

Parental Consanguinity and the Risk of Primary Immunodeficiency Disorders: Report from the Kuwait National Primary Immunodeficiency Disorders Registry

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Key Words

Primary immunodeficiency · Consanguinity · Epidemiology · Morbidity · Registry · Coefficient of inbreeding · Autosomal recessive · Genetic defects

Abstract

Background: It is proposed that consanguineous marriages increase the risk of primary immunodeficiency disorders (PID). The aim of this study is to review the frequency and pattern of parental consanguinity among PID patients and to determine its effects on the distribution of different PID, the patients' performance status and the risk of death. **Method:** The data was obtained from the Kuwait National Primary Immunodeficiency Disorders Registry. The coefficient of inbreeding was determined for each patient and the patients' overall performance status was assessed using the Lansky Play Performance Scale and the Karnofsky Performance Scale. **Results:** A total of 128 patients with PID from 99 families are reported. A family history suggestive of PID and parental consanguinity was reported in 44 and 75% of the patients respectively, while the mean coefficient of inbreeding was 0.044067. There were statistically significant associations between both a family history of PID and parental consanguinity and PID category, the risk of death and the patients' overall performance status. Evidence of autosomal

recessive transmission of disease was present in 44% of the patients. **Conclusions:** Parental consanguinity is a risk factor for the development of PID. There is a need to increase the public awareness of the health consequences of consanguineous marriages.

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Introduction

Primary immunodeficiency disorders (PID) are a diverse group of illnesses which are caused by a defect of the immune system and predispose the patients to both infectious and non-infectious complications. More than 200 clinical forms of PID have been described and more than 175 disease-related genes have been identified [1, 2]. Classical PID are usually monogenic disorders with mendelian inheritance [3]. Despite the recent emergence of dominant PID, and the well-documented existence of X-linked recessive traits, autosomal recessive (AR) PID are the most frequent types described [4]. Reports from Middle Eastern and Arab populations clearly show that both the prevalence and the pattern of PID are different compared to other populations, also reflecting the high consanguinity rate in these communities [5–10].

Consanguineous marriages, which are known to have adverse effects on morbidity and mortality [11], are a traditional practice in Middle Eastern and Arab cultures with a frequency of more than 50% in some countries [12–18]. Because of increased consanguinity, families of Middle Eastern origin have played a major role in the identification of novel and complex phenotypes associated with PID, including Veno-Occlusive Disease with Immune Deficiency (VODI) [19], CD40 deficiency [20], Jak3 deficiency [21] AICD deficiency [22], familial hemophagocytic lymphohistiocytosis type 5 [23], DOCK8 deficiency [24], and many forms of severe congenital neutropenia [25].

Kuwait is a small country located in the Arabian Peninsula and its population is characterized by a rapid rate of growth, large family size, and high rates of consanguineous marriages. About 45% of the patients evaluated at the Kuwait Genetic Diseases Center, which was established in 1981, suffered from disorders with AR inheritance [26]. PID in Kuwait are prevalent and characterized by a high frequency of combined T- and B-cell immunodeficiencies [5]. It was proposed that this could be due to the high rate of consanguinity among the population or due to racial backgrounds.

The aim of this study is to review the frequency and pattern of parental consanguinity among PID patients in Kuwait and to determine its effects on the distribution of different PID, the patients' performance status, and the risk of death.

Materials and Methods

Data Collection

The data was obtained from the Kuwait National Primary Immunodeficiency Disorders Registry (KNPIDR) which was approved by The Research and Ethics Committee of the Ministry of Health. The patients were classified according to both the clinical and laboratory criteria of PID reported by International Union of Immunological Societies (IUIS) Primary Immunodeficiency Diseases Committee [27]. The presence of secondary immunodeficiencies (drug- or virus-induced, immunodeficiencies associated with metabolic disorders, among others) in these patients was ruled out by obtaining their detailed medical history and by performing the appropriate tests.

Measures of Consanguinity

Parental consanguinity, which is defined as the union of individuals having at least one common ancestor, was recorded for each patient. The coefficient of inbreeding (F), which is the probability of homozygosity by descent, was determined depending on the degree of relationship between the parents as follows: double first cousins ($F = 1/8$), first cousins ($F = 1/16$), second cousins ($F = 1/64$), and beyond second cousins ($F = 1/128$). All other

types of unions were considered non-consanguineous with coefficient of inbreeding set at 0. The F value was calculated for each patient and the mean inbreeding coefficient was then computed. Furthermore, we categorized patients with parental consanguinity as 'more inbred' if they had $F \geq 1/16$, or as 'less inbred' if their $F < 1/16$.

Patients' Performance Status

The patients' overall performance status was assessed using the Lansky Play Performance Scale (LPPS) if the age was ≤ 16 years while the Karnofsky Performance Scale (KPS) was used for patients aged >16 years [28, 29]. The LPPS and KPS were scored in consultation with the patient or the family and were considered valid if assessed not more than 3 months before the manuscript preparation.

Statistical Analysis

Statistical analysis was performed using Minitab software package, version 15.1.1.0 (LEAD Technologies). The mean and standard deviation was computed for the scale variables. Two-sample t and Kruskal-Wallis tests were applied to assess whether scale variables have a significant effect on different categorical variables. In addition, Pearson's χ^2 test was used to determine the association between categorical variables. $p \leq 0.05$ was considered to be significant.

Results

A total of 128 patients (71 males and 57 females) with PID from 99 families were registered in KNPIDR and are presented in this report. The distribution of these patients according to PID categories is: combined T- and B-cell immunodeficiencies (30 patients, 23%), predominantly antibody immunodeficiency (31 patients, 24%), other well-defined immunodeficiency syndromes (38 patients, 30%), diseases of immune dysregulation (15 patients, 12%), congenital defects of phagocyte number, function or both (7 patients, 5.5%) and complement deficiencies (7 patients, 5.5%). No patients with either defects in innate immunity or autoinflammatory disorders were registered. None of the patients with combined T- and B-cell immunodeficiencies showed the immunologic phenotype suggestive of X-linked disease. There were 32 deaths (25%) among the registered patients.

A family history suggestive of PID was present in 56 patients (44%). The proportion of cases with a positive family history ranged from 27% in diseases of immune dysregulation to 86% in complement deficiencies (table 1). Parental consanguinity was reported in 96 patients (75%). The rate of parental consanguinity was different among PID categories ranging from 100% in both combined T- and B-cell immunodeficiencies and congenital defects of phagocyte number to 53% in other well-defined

Table 1. Measures of consanguinity in PID patients

Category	Family history of PID, %	Parental consanguinity, %	Double first cousins, %	First cousins %	Second cousins %	Beyond second cousins, %	Mean coefficient of inbreeding
All patients	43.8	75	9.4	49.2	4.7	10.9	0.044067
Combined T- and B-cell immunodeficiency	66.7	100	2.3	18	0.8	2.3	0.061719
Predominantly antibody deficiency	29	61.3	0	12.5	0.8	1.6	0.033266
Other well-defined immunodeficiency syndromes	36.8	52.6	3.9	5.5	2.3	3.1	0.030016
Diseases of immune dysregulation	26.7	93.3	3.1	5.5	0.8	1.6	0.064583
Congenital defect in phagocyte number, function or both	42.9	100	0	3.9	0	1.6	0.046875
Complement deficiency	85.7	85.7	0	3.9	0	0.8	0.045759

immunodeficiency syndromes (table 1). None of the families reported uncle-niece marriages because it is prohibited in Islam.

There were statistically significant associations between parental consanguinity and PID category, a family history of PID, and the risk of death (p values <0.0001 , <0.0001 , and 0.002 respectively). There was also a statistically significant effect of parental consanguinity on the patients' overall performance status (i.e. mean LPPS/KPS score for patients with parental consanguinity was 57.8 while it was 80.6 for patients with no parental consanguinity p value <0.0001). However, there was no statistically significant effect of being 'more inbred' or 'less inbred' on the tested variables.

There were statistically significant associations between a family history of PID and both PID category and the risk of death (p values 0.004 , and 0.007 respectively). There was also a statistically significant effect of a family history of PID on the patients' overall performance status (i.e. mean LPPS/KPS score for patients with a family history of PID was 53 while it was 71.9 for patients with no family history of PID, p value 0.007).

The mean delay in diagnosis, which is defined as the time between the initial presentation of symptoms and the time of definite diagnosis, was 27.3 months (0 month–31 years). However, there was no statistically significant effect of family history of PID on delay in diagnosis (i.e. mean delay of diagnosis for patients with a family history of PID was 27.4 months while it was 27.2 for patients with no family history of PID, p value 0.98).

Overall, the mean coefficient of inbreeding of the presented patients was 0.044067 and it ranged from 0.030016 in other well-defined immunodeficiency syndromes to 0.064583 in diseases of immune dysregulation.

Evidence of AR transmission of disease was present in 56 patients (44%). These patients were diagnosed with se-

vere combined immunodeficiency (27 patients), antibody deficiency syndromes (10 patients), ataxia-telangiectasia (7 patients), complement deficiency (5 patients), chronic granulomatous disease (3 patients), Chediak-Higashi syndrome (2 patients), cartilage-hair hypoplasia (1 patient) and hyper-IgE syndrome (1 patient). Genetic testing was performed in 63 patients (49%) and a genetic defect was identified in 52 patients (40%). The identified mutated genes were RAG1: 6 patients (severe combined immunodeficiency), DCLRE1C: 2 patients (severe combined immunodeficiency), ADA: 1 patient (severe combined immunodeficiency), ZAP-70: 1 patient (severe combined immunodeficiency), BTK: 4 patients (X-linked agammaglobulinemia), AICD: 4 patients (AR hyper-IgM syndrome), 22q11.2: 17 patients (DiGeorge syndrome), WAS: 3 patients (Wiskott-Aldrich syndrome), ATM: 5 patients (ataxia-telangiectasia), Fas: 3 patients (autoimmune lymphoproliferative syndrome), LYST: 1 patient (Chediak-Higashi syndrome), CYBA: 3 patients (chronic granulomatous disease), RMRP: 1 patient (cartilage hair hypoplasia), and PRF1: 1 patient (familial hemophagocytic lymphohistiocytosis type 2). Eleven patients (8.5%) presented with unique heretofore undescribed clinical and immunologic manifestations.

Discussion

PID represent a significant public health issue for Middle Eastern countries. We have found in the present study that the rate of parental consanguinity and the mean coefficient of inbreeding among our PID patients were 75% and 0.044067 respectively. These were higher than what is reported in the general population (54% and 0.0219 respectively) [12]. Accordingly, we can conclude with certainty that the previously reported high prevalence of

PID in our population [5] is caused by the high rate of parental consanguinity.

We found that parental consanguinity had adverse effects on the patients' quality of life, as assessed by the risk of death and the overall performance status. This can be explained by the high frequency of the severe forms of PID among the reported patients (i.e. combined T- and B-cell immunodeficiencies). It is possible that the poor outcome in some of the patients may reflect unique mutations or exposure to pathogens that are not as frequent in other populations. Additional studies are needed to address this issue. Interestingly, none of the presented patients with combined immunodeficiency suffered from X-linked severe combined immunodeficiency disease (SCID), whereas this is the most common form of SCID in other populations [30].

We have also found a high rate of positive family history suggestive of PID in our cohort of patients. While the presence of other affected members in the family should facilitate the diagnosis of PID, the presence of a positive family history was not associated with lower age at diagnosis in this study. This finding is consistent with a previous study where the diagnosis of about two thirds of patients with X-linked agammaglobulinemia, who could have been diagnosed at birth based on a positive family history, were diagnosed only later in life when they developed recurrent infections [31].

Forty-four percent of our patients had evidence of AR inheritance. This can be attributed to parental consan-

guinity since inbreeding tends to reveal recessive alleles present in heterozygous carriers and to increase the frequency of homozygous individuals for a given rare allele. In this regard, it is important to notice that availability of large consanguineous families may facilitate identification of novel disease-causing genes by linkage analysis and homozygosity mapping. Indeed, several PID-causing genes have been identified through the study of affected families from the Middle East, and it can be anticipated that study of the 11 patients in this series, who presented with unique clinical and immunologic manifestations, may also lead to the discovery of novel PID-related genes.

The findings in this study reinforce the need for implementation of strategies to increase the public awareness of the health burdens of consanguineous marriages. Furthermore, premarital and preconception carrier testing, genetic counseling, and prenatal diagnosis should be integral parts of the care of PID patients and their families. However, these measures should be undertaken with consideration of social and religious factors of the community.

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