused by combination cellular and humoral immunodeficiencies (24 patients) followed by 9 patients in phagocytic disorders, 6 patients in predominantly antibody deficiency and 4 patients in CID with syndromic features (**Table 6**).

Table (6): Outcomes for the group under study.

Outcome	The studied group (n=158)
Fate	
Alive	**115 (72.8%)**
Died	**43 (27.2%)**

Fate	Predominant antibody deficiency	Primary cellular and combined ID	Combined ID with syndromic features	phagocytic defect	Disorder of immune dysregulation	Test of significance	
						P value	P by MC test
Survived	26 (81.2)	33 (57.9%)	31 (88.6)	24 (72.7%)	1(100%)	χ^2=12.31	**0.009***
Died	6 (18.8%)	24 (42.1%)	4 (11.4%)	9 (27.3 %)	0(0 %)	**P=0.015***	

DISCUSSION

It has been reported that PID are considered to be a heterogeneous set of disorders having a broad geographical and ethnic distribution worldwide [(11)]. PID not a rare disease and it is more than expected in Egypt but due to lack of national registry and lack of knowledge between Paediatricians as regard early suspicion and referral of suspected cases.

The most common type was combined ID 92 (58%) patients as follow: 57 (36.1%) patients primary cellular and CID and 35 (22.2%) patients CID with syndromic features) followed by phagocytic dysfunction 33 patients including 22 patients with CGD that mean that more than 2/3 cases with phagocytic dysfunction were CGD. PAD was represented by 32 (20.3%) patients only with least presentation for immundysregulation.

By comparing our study with other studies, the Turk ethnic group has the highest prevalence of combined T- and B-cell immunodeficiency [(12)]. Also combined immunodeficiencies was represented by 59.7% in Saudi Arabia 2015 [(13)]**.** Unlike other research conducted in Iran and other nations, where predominantly antibodies. Another study in Oman 2016 reported that the most prevalent form of immunodeficiencies was phagocytic disorders (35.0%) followed by combined immunodeficiency (17.8%) [(14)].

Our study involved 158 patients, of them 105 were male and 53 were female with male to female ratio 1.9:1 with high prevalence in males and this finding was similar to most studies conducted on PID patients for example a study performed by Golan et al. (2002) reported a boy/girl ratio of 2/1 [(15)] in Iran revealed ratio 4:1[(16)]. Another Korian study the ratio was 3.6:1 sex ratio of boys to girls [(7)]**.** The ratio in China was 6:1 [(8)].

The high prevalence of x-linked disorders in males, like X-linked subtypes of CGD, X-linked agammaglobulnemia, Wiskott-aldrich, X-linked subtype of hyper IgM, and X-linked subtype of SCID, may be explained.

The patients' mean ages at the onset of symptoms were 9.00 (1.0-168) months, and at diagnosis, they were 24.00 (1.50-172) months. These findings matched data from Tunisia (24 months) [(15)] and Oman (21 months) [(10)]. But, South Africa (51 months) [(17)], Mexico (58.44 months) [(18)]**,** and Iran (42 months) all reported a delayed age of diagnosis [(19)].

The early age of diagnosis may be attributed to the severity of presentation and the predominance of primary cellular and CID with early presentation.

The time between the first presentations and the time of the definitive diagnosis is recognized as the average delay in diagnosis, and it has been found to equal 12 (0.00–108) months.

Consanguinity, a deeply rooted cultural trend in Egypt, ranges from 35.3 to 60 % causes a relative abundance in autosomal recessive disorders [(4)]**.**

Consanguinity showed high rates between our cases (58.2%) and this was near to an Egyptian study on PID patients 2022 [(20)] the rate was 52.8% .Other studies on PID patients showed also this high rate for example, a study in IRAN on PID [(21)] revealed consanguineous marriage in (60.1%) another study in Oman documented consanguinity in 76 % of patients [(10)] the same in sauidi Arabia (Al- In our study consanguinity rate was higher in rural areas than urban areas (76%) versus (23%) respectively and this is similar to most studies on Egyptian population either in the past [(22)] and recent studies [(23)] and this explain the higher rate of PID in rural areas than urban areas 70.9% vs 29.1%. the same in sauidi Arabia [(13)] 75% and Tunisia [(9)] (46%). However, there were lower consanguinity rates in South Africa (1.2%) [(17)] The UK (3%) [(24)] Germany (8.6%) [(25)] and France (15%) [(26)]**.**

It has been reported that a family history of known cases with PID has been detected in (24.1%). History of infections recurring in family members with no a recognized PID diagnosis was positive in 24.7% and 15.8%, a positive family history of siblings died at a young age by recurrent infections was recognized.

That was more or less similar to a study

conducted in Iran where 20.9% of participants had a family history of PID. Additionally, Family history of infections recurring with no a recognized PID diagnosis of was positive in 12.7% and 24.1%, a positive family history of mortality at a young age has been recognized.

However, another study in Saudi Arabia [13] documented a positive family history among 61% of patients with PID and this is due to higher rate of consanguinity.

In agreement with our study, 99 (62.7%) children had growth curves below the 5% percentile, 41 (25.9%) had growth curves between the 5% and 25%, 17 (10.8%) had growth curves between the 50% and 75%, and just one patient had a growth curve above the 75% percentile. This is nearly similar to a study on the Iranian population from 2006 [11].

Among the ten warning signs, recurrent pneumonia was the most common presenting sign (70.6%) of patient followed by ear infection 41% followed by recurrent abscess 44.3% followed by need for intravenous antibiotics 37%. Failure to thrive was represented by 32.9% and the least sign was family history of primary immunodeficiency 8.2%. And these findings were mostly similar in most studies [27,21].

The gastrointestinal (GI) system, which serves as a key barrier to infections and is regarded as the body's largest immune organ, is the next system commonly impacted by PIDs after the respiratory system, which is well known to be the most prevalent PID manifestation [28]. This affection may be infection, inflammatory, immune or malignancy. As regard GI manifestations diarrhea and vomiting were equally presented in 39% of cases without significant difference between different groups. But the majority of research revealed that between 20% and 50% of CVID patients have GI manifestations, which is a quite large prevalence [29,30]. Other GI manifestation was hepatosplenomegaly that was common among our cases; hepatomegaly was present in 36.6% of cases, splenomegaly in 16.5% of cases and hepatosplenomegaly in 11.3% of cases.

Also, inflammatory bowel disease was found in 4 cases and the four cases were combined ID. Autoimmune hepatitis was present in 2 cases in the group of syndromic CID. Hepatic abscess was present in 12 cases without significant difference between different groups.

Autoimmune manifestations are detected with substantial frequency in the cases suffering from 1ry deficiencies of antibody, involving selective immunoglobulin A deficiency (SIgAD) and common variable immunodeficiency (CVID), however can furthermore be evidenced in the cases suffering from CID [31,32].

Obviously autoimmune disorders were more common in PAD group as it was documented in almost all PID studies [33,34] especially CVID subgroup as mentioned above.

New studies involved large groups and a comparison cohort from Australia, The USA, and the Netherlands designated that the cases suffering from PIDs have represented a significantly elevated possibility of all cancers of 1.6-, 1.42-or 2.3-, fold, in that order, in comparison with the general population, much decreased than about 10,000-fold increase assessed in previous studies [35].

In our study 7 malignant cases were reported (3 lymphoma, 1 leukemia, 1 mylodysplasia, I pituitary carcinoma, 1 hemophagocytic lymphohistiocytosis "HLH"). Among different groups (4 case in syndromic CID {2 in hyper IGE syndrome (1 leukemia, 1 lymphoma), 2 in AT (1 mylodysplasia,1 pituitary carcinoma}, 2 cases in primary cellular and CID {1 HLH, 1 lymphoma}, 1 case phagocytic {lymphoma}) without significant difference.

Leukemia and lymphoma, particularly T-cell acute lymphoblastic leukemias [ALLs] and T-cell prolymphocytic leukemia, are the most prevalent types of malignancy in AT patients under the age of 20. These observations were typical as our study [34].

By comparison with other studies, in two Egyptian studies on PID patients [32,20] the mortality rate was 23.4% and 24.5%, respectively. Nonetheless, low death rates were observed in France [26] was (3.5%), Mexico [18] (6.82%), Saudi Arabia [13] (10.3%) and the United Kingdom [24] (13%).

Higher mortality rate in our country may be attributed to delayed diagnosis due to lack of knowledge between physicians as regard warning signs of PID so it is very important to raise the issue for early suspicion of PID between physicians to ensure early diagnosis and early intervention either by replacement therapy, prophylactic antibiotic, or bone marrow transplant.

Funding: Not funded.

Conflict of Interest: All researchers declared no conflict of interest.

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