

Combined immunodeficiency: The Middle East experience

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Previous reports about primary immunodeficiency disorders have shown variations in the frequency and distribution among populations from different ethnic and geographic backgrounds. In this review we describe peculiarities about combined immunodeficiencies (CIDs) in the Middle East. The frequency and type of genetic defects causing CIDs in this region differ in comparison with those in other populations because of the common practice of consanguineous marriage in the Middle East, which results in the relative increase in autosomal recessive diseases. We highlight some of the challenges in the awareness, diagnosis, and therapy of CIDs in the region and the research opportunities, especially those directed toward the identification of novel disease-causing genes. (*J Allergy Clin Immunol* 2013;■■■■:■■■-■■■.)

Key words: Primary immunodeficiencies, combined, Middle East, consanguinity

In our new mini-series "Allergy and clinical immunology around the world," we ask experts from different parts of the world to tell us about issues that are of particular interest in their regions, reflecting either distinctive diseases or unique approaches to common problems.

Combined immunodeficiencies (CIDs) are a group of phenotypically heterogeneous genetic disorders characterized by profound deficiencies of T- and B-cell function, which predispose the patients to both infectious and noninfectious complications. Mutations in 32 different genes have been found to cause these conditions,¹ which are potentially life-threatening unless immune reconstitution is accomplished.

The overall incidence of CID is estimated to be 1 in 75,000 to 100,000 live births.² Because most forms of CID are inherited as autosomal recessive traits, they would be expected to be more common in areas with high rates of consanguinity, such as the Middle East. Although accurate epidemiologic data remain scarce, anecdotal experience suggests that the incidence of

Abbreviations used

CID: Combined immunodeficiency
HSCT: Hematopoietic stem cell transplant
PID: Primary immunodeficiency disorder

CIDs is higher in the Middle East than in Western countries, probably exceeding 1 in 10,000 live births. Furthermore, review of published data from the Middle East in PubMed demonstrates differences in the genetic defects causing CIDs compared with that seen in subjects of other ethnicities and geographic areas (Fig 1).^{3,4} Although deficiencies in MHC class II and recombination-activating genes 1 or 2, which are transmitted in an autosomal recessive pattern, are the most common causes of CIDs in the Middle East, defects in the IL-2 common γ chain, which are X-linked, are the most common causes of CIDs in other geographic areas and ethnicities. Consanguineous marriages, which exceed 50% in many Middle Eastern countries,⁵ not only increase the frequency of CIDs but also affect the distribution and type of genetic defects causing these diseases, emphasizing the significance of knowing the local pattern and genetic background in each country or ethnicity before adopting the worldwide regular candidate gene approach. It is important to mention that we frequently encounter patients with CIDs who have unique clinical and immunologic phenotypes. This could be due to unique mutations in well-known genes, to pathogen exposures not as common in other populations, or to novel genes affecting disease in the Middle East.

CHALLENGES IN THE MIDDLE EAST

Lack of epidemiologic data

Few countries in the Middle East have established national registries to determine the prevalence of common primary immunodeficiency disorder (PID) phenotypes in their populations. Establishing such registries in the Middle East, as well as other countries, is essential not only for epidemiologic data but also for demonstrating to health authorities the magnitude of the health problem and the need for strategies to care for patients with these disorders.

Awareness and education about CIDs and consanguinity complications

Consanguineous marriage resulting from cultural and social practices is common in Middle Eastern countries, predisposing to the high incidence of autosomal recessive genetic disorders, including CIDs. Public awareness campaigns about CIDs and the medical consequences of consanguineous marriage might help in reducing the incidence of CIDs in the Middle East.

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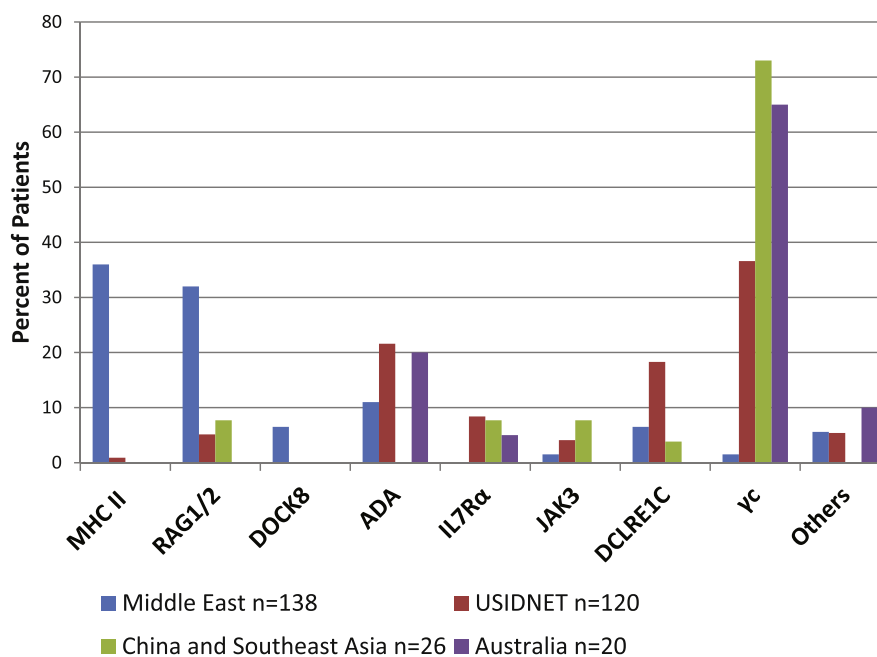


FIG 1. Mutation frequency in genes affecting Middle Eastern patients with CIDs based on published data in PubMed compared with other patients registered in USIDNET, China and Southeast Asia,³ and Australia.⁴ ADA, Adenosine deaminase; DCLRE1C, Artemis DNA recombinase repair protein; DOCK8, dedicator of cytokinesis 8; γ c, γ chain of receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21; IL7R α , IL-7 receptor α chain; JAK3, Janus-activating kinase 3; MHC II, major histocompatibility complex II; RAG1/2, recombination-activating gene 1/2.

Diagnosis

The extreme clinical, phenotypic, and genetic heterogeneity of many patients with CIDs represents a significant challenge to many Middle Eastern countries in which possibilities to perform extensive immunologic investigation and mutation analysis are often limited because of either financial or personnel limitations. These challenges are variable, and even with the rapid economic rise of many countries in the region, access to clinical immunology services and special immunologic and genetic testing is only available in limited specialized centers in major cities.

Therapy (clinical immunology and hematopoietic stem cell transplantation services)

Clinical immunology and hematopoietic stem cell transplantation (HSCT) facilities emerged as unique clinical services in a few countries since the early 1980s driven by the health demands of the population. A report from a single transplantation center in the Middle East showed that more than 80% of HSCT procedures were performed from HLA-matched related donors, whereas the remaining donor sources were either unrelated umbilical cord blood or haploidentical bone marrow.⁶ However, access to immunoglobulin therapy and HSCT is very limited or unaffordable for many patients in some of the Middle East countries.

FUTURE DIRECTIONS

Newborn screening

Because patients with CIDs are asymptomatic at birth and early diagnosis and initiation of therapy is essential for cure, CIDs have been recognized as candidates for population-based newborn

screening. The T-cell receptor recombination excision circle assay is already implemented in a few countries.^{7,8} Universal newborn screening is a cost-effective means to improve the quality and duration of life for children with CIDs, and disease incidence is a critical driving force affecting the incremental cost-effectiveness ratio.⁹ Implementing such a program in the Middle East is possible in resource-rich countries if health authorities recognize the seriousness of the health problem and provide all required resources to manage diagnosed patients.

Family-based preventive program for CIDs

In Middle Eastern countries the majority of patients with CIDs are from families known to have the disease.^{10,11} It would be cost-effective to establish programs to identify all family carriers and offer appropriate genetic counseling, premariage screening, and pregestational genetic diagnosis for affected couples. However, implementation of such programs should respect societal norms and individual beliefs.

Research

The importance of PID research is receiving more attention by the research community in the Middle East. Because Middle Eastern populations have a high prevalence of consanguinity, affected families provide the opportunity of identifying novel and complex phenotypes, such as veno-occlusive disease with immune deficiency,¹² Janus-activating kinase 3 deficiency,¹³ activation-induced cytidine deaminase deficiency,¹⁴ familial hemophagocytic lymphohistiocytosis type 5,¹⁵ dedicator of cytokinesis 8 deficiency,¹⁶ CD40 deficiency,¹⁷ and many forms of severe congenital neutropenia.¹⁸ Research laboratories in some Middle

Eastern countries offer genetic testing for PIDs. This genetic testing has identified specific genetic defects in 70% of affected subjects, primarily autosomal recessive defects. Because of the autosomal inheritance, whole-genome sequencing targeted to consanguineous families is likely to be productive in identifying the novel gene defects responsible for PIDs. The characterization of both novel mutations of known PID genes and novel genes will assist in the quantification of specific mutations, including the identification of founder effects. Finally, genotype-phenotype correlation studies might promote the development of patient-tailored prognosis and therapeutic plans.

Cooperation and commitment of clinical immunologists in the Middle East should be a strong impetus to develop clinical immunology services in the region. Multicenter collaborations and establishment of a common database will provide epidemiologic data on common PIDs. Creation of a Middle East society for PIDs would provide a forum and platform for enhanced medical education, dissemination of knowledge, and fostering of collaboration. Ultimately, formal subspecialty training in clinical immunology will be necessary for additional improvements in patient care. The lessons learned in the Middle East potentially will advance the understanding and care of patients with PIDs throughout the world.

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