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Review Article

Beyond Genes: The Social Dimensions of Inborn Errors of Immunity

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Abstract

Inborn errors of immunity (IEIs) necessitate a well-funded healthcare system and substantial financial resources for diagnosis and treatment. More than that, these diseases and socioeconomic status are inversely related. Immune deficiencies are better managed by those with higher socioeconomic position, but the emotional and financial tolls of living with a compromised immune system can be devastating for patients and their families, causing them to struggle financially for years to come. For a long time, the patient and people close to her are impacted by these conditions. Conversely, the national healthcare system and patients' socioeconomic situation determine the likelihood of early diagnosis and successful treatment. Development of the immune system throughout infancy is really crucial. Fetal development is regulated by maternal nutrition, psychological stress, the mother's mental health, and supporting social networks. The immune system develops from conception and matures during neonatal and early childhood. Effective IEI management and therapy require genetic and social factors to interact. Geneticists, immunologists, healthcare providers, and politicians must collaborate to address IEIs. Insufficient resources for complete newborn screening and genetic testing for all patients make treating the increased incidence of autosomal recessive and genetic diseases in MENA problematic. Primary immunodeficiency (PID) treatments including stem cell transplantation and gene therapy are limited in Latin America and Africa. Parental comprehension, awareness, and attitudes of PID genetic testing depend on service accessibility, familial history, and individual circumstances. Patients resist genetic therapy due to financial constraints, notably the high cost of genetic testing. Hematopoietic stem cell transplantation (HSCT) may treat nonmalignant lymphohematopoietic diseases, myeloid and lymphoid malignancies, immunological deficits, genetic disorders, and inborn metabolic problems. Improving PID outcomes requires correcting these discrepancies. This review aims to underscore the critical need for heightened awareness and improved diagnostic methods for IEIs by analyzing the interplay between genetic factors and societal influences.

Keywords: IEIs; PIDs; Immunological Dysregulation; Hematopoietic Stem Cell Transplantation

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Introduction

IEIs refer to a category of genetic disorders marked by the absence or malfunctioning of immune system components. The term "primary immunodeficiencies" has been updated to IEIs to reflect the varied clinical presentations, including immune deficiencies and exaggerated or unusual immunological responses (1). The pathogenic traits of specific monogenic variants underscore the critical and unique roles of particular genes, proteins, pathways, and cell types in the development and function of leukocytes and non-hematopoietic cells, which are essential for maintaining immune homeostasis and safeguarding the host. Consequently, IEIs function as a significant paradigm for linking particular monogenic abnormalities to clinical manifestations of immunological dysregulation (2). Clinically, IEIs are associated with recurrent infections, cancers, and immunological dysregulation, resulting in an unregulated immune response that causes inflammation and organ damage. Both children and adults are impacted by IEIs, with more than 50% of global IEI instances occurring in those aged over 25. IEIs are rather prevalent, with estimated rates reaching as high as 1 in 1200, and they are associated with considerable morbidity and mortality (1). Patients are often underdiagnosed due to symptom overlap and the intricate genetic framework of IEIs, characterized by incomplete penetrance, pleiotropy, and epistasis. Furthermore, several critical instances may culminate in mortality prior to identification, rendering the precise prevalence of IEIs ambiguous. Timely diagnosis is crucial, particularly in settings lacking newborn screening for inherited endocrine disorders, as insufficient care significantly increases mortality rates (3). The majority of IEIs have an autosomal recessive (AR) inheritance pattern, leading to a heightened frequency in populations with prevalent consanguineous marriages. The prognosis of a patient is influenced by factors such as immunization and perinatal screening policies, cultural and religious practices, and the accessibility of advanced diagnostic and therapeutic alternatives and examines genetic and sociocultural factors to emphasize the necessity for increased awareness of IEI and improved diagnostic methodologies. Contemporary medicine, public health, education, and culture are crucial for efficient management and treatment. Comprehending these ailments throughout healthcare systems and communities enhances diagnosis and outcomes. Geneticists, immunologists, healthcare professionals, and legislators must cooperate to tackle IEIs and ensure patients receive timely medications that enhance their quality of life and prognosis (4). This review aims to underscore the critical need for heightened awareness and improved diagnostic methods for IEIs by analyzing the interplay between genetic factors and societal influences. Efficient management and treatment depend not alone on medical advancements but also on public health initiatives, education, and cultural awareness. Enhancing understanding of these illnesses within healthcare systems and communities can promote earlier diagnoses and improve outcomes for affected persons. Ultimately, fostering collaboration among geneticists, immunologists, healthcare professionals, and legislators is crucial in addressing the challenges posed by IEIs, ensuring that patients receive timely treatments that significantly improve their quality of life and overall prognosis.

Development of the immune system and Influential factors

The immune system begins its development from conception and continues to mature throughout the neonatal period and early childhood. This ongoing process is delicate, as both accelerated and delayed development can be detrimental to the individual (5). Several organs, including the liver, bone marrow, thymus, spleen, skin, kidneys, intestines, and lungs, are essential in the formation of the immune system during fetal development (6). Hematopoiesis undergoes significant changes in the bone marrow and liver during fetal growth, producing all blood cells from a population of self-renewing, multilineage hematopoietic stem and progenitor cells (HSPCs). However, the concept of a single progenitor cell has evolved into a layered model, where various immune cells emerge from precursor cells in three distinct waves (7). The first wave of human hematopoiesis starts in the yolk sac, forming balloon-like structures near the embryo. Mesenchymal cells differentiate into hematopoietic cells, primarily producing nascent erythrocytes by 16-

18 days of gestation. During this time, primitive macrophages, megakaryocytes, and primitive erythroblasts also emerge, along with the first appearance of CD45+ cells. By four weeks of gestation, several progenitors, including HSC-like progenitors, NK cell progenitors, erythroid cells, mast cells, and ILC progenitors, can be detected. The fetal yolk sac acts as a source of macrophages, with the embryonic pancreas becoming populated with macrophages by six weeks of gestation. Fetal NK cells and ILCs contribute to tissue protection, while LTi cells support the formation of secondary lymphoid structures, playing a crucial role in the early development of innate lymphocytes in the human embryo (6). The second wave, beginning around six weeks post-conception, involves erythro-myeloid progenitors arising from hemogenic endothelial cells (7). These progenitors possess the ability to differentiate into macrophages, monocytes, granulocytes, and mast cells (8-10). Finally, around 10 to 12 weeks post-conception, the third wave, known as definitive hematopoiesis, occurs when adult-type HSPCs emerge from the aorta-gonad-mesonephros region, eventually seeding the fetal liver and later colonizing the fetal bone marrow (7).

Several factors influence the development of the immune system during the intrauterine period. Research shows that maternal nutrition and psychosocial stress can impact fetal immune responses, potentially leading to long-term health consequences for the child (11). For instance, poor mother nutrition has been linked to poor immune systems in infants, implying that the intrauterine environment is absolutely vital in determining immune development. (12). Moreover, maternal mental health, including stress and anxiety, can affect fetal immune programming, potentially increasing the child's susceptibility to infections later in life (13). Additionally, having supportive social networks during pregnancy can alleviate some of the negative effects of stress, highlighting the importance of social factors in the development of the immune system (14). Studies in humans and animals suggest that alcohol consumption during pregnancy can disrupt fetal immune development, increasing the risk of infections and diseases in newborns that may persist throughout life. Alcohol may indirectly affect the immune system by raising the risk of premature birth, which itself is a known risk factor for immune-related issues (15). Maternal obesity and over/undernutrition during critical periods, especially in the first 1000 days of life, can have lasting impacts on the child's health. Children born to mothers with obesity may have reduced immune responses, increasing their susceptibility to infections (7).

Consanguineous marriages and Inborn errors of immunity

It is well established that consanguineous couplings increase the risk of multifactorial diseases and autosomal recessive disorders (16). Autosomal recessive disorders are significantly linked to consanguinity in genetic anomalies. About 30% of sporadic, undiagnosed cases of intellectual disabilities, congenital malformations, and dysmorphism may arise from an autosomal recessive inheritance, with a possibility of recurrence in future pregnancies (17). The health repercussions of inbreeding mostly stem from the increased likelihood that offspring of consanguineous parents will be homozygous by descent, inheriting two identical alleles, a scenario less common among children of non-consanguineous unions (18). Consanguinity presents significant public health challenges due to the heightened probability of physical and psychological disorders in progeny (16). Research from countries with high consanguinity rates has highlighted a distinctive distribution of Primary Immunodeficiencies (PIDs), with a prevalence of severe forms such as Combined Immunodeficiencies (CIDs) and phagocytic dysfunction, contrasting with the predominance of antibody deficiencies observed in other populations (18). A study indicated that factors like parental consanguinity and early disease onset could help identify a subgroup of Common Variable Immunodeficiency (CVID) patients characterized by more complications, poorer prognosis, and a greater need for medical care (19). The prevalence of consanguineous marriages varies across populations, influenced by demographic, social, cultural, and religious factors (20-22). Notably, many countries in the Middle East and North Africa (MENA) region exhibit some of the world's highest rates of consanguineous marriages, ranging between 20% and 50%, with first

cousin marriages accounting for approximately 20-30% on average (23). The MENA region spans nearly 15 million square kilometers, from Morocco in the west to Iran in the east, encompassing 22 countries and territories with a population of 385 million, or about 6% of the global population (24). Populations in this region are of diverse ethnic origins, and the combination of high consanguinity rates and large family sizes in some communities leads to an increased prevalence of autosomal recessive Mendelian Inherited Disorders (MIDs) (25). Socio-cultural factors such as preserving family structure and property, ease of marital arrangements, improved relations with in-laws, and financial benefits related to dowry play a significant role in the preference for consanguineous marriages among Arab populations (26). These marriages are generally perceived as more stable than those between non-relatives, although no studies have directly compared divorce rates between consanguineous and non-consanguineous unions among Arabs. It is commonly believed that in marital disputes, the husband's family is more likely to support the consanguineous wife, who is seen as part of the extended family. When children with disabilities are born, more family members may contribute to their care. Contrary to common belief, consanguinity in the Arab world is not limited to Muslim communities; Christian populations in Lebanon, Jordan, and Palestine also practice it, albeit less frequently than Muslims (23). Demographically, the region is characterized by high consanguinity rates, large family sizes, and rapid population growth. There is a significant prevalence of autosomal recessive disorders, and increased frequencies of homozygosity for autosomal dominant traits, such as familial hypercholesterolemia, and X-linked traits, such as glucose-6-phosphate dehydrogenase deficiency (27). Recent improvements in the MENA region include an increase in the number of patients receiving intravenous immunoglobulin (Ig) replacement therapy. However, there is still a shortage of resources for newborn screening and the availability of genetic tests for all patients. Advancing pre-symptomatic diagnosis of patients with other IEIs, including those with high morbidity and mortality rates, such as phagocytic and complement deficiencies, is necessary in MENA countries. Enhancing awareness of IEI and improving diagnostic capabilities will lead to more referrals for Hematopoietic Stem Cell Transplantation (HSCT) (28).

Awareness of PIDs

Access to healthcare for individuals with primary immunodeficiency (PI) continues to be a substantial global concern. Despite the increasing incidence of PI, which currently impacts over six million individuals globally, awareness and access to prompt diagnosis and treatment varied significantly across various locations. Although modern therapies like as stem cell transplantation and gene therapy are accessible in developed regions like North America and Europe, their availability is significantly restricted in places such as Latin America and Africa (29). PIDs are more prevalent than formerly recognized, highlighting an urgent necessity to enhance awareness among healthcare practitioners. Heightened awareness is crucial for facilitating prompt diagnosis and treatment, as several instances of PIDs are frequently overlooked due to insufficient comprehension of the illnesses. This error results in postponed treatment, potentially causing serious repercussions from infections (30). Parental knowledge, awareness, and perceptions regarding genetic testing for PID are shaped by several factors, including access to services, family history, and personal circumstances. Access to genetic services is particularly crucial in shaping awareness and understanding of genetic testing (31). One of the key measures to achieve early diagnosis is enhancing the medical community's knowledge of PID (32).

Research has highlighted a significant lack of awareness about primary immunodeficiencies among graduating medical students. On average, only 59.2% of questions were answered correctly, indicating that many students are not sufficiently informed about these conditions (33). A study conducted in Japan revealed a notable gap in knowledge among physicians regarding PIDs, with many unaware of the optimal IgG trough levels necessary for diagnosing and managing these disorders (32). A study conducted at a national pediatric reference hospital in Peru revealed that although physicians possessed some acquaintance with primary immunodeficiencies (PIDs), their overall awareness and comprehension of these illnesses and their warning indications were

inadequate (34). In Ukraine, it was found that 59.2% of physicians correctly answered more than half of the questions regarding PID, indicating a moderate level of awareness. Pediatricians and general practitioners had superior performance compared to other specialties, achieving a larger percentage of accurate responses (35). 2010 research in the United States indicated that merely 32% of surveyed physicians had diagnosed, treated, or referred a patient with PID in the preceding five years, underscoring a substantial deficiency in the recognition and management of these illnesses among primary care clinicians (36). In Brazil, there is a significant shortage of medical awareness of PID among healthcare practitioners (37). This knowledge gap persists even among pediatricians, who generally have more exposure to these conditions. Approximately 70% of the surveyed physicians reported acquiring knowledge of PID throughout their medical education or residency training; nevertheless, this education is inadequate in translating into significant clinical knowledge or practice (38). A study conducted in Iran on physicians' awareness of PID revealed that only 20.4% of the 794 participants answered more than two-thirds of the questions correctly, indicating a deficiency in awareness (39, 40). Similar studies have indicated a significant need for improved pre- and postgraduate education in primary immunodeficiencies for physicians in regions such as Southeast and East Asia, Turkey, India, and South Africa (41-44). (**Table 1**)

Medical education and public awareness initiatives have been essential in enhancing the diagnosis of many conditions (45). In Eastern Europe, initiatives under the J Project, spearheaded by Professor Lazlo Marodi, have been established to rectify the discrepancies in PID diagnosis and patient care between Eastern and Western European nations, primarily attributed to insufficient physician awareness and restricted access to genetic testing (46, 47). A 2020 study assessed physician awareness of PID prior to and following the introduction of a teaching program, revealing a substantial rise in awareness. The proportion of correct responses in survey questions increased from 58.3% in 2016 to 79.0% in 2019, indicating a significant enhancement in participants' knowledge. Pediatricians demonstrated significant improvement, with over 80% correct responses in the 2019 study, highlighting the necessity of focused educational initiatives in specialties more prone to encountering PIDs (48). Extensive undergraduate and postgraduate education, continuing medical education (CME) courses, and the dissemination of educational materials, including posters, pamphlets, and articles, have positively influenced the enhancement of physicians' knowledge (39). Awareness programs have proven beneficial in enhancing diagnoses, minimizing delays, and facilitating earlier discovery of primary immunodeficiencies (49). A summary of the most significant studies assessing PID awareness among various populations can be found in **Table 1.**

Early diagnosis of primary immunodeficiency

The timely identification of PID is essential because of its diverse symptoms and limited clinical recognition, frequently resulting in underdiagnosis and elevated mortality rates (50). Timely diagnosis yields improved outcomes and reduced healthcare expenditures by facilitating the swift commencement of suitable therapy. For instance, early identification facilitates prompt referral for antibiotic and immunoglobulin therapy in patients with antibody deficiencies, thus averting chronic pulmonary illness and minimizing further hospitalizations. Moreover, in individuals with severe combined immunodeficiency (SCID), prompt diagnosis enables timely referral for hematopoietic stem cell transplantation, which is crucial for their survival (51).

Despite this, early diagnosis of primary immunodeficiencies is particularly challenging because there are no distinctive signs, resulting in a wide variety of clinical presentations in children, especially in infancy. Advancements in gene sequencing technology are leading to a rising number of diagnosed PIDs. Next-generation sequencing (NGS) has demonstrated efficacy as a robust instrument for the prompt detection of PIDs in babies, facilitating swift molecular diagnoses that can profoundly influence medical care and treatment results for affected children. Whole-exome sequencing (WES) is progressively being utilized by numerous laboratories as the preferred way for identifying various PIDs due to its capacity for facilitating swift detection (52). Population-based newborn screening is essential for the early identification of asymptomatic infants with a range

of severe diseases, for which effective treatments are available and where early diagnosis and intervention can prevent serious sequelae (53). Neonatal screening has been proposed for the early recognition of treatable, severe forms of PIDs that are characterized by profoundly low T and B cell numbers. This screening is conducted by quantifying T-cell receptor excision circles (TRECs) and

Table 1. Studies that conducted to assess the level of awareness of primary immunodeficiency disorders (PIDs) among various groups.

Study group	Number of participants	Findings	Ref.
Medical students in Ukraine	271	The questionnaire comprised 25 questions. The average percentage of correct answers provided by the surveyed students for each question was 59. 2% (with a range of 22. 5% to 82. 3%). 223 medical students (82. 3%) answered more than 50% of questions correctly, while only 21 students surveyed (7. 7%) answered more than 75% of questions correctly.	(33)
Japanese physicians	355(which included 121 pediatricians, 116 hematologists, and 118 general internal medicine physicians)	Results from the hypothetical case study indicated that more than 70% of physicians considered PID after reviewing patients past medical histories, and 75. 2% expressed interest in acquiring additional knowledge about PID	(32)
pediatricians employed at the Instituto Nacional de Salud del Niño, a national pediatric reference center in Peru	83	Among pediatricians, 50% had completed courses on primary immunodeficiency diseases, and 53. 1% had participated in conferences concerning this topic. Only 39. 8% of physicians reported being aware of the list of 10 warning signs created by the Jeffrey Modell Foundation.	(34)
Physicians in the United States	1250	Overall, 32% of physicians have diagnosed, treated, or referred a patient with primary immunodeficiency disorder	(36)
Brazil's Physicians	4026(1628 pediatricians, 1436 clinicians, and 962 surgeons)	Approximately 67% of the physicians were educated on primary immunodeficiency disorders (PIDs) during their medical school or residency training. Seventy-seven percent of the physicians involved in the study were unfamiliar with the warning signs of primary immunodeficiency disorders (PIDs). The average score of accurate responses for the 25 clinical scenarios was 48. 08%. Only 18. 3% of pediatricians, 7. 4% of clinicians, and 5. 8% of surgeons responded appropriately to at least two-thirds of scenarios	(37)
Physicians in Nine states of Iran	794(466 general practitioners, 90 pediatric residents, 124 pediatric specialists, and 20 pediatric)	The average total knowledge score of participants was 51. 30, with a standard deviation of 18. 76. Only 161 participants (20. 4%) answered more than two-thirds of all questions correctly. The average score in the management of PIDs was 66. 25±54. 55, followed by laboratory findings at 49. 57±25. 07, clinical symptoms at 54. 42±17. 85, and associated syndromes at 42. 32±28. 57. Only 207 physicians completed the continuing medical education (CME) curricula.	(39)
Iranian general practitioners and pediatricians	333(50 general practitioners, 52 pediatric residents, 182 pediatric specialists, and 49 pediatric)	105 participants (31. 9%) correctly answered more than two-thirds of all questions. A ranking system was utilized to qualitatively compare the groups. The total scores exhibited significant variation among the groups of physicians. Pediatric subspecialties achieved the highest ranking, surpassing the other participants significantly.	(40)

kappa-deleting recombination excision circles (KRECs). Newborn screening is critical for the early diagnosis and management of PIDs, reducing morbidities, and potentially saving lives, particularly in cases of SCID. However, there are still no available screening tests for many other PIDs, and their diagnosis requires clinical expertise (54). The emphasis on implementing newborn screening programs differs across high-income and middle- to low-income countries due to conflicting health goals, including infectious illness management, vaccination, and malnutrition. Economic variables, such as restricted resource access, weak economies, and governmental instability, together with local cultural and geographic influences, affect government prioritizing, public acceptance, and the engagement of health practitioners in these initiatives (55). The high cost of advanced technology and the limited availability of innovative diagnostic tools like next-generation sequencing (NGS) are restricting access to innovative diagnostic tools in many nations. Nonetheless, a mere minority of the population has access to genome sequencing (GS), and this testing predominantly remains unattainable in low- and middle-income nations. Despite comprehensive coverage for genetic testing in certain areas, substantial underutilization persists, frequently intensified by insufficient physician awareness, prolonged wait times for specialist consultations, and difficulties encountered by patients and clinicians in maneuvering through the health insurance system (56). The extensive implementation of exome sequencing (ES) and whole genome sequencing (WGS) in Brazil is impeded by multiple problems, including elevated costs, insufficient funding, inadequate reimbursement, little knowledge and education, a scarcity of specialists, and different policy challenges (57). Due to the high prevalence of hereditary diseases in the MENA region, extensive genomic programs are required. Several challenges may be encountered by precision genomic projects (PGPs) in the MENA region. These include problems with finance, infrastructure, and institutional collaboration as well as problems with accessing biobanks and health records. (58).

Research shows that even though there are immunology referral centers, hematopoietic stem cell transplantation, and intravenous immunoglobulin replacement therapy available, very few countries have implemented newborn screening (NBS) for inborn errors of immunity (IEI). Findings highlight technical and budgetary obstacles to widespread NBS implementation. Possible solutions to these problems might emerge from a worldwide exchange of knowledge, skills, and resources. (59). Financial obstacles are frequently cited as significant impediments to patients' adoption and utilization of genetic therapies. Despite insurance coverage and government subsidies in certain low- and middle-income countries (LMICs) enhancing access to these treatments, the exorbitant cost of genetic testing continues to be a substantial obstacle, particularly for low-income and rural patients. When genetic services are scarce, patients frequently must traverse considerable distances to obtain them, resulting in substantial expenses. Healthcare systems face financial difficulty in delivering the services required to satisfy demand. Awareness and understanding of genetic disorders and services, along with the acceptance of genetic testing and counseling, are favorably associated with education and socioeconomic position. Individuals from remote regions and lower socioeconomic strata encounter financial and various obstacles in obtaining these services (60). The use and acceptance of genetic services may be hindered by religious beliefs. Multiple studies have demonstrated that religious beliefs against pregnancy termination significantly hinder the acceptance and use of genetic services. In Islam, fatwas (religious rulings) guide decisions on abortion, depending on the severity of the condition and the gestational age (61-65).

Infections and inborn error of immunity

Infections can have a profound impact on individuals with inborn errors of immunity (IEI), as these genetic defects often compromise the immune system's ability to effectively respond to pathogens. Research has shown that patients with IEI are at an increased risk for recurrent and severe infections due to their impaired immune responses, which can lead to chronic health issues and elevated morbidity rates (66). These infections are often severe and frequent, typically

caused by organisms that are generally harmless in healthy individuals. This heightened susceptibility is a defining characteristic of these disorders (67). Social determinants of health, including socioeconomic position, education, and housing, significantly influence the risk of infection and disease transmission. Individuals from lower socioeconomic backgrounds frequently encounter heightened exposure to infectious diseases due to overcrowded living circumstances and restricted access to healthcare facilities, hence exacerbating health inequities (68). Socio-demographic and economic aspects are significant determinants influencing the dynamics of epidemic transmission. These features influence both the outcome of epidemics within the host population and significantly dictate the progression and severity of the disease in infected individuals (69). In any society, disparities in social, demographic, and economic characteristics, such as age, income, or employment status, result in variations in medical outcomes (e.g., immunity, overall health conditions, or chronic diseases) and differences in adaptive capacities and behaviors, rendering specific groups more vulnerable to infection (70). The physical environment, encompassing housing and occupational circumstances, significantly influences the transmission of fungal infections. Substandard living conditions can exacerbate the incidence of these diseases. Specific occupations are linked to an elevated risk of fungal infections, frequently attributable to inadequate compensation and congested living environments that enhance exposure to fungal pathogens. These vocations encompass agricultural labor, military duty, incarceration-related jobs, archaeological excavation, building, farm labor, firefighting, and cotton mill operations (71). Barriers to seeking care among tuberculosis (TB) patients include negative perceptions of health issues, expenses related to care, and distance to healthcare facilities. Additionally, socioeconomic status, inadequate housing, and environmental conditions, food insecurity, malnutrition, alcohol consumption, tobacco use, substance abuse, comorbidities such as HIV/AIDS, diabetes, mental illness, and imprisonment appear to predispose individuals to develop TB (72, 73). Addressing these social determinants is essential for reducing infection rates and improving public health outcomes.

Social factors influence the management of IEIs

Hematopoietic stem cell transplantation (HSCT), introduced in the mid-20th century, has since been utilized as a potential cure for nonmalignant lymphohematopoietic disorders, myeloid and lymphoid malignancies, immune deficiencies, genetic disorders, and inborn errors of metabolism (74). HSCT remains the only treatment option for many patients with primary immunodeficiencies (PID). European centers have been performing transplants for over 50 years, with improvements in survival rates documented over time. Advances include refinements in HLA-tissue typing methods, the availability of new stem cell sources such as umbilical cord blood, and enhanced methods for isolating hematopoietic stem cells, such as CD34+ stem cell selection and CD3+/CD19+ depletion (75). Recent concerns have emerged regarding the mental health, quality of life, and overall well-being of patients and their families who have undergone HSCT. Long-term follow-up reports indicate that immunodeficient children treated with HSCT have achieved educational milestones and, in some cases, produced healthy offspring (76).

Access to HSCT is influenced by multiple factors including patient demographics, healthcare infrastructure, and socioeconomic status. Studies show that disparities in HSCT access, particularly among minority groups and those in lower socioeconomic brackets, can lead to poorer outcomes and higher mortality rates (77). Financial toxicity (FT), defined as the distress and financial burden related to the disease, is a significant concern among patients who have undergone allogeneic HSCT (allo-HSCT). FT is characterized by financial distress that can negatively impact health outcomes. Key factors influencing FT include gender, income level, and perceived financial loss post-transplant (78). Insurance status also significantly affects access to HSCT. Research indicates that the type of insurance (private vs. non-private, managed vs. non-managed care) impacts HSCT utilization, highlighting economic factors as crucial in treatment decisions, particularly regarding referral and transplantation (79). A study exploring psychosocial factors, such as the Stanford Integrated Psychosocial Assessment for

Transplantation (SIPAT) score and educational status, found that higher educational attainment correlates with better overall survival and lower readmission rates. This suggests that education enhances patients' understanding of their treatment and adherence to medical advice, leading to improved health outcomes (80).

In the United States, about one in three patients who may need allo-HSCT actually receive it, indicating a significant unmet need. The study found a correlation between county-level social vulnerability and unmet need for allo-HSCT, with higher social vulnerability index (SVI) scores linked to greater unmet needs, suggesting that social factors are critical in accessing care (81). Distance from an HCT facility also plays a crucial role in access. Patients with limited geographic access must choose between making frequent long trips or relocating near the facility, both of which can be financially burdensome. Published data on the impact of distance from transplant centers or urban/rural status on outcomes after allo-HSCT are mixed (82).

Globally, access to and rates of allo-HSCT are closely tied to the socioeconomic status of countries and regions. International data reveal significant differences in transplant numbers and access, influenced primarily by macroeconomic and infrastructural factors (83). In the MENA (Middle East and North Africa) region, HSCT is conducted in several centers in Saudi Arabia, Iran, Jordan, Turkey, Tunisia, and Israel. However, experience with HSCT is limited in countries such as Egypt, Algeria, and Morocco.

In these regions, demand often exceeds supply, making timely access to HSCT challenging. A report from Latin America estimates that less than 10% of required transplants are performed, due to challenges including cost, donor availability, number of transplant centers, and lack of expertise. The absence of local registries, additional costs for unrelated donor searches and graft shipments, and the prevalence of large, consanguineous families contribute to the increased use of matched sibling and related donor transplants in the MENA region and Latin America (4). Addressing these disparities necessitates a comprehensive approach, including policy changes and community outreach, to improve access to HSCT for all patients (81).

Conclusion

IEIs result from a complicated interaction between genetic predisposition and environmental influences. The disease is biologically based, although its effects and management are significantly shaped by social determinants of health. Rectifying these discrepancies is essential for enhancing outcomes for patients with PID.

The complex interplay between social determinants and IEIs highlights the necessity for a holistic approach to patient management. Our research underscores the substantial influence of socioeconomic position, geographic location, and healthcare accessibility on disease awareness, early diagnosis, and infection management. Enhancing awareness of IEIs is the initial step toward prompt diagnosis and efficient management. By recognizing the signs and symptoms, healthcare professionals and the public can swiftly detect potential cases. Timely action is crucial for averting life-threatening infections and consequences. Moreover, guaranteeing fair access to specialized healthcare is essential.

Ethics approval

This study was reviewed and approved by Abadan University of Medical Sciences with the approval number: IR.ABADANUMS.REC.1402.086, dated 8 October 2023.

Conflict of interests

The authors declare that they have no conflict of interest.

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Authors' contributions

A-SB the study and edited the manuscript. E-KS, P-A, and F-P contributed to comprehensive research and writing the original draft. E-KS and A-SB participated in manuscript editing and design of the figures. All authors read and approved the final manuscript.

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Availability of data and materials

Data sharing does not apply to this article as no new data were created or analyzed in this study.

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