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DOI: <https://doi.org/10.28942/atuj.v6i3y2026.160>INBORN ERRORS OF IMMUNITY IN THE ERA OF GLOBALIZATION:
EVOLVING CONCEPTS AND CLINICAL IMPLICATIONSNasrullayeva G.M.^{1,2}, Mammadova V.R.^{1*}, Nazirzade M.M.¹, Mollayeva N.O.²**Abstract**

Globalization, migration, urbanization, and environmental changes exert a significant impact on human health, particularly on immune system function. These factors have contributed to evolving perspectives on congenital immunodeficiencies, now more accurately referred to as inborn errors of immunity (IEI). Previously considered rare and underdiagnosed, these disorders are currently recognized as a major global health concern.

Advances in molecular genetic technologies have enabled early and precise diagnosis of IEI. International collaboration, the development of global registries, and the standardization of clinical protocols have increased detection rates worldwide. Environmental influences also affect immune function through modulation of the microbiota and microbiome.

Neonatal screening using TREC/KREC assays is increasingly becoming standard practice in many countries for the early detection of severe forms of IEI, such as severe combined immunodeficiency (SCID). The concept of IEI reflects a paradigm shift, recognizing immune disorders as complex, dynamic conditions. The immune system is now viewed not only as a collection of cells and molecules but as an integrated ecosystem interacting with genetic and environmental factors.

Keywords: *Inborn Errors of Immunity, Primary Immunodeficiency, Globalization, Neonatal Screening, Microbiome*

INTRODUCTION

In recent decades, globalization has profoundly influenced medicine alongside

economic and communication systems. It has facilitated the discovery of previously unrecognized diseases and enabled the rapid global exchange of scientific knowledge regarding diagnosis and treatment. Enhancing the translation of scientific findings into clinical practice has become a key priority in modern healthcare [1,4].

Globalization, migration, urbanization, and environmental changes significantly affect immune system function. Increasing

Yazışma üçün əlaqə:

Nasrullayeva G.M.^{1,2}, Mammadova V.R.^{1*}, Nazirzade M.M.¹, Mollayeva N.O.²

1Azerbaijan Medical University, Scientific Research Laboratory of Immunology

2Azerbaijan Medical University, I children department, Baku, Azerbaijan

*For correspondence E-mail: vafaimmun26@gmail.com



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interactions across geographical, ethnic, and social boundaries have further shaped immune responses. These developments have led to a transformation in the understanding of congenital immunodeficiencies. Once considered rare and poorly characterized, these conditions are now recognized as a significant global health issue [2,3,8]. Historically, primary immunodeficiencies were frequently misdiagnosed or overlooked, with patients receiving only symptomatic treatment for recurrent infections. Advances in immunology and genetics have demonstrated that these disorders comprise a heterogeneous group of diseases with diverse clinical manifestations. Consequently, the term

inborn errors of immunity (IEI) has been adopted to reflect this complexity [2,7,8].

Changing Perspectives in a Globalizing World

Globalization has accelerated progress in medical technologies and genetic research. Modern molecular diagnostic methods allow early and accurate identification of IEI. International cooperation, global databases, and standardized clinical protocols have significantly increased detection rates. Although these conditions were previously under recognized, substantial progress has been achieved in recent years. Nevertheless, globalization presents both advantages and challenges (Figure 1) [1,3].

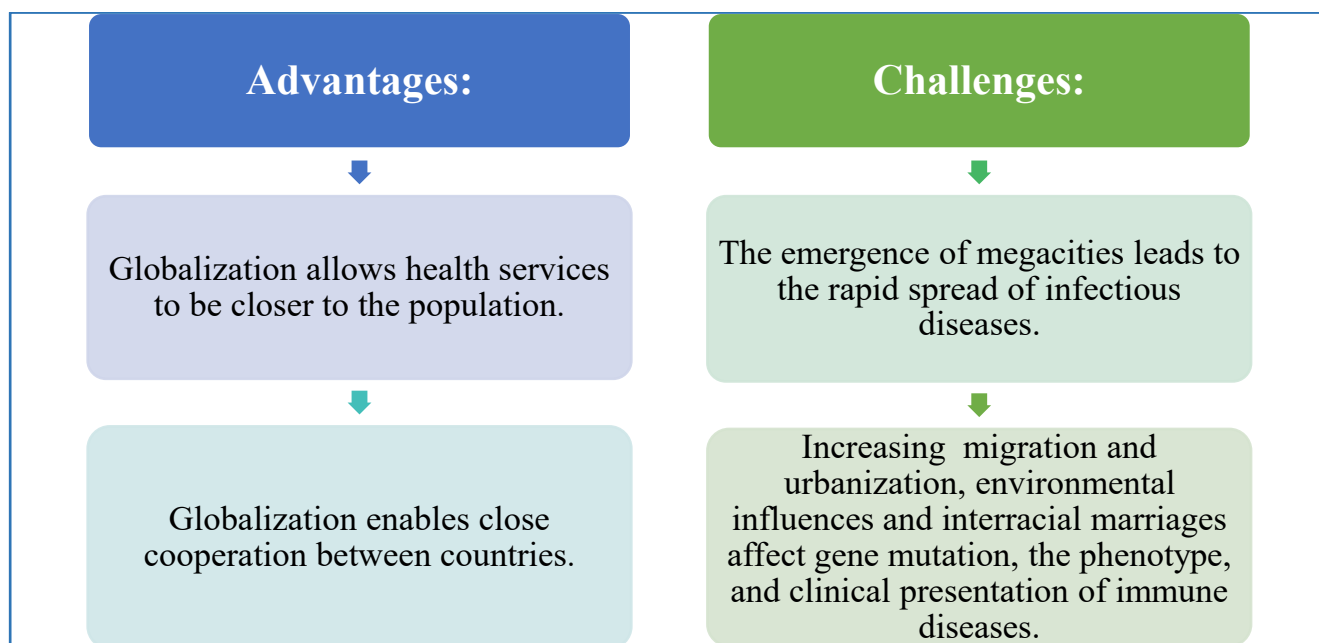


Figure 1. Advantages and challenges of globalization.

The foundation of immune function lies within the human genome. Epigenetic modifications regulate gene expression and are highly sensitive to environmental factors such as infections, microbiome composition, toxins, and stress. As a result, individuals with the same genetic mutation may exhibit markedly different phenotypes,

ranging from severe combined immunodeficiency (SCID) to mild antibody deficiencies. Conversely, similar clinical phenotypes may arise from different genetic mutations [5,12].

Key mechanisms underlying genetic variability include:

- Gene frequency

- Diversity of gene expression
- Gene–gene interactions
- Environmental influences [6,7]

Globalization, urbanization, environmental pollution, and changes in the microbial environment can lead to the following consequences: increased incidence of certain genetic diseases in the population, changes in the clinical symptoms of genetic diseases, increased risk of genetic predisposition, and the spread of rare mutations in consanguineous marriages. From the perspective of modern genetics and immunology, immunodeficiency diseases are of particular interest.

Previously, many children with severe primary immunodeficiencies died at an early age. Today, thanks to modern and effective treatments such as immunoglobulin therapy, bone marrow transplantation, and gene therapy, patients survive into adulthood and have children.

As a result, some rare mutations (CTLA4 deficiency, LRBA deficiency, APDS (PIK3CD), STAT3, and ADA deficiency) can persist and become more common in the population.

Environmental factors also influence immune function through their effects on the microbiota and microbiome. The microbiome comprises all microorganisms and their genetic material residing in and on the human body, forming a complex ecosystem that affects metabolism, immunity, and overall health. Its composition is highly individualized and influenced by diet, lifestyle, and environmental exposures.

The microbiota plays a critical role in immune system development, immune memory formation, and immune regulation. Under normal conditions, the immune system and microbiota maintain a balanced relationship that ensures protection against pathogens while preserving tolerance to

harmless antigens. However, factors such as excessive antibiotic use and dietary additives may disrupt this balance, leading to immune dysregulation.

The development of the immune system and the maintenance of homeostasis are just two of the many areas in which the microbiota is important. It is known that a healthy microbiota balance is important in the management of inflammatory responses by supporting immune tolerance. In this regard, first of all, the interactions between the microbiota and the immune system are investigated, and the influence of the microbiota on the immune system is studied in detail. Then, the molecular and cellular mechanisms of the microbiota balance in specific autoimmune diseases can be evaluated. In this regard, the interactions and clinical manifestations of these two mechanisms should be studied, and therapeutic approaches targeting the microbiota, such as prebiotics, probiotics, and fecal microbiota transplantation, may be prescribed [12].

Microbiome alterations in patients with IEI may result in dysbiosis, microbial translocation, mucosal immune dysfunction, chronic inflammation, and impaired immune regulation. These processes contribute to complications such as autoimmunity, lymph proliferation, and malignancy, significantly affecting patient outcomes and quality of life [9,10,12].

IEI in the Context of the COVID-19 Pandemic

The COVID-19 pandemic highlighted variability in immune responses across populations. Environmental factors such as urban density, pollution, and microbiome diversity may influence susceptibility and disease severity.

The pandemic also exposed vulnerabilities in healthcare systems, particularly affecting patients with IEI. Disruptions in plasma

donation negatively impacted the availability of immunoglobulin replacement therapy, a cornerstone of treatment. Patients with IEI are at increased risk of infections, and ongoing research explores genetic predisposition to severe COVID-19. Additionally, vaccine responses in these patients may be suboptimal due to impaired B- and T-cell immunity. Consequently, efforts have intensified to develop more effective and durable immunization strategies [5].

New Concepts in Inborn Errors of Immunity

Advances in molecular genetics have redefined the classification of immune disorders, leading to the adoption of the term *inborn errors of immunity (IEI)*. The immune system is now conceptualized as a dynamic and integrated ecosystem. The concept of the *immunome* has emerged, reflecting the interaction between genetic factors and environmental influences [3,4,6].

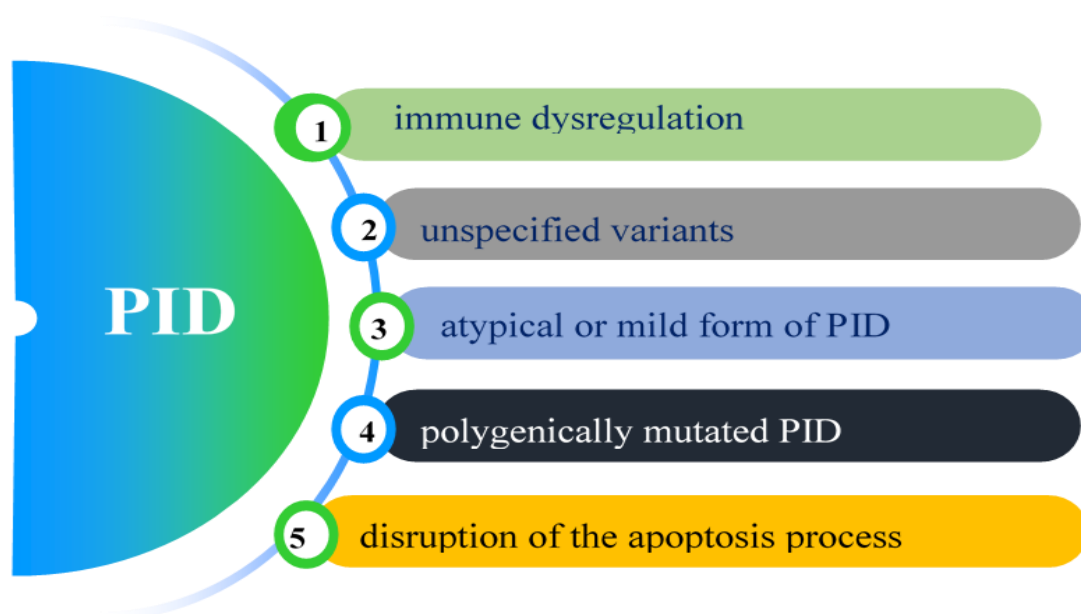


Figure 2. New forms of primary immunodeficiency

Next-generation sequencing (NGS) has identified more than 690 gene defects associated with IEI. Thus, there has been a shift the paradigm from isolated genetic defects to complex networks of immune dysregulation, from the importance of a single gene to the multiple interactions of genetic changes [1, 5, 12]. As a result, new forms of PID have emerged (Figure 2).

Newborn Screening Programs

Newborn screening programs are implemented in many countries and now it is part of routine healthcare, although the

range of screened conditions varies widely. Initially introduced for the detection of phenylketonuria, these programs now have expanded significantly over time [12, 13]. This program allows us to detect several serious hereditary diseases before clinical symptoms even appear. Also, it plays a critical role in preventing severe complications. This is particularly important for primary immunodeficiencies, where early diagnosis can be life-saving.

In 2022, this program in Azerbaijan is dedicated to the following diseases: phenylketonuria, cystic fibrosis, adrenogenital syndrome, hypothyroidism,

and galactosemia. In 2026-2027, the program plans to include testing for severe combined immunodeficiency (SCID) using a heel-prick blood test.

TREC/KREC-based screening is increasingly used for early detection of severe IEI, particularly SCID. TREC reflects newly formed T-lymphocytes. It is a small DNA fragment formed during T-cell development in the thymus and indicates the number of naive T cells. KREC reflects newly formed B cell.

SCID is characterized by: impaired T-cell development, reduced or absent B cells, dysfunction of natural killer (NK) cells

Early diagnosis enables timely hematopoietic stem cell transplantation (HSCT), significantly improving outcomes. This underscores the importance of early identification in reducing morbidity and mortality [1, 6].

Future Directions

- Integration of artificial intelligence in immunological diagnostics
- Development of global registries combining genomic and clinical data
- Strengthening multidisciplinary collaboration
- Expansion of telemedicine to improve access in low-resource settings [4,5]

CONCLUSION

A multidisciplinary approach is essential in the management of patients with IEI, involving immunologists, pediatricians, geneticists, infectious disease specialists, and other healthcare professionals.

Globalization has transformed the understanding and management of primary immunodeficiencies. Advances in diagnostics, treatment, and international collaboration have improved patient outcomes. Continued progress in this field will further enhance our understanding of immune system disorders and support the

development of innovative therapeutic strategies.

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QLOBALLAŞMA DÖVRÜNDƏ İMMUNITETİN ANADANGƏLMƏ SƏHVLƏRİ: ELMI KONSEPSİYALARIN İNKİŞAFI VƏ KLİNİK ƏHƏMİYYƏTİ

Nasrullayeva G.M.^{1,2}, Məmmədova V.R.^{1*}, Nazirzadə M.M.¹, Mollayeva N.O.²

¹ Azərbaycan Tibb Universiteti, İmmunologiya Elmi-Tədqiqat Laboratoriyası

² Azərbaycan Tibb Universiteti, I Uşaq xəstəlikləri kafedrası, Bakı, Azərbaycan

* Yazışma üçün E-mail: vafaimmun26@gmail.com

Xülasə

Qloballaşma, miqrasiya, urbanizasiya və ətraf mühitdə baş verən dəyişikliklər insan sağlamlığına, xüsusilə immun sisteminin funksional vəziyyətinə əhəmiyyətli təsir göstərir. Bu amillərin təsiri nəticəsində anadangəlmə immun çatışmazlıqları haqqında elmi təsəvvürlər əhəmiyyətli dərəcədə dəyişmiş və hazırda bu xəstəliklər daha geniş anlayış olan *immunitetin anadangəlmə səhvləri* (Inborn Errors of Immunity – IEI) termini ilə ifadə olunur. Əvvəllər nadir və çox zaman gec diaqnostika olunan xəstəliklər kimi qiymətləndirilən bu patologiyalar hazırda qlobal səhiyyənin mühüm problemlərindən biri hesab edilir.

Molekulyar-genetik texnologiyaların sürətli inkişafı immunitetin anadangəlmə səhvlərinin erkən və dəqiq diaqnostikasına imkan yaratmışdır. Beynəlxalq əməkdaşlığın genişlənməsi, qlobal xəstə registrlərinin yaradılması və klinik protokolların standartlaşdırılması bütün dünyada bu xəstəliklərin aşkar edilmə səviyyəsinin yüksəlməsinə şərait yaratmışdır. Eyni zamanda, ətraf mühit amillərinin mikrobiota və mikrobiomun tərkib və funksiyasına təsiri immun sisteminin fəaliyyətinin formalaşmasında mühüm rol oynayır.

TREC/KREC analizlərindən istifadə etməklə neonatal skrining bir sıra ölkələrdə ağır immun çatışmazlığı formalarının, xüsusilə ağır kombine olunmuş immun çatışmazlığının (SCID) erkən aşkarlanması məqsədilə getdikcə daha geniş tətbiq olunur və standart diaqnostik yanaşmaya çevrilməkdədir.

İmmunitetin anadangəlmə səhvləri konsepsiyasının formalaşması immun pozğunluqlarına yanaşmada yeni paradigmanı əks etdirir. Bu konsepsiyaya əsasən, immun sisteminin xəstəlikləri sadəcə ayrı-ayrı immun hüceyrələrinin və ya molekulalarının funksional pozğunluğu kimi deyil, genetik və ətraf mühit

amilləri ilə qarşılıqlı əlaqədə olan mürəkkəb və dinamik proseslər kimi qiymətləndirilir. Müasir yanaşmada immun sistemi yalnız hüceyrə və molekulların məcmusu deyil, genetik xüsusiyyətlər və ətraf mühit amilləri ilə qarşılıqlı əlaqədə fəaliyyət göstərən inteqrasiya olunmuş bioloji ekosistem kimi nəzərdən keçirilir.

Açar sözlər: *immunitetin anadangəlmə səhvləri, birincili immun çatışmazlığı, qloballaşma, neonatal skrining, mikrobiom.*

ВРОЖДЕННЫЕ ОШИБКИ ИММУНИТЕТА В ЭПОХУ ГЛОБАЛИЗАЦИИ: ЭВОЛЮЦИЯ КОНЦЕПЦИЙ И КЛИНИЧЕСКИЕ АСПЕКТЫ

Насруллаева Г.М.^{1,2}, Мамедова В.Р.^{1*}, Назирзаде М.М.¹, Моллаева Н.О.²

¹ *Азербайджанский медицинский университет, Научно-исследовательская лаборатория иммунологии, Баку*

² *Азербайджанский медицинский университет, кафедра детских болезней I, Баку, Азербайджан*

** Для корреспонденции E-mail: vafaimmun26@gmail.com*

Резюме

Глобализация, миграция, урбанизация и изменения окружающей среды оказывают существенное влияние на здоровье человека, в частности на функционирование иммунной системы. Воздействие этих факторов обусловило изменение современных представлений о врожденных иммунодефицитах, которые в настоящее время более корректно обозначаются термином *врожденные ошибки иммунитета* (Inborn Errors of Immunity, IEI). Ранее рассматривавшиеся как редкие и часто недодиагностируемые заболевания, данные состояния в настоящее время признаны значимой глобальной проблемой здравоохранения.

Достижения в области молекулярно-генетических технологий обеспечили возможности для ранней и точной диагностики врожденных ошибок иммунитета. Международное сотрудничество, создание глобальных регистров и стандартизация клинических протоколов способствовали повышению выявляемости данных заболеваний во всем мире. Существенное влияние на функционирование иммунной системы оказывают также факторы окружающей среды, в том числе посредством модуляции микробиоты и микробиома.

Неонатальный скрининг с использованием методов определения TREC/KREC все чаще становится стандартной практикой в ряде стран для раннего выявления тяжелых форм врожденных ошибок иммунитета, в частности тяжелого комбинированного иммунодефицита (SCID).

Современная концепция врожденных ошибок иммунитета отражает смену парадигмы в понимании иммунных нарушений как сложных и динамических состояний. Иммунная система в настоящее время рассматривается не только как совокупность клеток и молекул, но и как интегрированная биологическая система, функционирование которой определяется взаимодействием генетических факторов и факторов окружающей среды.

Ключевые слова: *врожденные ошибки иммунитета, первичные иммунодефициты, глобализация, неонатальный скрининг, микробиома.*