Consanguinity in Primary Immunodeficiency Disorders; the Report from Iranian Primary Immunodeficiency Registry

Nima Rezaei¹, Zahra Pourpak¹, Asghar Aghmohammadi¹, Abolhassan Farhoudi¹, Masoud Movahedi¹, Mohammad Gharagozlou¹, Bahram MirSaeid Ghazi¹, Lida Atarod¹, Kamran Abolmaali¹, Maryam Mahmoudi¹, Davoud Mansouri², Saba Arshi³, Naser Javaher Tarash³, Roya Sherkat⁴, Reza Amin⁵, Sara Kashef⁵, Reza Farid Hosseini⁶, Iraj Mohammadzadeh⁷, Mehrnaz Sadeghi Shabestari⁸, Mohammad Nabavi⁹, Mostafa Moin¹

¹Department of Allergy and Clinical Immunology, Children Medical Center, Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran;
²Division of Infectious Diseases and Clinical Immunology, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran;
³Department of Immunology and Allergy, Rasoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran;
⁴Al Zahra Hospital, Isfahan University of Medical Sciences, Tehran, Iran;
⁵Department of Immunology and Allergy, Namazi Hospital, Shiraz University of Medical Sciences, Tehran, Iran;
⁶Department of Immunology and Allergy, Mashhad University of Medical Sciences, Tehran, Iran;
⁷Amirkola Hospital, Babol University of Medical Sciences, Tehran, Iran;
⁸Tabriz University of Medical Sciences, Tehran, Iran;
⁹Semnan University of Medical Sciences, Tehran, Iran

Keywords
Consanguinity, family history, Iran, primary immunodeficiency disorders

Correspondence
Zahra Pourpak, Immunology, Asthma and Allergy Research Institute, Children Medical Center, No. 62, Dr Gharib St, Keshavarz Blvd, PO Box 14185-863, Tehran 14194, Iran.
E-mail: rezaei_nima@hbi.ir; zpourpak@hbi.ir

Submitted August 27, 2005; accepted May 9, 2006.

Citation
doi:10.1111/j.1600-0897.2006.00409.x

Problem
Primary Immunodeficiency Disorders (PiD) are a heterogeneous group of genetic disorders, with different modes of inheritance. This study was accomplished in order to determine the frequency of consanguineous marriages in the families of patients with PiD.

Method
In this study, the records 515 Iranian PiD patients were reviewed during a 25-year period.

Results
The mean proportion of consanguineous marriages was 65.6% among PiD patients, while the overall rate was 38.6% in the country. The rate of consanguinity was 77.8% in cellular immunodeficiencies, 75.8% in combined immunodeficiencies, 72.5% in defects of phagocytic function, 58.6% in other immunodeficiencies, 54.1% in predominantly antibody deficiencies, and 50% in complement deficiencies. Moreover all patients with immunodeficiency associated with other diseases had consanguineous parents. Such marriages were most common in the parents of patients with Chediak-Higashi syndrome, severe combined immunodeficiencies, primary CD4 deficiency, ataxia-telangiectasia, seletive IgG class deficiencies, chronic granulomatous disease, and Schwachman syndrome.

Conclusions
It is important to inform the general population about the dangers of consanguinity, which is very common in some areas such as Iran. Premarital examination to avoid genetic diseases could be suggested, especially in a community where the rate of consanguineous marriage is high.
Introduction

Primary immunodeficiency disorders (PiD) are relatively rare disorders, characterized by unusual susceptibility to infections and predisposition to the development of autoimmune diseases and malignancies. More than 100 different disorders have been identified and categorized in PiD classification to date. The frequency of different types of immunodeficiency disorders varies among different regions of the world. PiD constitutes a wide group of genetic disorders, with different modes of transmission. Although the genes responsible for some of these disorders have been identified, much needs to be elucidated about these disorders.

Consanguineous marriages may increase the risk of autosomal recessive disorders and multifactorial diseases. Considering the increased risk of physical and mental disorders in the offspring, consanguinity has important public health consequences. Consanguineous marriages have been a long-standing social habit among Iranians. Early records of consanguinity were described in Iranian mythological literature. The prevalence of consanguineous marriages in a population depends on demographic, social, cultural and religious factors; so the frequency of consanguineous marriages varies across the world. Although this frequency is very low in USA and in many European countries, marriage with relatives is a common feature of the family systems in the Middle East and some Asian countries. Studies indicated that the rate of consanguinity varied from 20% to more than 70% in Muslim populations of the Middle East. Iran is one of the countries in the Middle East with a high rate of consanguineous mating.

Although there are a number of studies on the frequency of PiD and consanguinity in Iran, the frequency of consanguinity in PiD had not been studied. The present study was conducted to determine the frequency and patterns of consanguineous marriages in the parents of Iranian patients with PiD.

Materials and methods

Files of all patients with PiD, who had been referred to Iranian Primary Immunodeficiency Registry (IPIDR) during a 25-year period (1980–2005), were reviewed in this study. Patients were diagnosed based on a standard criteria; so, only well established immunodeficient patients were included in this registry. This survey was performed in collaboration by eight medical universities, which had immunodeficiency clinics, from six major provinces of Iran, including Tehran, Fars (Shiraz), Khorasan (Mashhad), Isfahan, Azarbayjan (Tabriz), and Mazandaran (Babol).

A consanguineous marriage was defined as one in which two partners had at least one ancestor in common, with the ancestor being no more distant than a great great grandparent. For descendants who were of the same generation, a consanguineous marriage was between one person and a third cousin or a closer relative. Consanguineous marriages were classified by the degree of relatedness between partners: first cousins, second cousins, and beyond-second cousins. For a given degree of relatedness, a second level of classification was noted, according to the sex of the individuals occupying the different points in the pedigree. That is, first cousins may either be the children of two brothers (patrilateral parallel cousins), of two sisters (matrilateral parallel cousins), or of a brother and a sister (cross-cousins).

Results

Five hundred and fifteen patients (324 men and 191 women) with the diagnosis of PiD were recorded in IPIDR till April 2005. Patients predominantly presented with antibody deficiencies (40.2%), followed by defects of phagocytic function (26.8%), cellular immunodeficiencies (17.3%), combined immunodeficiencies (6.4%), other immunodeficiencies (5.6%), immunodeficiency associated with other diseases (2.1%), and complement deficiencies (1.6%). In our patient population, common variable immunodeficiency was the most frequent disorder (n = 107), followed by chronic granulomatous disease (n = 89), ataxia-telangiectasia (n = 74), X-linked agammaglobulinemia (n = 45), selective IgA deficiency (n = 33), leukocyte adhesion defects (n = 25), severe combined immunodeficiency (n = 21), hyper-IgE syndrome (n = 16), and the rest of PiD were less than 15 in number (Table I). The mean age of our patients at the time of study was 14.95 ± 8.69 years (1 month–81 years). Fifty-six of these patients have died because of recurrent infections (10.9%) (Table I).

The overall rate of consanguineous marriages was 65.6%. Considering the major groups of PiD, the rate of consanguinity was high in cellular immunodeficiencies (77.8%), combined immunodeficiencies (75.8%), and defects of phagocytic function (72.5%), followed by predominantly antibody deficiencies (54.1%), other immunodeficiencies (58.6%), and complement deficiencies (50.0%). Moreover all patients in the group of immunodeficiency associ-
ated with other diseases had consanguineous parents. The rate of such marriages varied among different types of PID (Table II). Consanguineous marriages were most common in parents of patients with Chediak-Higashi syndrome, severe combined immunodeficiency, primary CD4 deficiency, ataxia telangiectasia, selective IgG class deficiencies, chronic granulomatous disease, Shwachman-Diamond syndrome, severe congenital neutropenia, leukocyte adhesion defects, common variable immunodeficiency, chronic mucocutaneous candidiasis, combined immunodeficiencies, and hyper-IgE syndrome.

According to the classification of consanguineous marriages, first cousin marriages were found in the parents of 220 cases (65.1%), including 68 patrilateral parallel cousins, 56 matrilateral parallel cousins, and 96 cross-cousins. Second cousin and beyond- second cousin consanguineous marriages accounted for 16.0% (54 cases) and 18.9% (64 cases), respectively (Table II).

Ninety-eight patients had positive history of immunodeficiencies in their families (19.0%). This rate was considerable in patients with selective IgG class deficiencies, C1 inhibitor deficiency, X-linked agammaglobulinemia, severe combined immunodeficiency,
### Table II

#### Frequency of Consanguineous Marriages in the Parents of Patients with Primary Immunodeficiency Disorders

<table>
<thead>
<tr>
<th>Category of Disorders</th>
<th>Name of disease</th>
<th>Patrilateral parallel cousins</th>
<th>Matrilateral parallel cousins</th>
<th>Cross-cousins</th>
<th>Total cousins</th>
<th>Total Number (n)</th>
<th>Consanguinity, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predominantly antibody deficiencies</strong></td>
<td>X-linked agammaglobulinemia</td>
<td>11 (37.8)</td>
<td>28 (62.2)</td>
<td>1</td>
<td>5</td>
<td>38 (62.2)</td>
<td>16 (36.4)</td>
</tr>
<tr>
<td></td>
<td>Hyper-IgM syndromes</td>
<td>66 (63.6)</td>
<td>39 (36.4)</td>
<td>12</td>
<td>5</td>
<td>75 (45.9)</td>
<td>22 (32.6)</td>
</tr>
<tr>
<td></td>
<td>Common variable immunodeficiency</td>
<td>14 (21.2)</td>
<td>55 (68.8)</td>
<td>2</td>
<td>4</td>
<td>61 (68.8)</td>
<td>4 (6.4)</td>
</tr>
<tr>
<td></td>
<td>Selective IgA deficiency</td>
<td>7 (35.2)</td>
<td>17 (84.8)</td>
<td>2</td>
<td>4</td>
<td>28 (84.8)</td>
<td>5 (17.8)</td>
</tr>
<tr>
<td></td>
<td>Selective IgG class deficiencies</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td>0</td>
<td>0</td>
<td>3 (33.3)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td></td>
<td>Antibody deficiency with normal or elevated Igs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Transient hypogammaglobulinemia of infancy</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
<td>0</td>
<td>0</td>
<td>2 (50.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>112 (54.1)</td>
<td>95 (45.9)</td>
<td>17</td>
<td>24</td>
<td>154 (45.9)</td>
<td>50 (22.7)</td>
</tr>
<tr>
<td><strong>Combined immunodeficiencies</strong></td>
<td>Combined immunodeficiency</td>
<td>7 (58.3)</td>
<td>5 (41.7)</td>
<td>2</td>
<td>0</td>
<td>14 (25.0)</td>
<td>4 (8.3)</td>
</tr>
<tr>
<td></td>
<td>Severe combined immunodeficiency</td>
<td>66 (76.4)</td>
<td>21 (23.6)</td>
<td>21</td>
<td>8</td>
<td>88 (23.6)</td>
<td>21 (23.6)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>100 (72.5)</td>
<td>38 (27.5)</td>
<td>25</td>
<td>13</td>
<td>148 (22.5)</td>
<td>26 (18.8)</td>
</tr>
<tr>
<td><strong>Other cellular immunodeficiencies</strong></td>
<td>Wiskott-Aldrich syndrome</td>
<td>1 (37.5)</td>
<td>6 (62.5)</td>
<td>0</td>
<td>1</td>
<td>8 (62.5)</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td></td>
<td>Ataxia-telangiectasia</td>
<td>60 (81.1)</td>
<td>14 (18.9)</td>
<td>2</td>
<td>1</td>
<td>66 (18.9)</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td></td>
<td>DiGeorge anomaly</td>
<td>1 (100.0)</td>
<td>0 (0.0)</td>
<td>0</td>
<td>0</td>
<td>1 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Primary CD4 deficiency</td>
<td>5 (83.3)</td>
<td>1 (16.7)</td>
<td>2</td>
<td>5</td>
<td>12 (16.7)</td>
<td>5 (8.3)</td>
</tr>
<tr>
<td></td>
<td>Severe congenital neutropenia (Kostmann)</td>
<td>6 (66.7)</td>
<td>3 (33.3)</td>
<td>1</td>
<td>0</td>
<td>10 (33.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Primary lymphocyte adhesion deficiencies</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td>0</td>
<td>0</td>
<td>3 (33.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Chronic granulomatous disease</td>
<td>66 (76.4)</td>
<td>21 (23.6)</td>
<td>21</td>
<td>8</td>
<td>88 (23.6)</td>
<td>21 (23.6)</td>
</tr>
<tr>
<td></td>
<td>Chronic atypical neutropenia (Rothmann)</td>
<td>6 (66.7)</td>
<td>3 (33.3)</td>
<td>1</td>
<td>0</td>
<td>10 (33.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Leukocyte adhesion deficiencies</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>112 (54.1)</td>
<td>95 (45.9)</td>
<td>17</td>
<td>24</td>
<td>154 (45.9)</td>
<td>50 (22.7)</td>
</tr>
<tr>
<td><strong>Defects of phagocytic function</strong></td>
<td>Chronic granulomatous disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Leukocyte adhesion deficiencies</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Complement deficiencies</strong></td>
<td>C1 inhibitor deficiency</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>C4 deficiency</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Immunodeficiency associated with other diseases</strong></td>
<td>Chronic mucocutaneous candidiasis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hyper-IgE syndrome</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Other immunodeficiencies</strong></td>
<td>Chronic mucocutaneous candidiasis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hyper-IgE syndrome</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
hyper-IgM syndromes, chronic granulomatous disease, and common variable immunodeficiency (Table II). Sixty-six of 98 cases had two patients of PiD in their families, 15 had three patients, 12 had four patients, and five had more than four patients with PiD in their families. The pedigrees of a number of families with consanguineous marriages and multi-cases are depicted in Fig. 1.

Discussion

Consanguinity is prevalent in many regions of Asia and Africa because of socioeconomic, cultural and religious factors. Historical sources report a strong preference of Iranians for marriage with relatives. Despite the fact that Iranians are prohibited against close relative marriage (e.g. a man’s mother, daughters, sisters, aunts, nieces, and some of his wife’s relatives) according to the Islamic rules mentioned in the Koran, men are allowed to marry with any of their parallel or cross-cousins. The mean proportion of consanguineous marriages in this country was 38.6%, ranging from 15.9% in the northern provinces to 47.0% in the eastern provinces. The overall rate of consanguineous marriages in our patients with PiD was 65.6%, which is much higher than the rate in the normal population. This rate was not lower than 50% in none of the major groups of PiD. Even though studies in Arab countries report a very high proportion of consanguineous marriages, the rate of such marriages in Iranian patients with PiD is higher than in other countries.

Consanguineous marriages were most common in the patients with autosomal recessive inheritance such as Chediak-Higashi syndrome, severe combined immunodeficiency, ataxia-telangiectasia, Shwachman-Diamond syndrome, severe congenital neutropenia, leukocyte adhesion defects, and chronic mucocutaneous candidiasis. It should be noted that several types of PiD do not follow a single pattern of inheritance, while they are clearly influenced by genetic factors; such examples are common variable immunodeficiency and selective IgA deficiency, which have variable inheritance, and primary CD4 deficiency, selective IgG class deficiencies, and hyper-IgE syndrome, which have unknown inheritance. Consanguineous marriages were also high in the parents of patients with chronic granulomatous disease. This disease may be inherited either X-linked or autosomal recessive, of which X-linked accounts for about 70% of all patients. Male patients constituted two-thirds of our patient group, which is lower than that observed in other studies. It may arise from a higher frequency of autosomal recessive inheritance.
due to an increased consanguinity in Iranians. However, a more accurate description of hereditary patterns needs a precise determination of the patients’ genotype, which is not feasible because of poor facilities in our country. As expected, the rate of consanguineous marriages in the patients with X-linked inheritance like X-linked agammaglobulinemia, hyper-IgM syndromes and Wiskott-Aldrich syndrome was 38%, which was similar to that observed in the normal population.

First cousin marriages were the most common form of consanguineous union in the parents of our patients, with cross-cousins favored. The rates of first cousin, second cousin, and beyond-second cousin consanguineous marriages were 42.7%, 10.5%, and 12.4%, respectively. This order is similar to the Iranian population with 27.9%, 4.3%, 6.3%, respectively. In first cousin marriages, cross-cousin type was much higher than patrilateral parallel cousins and matrilateral parallel cousins. Unlike many other populations in the Middle East, Iranian men do not have any special preference for marriage with close kin. In fact, a general bilateral preference for marriage with close kin has been reported in many regions of Iran. The highest risk of transmission of the genetic disorders belongs to first-degree marriages, which is approximately 30% in Iran. It would increase the frequency of all autosomal recessive disorders. Moreover, the gene of autosomal recessive disorders in the community is expressed more in first cousin marriages.

A positive family history of PiD was found in 19% of our patients. The family history is very important in assessing the patients for possible immunodeficiencies. A relevant family history may suggest a diagnosis before clinical symptoms appear. As seen in some pedigrees (Fig. 1), there are also some affected members in the non-consanguineous generation. Consanguinity in rural regions of Iran is complex. There are many consanguineous marriages in each family; maybe the patients’ parents could not describe the exact pedigrees in the previous generations. So, we guess that they may have a common ancestor as they have the same family name.

As PiD are caused by genetic factors, genetic counseling for the affected child’s parents, siblings and the extended family is indispensable. Genetic counseling issues vary depending on the mode of inheritance of the PiD. In families with autosomal recessive immunodeficiencies, the major concern is prenatal diagnosis for the patient’s siblings to be at risk of having affected children. In families with X-linked or autosomal dominant disorders, the genetic risks should be discussed again during the reproductive age. As sisters, cousins, and aunts of boys with X-linked immunodeficiencies are at risk of having affected children, carrier detection as well as prenatal diagnosis is a concern for these families. In other immunodeficiencies that follow less clearly defined patterns of inheritance, genetic issues should also be addressed. To avoid genetic diseases premarital examination could be recommended, especially in a community where the rate of consanguineous marriage is high. Important factors such as religious beliefs need to be considered when offering prenatal diagnosis to certain families.

Consanguineous marriage is an important social and health problem which should be addressed by an intensive health education campaign. In some countries such as Iran, where consanguineous marriages are common, there is an urgent need for public education programs and for providing the facilities for genetic counseling and reproductive risk assessment. The educational programs could be directed toward unmarried young females and males, especially those who had a genetic disorder in their families, in order to increase their awareness of the potential risks of consanguineous marriages.

Acknowledgments

We thank all colleagues who contributed to this study. We gratefully acknowledge the efforts of Dr Akefeh Ahmadi Afshar, Dr Hengameh Abdollahpour, Dr Laleh Amiri Kordestani, Dr Ali Babaei Jandaghi, Dr Jafar Bakhshaei, Dr Nasrin Bazargan, Dr Mohammad Hassan Bemanian, Dr Leila Emami, Dr Mohammad Reza Fazlollahi, Dr Zohreh Habibi, Dr Taha Hojjati Ashrafi, Dr Mahboubeh Mansouri, Dr Fereshteh Rafiei Samani, Dr Afshaneh Shirani, Dr Mojdeh Vaziri, and Dr Fariborz Zandieh for their role in collecting the data. We are also thankful to Dr Katayoun Bidad for editing the English of this manuscript, to laboratory personnel Mrs Anna Isaeian and Mrs Anahita Azimdoost, and to secretarial personnel Ms Tahereh Aghabaraghi Kashi, Ms Zahra Arij, and Ms Zahra Shobayri for their arrangements and administrative efforts.

References

1 Aghamohammadi A, Moein M, Farhoudi A, Pourpak Z, Rezaei N, Abolmaali K, Movahedi M, Gharagozlou M, Ghazi BM, Mahmoudi M, Mansouri D, Ashrafi, Dr Mahboubeh Mansouri, Dr Fereshteh Rafiei Samani, Dr Afshaneh Shirani, Dr Mojdeh Vaziri, and Dr Fariborz Zandieh for their role in collecting the data. We are also thankful to Dr Katayoun Bidad for editing the English of this manuscript, to laboratory personnel Mrs Anna Isaeian and Mrs Anahita Azimdoost, and to secretarial personnel Ms Tahereh Aghabaraghi Kashi, Ms Zahra Arij, and Ms Zahra Shobayri for their arrangements and administrative efforts.

References


