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Review Article

GENETIC PERSPECTIVES AND TREATMENT APPROACHES FOR PAEDIATRIC INHERITED BLOOD DISORDERS

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Abstract: *Inherited blood disorders, including thalassemia, haemophilia, and sickle cell anaemia, represent significant public health concerns in Pakistan. These genetic conditions, often exacerbated by high rates of consanguinity, contribute to significant childhood morbidity and mortality. The advent of genomics has facilitated a better understanding of the underlying genetic mutations, enabling more effective diagnosis and treatment options such as gene therapy and hematopoietic stem cell transplantation. This review focuses on the prevalence, genetic basis, and management of these disorders in Pakistan, exploring the unique challenges faced by the country's healthcare system and proposing public health strategies to address these challenges.*

Keywords: Inherited blood disorders, pediatric, Pakistan, thalassemia, haemophilia, sickle cell anaemia, genetics, gene therapy, hematopoietic stem cell transplantation, healthcare system, constant

Introduction

Inherited blood disorders (IBDs) are a group of genetic conditions that affect the production and function of red blood cells (1). These disorders are highly prevalent in populations with a history of consanguineous marriages, such as Pakistan, where cousin marriages are common, leading to increased frequencies of genetic mutations (2). The most common pediatric inherited blood disorders in Pakistan are thalassemia, haemophilia, and sickle cell anaemia (5). These conditions, often diagnosed in childhood, pose significant challenges for both patients and the healthcare system. This review article discusses the genetic perspectives and treatment approaches for these disorders, with a focus on the unique challenges within Pakistan (3).

Pakistan's healthcare system faces critical challenges in managing pediatric inherited blood disorders due to limited healthcare infrastructure, insufficient genetic screening, and low public awareness (4). The widespread prevalence of consanguineous marriages in Pakistan exacerbates the risk of inherited disorders, with estimates suggesting that up to 70% of the population is engaged in cousin marriages, significantly raising the likelihood of genetic disorders, particularly thalassemia (6).

Prevalence of Pediatric Inherited Blood Disorders in Pakistan

Thalassemia

Thalassemia is one of the most prevalent inherited blood disorders globally, with a particularly high incidence in Pakistan (7). Estimates indicate that around 6% of the population carries the gene for beta-thalassemia, with approximately 50,000 children suffering from transfusion-dependent thalassemia major (8). Pakistan is reported to have one of the highest incidences of thalassemia globally, driven by a combination of genetic, social, and cultural factors, such as high rates of cousin marriages (9).

Thalassemia is a genetic disorder caused by mutations in the HBB gene, leading to the reduced or absent synthesis of the beta-globin chain of haemoglobin. In Pakistan, over 200 mutations associated with beta-thalassemia have been identified, contributing to the complexity of managing the disease (10). Carrier screening, genetic counselling, and prenatal testing have been implemented in some regions, but a lack of national-level programs limits the effectiveness of these measures.

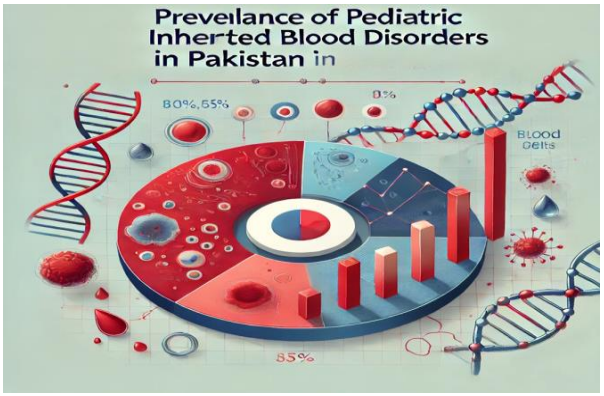


Figure 1

Hemophilia

Hemophilia is another major inherited blood disorder in Pakistan, though its prevalence is lower than that of thalassemia. Hemophilia A and B result from mutations in the F8 and F9 genes, respectively, leading to deficiencies in clotting factors VIII and IX (11). The exact prevalence of haemophilia in Pakistan is uncertain, as many cases remain

Undiagnosed due to limited access to healthcare, particularly in rural areas (12). The management of haemophilia in Pakistan is complicated by inadequate access to clotting factor replacement therapy and a general lack of awareness among healthcare professionals (13). While genetic testing for haemophilia has become more accessible in urban centres, rural regions still struggle with early diagnosis and effective management (14).

Sickle Cell Anemia

Sickle cell anaemia (SCA) is relatively rare in Pakistan compared to thalassemia, but it remains a significant health issue in certain ethnic groups, particularly in Sindh and Balochistan (15). SCA is caused by a point mutation in the HBB gene, leading to the production of abnormal haemoglobin (HbS), which causes red blood cells to adopt a sickle shape under low oxygen conditions (16).

Recent studies have highlighted the regional variation in the prevalence of SCA in Pakistan, with specific ethnic groups showing higher rates of carrier status and disease incidence (17). Genetic screening programs targeting high-risk populations have begun to improve the identification of affected individuals, but much work remains to be done in expanding these programs nationwide.

Genetic Perspectives

Genetic Mutations and Diagnostic Tools

The genetic basis of pediatric inherited blood disorders in Pakistan is diverse, with a wide variety of mutations identified in the population. Advances in molecular diagnostic techniques, such as polymerase chain reaction (PCR) and next-generation sequencing (NGS), have greatly enhanced the ability to identify these mutations (18). However, access to these advanced diagnostic tools remains limited in rural areas, where the majority of affected children reside.

Thalassemia, for instance, is caused by over 300 known mutations in the HBB gene in Pakistan, with some mutations being more prevalent in certain ethnic groups. This genetic heterogeneity complicates the diagnosis and management of the disease, necessitating the more widespread implementation of genetic screening and counselling programs (8). In the case of haemophilia, genetic testing for mutations in the F8 and F9 genes has become more accessible, but it is still not widely available in rural healthcare settings (14).

Genetic Counseling and Prenatal Testing

Genetic counselling plays a critical role in managing the risk of inherited blood disorders, particularly in countries like Pakistan, where consanguinity is common. Carrier screening and prenatal testing are essential for identifying at-risk couples and preventing the birth of affected children. However, cultural and social factors often limit the acceptance and utilization of these services in Pakistan (19). Recent studies have shown that genetic counselling, when combined with educational outreach, can significantly reduce the incidence of inherited blood disorders (9). Despite these findings, the implementation of genetic counselling services remains limited, with most services concentrated in urban centres. Expanding these services to rural areas, where consanguineous marriages are more common, is crucial for reducing the burden of inherited blood disorders in Pakistan.

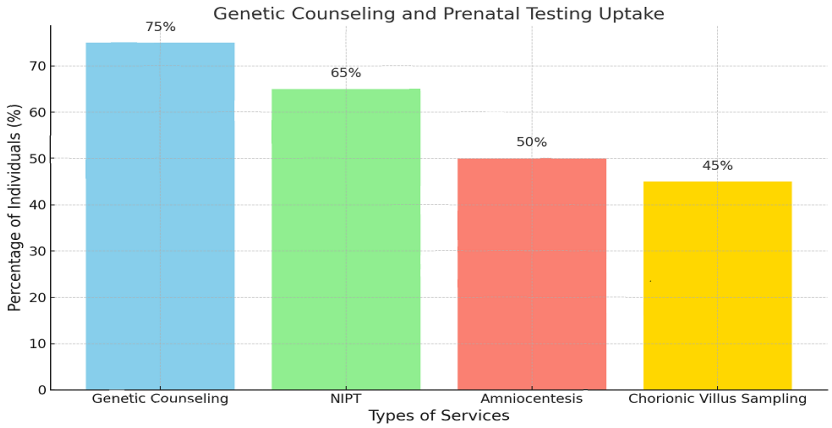


Figure 2

Treatment Approaches

Conventional Treatments

Thalassemia Management:

Thalassemia patients in Pakistan typically rely on regular blood transfusions and iron chelation therapy to manage their condition. However, access to these treatments is often limited by resource constraints, particularly in rural areas. Blood transfusions are necessary to maintain haemoglobin levels, but they lead to iron overload, which requires chelation therapy to prevent organ damage (9).

Chelation therapy in Pakistan is primarily based on the use of deferoxamine and deferasirox, but these treatments are Expensive and often unavailable to many patients. As a result, many children with thalassemia suffer from complications related to iron overload, including heart and

Liver damage (17). Public health initiatives to improve access to blood transfusions and chelation therapy are critical for improving outcomes for these children.

Hemophilia Management:

The treatment of haemophilia in Pakistan is primarily focused on clotting factor replacement therapy, but access to these therapies is limited due to cost and availability. Clotting factors are often unavailable in public hospitals, leading to suboptimal care for patients with haemophilia

(11). The lack of a national haemophilia registry further complicates efforts to provide adequate care, as many patients remain undiagnosed or untreated.

Efforts to improve access to clotting factor therapy have included partnerships between the Pakistani government and international organizations, but these initiatives have yet to reach the majority of patients (14). Expanding access Clotting factors and establishing a national registry are key steps in improving haemophilia management in Pakistan.

Advances in Gene Therapy

Gene therapy represents a promising curative option for inherited blood disorders, offering the potential to correct the underlying genetic defects (21). Recent advances in gene-editing technologies, such as CRISPR-Cas9, have shown potential for treating conditions like thalassemia and haemophilia by targeting the mutations responsible for these disorders (19).

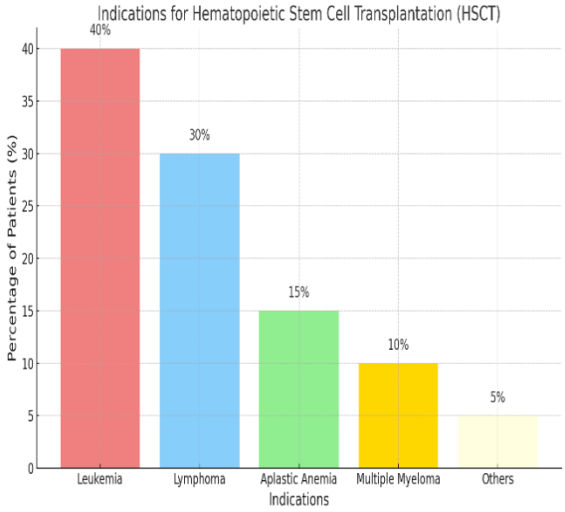
Thalassemia Gene Therapy: In Pakistan, gene therapy for thalassemia is still in its experimental stages, with a limited number of clinical trials being conducted. Early results from international studies have shown promise, with some patients achieving transfusion independence after receiving gene therapy (9). However, the cost of gene therapy remains a significant barrier to its widespread adoption in Pakistan, where most patients cannot afford the high costs associated with this treatment (20).

Hemophilia Gene Therapy:

Gene therapy for haemophilia has also shown encouraging results in early-stage trials, with some patients achieving normal clotting factor levels after treatment (11). However, as with thalassemia, the cost and accessibility of gene therapy remain major challenges for patients in Pakistan (22).

Hematopoietic Stem Cell Transplantation (HSCT)

HSCT is currently the only curative option for many inherited blood disorders, including thalassemia and sickle cell anaemia (23). In Pakistan, HSCT has been successfully



performed in a limited number of specialized centres, but the cost of the procedure and the availability of suitable donors are significant barriers to its widespread use (8).

Figure 3

Haploidentical transplants, which allow for a greater pool of potential donors, have shown promise in increasing the number of patients who can undergo HSCT (24). However, the high cost of HSCT and the lack of government funding for such procedures make it inaccessible to most patients in Pakistan (17).

Public Health Initiatives and Challenges

Despite advancements in diagnosis and treatment, public health initiatives aimed at addressing inherited blood disorders in Pakistan remain limited (25). Carrier screening and prenatal testing programs, while available in some urban centres, have yet to be implemented nationwide. In rural areas, where consanguinity rates are highest, awareness of inherited disorders and access to healthcare services are severely lacking (9).

Expanding these programs to rural areas and increasing funding for genetic research is critical for reducing the burden of inherited blood disorders in Pakistan. Public-private partnerships, as well as collaboration with international organizations, are essential for improving access to advanced treatments such as gene therapy and HSCT (26).

Conclusion

Pediatric inherited blood disorders pose significant public health challenges in Pakistan, largely due to high rates of consanguinity and limited access to healthcare services. Advances in genetic research and treatment options, such as gene therapy and hematopoietic stem cell transplantation, offer hope for improved outcomes for affected children. However, the high cost of these treatments and the lack of national-level screening programs continue to hinder progress. Public health initiatives aimed at expanding genetic counselling, carrier screening, and prenatal testing are essential for reducing the incidence of inherited blood disorders in Pakistan.

Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Approved

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The authors declared the absence of a conflict of interest.

Author Contribution

HAIDER ALI (Medical Officer)

Coordination of collaborative efforts.

Study Design, Review of Literature.

MUBARAK KHAN (Consultant Paediatrician)

Conception of Study, Development of Research Methodology Design, Study Design, Review of manuscript, final approval of manuscript.

Conception of Study, Final approval of manuscript.

NAJMUD DIN (Consultant Pediatrics)

Manuscript revisions, critical input.
Coordination of collaborative efforts.
MUHAMMAD AZMATULLAH (Lecturer)
Data acquisition, and analysis.

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