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Research Article

Effectiveness of Cascade Screening in the Detection of β-Thalassemia Carriers and Prevention of Thalassemia Major

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ABSTRACT

Background & Objectives: Beta-thalassemia is one of the most common autosomal recessive hemoglobinopathies worldwide, imposing a substantial financial, psychological, and clinical burden on affected families and healthcare systems. Because universal population screening is often resource-prohibitive in developing nations, targeted screening mechanisms are urgently required. This study aimed to evaluate the diagnostic yield and practical utility of targeted 'cascade screening' among extended family members of known index cases for carrier state identification.

Materials & Methods: A prospective observational study was conducted over a one-year period (2010–2011) at the Thalassemia Day Care Centre, Indira Gandhi Institute of Child Health, Bangalore. Extended family members—specifically second- and third-degree relatives (n = 138) of 20 confirmed β-thalassemia major index cases—were enrolled following informed written consent. Screening for thalassemia carrier status was performed using alkaline and/or citrate agar hemoglobin electrophoresis.

Results: Among the 138 extended relatives evaluated (28 males, 27 females in primary socio-demographic cohort), 55 individuals were identified as heterozyous β-thalassemia carriers, representing a high diagnostic yield of 39.86% (approximately 40%). Notably, 3 pregnant women were identified as carriers; subsequent chorionic villus sampling (CVS) revealed 2 fetuses with carrier trait and 1 fetus with β-thalassemia major, leading to informed genetic counseling and therapeutic termination of the affected pregnancy. On average, for every index patient evaluated, approximately 3 carrier relatives were successfully identified.

Conclusion: Cascade screening of extended family members demonstrates high diagnostic efficacy, cost-effectiveness, and feasibility. Targeting high-risk family lineages provides an optimal strategy to reduce the incidence of homozygous β-thalassemia major in resource-limited settings.

Keywords: Beta-thalassemia, cascade screening, carrier detection, hemoglobinopathy, genetic counseling, prenatal diagnosis, disease prevention.

Introduction

Beta-thalassemia represents one of the most prevalent inherited monogenic blood disorders globally, characterized by reduced or completely absent synthesis of the β-globin chains of hemoglobin. Inherited in an autosomal recessive pattern, the clinical spectrum ranges from

asymptomatic heterozygous carriers (thalassemia minor) to severe, transfusion-dependent anemia in homozygous or compound heterozygous individuals (thalassemia major). The global epidemiological burden is concentrated primarily across the Mediterranean basin, the Middle East, the Indian subcontinent, and Southeast Asia.

World Health Organization (WHO) estimates indicate that approximately 1.5% of the global population are trait carriers for β-thalassemia, resulting in over 68,000 affected births annually worldwide. In India alone, over 30 million individuals carry the mutant β-thalassemia gene, with an estimated overall carrier frequency of 3% to 4%. Consequently, India accounts for nearly 10% of the total global burden of children born with severe thalassemic syndromes each year.

Management of β-thalassemia major requires lifelong hypertransfusion regimens coupled with complex iron-chelation therapy to prevent secondary hemochromatosis and organ toxicity. The economic, psychological, and social toll on affected families is immense, frequently compounded by limited regional care centers and inadequate financial resources. Because definitive curative options such as hematopoietic stem cell transplantation (HSCT) remain out of reach for the vast majority of patients, primary prevention remains the cornerstone of public health management.

While general population screening is ideal in theory, mass universal screening programs in highly populated, resource-constrained settings present substantial financial and logistical hurdles. In contrast, inductive or 'cascade screening'—a targeted methodology in which the extended biological relatives of an established index case are systematically screened—offers a highly focused and economically viable alternative. This study was undertaken to evaluate the diagnostic yield and clinical feasibility of cascade screening among second- and third-degree relatives of β-thalassemia major patients in Karnataka, South India.

Materials and Methods

Study Design and Setting

This prospective observational clinical study was conducted over a 12-month period (2010–2011) at the Thalassemia Day Care Centre of the Indira Gandhi Institute of Child Health (IGICH), Bangalore, Karnataka, India.

Study Population and Sampling

The primary study cohort comprised second- and third-degree biological relatives (n = 138) derived from 20 confirmed index cases of β-thalassemia major receiving regular care at the institution. Informed written consent was obtained from all adult participants and from the legal guardians of minor pediatric subjects prior to enrollment.

Diagnostic Methodology

Venous blood samples were collected in EDTA tubes and processed for complete blood counts (CBC) and red cell indices. Definitive carrier detection was performed via quantitative hemoglobin electrophoresis using alkaline and/or citrate agar gel methods. Trait identification was defined by elevated HbA2 levels (>3.5%) and characteristic microcytic hypochromic erythrocyte parameters. Antenatal carrier testing and prenatal diagnostic procedures—specifically Chorionic Villus Sampling (CVS) followed by fetal DNA analysis—were offered to pregnant female carriers identified during cascade tracing.

Results

A total of 20 index cases of β-thalassemia major led to the identification and screening of 138 extended relatives (second- and third-degree). Detailed carrier tracing yielded 55 confirmed β-thalassemia carriers, establishing a overall diagnostic carrier detection rate of 39.86% (40.0%).

Table 1: Summary of Cascade Screening Diagnostic Yield

Parameter / Category	Enrolled Cohort Count	Percentage / Yield
Total Index Cases Evaluated	20	—
Extended Relatives Screened (2nd & 3rd Degree)	138	100.0%
Confirmed β-Thalassemia Carriers Identified	55	39.86%
Non-Carrier Extended Relatives	83	60.14%
Identified Pregnant Carrier Females	3	—
Ratio of Carriers Detected per Index Case	2.75 : 1 (~3:1)	—

Antenatal Outcomes

Among the 55 carriers detected, 3 were pregnant females at early gestations. Following non-directive genetic counseling, all 3 underwent prenatal diagnosis via Chorionic Villus Sampling (CVS). Molecular analysis confirmed that 2 fetuses were heterozygous carriers, while 1 fetus was homozygous for β-thalassemia major. Following thorough clinical consultation, the parents elected for legal therapeutic termination of the affected pregnancy.

Discussion

In South India, the background carrier frequency for β-thalassemia is estimated between 1% and 3%. However, high rates of endogamy and consanguineous marriages within specific regional communities significantly elevate the risk of producing homozygous offspring. Because unselected general population screening programs lack cost-effectiveness in developing economic landscapes, selective screening focused on high-risk pedigrees represents the most practical pathway.

Our findings demonstrate a carrier detection rate of ~40% through cascade screening, confirming that screening biological relatives of index cases yields a significantly higher prevalence of gene carriers than general population surveys. Crucially, each index case evaluated led to the detection of approximately 3 carriers, underlining the high sensitivity of family-centered genetic tracing.

Historically, socio-cultural barriers such as social stigmatization, fear of altered marital prospects, and lack of awareness have hindered carrier disclosure within extended families. For instance, early studies by Sangani et al. (1990) in Mumbai and Yagnik (1997) highlighted that nearly half of identified carriers did not inform their immediate siblings due to social stigma. However, recent trends demonstrate rising health literacy and willingness among parents of affected children to share genetic information across extended family networks (Saxena & Phadke, 2002).

The success of national prevention initiatives in Cyprus, Greece, and Sardinia demonstrates that public awareness, combined with targeted carrier identification, premarital counseling, and prenatal diagnosis, can lead to the near-complete eradication of new thalassemia major births.

Conclusion

Cascade screening represents an exceptionally high-yield, cost-effective, and logistically feasible strategy for identifying β-thalassemia carriers in India. Establishing strong public-private healthcare partnerships to incorporate family-based cascade tracing into routine pediatric and hematological practice will play a vital role in lowering the overall incidence of thalassemia major nationwide.

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