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SCID Across Decades: Changes and Challenges in SCID Management

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Abstract

Severe Combined Immunodeficiency (SCID), often termed "bubble boy disease", is a rare but life-threatening group of genetic disorders characterized by profound defects in T-cell and B-cell immunity. Over the decades, advancements in understanding and managing SCID have revolutionized outcomes, yet challenges remain. The discovery of SCID in the mid-20th century marked the advent of recognizing primary immunodeficiencies as distinct medical entities. Early management relied on isolation to prevent infections, emphasizing the urgency of a definitive cure. Introduction of hematopoietic stem cell transplantation (HSCT) from matched sibling donors in 1968 transformed SCID prognosis, achieving survival rates exceeding 90% in optimal cases. Over time, donor selection expanded to include matched unrelated and haploidentical donors, addressing limitations posed by donor scarcity. The 1990s witnessed the emergence of gene therapy, offering a curative approach for SCID caused by specific genetic mutations. Initial setbacks, including treatment-related leukemia, underscored the complexities of modifying the human genome. However, refinements in vector design and delivery have revived its promise, with newer trials demonstrating remarkable efficacy. Neonatal screening, now implemented in many regions, has significantly improved early SCID diagnosis, enabling timely intervention. However, disparities in access to screening and treatment persist globally. The cost of advanced therapies, immune reconstitution variability, and long-term follow-up challenges remain critical issues. Addressing these challenges requires continued research, equitable healthcare policies, and innovations in therapy and screening. SCID management exemplifies the intersection of scientific progress and medical ethics, highlighting the need for vigilance in translating discoveries into accessible, life-saving interventions.

Keywords: Severe Combined Immunodeficiency, Primary Immunodeficiency, Lymphocyte, Immunoglobulin

1. Introduction

Immunodeficiency occurs when the immune system fails to function appropriately, leaving the body vulnerable to infections. It can be either primary (inherited) or secondary (acquired). Primary immunodeficiencies are classified based on the affected components, including T-cells, B-cells, both T and B cells, phagocytes, complement proteins, or immunoglobulin A.[1] The clinical manifestations of primary immunodeficiencies (PIDs) are diverse but commonly involve heightened infection vulnerability. These conditions can be present at any age. Many PIDs initially appear as typical infections, such as those affecting the sinuses, ears, or lungs, which can easily be overlooked in primary care.[2]

Severe Combined Immunodeficiency (SCID) is a genetic disorder caused by T and B Lymphocyte defects.[3] SCID is mainly due to mutations in genes essential for the development and function of T and B lymphocytes. While some mutations affect only T-cell function, leaving B cells intact, others impair both. Natural killer (NK) cells, which

develop independently of T and B cells and possess cytotoxic properties, are present in about half of SCID patients, offering partial protection against infections and contributing to improved outcomes. SCID immunophenotypes are classified based on the presence (T–B+) or absence (T–B–) of B cells in the blood, with both groups including forms with or without NK cells. Additionally, SCID is categorised by the functional role of the defective gene, involving cytokine signaling, antigen presentation, V(D)J recombination, T-cell receptor signaling, or basic cellular functions.[4]

According to Fischer[5], the most common type, X-linked SCID, results from mutations in the IL-2 receptor γc chain gene, impairing T and NK cell development. Adenosine Deaminase deficiency, the second most common form, leads to toxic metabolite accumulation, causing lymphopenia and neurological issues. RAG-1 and RAG-2 mutations disrupt T-cell receptor development, while IL-7R deficiency affects both T and B cells. Leaky SCID features partial T-cell presence with autoimmune tendencies, and Omenn Syndrome involves dysfunctional T cells with severe autoimmunity. Other forms include CD3 complex and JAK3 deficiencies and rare variants like bare lymphocyte syndrome and Griscelli syndrome.[6]

SCID occurs at a frequency ranging from 1 in 40,000 to 1 in 75,000 live births globally.[7] The incidence of SCID varies across different countries and is influenced by the prevalence of recessive genetic disorders and the effectiveness of case detection. Differences in detection rates are particularly pronounced based on the availability and implementation of SCID newborn screening programs (NBS), the process by which infants are screened for genetic defects. The introduction of these programs has also revealed that SCID is more common than previously estimated. In regions with high rates of consanguineous marriages, the incidence is notably higher compared to areas where such practices are less common. The median annual incidence of SCID is estimated at 4.5 cases per 100,000 live births among the Omani population[8], 1 case per 2,906 live births among the Saudi population[9], while the incidence of typical SCID, leaky SCID, and Omenn syndrome in India is approximately 1 in 58,000 live births[10] and in the USA is 1 in 58 000 infants.[11] SCID is the most common immune deficiency condition in Sri Lanka. Prevalence is significantly higher than in countries such as Europe (4.5%). However, it is lower than in other MENA region countries such as Saudi Arabia (22%).[12]

This condition constitutes a pediatric emergency, as affected infants face a high risk of severe, recurrent infections. SCID treatment involves isolating newborns to prevent infections, addressing nutritional challenges through intravenous feeding, and managing secondary infections with antimicrobial medications. Definitive therapies include hematopoietic stem cell transplantation (HSCT), gene therapy, enzyme replacement therapy (ERT), and chemotherapy, depending on the genetic cause.[9] Without timely treatment, such as stem cell transplantation or gene therapy, SCID is nearly always fatal within the first years of life.[13]

Early diagnosis through family history, clinical signs, or newborn screening is vital to improving outcomes for this life-threatening condition.[13] A thorough evaluation is required to diagnose SCID, including a detailed patient history (infections, prematurity, family history) and physical examination for signs of related conditions. Key laboratory tests include lymphocyte phenotyping, T-cell quantification, and T Cell Receptor Excision Circle (TREC) quantification to assess thymic function. Genetic sequencing is crucial for identifying SCID-causing mutations. Testing for T-cell

receptor diversity and proliferative responses may further help differentiate SCID from other disorders with low T-cell numbers. Secondary causes of T-cell lymphopenia, like HIV or prematurity, must also be ruled out.[14]

This review summarizes findings from 10 SCID case studies conducted in different countries, including developed and developing countries. The studies include clinical presentations, diagnostic approaches, treatment methods, discussion, and a prognosis. By comparing these cases, this discussion identifies patterns and differences in SCID diagnosis, management and treatment through the decades.

2. Demographics, Consanguinity and Family History

In a study done in France from 1970 to 1993, a cohort of 117 patients was studied. Most patients were placed in a sterile environment, such as the Isolator Bubble System, from 1981 onward. The mean age of diagnosis was 9.5 months. Retrospectively, family history of SCID was found in 74 of the cases.[15] 2010 to 2011, a study on 47 patients in India aimed to understand severe combined immunodeficiency (SCID). The findings focused on identifying and characterizing the disease in the region without delving into specifics like consanguinity or family history.[16]

Between 2000 and 2011, a study conducted in Brazil involving 70 patients reported 16% of cases with consanguinity. The mean age at diagnosis was approximately 6.7 months, with a median of 8 months. Eight children were diagnosed at birth or before clinical manifestations due to a previously affected sibling.[17] From 2010 to 2011, a cohort of 24 patients was studied in Taiwan.[18]

A study conducted in Saudi Arabia from 2010 to 2013, involving 502 patients, showed a consanguinity rate of 75%. A majority (93%) of patients were diagnosed during childhood. The mean age of symptom onset was 17 months.[19] From 2010 to 2014, in the United States and Canada, 118 cases were reviewed.[20]

A cohort of 10 patients was examined in Iran between 2006 and 2013. Parental consanguinity was observed in 9 of the 10 cases. Among them, seven had second-degree consanguineous parents, two had third-degree consanguineous parents, and one had non-consanguineous parents. Additionally, six patients had a history of early infant deaths among siblings, while two had relatives diagnosed with SCID.[21] Between 2013 and 2018, another study conducted in India examined 57 SCID patients. Of these, 36% had consanguineous parents, and a family history of SCID was observed in 56% of cases. The median age of diagnosis was 60 days, with two patients identified pre-symptomatically due to a strong family history.[22]

Between 2010 and 2020, 36 patients were reviewed in Oman. In 24 cases (66.7%), a positive family history of SCID was identified, and 91.7% of children were born to consanguineous parents. The median age of diagnosis was 54 days. Additionally, 33.3% of cases involved a history of sibling death[11]. From 2016 to 2019, three cases were studied in Kenya. None of the parents showed first- or second-degree consanguinity. However, all cases involved sibling deaths attributed to SCID.[23]

3. Clinical manifestations

Clinical manifestations of severe combined immunodeficiency (SCID) vary widely across countries, reflecting the diversity of immune disorders and healthcare systems. For instance, pneumonia and failure to thrive are common features globally, with additional complications like chronic diarrhea, recurrent candidiasis, and autoimmune conditions seen in countries like India, Brazil, and Saudi Arabia.[17,19,22] Unique presentations such as disseminated BCG infections in Saudi Arabia or Omenn syndrome

in the USA and France highlight the spectrum of PID manifestations and the importance of timely diagnosis and intervention.[15,19,20]

In Oman, SCID presentations paralleled those in the USA and Canada. Typical SCID was marked by severely reduced CD3 T-cell counts, impaired T-cell proliferation, and maternal T-cell engraftment in some cases. Atypical SCID exhibited reduced CD3 T-cell counts adjusted for age and partially impaired T-cell functions. Common symptoms included pneumonia, septicemia, and chronic diarrhea. This study reiterated the significance of age-adjusted immunologic criteria for diagnosing SCID.[8]

In a case study done in France, the onset of clinical symptoms occurred earlier in patients with ADA (-) SCID compared to other forms. In fact, life-threatening interstitial pneumonitis developed as early as one month after birth in ADA (-) SCID patients. Common clinical manifestations included oral candidiasis, erythema, persistent diarrhea leading to growth failure, and interstitial pneumonitis. In addition, six infants with ADA (-) SCID exhibited developmental delays, although there was no evidence of central nervous system infections. One case involved early-onset encephalopathy associated with tubular acidosis, marasmus, and abnormal fundoscopic findings. Five ADA (-) SCID patients also presented with typical skeletal abnormalities such as cupping and flaring at the costochondral junctions, as well as dysplasia of the pelvis. Furthermore, characteristics of Omenn syndrome were observed, including erythroderma with thickened skin (pachyderma), chronic diarrhea, lymphadenopathy, hepatosplenomegaly, significant eosinophilia, and elevated serum IgE levels.[15]

The study in India from 2013, involving 47 patients highlighted the diversity of immune deficiencies, with immune dysregulation observed in 29%, B- and T-cell abnormalities in 28%, predominant antibody deficiencies in 23%, well-defined immunodeficiencies in 15%, and phagocyte disorders in 4% of cases. Recurrent infections, failure to thrive, and autoimmune manifestations were common clinical features, reflecting the varied presentations of immunodeficiency disorders.[16]

In Brazil, the study of 64 patients revealed pneumonia (64.1%) as the most common symptom, followed by chronic or acute diarrhea (46.9%), candidiasis (45.3%), and sepsis (40.6%). Failure to thrive and skin conditions such as eczema or erythroderma were each observed in 35.9% of patients, while lymphadenopathy and hepatosplenomegaly were documented in 34.4% of cases. Acute otitis media was also common, indicating the widespread and severe infections associated with immunodeficiencies in the cohort.[17]

In Taiwan, two confirmed SCID cases, two suspected SCID cases, four patients with persistent T-cell lymphopenia, and five cases of chromosome 22q11.2 microdeletion syndrome were analyzed from a Chinese population. While newborns with SCID may initially appear asymptomatic, they rapidly develop severe infections. T-cell lymphopenia was a consistent finding, and patients with chromosome 22q11.2 microdeletion syndrome often exhibited congenital heart defects or cleft palate, showcasing the spectrum of presentations in primary immunodeficiencies.[18]

In Saudi Arabia, among 114 SCID patients who received the BCG vaccine, 43% developed disseminated *Mycobacterium bovis*. The mean age of symptom onset was 17 months. Common infections included lower respiratory tract infections (50%), skin infections such as cellulitis and abscesses (25%), chronic diarrhea (24%), and oral thrush (13%). Deep abscesses were noted in 6% of patients. These findings illustrate the high burden of infections and complications in SCID patients, emphasizing the need for early

diagnosis and vaccination policies tailored to this population.[19]

In the USA and Canada, SCID patients were classified into typical and atypical forms.[20] Typical SCID was characterized by extremely low CD3 levels (<300/μL), maternal engraftment, and minimal response to phytohemagglutinin (PHA). Atypical or leaky SCID showed age-dependent CD3 level reductions, no maternal engraftment, partial PHA responses, and low response to tetanus toxoid. Omenn syndrome was identified by generalized rash, a high percentage of CD45RO T cells, and distinct genetic markers. The detailed characterization of immune profiles highlighted age-related differences and the importance of genetic diagnosis.[20]

In Iran, a study of ten patients with Severe Combined Immunodeficiency (SCID) revealed pneumonia as the most common clinical presentation. In which, seven cases were pneumonia followed by failure to thrive and Lymphopenia in nine patients. The initial symptoms included chronic cough, diarrhea, gastroenteritis, and prolonged fever. A positive family history of immunodeficiency was noted in some patients. Secondary complications such as invasive pulmonary aspergillosis, encephalitis, membranous colitis, and sepsis were also documented. Unique findings included disseminated Bacille Calmette-Guérin (BCG) infections in three patients, eczematous skin rashes, and lymphadenopathy, emphasizing the heterogeneity of SCID manifestations and the need for early intervention.[21]

In the 2019 Indian case study, pneumonia emerged as the most frequent clinical manifestation, affecting 66% of patients, followed by failure to thrive in 60%, chronic diarrhea in 35%, gastrointestinal infections and oral candidiasis in 21% each, and BCGiosis in 12% of cases. Additional features included erythematous skin rash in 29%, dysmorphism and abscesses in 8% each, and hepatosplenomegaly in 3% of the patients. Immunologically, 67% of the cohort (38 out of 57 patients) exhibited absent or severely diminished T-cell counts (<300 cells/μL), while lymphopenia (<2,500 lymphocytes/μL) was observed in 63% (36 of 57 patients). Isolated T-cell lymphopenia was identified in 12% (7 of 57 patients), further highlighting the immunodeficiency spectrum in these cases.[22] This diverse clinical and immunological presentation underscores the complexity and severity of immune dysfunction in the Indian cohort.

In Kenya, three patients presented with pneumonia and reduced immunoglobulin levels, with additional unique symptoms in each case. Patient 1 included persistent irritability, seizures unresponsive to treatment, congestive heart failure, and failure to thrive. Patient 2 developed severe pneumonia progressing to Acute Respiratory Distress Syndrome (ARDS) with septic shock, severe gastroesophageal reflux disease, atopy, and failure to thrive. Patient 3 experienced severe pneumonia with rotavirus gastroenteritis, severe progressive dermatitis, and failure to thrive. Following a protracted rotavirus infection—possibly a vaccine-acquired illness—the patient experienced severe sepsis. These cases underscore the life-threatening complications associated with immune deficiencies in pediatric patients.[23]

4. Diagnosis

The diagnostic methods for severe combined immunodeficiency (SCID) vary significantly across the different countries, reflecting diverse approaches and levels of healthcare development. In the study done in Sri Lanka from 2010 to 2022, a total of 206 patients were diagnosed of inborn errors of Immunity out of which SCID was the commonest (14.9%).[12]

In Oman, a combination of microbiological and molecular techniques was employed. These included cultures for bacteria, mycobacteria, and fungi, along with PCR for

pathogens in plasma, fluids, feces, and cerebrospinal fluid. Histopathology identified virus-specific inclusion bodies, and flow cytometry was used for immune profiling. Although TREC analysis for newborn screening was unavailable, the whole exome sequencing by Centogene® facilitated genetic assessment.[8]

In France, diagnostic methods evolved over time. T-cell counts were initially determined by E-rosetting until 1981, replaced by indirect immunofluorescence. B-cell counts employed direct immunofluorescence, while serum immunoglobulin levels transitioned from radial immunodiffusion to nephelometry. PCR and Southern blotting became standard for lymphocyte analysis, enhancing diagnostic precision.[15]

In India (2013), molecular diagnostics were performed in 12 cases, with positive findings in seven. Disorders were categorized into immune dysregulation (29%), B- and T-cell abnormalities (28%), predominant antibody deficiencies (23%), well-defined immunodeficiencies (15%), and phagocyte disorders (4%). Molecular testing played a pivotal role, particularly in identifying genetic mutations in 14 hemophagocytic lymphohistiocytosis (HLH) cases.[16]

In Brazil, diagnostic methods included absolute lymphocyte CD3+ T-cell and NK cell counts, lymphocyte proliferation tests, and maternal T-cell engraftment analysis. Flow cytometry examined peripheral T-cell subpopulations, while TREC assays, adenosine deaminase, uric acid, eosinophil counts, and serum IgE levels were assessed. Chest X-rays evaluated thymic shadow, and fluorescence in situ hybridization (FISH) provided additional insights.[17]

In the Chinese population of Taiwan, newborn screening using the T-cell receptor excision circle (TREC) assay was the cornerstone of diagnosis. Modifications to the TREC assay involved adjustments in elution and RT-qPCR volumes. Infants with low or zero TREC levels underwent complete blood counts, flow cytometry, and TUPLE1 gene analysis to detect chromosome 22q11.2 microdeletion syndrome. Confirmatory genetic diagnoses employed multiplex ligation-dependent probe amplification (MLPA), ensuring precise identification of immune deficiencies.[18]

In Saudi Arabia, 26% of PID cases were diagnosed at birth through targeted screening for affected families. Genetic testing identified familial HLH mutations and a novel ELANE mutation in congenital neutropenia. Flow cytometry revealed SCID phenotypes such as $T^{-}B^{+}NK^{-}$ and $T^{-}B^{-}NK^{+}$. Molecular studies identified mutations in approximately 14.9% of cases, underscoring the importance of genetic evaluations.[19]

In the USA and Canada, diagnostic approaches included lymphocyte phenotyping, in vitro lymphocyte proliferation tests, and quantitative immunoglobulin measurements. Screening for TRECs and T-cell receptor spectratyping further aided diagnosis. Additional evaluations, such as maternal T-cell engraftment, were conducted to assess immune function comprehensively and guide therapeutic decisions.[20]

In Iran, diagnostic techniques included CT scans and Polymerase Chain Reaction (PCR). CT scans identified splenomegaly, hypodense lesions in the spleen and liver, and lymphadenopathies. PCR confirmed *Mycobacterium bovis* in lymph node and bone marrow specimens in one case. Abdominal CT scans further revealed hypoechoic lesions in the liver and spleen. Skin biopsies showed acid-fast bacilli in one patient, aiding in the diagnosis of BCGosis. Flow cytometry delineated SCID phenotypes, such as $T^{-}B^{-}NK^{+}$, $T^{-}B^{-}NK^{-}$, $T^{-}B^{+}NK^{-}$, and $T^{-}B^{+}NK^{+}$, with an average diagnostic age of 131.8 days.[21]

In India (2019), diagnostic techniques included automated complete blood counts,

lymphocyte subset analysis through flow cytometry, and serum immunoglobulin level measurement by nephelometry. Newborn screening employed TREC assays, while advanced studies like phospho-STAT5 analysis and CellTrace Violet dye were used for T-cell proliferation. Molecular diagnostics included Sanger sequencing, and ADA activity was assessed calorimetrically. These comprehensive methods provided detailed insights into immune dysfunction and deficiencies.[22]

In Kenya, chest X-rays and echocardiography were key diagnostic tools. Chest X-rays revealed pneumonia in two cases and ARDS in one, while echocardiography showed dilated cardiomyopathy in one case but was normal in another. Patients were diagnosed with $T^{-}B^{-}$ SCID and low immunoglobulin (Ig) levels based on these findings, with diagnoses occurring within 10 months to 1 month of admission.[23]

This global overview highlights the diversity in diagnostic approaches to SCID, emphasizing advancements in genetic, molecular, and immunological testing.

5. Treatment methods

Multiple techniques have been used to treat severe combined immunodeficiency (SCID), with the goal of increasing survival and quality of life. Hematopoietic stem cell transplantation (HSCT) is the treatment, with the use of matched related donors (MRD) yielding the best results.[1] When an MRD is unavailable, mismatched related donors (MMRD), unrelated donors (URD), and umbilical cord blood transfusions are viable options. Intravenous immunoglobulin (IVIG) is given on a regular basis to compensate for antibody shortages, and antibiotics, antivirals, and antifungals are used to prevent opportunistic infections.[3] In some areas, mainly North America and Europe, gene therapy has been investigated as a treatment option for specific genetic disorders.[20] Furthermore, supportive care includes the management of organ dysfunctions such as heart failure or sepsis, and the provision of nutritional support is critical for addressing complications and ensuring comprehensive patient care.

In 1993 in France, immunoglobin substitution was used for patients who were unable to produce sufficient antibodies. Immunoglobulin substitution provides the necessary antibodies to help fight infections. Subsequently, fetal liver transplant was carried out, liver contains hematopoietic stem cells (HSCs) capable of producing blood cells, including T cells and B cells. These cells can help restore normal immune function by providing the recipient with the ability to generate a functional immune system. Prophylactic antibiotics were used to prevent these infections, especially during the first few months or years of life before the immune system can be restored through treatments.[15]

The high costs of supportive care and definitive treatments pose significant barriers to improving patient outcomes. Intravenous immunoglobulin (IVIG), antibiotics and antifungals as well as definitive cure in the form of Stem Cell Transplantation are major barriers to improving prognosis of the patients. In addition, any improvement in the survival of these patients in developing countries like India would require a networked, financially sound and possibly government-backed effort to set up a national registry, improve awareness among pediatricians, and establish specific centers offering genetic diagnosis and definitive therapy.

A 2017 publication in the United States reported the use of gene therapy for X-linked SCID, which is typically caused by mutations in the IL2RG gene. Gene therapy was conducted to introduce a functional copy of the IL2RG gene into the patient's hematopoietic stem cells (HSCs), allowing these cells to produce functional T cells and restore immune function. Enzyme Replacement Therapy (ERT)

is primarily used for treating enzyme deficiency disorders where a particular enzyme is malfunctioning. ERT offers several key advantages, including direct correction of the metabolic defect, stabilization of immune function, and the ability to delay disease progression. Thymus Transplant before Hematopoietic stem cell transplantation was performed; this has several key advantages in the treatment of SCID, particularly in improving T cell reconstitution, reducing graft-versus-host disease (GVHD), and accelerating overall immune recovery. By providing a functional thymus, it enhances the success of HCT, leading to better long-term outcomes and overall survival in patients with T-cell deficiencies.[20]

In 2020, in Oman eleven children (30.6%) have received hematopoietic stem cell transplant (HSCT) with a survival rate of 73%. Hematopoietic Stem Cell Transplant (HCT) is considered the most successful and definitive treatment option for SCID. HCT is most successful when performed early in life, especially in newborns who have been diagnosed with SCID through newborn screening. Early transplantation significantly increases the chances of immune reconstitution, providing a higher likelihood of survival and preventing severe infections. One of the main advantages of HCT are the ability to use different sources of hematopoietic stem cells, such as matched sibling donors, haploidentical family members, or unrelated bone marrow donors, as well as umbilical cord blood. Advances in HLA matching and immune suppression protocols have increased the success of HCT even with mismatched donors.[8]

Hematopoietic stem cell (HSC) transduction is undergoing remarkable advancements in recent years, revolutionizing the landscape of gene therapy specifically for inherited disorders like SCID. The evolution of viral vector-based transduction technologies, including retroviral and lentiviral vectors, has significantly enhanced the efficiency and specificity of gene delivery to HSCs. Furthermore, the advent of gene editing technologies, notably CRISPR-Cas9, has empowered precise genome modification in HSCs, paving the way for targeted gene correction. These striking progresses have led to the clinical approval of medicinal products based on engineered HSCs with impressive therapeutic benefits for patients.[20]

In Sri Lanka, the treatment of Inborn Errors of Immunity (IEI) is a complex issue with significant gaps. Intravenous immunoglobulin replacement therapy is crucial for managing antibody deficiencies like Common Variable Immune Deficiency (CVID) and X-Linked Agammaglobulinemia (XLA). Hematopoietic Stem Cell Transplantation (HSCT) has been introduced for severe cases like SCID, but its availability is limited, leading to high mortality rates (83.6%). The administration of the BCG vaccine at birth often worsens the condition, with delayed diagnosis and low awareness of unexplained infant deaths. Chronic Granulomatous Disease (CGD) also faces challenges, with higher mortality rates than in Europe due to insufficient access to HSCT and limited multidisciplinary care. Genetic testing, a crucial component of IEI diagnosis, relies heavily on next generation sequencing due to the lack of local facilities. Supportive care, including antimicrobial prophylaxis and management of complications, is essential for enhancing quality of life. Expanded HSCT services, improved diagnostic capabilities, and increased awareness are needed to address these gaps in IEI care in Sri Lanka.[12]

6. Mortality

The mortality rates vary significantly depending on the region and the availability of timely interventions. In India (2013), the mortality rate stands at 51%, largely due to delays in diagnosis and limited access to HSCT.[16] In the Chinese population of Taiwan, the mortality is relatively lower at 17%, with

early detection through newborn screening and prompt HSCT improving survival outcomes.[18] Kenya reported a 100% mortality rate in a small cohort, mainly due to the lack of access to HSCT and delayed diagnosis.[23] In Oman, where consanguinity is common, and there is no national newborn screening program, the mortality rate is 69%, with late diagnosis and the complexity of the disease contributing to poor outcomes.[8] In Saudi Arabia, the overall mortality rate is 10.3%, with HSCT significantly improving survival, particularly for patients who received early treatment.[19] These findings highlight the crucial role of early diagnosis, access to advanced treatments like HSCT, and appropriate prophylactic care in improving survival rates for children with SCID. Table 1 summarizes the mortality rate and emphasizes the cause of death.

Table 1. Consolidated Mortality Data.

Region	Number of patients	Mortality Rate	Comments
India (2013)	47	51%	High due to limited HSCT and delayed diagnosis.[16]
Taiwan	24	17%	Early HSCT improved prognosis.[18]
Kenya	3	100%	Lack of infrastructure and diagnostic delays.[23]
Oman	36	69%	High consanguinity rates, no NBS program.[8]
Saudi Arabia	502 (85 SCID)	10.3%	HSCT widely available; most deaths under 5 years.[19]

7. Discussion

Severe combined Immunodeficiency (SCID) represents one of the most severe forms of primary immunodeficiency (PID) disorders characterized by impaired cellular and humoral immune responses. This report analyzes patient records from regions all over the world, which includes Saudi Arabia, United States, France, Oman, Taiwan, Iran, France, Kenya, India and Sri Lanka.

Diagnosis is crucial to establish a clear understanding of the patient's clinical presentation, medical history and other preliminary findings. This review attempts to delve into case studies, which highlight the key diagnostic tools and to uncover the evolving of diagnostic methods over the years. Majority of the patients were diagnosed from the age of 7 months to 1 year.

According to a case study conducted and published in 1993, in France, initially blood T-cell counts were determined by E-rosetting until 1981, later diagnosis was transitioned to more accurate methods like indirect immunofluorescence. Serum immunoglobulin levels, crucial for understanding immune deficiencies, were first measured using radial immunodiffusion until 1983, after which the more sensitive and automated technique of Nephelometry was introduced.[15]

Fast forward to 2005, in Iran, diagnosis significantly improved through the integration of advanced diagnostic tools such as positive serum galactomannan testing, computed tomography (CT) scans, PCR analysis and flow cytometry. Serum galactomannan testing aids in identifying opportunistic fungal infections, which are common in SCID patients due to profound immunosuppression. CT scans provide detailed imaging of lymphoid tissues, lungs, and other organs, identifying structural abnormalities or infections indicative of immunodeficiency complications.[21]

During a study conducted in Taiwan between 2010 and 2011, T-cell receptor excision circle (TREC) assay was introduced which was utilized to detect T-cell deficiencies, as particularly methods like newborn screening was used to measure complete blood counts,

which provided broader but less specific insights into immune function, the TREC assay directly assesses thymic output, making it highly sensitive and specific for identifying severe combined immunodeficiency (SCID) and other T-cell deficiencies. Its ability to detect low or absent TRECs at birth enables early identification of immune deficiencies, often before symptoms appear. TREC assay made a profound difference and was significantly advantageous over traditional diagnosis methods.[18]

By 2011, Lymphocyte flow cytometry was the commonest diagnostic technique that was used in India.[16] Lymphocyte flow cytometry is a cornerstone in the diagnosis of SCID because it allows for a comprehensive and detailed analysis of T, B and Natural Killer Cells. Similarly, Lymphocyte Phenotyping was widely used in North America which aided in characterizing immune cell populations and identifying deficiencies or imbalances in lymphocyte subsets. In vitro Lymphocyte Phenotyping, which assesses lymphocyte function, such as proliferation and cytokine production has been useful in SCID diagnosis. T-cell Receptor spectratyping is used in analyzing T-cell repertoire and identifying clonal expansions or reduced diversity. These remarkable advancements in diagnostic techniques have enabled early patient diagnosis, ensuring timely treatment delivery.[24]

By 2015, Arab populations have showed that the rate of combined immunodeficiency is higher than that in the rest of the world.[22] During the study period, 26% of the cases, comprising 132 patients, were diagnosed at birth through targeted newborn screening programs specifically designed for families with a known history of immunodeficiency disorders. Consanguineous marriages have been a major reason for mortality.[19] Inbreeding tends to reveal recessive alleles present in heterozygous carriers and to increase the frequency of homozygous individuals for a given rare allele. Therefore, it is ideal that families with an affected member could utilize preconception carrier testing and prenatal diagnosis.

By 2017, the United States and Canada had made significant advances in the early diagnosis of SCID. Among the diagnostic techniques used in USA and Canada, T cell receptor excision circle (TREC) testing stands out as the most significant, particularly in the context of early detection of T-cell deficiencies. Both countries have robust newborn screening programs that include TREC testing. Another important diagnostic technique is Transplacental Maternal Engraftment, this detects the presence of maternal cells in the infant's blood, a phenomenon known as maternal engraftment. It can be useful for diagnosing conditions like graft-versus-host disease (GVHD) or assessing the impact of maternal immune cells on the newborn's immune system.[20]

In 2019, India had made significant advances in genetic testing. Phospho-STAT5 analysis is a test that evaluates the activation of STAT5, a transcription factor critical for T-cell receptor signaling. T-cell proliferation assays evaluate the ability of T cells to proliferate in response to stimuli, which is typically impaired in SCID patients. A common method uses CellTrace Violet dye to label T cells, allowing for tracking their proliferation after stimulation with mitogens or antigens. Sanger sequencing is a method for determining the nucleotide sequence of DNA and is used to identify mutations in genes associated with SCID. This method allows for the precise identification of mutations in SCID-related genes such as IL2RG**,** RAG1**,** and RAG2**.** Sanger sequencing has been a gold standard in diagnosis for decades, as it stands out due to its high accuracy and versatility.[22]

According to a published study in 2020, Oman was introduced to a comprehensive diagnosis tool, Whole Genome Sequencing (WES) which provided a

comprehensive analysis of the exome (the protein-coding regions of the genome), allowing for the identification of mutations in any of these genes or other novel genes linked to SCID. WES revolutionized the diagnosis of SCID by enabling the rapid and detailed identification of rare genetic mutations which reduced diagnostic delays allowing for earlier interventions.[8]

By 2021, in Kenya Flow cytometry was used, which is a powerful tool used to analyze the characteristics of individual cells in a heterogeneous population, such as peripheral blood leukocytes.[23] The BD FACSCalibur™ is a flow cytometer used to analyze immune profiles by measuring specific cell surface markers on blood cells. It can provide a detailed profile of different immune cell populations, such as the enumeration of T cell subsets (CD4+, CD8+), B cells (CD19+), and NK cells (CD56+). While flow cytometry offers a cellular view, immunoglobulin testing directly evaluates the humoral aspect of immunity. This method is essential for identifying deficiencies in antibody production, which is particularly helpful in diagnosing conditions like specific Ig deficiencies.[25]

In Sri Lanka, 10 patients have been confirmed with SCID through diagnostic tests such as Full Blood Count (FBC), T Cell Proliferation Assay, and Functional Hemolytic Complement Assays. FBC identifies abnormalities in white blood cells, while T Cell Proliferation evaluates immune functionality, and complement assays assess the complement system's role in immunity. However, molecular and genetic diagnostics remain limited to X-linked SCID, XLA, and chromosomal deletion 22q11.2. Expanding diagnostic facilities could drastically reduce mortality in Sri Lanka.[26]

Diagnosis has evolved rapidly over the years, and future advancements promise to bring a great revolution. Newborn screening and Whole Genome Sequencing have brought in a drastic change in diagnosis. Apart from TREC, advanced methods of screening have been suggested in Italy.[23] TREC Assay is combined with Tandem mass spectrometry for adenosine deaminase deficiency detection (including the combination of molecular and biochemical techniques to improve early diagnosis of SCID and related conditions). Building on these advancements, multiples assays play a vital role by enabling comprehensive analysis of the genetic condition. Furthermore, advancements in automation and robotics have enabled high-throughput screening platforms by speeding up sample processing. Ongoing research and innovation in this field are crucial to enhance diagnosis of SCID on a global scale.

8. Conclusion

Severe Combined Immunodeficiency is a group of rare and life-threatening genetic disorders characterized by profound defects in the immune system, particularly affecting T cells, and often B cells and NK cells. SCID patients are highly susceptible to recurrent, severe infections, which can be fatal if not diagnosed and treated early. Early diagnosis is crucial for improving outcomes, as the condition is usually detected in infancy or early childhood. The most effective diagnostic tool for SCID is lymphocyte flow cytometry, which provides details of immune cell populations. Subsequently, TREC assay was introduced which provided detailed analysis of T cell deficiencies. Whole genome sequencing (WGS) has revolutionized the diagnosis SCID by providing a comprehensive and precise method for identifying genetic mutations. Unlike traditional diagnostic methods, which may focus on specific genes or symptoms, WGS allows for the analysis of an individual’s entire genetic makeup, enabling the detection of a wide range of mutations. Bone marrow and fetal liver transplantation, and in some cases gene therapy, offer the potential for long-term immune reconstitution and are considered curative options for SCID. Advances in

treatment have significantly improved survival rates, especially when these therapies are initiated early in life. Recent advancements in hematopoietic stem cell (HSC) transduction have revolutionized gene therapy for inherited disorders like SCID. The development of viral vector-based technologies, including retroviral and lentiviral vectors, has greatly improved the efficiency and specificity of gene delivery to HSCs. Despite the challenges, timely diagnosis and comprehensive treatment approaches, including immune system restoration and supportive care, can offer SCID patients the best chance for survival and improved quality of life.

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