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Combined immunodeficiency in the United States and Kuwait: Comparison of patients' characteristics and molecular diagnosis

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ABSTRACT

Aim: To compare different variables among (S)CID patients diagnosed in the USA and Kuwait.
Methods: Review of patients registered in The US Immune Deficiency Network registry or Kuwait National PID Registry between 2004 and 2014.
Results: Totals of 98 and 69 (S)CID patients were registered during the study period in the USIDNET registry and the KNPIDR, respectively. The average annual incidence rate for the period 2004–2014 of (S)CID in children in Kuwait was 13.01/100,000 children, with an estimated occurrence of 1/7500 live births. There were differences between the two countries in the following variables: age at onset and diagnosis, family history of (S)CID, parental consanguinity, and outcome. More than 14% of (S)CID patients from USIDNET registry were diagnosed through newborn screening.
Conclusions: Patients' characteristics and molecular causes of S(CID) are different between USA and Kuwait. NBS for SCID should be started in countries where the incidence of (S)CID is high.

1. Introduction

Combined immunodeficiencies (CID) are characterized by defects in T-lymphocyte differentiation or function and variably associated with defects of B- or NK-lymphocytes. Over 40 different molecular defects can result in CID [1] and the list is growing due to availability of next generation sequencing (NGS) and advances made in functional assays. CID are characterized by a high level of genetic, immunologic and clinical heterogeneity. Patients with severe combined immune deficiency (SCID) present very early in life with interstitial pneumonia, failure to thrive, candidiasis and chronic diarrhea [2]. However, atypical SCID and CID are often characterized by delayed clinical presentation (beyond 1 year with recurrent infections, autoimmunity, granuloma, skin manifestations, lymphoproliferation and increase risk of malignancies) [3–5]. These patients often harbor hypomorphic mutations in SCID-causing genes, or have defects in gene less critical for T-lymphocyte development and/or function. In many cases, the genetic defect remains unknown. Early diagnosis of CID is of critical importance for prompt medical intervention, including prophylactic antibiotics, avoidance of live vaccines and non-irradiated blood products, and initiation of immunoglobulin replacement therapy. However, immune reconstitution can only be achieved with allogeneic hematopoietic stem cell transplantation (HSCT) or gene therapy [6], and in the case of adenosine deaminase (ADA) deficiency with enzyme replacement therapy.

Based on newborn screening (NBS) results in eleven of the United States of America (USA), typical and atypical SCID were found to affect 1 in 58,000 newborns [7]. Registry reports of several countries and regions show wide variations in geographical and racial prevalence as well as the frequencies of different types of PID [8–15]. Because most of (S)CID-causing gene defects are inherited in an autosomal recessive pattern, it is expected that (S)CID would be more prevalent in countries in which consanguineous marriages are common.

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The aim of this study is to compare different variables among (S)CID patients diagnosed in the USA and Kuwait.

2. Method

Patients included in this study were diagnosed between January 2004 and December 2014 and registered in the United States Immune Deficiency Network (USIDNET) registry or Kuwait National Primary Immunodeficiency Disorders Registry (KNPIDR). Details about both registries can be found elsewhere [11,15]. The registries were queried for the following patients' data: gender, age at onset, age at diagnosis, family history of CID, parental consanguinity, molecular diagnosis, outcome (alive/dead) at the time of data retrieval and whether the patient was diagnosed through NBS. NBS in Kuwait was limited to the use of flow cytometry for patients who had a family member affected by (S)CID. The same was applied in the United States until 2008 when NBS was started in Wisconsin by quantifying levels of T-cell receptor excision circles (TRECs) in dried blood spots collected at birth followed by flow cytometry for confirmation. In the United States, TREC assay is currently implemented in 30 states, the District of Columbia and the Navajo Nation. For patients who were treated with HSCT, age at transplant and type of donor were also queried.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 22, IBM Corp., Armonk, NY, USA). Pearson's Chi-square test was used to assess the association or significant differences between two qualitative variables, while Z-test was applied to compare two proportions. Two-sample non-parametric Kolmogorov–Smirnov test was used for the quantitative variables. A probability value of $p < 0.05$ was considered as the cut-off level for statistical significance.

3. Results

Totals of 98 and 69 (S)CID patients were registered during the study period in the USIDNET registry and the KNPIDR, respectively. There were missing data from USIDNET registry as shown in Supplementary Table 1. Patients from the USIDNET registry presented at an earlier age [mean: 2.78 months, standard deviation (SD): 2.65, standard error (SE): 0.41] compared to those from KNPIDR [mean: 7.99 months, SD: 18.21, SE: 2.20], p: <0.001. They were also diagnosed at an earlier age [mean: 3.06 months, SD: 3.07, SE: 0.527] compared to patients from KNPIDR [mean: 20.71, SD: 35.28, SE: 4.247], p: <0.001. Patients' characteristics from both registries are shown in Fig. 1. There were differences between the two countries in the following variables: family history of (S)CID, parental consanguinity, and outcome. More than 14% of (S)CID patients from USIDNET registry were diagnosed through NBS. They constituted 23% of patients who were diagnosed in 2008 onward.

While there were no statistical differences in the frequency of molecularly-confirmed diagnosis in the two registries, there were important differences in the distribution of individual genotypes. In particular, most of the (S)CID patients from the USIDNET registry had adenosine deaminase (ADA) or γc deficiencies, while those from KNPIDR had recombinase activating gene (RAG) 1 or 2, major histocompatibility complex (MHC) II and dedicator of cytokinesis 8 (DOCK8) deficiencies (Fig. 2). The frequency of X-linked disease-causing gene defects (γc and CD40L) in USIDNET registry was 28% compared to none in KNPIDR (p: <0.001).

The frequency of HSCT performance in both registries was comparable (Fig. 1). However, most of the transplants in USIDNET registry were from haploidentical donors, whereas the majority of transplants in the KNPIDR were from matched related donors (Table 1), p: <0.001.

4. Discussion

In this report, we have compared patients' characteristics and molecular profile of (S)CID patients diagnosed in the USA and Kuwait between 2004 and 2014. The average annual incidence rate for the study period was 13.01/100,000 children born in Kuwait, with an estimated occurrence of 1/7500 live births. This is almost 8-fold higher than the reported incidence of 1 in 58,000 infants in the USA [7]. This high incidence is most probably due to the common practice of consanguineous marriages in Kuwait (94% in the current report). A similar high incidence of CID (1 per 2000 births) was documented in the Navajo Nation [16] and in Konya, a city in central Turkey, where the incidence of CID was found to be 1 per 10,000 live births [17], demonstrating that the high incidence of CID can also be caused by other variables such as ethnic, genetic (founder effect, genetic isolates) and geographical factors. Consanguineous marriages not only increase the frequency of CID, but also affect the distribution and the type of genetic defects causing these diseases as apparent by the fact that none of the presented CID patients from KNPIDR suffered from X-linked forms of (S)CID, whereas they accounted for 28% of all cases in the USIDNET registry. A recent review of published CID-related data in PubMed showed that deficiencies in MHC II and RAG1/2, which are transmitted as autosomal recessive traits, are the most common causes of CID in the Middle East, while γc deficiency, which is responsible for X-linked SCID, represents the most common cause of SCID in other geographical areas and ethnicities [18]. Most of the (S)CID patients from the USIDNET in the current study were caused by ADA deficiency (30%) followed by γc deficiency (20%). This seems to contradict previous reports from the

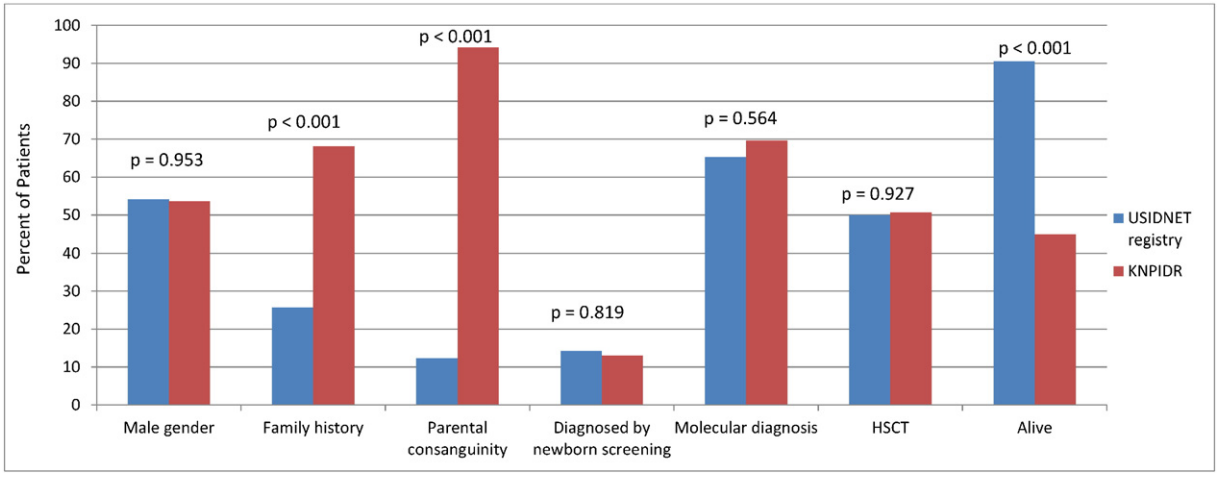

Fig. 1. Characteristics of S(CID) registered in the United States Immune Deficiency Network (USIDNET) registry and Kuwait National Primary Immunodeficiency Disorders Registry (KNPIDR).