Performance status and deaths among children registered in Kuwait National Primary Immunodeficiency Disorders Registry

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Summary

Children with primary immunodeficiency disorders (PIDD) have an increased risk of suffering from physical, social, and psychological problems. The aim of this study was to evaluate the performance status and mortality of children with PIDD in Kuwait and to determine the variables and co-morbidities that may affect their performance and risk of death. The data for the children were obtained from Kuwait National Primary Immunodeficiency Disorders Registry describes the patients' characteristics, co-morbidities and their treatment regimens. Each patient was scored using the Lansky Play Performance Scale (LPPS), and we evaluated the number of deaths among the children and the effects of different variables on their LPPS scores and mortality. We examined 98 pediatric patients with a mean delay in diagnosis of 21.2 months. Antimicrobial prophylaxis was administered to 57.2% of the patients, whereas intravenous immunoglobulin (IVIG) therapy was used in 44%. Eight patients underwent bone marrow transplants. The mean LPPS score for all the patients was 65.5, and there was a significant disparity in the mean LPPS scores across PIDD categories. Twenty-one patients died. The variables that were found to have a significant effect on both the LPPS score and the risk of death were an age of onset of less than 6 months, a history of CMV infection, parental consanguinity, the use of antimicrobial prophylaxis and IVIG therapy. In conclusion, patients with PIDD have a poor performance status and a high rate of mortality. Early diagnosis and aggressive therapeutic interventions directed at patients with early onset of symptoms and CMV infections can help improve the quality of life of patients with PIDD. *(Asian Pac J Allergy Immunol 2010;28:141-6)*

Key words: *primary immunodeficiency, quality of life, immunoglobulins, mortality, cytomegalovirus*

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Introduction

Primary immunodeficiency disorders (PIDD) are a heterogeneous group of genetic disorders that affect the development or function of the immune system. Patients with PIDD suffer from recurrent or severe infections and have a far higher incidence of autoimmune diseases and malignancies than the general population.[1-4] Early diagnosis and adequate therapy are important for the survival and quality of life of patients with PIDD; delays in diagnosis and/or inadequate management can lead to permanent organ damage and a shortened lifespan.[5-8] The true prevalence of PIDD is not known. However, previous reports have suggested that the prevalence of PIDD varies according to race and geography. A recent study suggested that PIDD are so common that primary care physicians are likely to see patients with PIDD in their practice.[9] Unfortunately, the failure of clinicians to recognize PIDD is still a major

worldwide problem. As a result, the diagnosis of PIDD in children and adult patients is usually delayed between 2½ to 5 years.[10-13]

In the last 15 years, molecular defects in approximately 130 PIDD patients have been defined,[14] and a genotype-phenotype correlation has been established for some of these patients, which has important prognostic and therapeutic implications.[15-17] In spite of these advances and the improved survival rates, children with PIDD have been found to be at risk for physical, social, and psychological problems due to their chronic health conditions and need for constant treatment.[18-25]

The aim of this study was to evaluate the overall performance status and deaths of children with PIDD in Kuwait and to determine the variables and co-morbidities that may affect their performance status and the risk of death.

Methods

Patients and data collection

The data for the children was obtained from Kuwait National Primary Immunodeficiency Disorders Registry (KNPIDR), which was approved by the Research and Ethics Committee of the Ministry of Health of Kuwait. The data corresponded to children under 16 years of age who were diagnosed and classified with PIDD according to the clinical and laboratory criteria for these diseases reported by the International Union of Immunological Society's (IUIS) Primary Immunodeficiency Diseases Classification Committee.[14] The presence of secondary immunodeficiencies (drug- or virus-induced, immunodeficiencies associated with metabolic disorders, among others) in these children was ruled out by obtaining their detailed medical history and by performing the appropriate tests. The data collected for the children included the age at onset of PIDD, the time of delay in diagnosis, gender, use of antimicrobial prophylaxis and/or intravenous immunoglobulin (IVIG) therapy, history of *Aspergillus* and cytomegalovirus (CMV) infections, sepsis, autoimmune manifestations, bronchiectasis, gastrointestinal and skin manifestations, and/or bone marrow transplants (BMT). The Lansky Play Performance Scale (LPPS), which ranges from 0 (unresponsive/death) to 100 (fully active/normal), was used to assess the overall performance status for each patient.[26] The children were scored using the LPPS in consultation with their families and was considered valid if assessed not more than 3 months before the preparation of this manuscript. The effect of different variables on both the LPPS score and mortality were evaluated.

Statistical analysis

Statistical analysis was performed using the Minitab software package, version 15.1.1.0 (LEAD Technologies). The mean and standard deviation was measured for the scale variables. Although the number of patients included in this study was large enough to assume normality using the CLT, in most of the tests conducted, we performed parametric and nonparametric tests to ensure the consistency of the results. Two-sample *t*- and Mann-Whitney tests were used to determine whether different categorical variables had a significant effect on the patients' LPPS scores or in the delay in diagnosis. In addition, a one-way ANOVA and the nonparametric Kruskal-Wallis test were used to assess the effect of the PIDD categories on the LPPS score and the delay in diagnosis after excluding 2 patients with complement deficiencies. Furthermore, the Pearson correlation test was used to determine whether there were any associations between the scale variables. Finally, the Pearson chi-Square test was used to determine whether the death of a patient was dependent on the categorical variables evaluated. *P*-values of ≤ 0.05 were considered statistically significant, and unless only one test was used, the reported *p* -values are from those tests that yielded a higher value, in the case of significance, and a lower value, in the case of insignificance.

Results

Frequency and distribution of PIDD

Here, we evaluated 98 pediatric patients (52 males and 46 females) with PIDD who were registered in KNPIDR. The patients were classified into the following PIDD categories: combined T- and B-cell immunodeficiencies (24 patients, 24%); predominantly antibody immunodeficiency (27 patients, 28%); other well defined immunodeficiencies (30 patients, 31%); diseases of immune dysregulation (8 patients, 8%); congenital defects in the number and/or function of phagocytes (7 patients, 7%); and complement deficiencies (2 patients, 2%). No patients with either defect in innate immunity or autoinflammatory disorders were registered.

Patient characteristics

The mean age of the patients at the onset of symptoms was 11 months (Standard Deviation 18.6). Seventy-eight patients (79%) presented symptoms before the age of 1 year, 13 (14%) presented symptoms between 1 and 3 years of age and 7 (7%) presented symptoms after the age of 3 years. The mean delay in diagnosis, which is defined as the time between the initial presentation of symptoms and the time of definite diagnosis, was 21.2 months (Standard Deviation 29 months). There were significant differences in the means of delay in diagnosis across patients in the different PIDD categories (p = 0.005). History of parental consanguinity was reported in 75% of the patients. Table 1 shows the details of the patients' characteristics and the frequency of different manifestations according to PIDD category. Infectious complications affected 85% of the patients, with the most common infections being pneumonia (59%), otitis media (38%), urinary tract infections (18%), skin abscesses (15%), sepsis (12%), sinusitis (7%), and infectious diarrhea (7%). Skin manifestations affected 39% of the patients, with the most common manifestations being skin infections (20%), eczema (18%), and erythroderma (8%). Gastrointestinal complications affected 40% of the patients, and the most common manifestations were chronic diarrhea (16%), gastroesophageal reflux (7%), and granulomatous disease of the gut (4%). Autoimmune complications affected 12% of the patients, and the most common manifestations were hemolysis and (6%) and thrombocytopenia 4%.

The Lansky Play-Performance Scale

The mean LPPS score for all the patients was 65.5 (Standard Deviation 37.7. We found a significant disparity in the mean LPPS scores across the different PIDD categories (p <0.0001) (Table 1). However, there was no statistically significant association between the LPPS score and the delay in diagnosis.

We found a statistically significant effect of CMV infection, parental consanguinity, use of

Table 1. Patients characteristics, co-morbidities and treatment used

Category	Number of patients Males/ Females	Onset age (months)*	Diagnosis delay (months)*	Lansky index*	Aspergillus Infection (%)	CMV Infection (%)	Sepsis (%)	Autoimmune Manifestations (%)	Bronchiectasis (%)	Gastrointestinal Manifestations (%)	Skin Manifestations (%)	Use of prophylaxis antimicrobials (%)	Use of IVIG (%)	Bone Marrow transplant (%)	Deaths (%)
All patients	98 52/46	11.1	21.2	65.8	4.1	9.2	13.3	12.2	10.2	37.7	36.8	57.2	43.9	8	21.4
Combined T and B cell immuno-deficiency	24 8/16	2.1	5.3	30.8		12.5	25	4.2	8.4	50	37.5	87.5	92	21	62.5
Predomi-nantly antibody deficiency	27 20/7	24.8	27.7	84.8	7.4	3.7	7.4	14.8	18.5	29.6	11.1	25.9	55.5		3.7
Other well defined immuno-deficiency syndromes	30 16/14	7.4	24.6	69.6		13.4	6.7	13.4	6.7	43.4	56.7	60	6.6		10
Diseases of Immune dysregu-lation	8 3/5	9.5	33.6	83.7		12.5		37.5	12.5	12.5	62.5	50			
Congenital defect in phagocyte number, function or both	7 5/2	1.3	6.7	65.7	28.6		28.6			42.9	14.3	71.5	14.3	42	28.5
Comple-ment deficiency	2 0/2	16	74	100			50				50	50			

*mean

antimicrobial prophylaxis and IVIG therapy on the LPPS score (p - values of 0.0009, 0.01, <0.0001 and 0.009, respectively). However, there was no statistically significant effect of gender, *Aspergillus* infection, sepsis, autoimmune manifestations, bronchiectasis, and gastrointestinal and skin manifestations on the LPPS score. When we analyzed only the patients with combined T- and B-cell immunodeficiencies, a history of BMT was found to have a significant effect on the LPPS score ($p = 0.0269$).

After dividing the patients into groups according to the their age at disease onset, we found that patients who presented symptoms when they were under 6 months of age had a lower LPPS score when compared to the patients in the other age groups ($p = 0.013$).

Patient management

Antimicrobial prophylaxis was used in 57.2% of the patients, whereas antibody replacement therapy in the form of IVIG infusion was used in 44% (Table 1). To reach a serum IgG level of >500 mg/dl, the dose of IVIG administered to the patients was of at least 400 mg/kg/dose every 4 weeks. To control infections and autoimmune manifestations, some patients received higher doses and/or more frequent infusions of IVIG. BMT was performed in 8 patients, of whom 5 had combined immunodeficiency and 3 had chronic granulomatous disease.

Mortality

Of the patients examined, 21 died (Table 1), and their mean age at the time of death of was 21 months (range: 2-192 months). Fifteen patients who were in the combined T- and B-cell immunodeficiencies group died, and their mean age at the time of death was 11 months (range: 2-30 months). The causes of death of the patients included respiratory failure with ARDS secondary to pneumonia, sepsis, and multiorgan, liver or renal failure. The same variables which were found to have a significant effect on the LPPS score (i.e., onset age under 6 months, CMV infection, parental consanguinity, use of antimicrobial prophylaxis and IVIG infusion) were also found to have a significant effect on the risk of death (p - values of 0.003, 0.009, 0.002, <0.0001 and, 0.004, respectively), whereas the other variables tested did not.

When we analyzed only the patients with combined T- and B-cell immunodeficiencies, 80% of the patients who underwent a BMT survived, whereas only 26% of the patients who did not undergo BMT were still alive at the time of preparation of this manuscript.

Discussion

We have shown in this report that patients with PIDD have a poor performance status and a high rate of mortality. The low LPPS scores and the high rate of mortality that we observed can be explained by the high frequency of severe forms of PIDD (i.e., combined T- and B-cell immunodeficiencies) and by the lack of a BMT in the majority of these patients. The observed variability in the LPPS scores among the patients in the different PIDD categories was expected because the severity and complications of disease are different between patients in different PIDD categories. In fact, it is also expected that the LPPS score will be variable for patients within the same PIDD group who have different diagnoses (i.e., for the group of patients who have predominantly antibody deficiencies, the mean LPPS scores between the patients with common variable immunodeficiency, Bruton's disease and selective IgA deficiency are expected to be different).

Our finding that CMV infection has a significant effect on both the LPPS score and the risk of death should prompt physicians to be more aggressive in diagnosing and treating CMV-infected PIDD patients earlier. Our results showing that antimicrobial prophylaxis, IVIG and BMT are beneficial therapeutic options for patients with PIDD are in agreement with the results of previous studies. However, additional studies are required to determine the optimal dose of IVIG, the target serum IgG levels to be reached and the choice of antimicrobial prophylaxis to use for treating patients with PIDD.

We did not find significant statistical evidence for an association between the LPPS score and the delay in diagnosis. In addition, we did not find evidence for an effect of co-morbidities, such as autoimmune manifestations, bronchiectasis, and gastrointestinal and skin manifestations, on the LPPS score or the risk of death. Interestingly, Aghamohammadi and colleagues also found that the survival rate of patients with PIDD is not influenced by a delay in diagnosis or by the complications associated with PIDD.[27] Our results can be explained by the fact that the patients' LPPS scores were measured after the initiation of treatment, which raises the possibility that a delay

in diagnosis may cause a significant effect on the performance status of the patients before being diagnosed and starting therapy. The lack of an effect of co-morbidities on the LPPS score and the risk of death indicates that the treatments administered to the patients to treat their co-morbidities are effective in preventing a poor performance status. Accordingly, we recommend implementing strategies that can help in the early diagnosis of PIDD and its associated co-morbidities so the appropriate therapies can be administered to prevent irreversible tissue damage, morbidity and mortality. These strategies may include neonatal screening programs and activities to improve physician awareness about PIDD. It is important to mention that co-morbidities and complications, which can evolve over time, affect a significant number of patients with PIDD.[28-30] As such, these patients require highly specialized management programs that are best delivered by multi-specialized care.

Our finding that patients who present symptoms before the age of 6 months have a poor performance status and a high rate of mortality when compared to other patients can be explained by findings which have demonstrated that patients with severe forms of PIDD, such as severe combined immunodeficiency, Wiskott-Aldrich syndrome and chronic granulomatous disease, present symptoms earlier in life than do patients with milder forms of PIDD, such as predominantly antibody deficiency.

Compared to patients on other PIDD registries,[13,31-34] the patients registered in the KNPIDR show a high frequency of severe forms of PIDD (i.e., combined T- and B-cell immunodeficiencies) and a lower frequency of the more benign predominantly antibody immunodeficiencies. This finding can be explained by the high consanguinity rate in our population of patients[35] and/or the effect of their racial background. As such, our finding that patients with PIDD have low quality of life indexes does not apply to the general PIDD population.

Conclusions

Our results show that patients with PIDD have a poor performance status and a high rate of mortality. Early diagnosis and aggressive therapeutic interventions specifically targeted to PIDD patients with early presentation of symptoms and CMV infections may help improve their quality of life. In addition, the public should be educated about the potential adverse effects of consanguinity. Furthermore, collaborative efforts should be continued to design the best therapeutic protocols to treat these patients.

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