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Fetal Hemoglobin (HbF) as a Genetic Modulator in Various Clinical Phenotypes of Sickle Cell Anemia in Tribal and Non-Tribal Ethnic Group of Saurashtra Region in Gujarat

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Abstract

Objectives: To compare fetal hemoglobin (HbF) levels and clinical manifestations between Tribal and non-Tribal Sickle Cell Anemia (SCA) patients in Gujarat's Saurashtra region and investigate HbF's role in modulating disease severity. ***Methods:*** This retrospective study analyzed 68 SCA patients (33 Tribal, 35 non-Tribal) at a tertiary care center from January 2023-2024. HbF levels were measured via high-performance liquid chromatography, and clinical data on Acute Chest Syndrome (ACS), Vaso-occlusive Events (VOE), Pain Crisis, and hospitalization duration were collected from medical records. ***Results:*** Tribal patients exhibited significantly higher mean HbF levels compared to non-Tribal patients (17.8% vs. 13.0%, p<0.01). This correlated with lower incidence of ACS (36% vs. 65%, p=0.0176) and VOE (39% vs. 77%, p=0.0016) among Tribal patients. Pain Crisis incidence showed no significant difference between groups (36% vs. 45%, p=0.4535). Notably, Tribal patients experienced shorter mean hospital stays (2.12 vs. 3.37 days, p<0.01). ***Conclusion:*** Higher HbF levels in Tribal SCA patients correlate with reduced ACS and VOE incidence and shorter hospitalizations, suggesting a protective effect. These findings enhance understanding of SCA heterogeneity across ethnic groups and may inform development of population-specific management approaches. Further investigation into genetic and environmental factors underlying these differences is warranted.

Keywords: ***Sickle Cell Anemia, Fetal Hemoglobin, Tribal (Ahir, Bharwad, Rabari, and Kharwa), Genetic Modulator, Ethnic Variation.***

Introduction

Sickle Cell Anemia (SCA) is a genetic disorder characterized by the production of abnormal hemoglobin S, leading to erythrocyte sickling, vaso-occlusion, and hemolysis. It affects millions worldwide, with a particularly high prevalence in sub-Saharan Africa, the Middle East, and certain regions of India [1]. In India, SCA is especially prevalent among tribal populations, including the Tribal communities, where carrier frequencies can reach up to 40% in some groups [2]. The clinical manifestations of SCA are diverse and can include acute pain crises, acute chest syndrome (ACS), stroke, and organ damage. However, the severity and frequency of these complications vary significantly among patients, even within the same geographical or ethnic group [3]. This heterogeneity in clinical presentation has led researchers to investigate various genetic and environmental factors that might modulate disease severity.

One of the most well-established genetic modifiers of SCA severity is fetal hemoglobin (HbF). HbF, which comprises two α-globin and two γ-globin chains, is the primary hemoglobin during fetal development and is normally replaced by adult hemoglobin (HbA) shortly after birth. However, some individuals continue to produce significant amounts of HbF into adulthood, a condition known as hereditary persistence of fetal hemoglobin (HPFH) [4].

Higher levels of HbF have been consistently associated with milder clinical courses in SCA patients. HbF inhibits the polymerization of deoxygenated hemoglobin S, thereby reducing erythrocyte sickling and its consequent complications [5]. Studies have shown that SCA patients with HbF levels above 8-10% experience fewer pain crises, less frequent ACS episodes, and improved survival compared to those with lower HbF levels [6].

Interestingly, HbF levels and their distribution within erythrocytes can vary significantly between different ethnic groups. For instance, some populations in the Eastern Province of Saudi Arabia and certain regions of India have been reported to have higher baseline HbF levels and milder SCA phenotypes [7]. These observations suggest that genetic factors influencing HbF production may have been selected for in populations with a high

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prevalence of the sickle cell gene, possibly as an evolutionary response to malaria [1].

In India, the Tribal communities, who are indigenous tribal populations, have been living in malaria-endemic regions for millennia. This long-term exposure to malaria may have led to the selection of genetic variants that confer protection against severe malaria, including the sickle cell trait. However, limited research has been conducted to compare HbF levels and SCA severity between Tribal and non-Tribal populations in India [8].

Understanding the differences in HbF levels and clinical manifestations of SCA between these populations could provide valuable insights into the genetic and environmental factors modulating disease severity. Such knowledge could inform more tailored approaches to SCA management and potentially guide genetic studies aimed at identifying novel therapeutic targets.

Therefore, this study aims to compare HbF levels and the incidence of key SCA complications (acute chest syndrome, vaso-occlusive events, and pain crises) between Tribal and non-Tribal SCA patients. By elucidating these differences, we hope to contribute to a better understanding of SCA heterogeneity in the Indian context and pave the way for more personalized treatment strategies.

Methodology

Study Design

This study employed a retrospective, record-based design to investigate the differences in fetal hemoglobin (HbF) levels and clinical manifestations of Sickle Cell Anemia (SCA) between Tribal and non-Tribal communities.

Study Setting

The study was conducted at [Shri M P Shah Medical College, GG Hospital], a tertiary care center located in [Saurashtra Region of Gujarat]. This center serves as a major referral hospital for SCA patients from both Tribal and non-Tribal communities in the region. The tribal population primarily comprises Ahir, Bharwad, Rabari, and Kharwa communities.

Study Period

The study included medical records from [23/01/2023] to [22/01/2024], covering a period of 1 years.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee of [Shri M P Shah Medical College, GG Hospital] (Approval number: [199/05/2022]). As this was a retrospective study using anonymized data, the requirement for individual patient consent was waived.

Study Population

Inclusion Criteria

The study population comprised patients diagnosed with Sickle Cell Anemia, specifically those with confirmed HbSS genotype through appropriate laboratory testing. All participants were required to be above one year of age at the time of enrollment. To ensure comprehensive data collection and analysis, only patients with complete medical records spanning the entire study period were included in the research cohort.

Exclusion Criteria

The study excluded patients diagnosed with hemoglobinopathies other than sickle cell disease or those with concurrent hematological disorders to maintain homogeneity in the study population. Additionally, patients with incomplete or inadequate medical documentation were not considered for enrollment to ensure data accuracy and completeness. Furthermore, individuals receiving hydroxyurea therapy or other hemoglobin F-inducing medications were excluded from the study cohort, as these interventions could potentially influence the natural course of the disease and affect the study outcomes.

Sample Size

A total of 68 patient records meeting the inclusion criteria were included in the study. These comprised 33 patients from the Tribal community and 35 patients from other communities. Figure-1 illustrates the participants recruitment process [**Figure 1**].

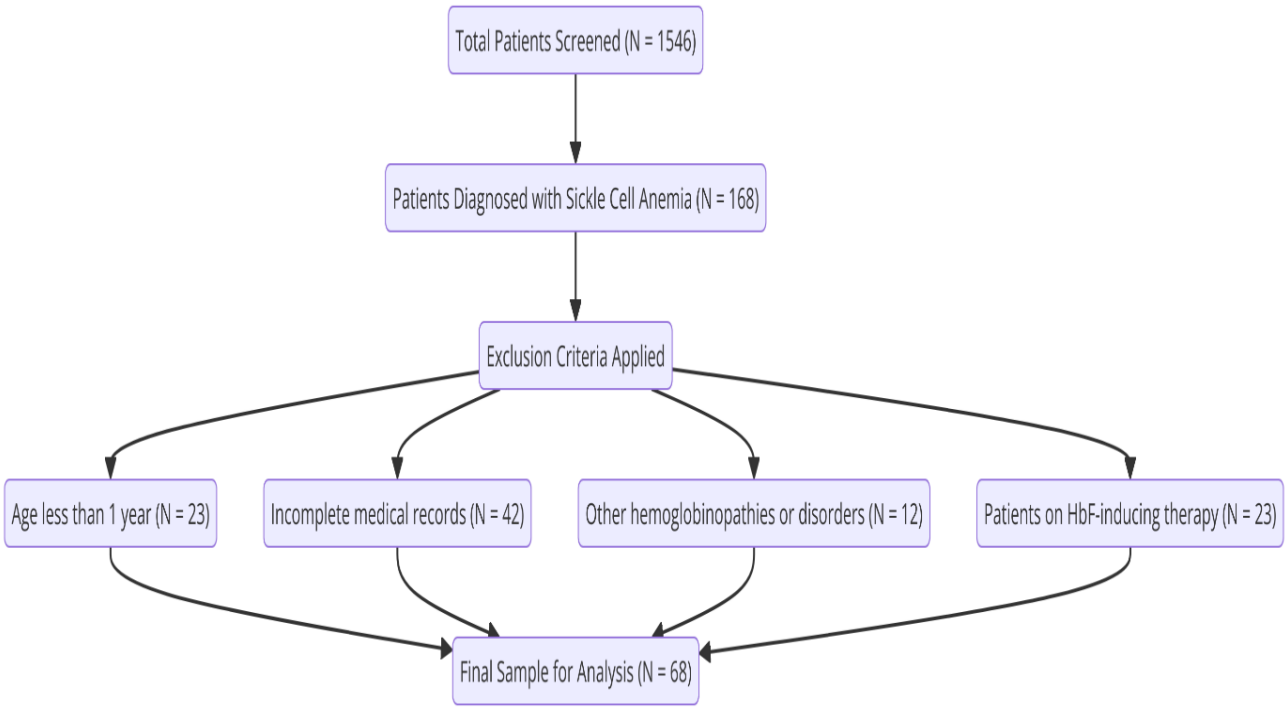

Figure 1: participant requirement process

Data Collection

Source of Data

Data were extracted from electronic medical records and paper-based patient files maintained at the [Shri M P Shah Medical College, GG Hospital].

Data Extraction Process

The data extraction process followed a systematic approach where a standardized data extraction form was initially developed and validated through pilot testing on ten medical records. Data collection was conducted independently by two trained research assistants to minimize bias and ensure data quality. To maintain accuracy and reliability of the extracted information, a third researcher independently cross-verified 20% of the collected data, serving as an additional quality control measure throughout the data collection process.

Variables Collected

The study collected comprehensive participant data across several key domains. The demographic information included participants' age, sex, and ethnicity, specifically noting whether individuals were of Tribal or non-Tribal background. Clinical data encompassed multiple parameters, including the most recent hemoglobin F (HbF) level measurements, along with documented incidents of Acute Chest Syndrome (ACS), Vaso-occlusive Events (VOE), and Pain Crisis. Laboratory investigations consisted of complete blood count analysis and results from High-Performance Liquid Chromatography. The treatment history documented all blood transfusions received, approaches to pain management, and records of hospitalizations.

Laboratory Methods

HbF levels were determined using high-performance liquid chromatography (HPLC) on a [ADAMS A1c HA-8180T System] analyzer, following the manufacturer's protocol.]

Case Definitions

The study established clear diagnostic criteria for key clinical conditions. Acute Chest Syndrome was characterized by the detection of a new pulmonary infiltrate through chest X-ray imaging, coupled with either fever, respiratory symptoms, or both. A Vaso-occlusive Event was identified when patients experienced pain episodes affecting the extremities, back, abdomen, or chest that were severe enough to necessitate either hospital admission or a visit to the emergency department. Pain Crisis was specifically defined as any pain episode with a duration exceeding 4 hours that required the administration of opioid analgesia for management.

Data Analysis

Data were entered into statistical software (SPSS version 26) for analysis. Descriptive statistics were utilized to summarize the demographic and clinical characteristics of the study population. Continuous variables, such as HbF levels, were presented as mean ± standard deviation, while categorical variables, such as the incidence of clinical events, were expressed as percentages. Differences in HbF levels between the Tribal and non-Tribal groups were analyzed using Student's t-test. Chi-square tests were employed to compare the incidence proportions of clinical events between the two groups. A p-value of less than 0.05 was considered statistically significant for all analyses.

Quality Control Measures

The study implemented rigorous quality control measures throughout the data management process. All data underwent double entry procedures to minimize potential entry errors and ensure accuracy. The research team conducted regular meetings to identify and resolve any discrepancies or issues that arose during the data collection phase. To maintain analytical integrity, an independent statistician was engaged to review the entire data analysis process.

Results

In our research, we analyzed a total of 68 Sickle cell Anemia out of which 33 cases were from the Tribal community and 35 cases were from other communities findings are as follows:

Table 1 presents a comparison of fetal hemoglobin (HbF) values between Tribal and Non-Tribal groups with Sickle Cell Anemia. The study included 33 Tribal patients and 35 Non-Tribal patients, for a total of 68 participants. The Tribal group showed a higher mean HbF level of 17.8% with a standard deviation of 5.46, while the Non-Tribal group had a lower mean HbF level of 13.0% with a standard deviation of 5.42. The mean difference between the two groups was -4.87, indicating that the Tribal group had significantly higher HbF levels. This difference was found to be statistically significant with a p-value of less than 0.01, suggesting that the observed difference in HbF levels between the two groups is unlikely to be due to chance **[Table 1]**.

Table 2 compares various clinical phenotypes of Sickle Cell Anemia between Tribal and Non-Tribal groups. The table presents data on three key complications: Acute Chest Syndrome (ACS), Vaso-occlusive Events (VOE), and Pain Crisis. For ACS, 15 Tribal patients (36% incidence) and 23 Non-Tribal patients (65% incidence) were affected. The difference in ACS incidence was statistically significant with a p-value of 0.0176. VOE occurred in 13 Tribal patients (39% incidence) compared to 27 Non-Tribal patients (77% incidence), with a highly significant p-value of 0.0016. Pain Crisis affected 12 Tribal patients (36% incidence) and 16 Non-Tribal patients (45% incidence), but this difference was not statistically significant (p-value 0.4535). Overall, the data suggests that Tribal patients experienced fewer complications, particularly ACS and VOE, compared to their Non-Tribal counterparts [**Table 2**].

Table 3 examines the duration of hospitalization for Sickle Cell Anemia patients in Tribal and Non-Tribal groups. Tribal patients had a mean hospitalization duration of 2.12 days with a standard deviation of 0.696, while Non-Tribal patients stayed longer with a mean of 3.37 days and a standard deviation of 1.14. The mean difference in hospitalization duration was 1.25 days, with Non-Tribal patients requiring longer hospital stays. This difference was statistically significant with a p-value of less than 0.01, indicating that Tribal patients generally had shorter hospital stays compared to Non-Tribal patients **[Table 3]**.

Figure 2 presents a correlation between days of hospitalization and HbF levels ($r=0.719$, $p<0.001$). While the specific details of the graph are not provided, it can be inferred that this figure likely demonstrates an inverse relationship between HbF levels and the duration of hospitalization. This would align with the study's findings that higher HbF levels, as seen in the Tribal group, are associated with shorter hospital stays and potentially milder disease severity [**Figure 2**].

Table 1: Comparison of HbF values in Sickle cell Anemia between Tribal and Non Tribal group

Caste Group	Total Patients	Hb F Mean	HbF Standard Deviation	Mean Difference	P Value
Tribal	33	17.8	5.46	-4.87	<0.01
Non-Tribal	35	13.0	5.42		
Total	68	-	-		

A p-value < 0.05 was considered statistically significant. Hb F-Fetal Hemoglobin

Table 2: Comparison of various Clinical phenotypes of Sickle cell Anemia of Tribal and Non Tribal Group

Caste Group	Acute Chest Syndrome	Vaso occlusive events	Pain Crisis	ACS Incidence Proportion (%)	VOE incidence Proportion (%)	Pain Crisis Incidence Proportion (%)
Tribal	15	13	12	36	39	36
Non-Tribal	23	27	16	65	77	45
Total	38	40	28	55	58	41
P Value	-	-	-	0.0176	0.0016	0.4535

A p-value < 0.05 was considered statistically significant. ACS- Acute Chest Syndrome, VOE- Vaso occlusive events

Table 3: Comparison of Duration of Hospitalization in sickle cell anemia between Tribal and non Tribal group

Caste Group	Duration of Hospitalization		Mean Difference	P Value
	Mean	SD		
Tribal	2.12	0.696	1.25	<0.01*
Non-Tribal	3.37	1.14		

P<0.05- Statistically significant.*

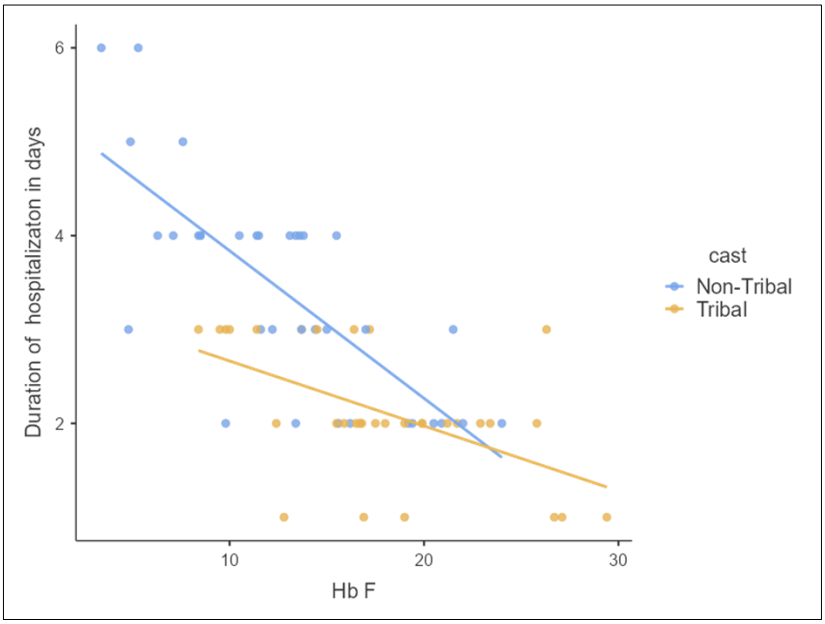

Figure 2: Correlation between days of hospitalization and HbF

Discussion

The results of our study reveal significant differences in fetal hemoglobin (HbF) levels and clinical manifestations of Sickle Cell Anemia (SCA) between Tribal and non-Tribal communities. These findings have important implications for understanding the genetic and environmental factors influencing SCA severity and for developing targeted interventions.

The higher mean HbF levels observed in Tribal patients (17.8% vs. 13.0% in non-Tribal) align with previous studies suggesting that elevated HbF levels can ameliorate SCA symptoms (Steinberg et al., 2014). This difference may be attributed to genetic factors specific to the Tribal population, possibly resulting from evolutionary adaptations to malaria-endemic regions [9].

The lower incidence of Acute Chest Syndrome (ACS), Vaso-occlusive Events (VOE), and Pain Crises in the Tribal group correlates with their higher HbF levels. This supports the protective role of HbF in reducing SCA complications, as documented in other populations [10]. The particularly striking difference in VOE incidence (39% in Tribal vs. 77% in others) warrants further investigation into potential genetic or environmental factors contributing to this disparity.

However, the considerable overlap in HbF distributions between the two groups, as shown in Figure 1, suggests that factors beyond HbF levels also influence SCA severity. These may include other genetic modifiers, environmental conditions, or healthcare access disparities between Tribal and non-Tribal communities [11].

The similar standard deviations in HbF levels between the groups indicate comparable variability within each population. This suggests that while the Tribal community has a higher average HbF level, individual variation remains significant. Consequently, personalized approaches to SCA management may be beneficial across both communities.

Our findings have potential clinical implications. The higher HbF levels and lower complication rates in the Tribal population suggest that genetic factors in this community could be targets for novel therapeutic approaches. Additionally, the results underscore

the importance of considering ethnic background in SCA prognosis and treatment planning.

This study, while providing valuable insights into the role of fetal hemoglobin (HbF) in Sickle Cell Anemia (SCA) among Tribal and non-Tribal populations, has several limitations. The relatively small sample size of 68 patients and the single-center design limit the generalizability of the findings to the broader SCA population in India. The retrospective nature of the study introduces potential for selection bias and limits control over confounding variables. The broad categorization of patients into "Tribal" and "non-Tribal" groups may overlook important subgroup differences. Additionally, the study lacks comprehensive genetic data that could explain the observed differences in HbF levels. Other potential confounding factors such as socioeconomic status, healthcare access, and treatment adherence were not fully accounted for. The cross-sectional design provides only a snapshot of HbF levels and clinical manifestations, without capturing their dynamic nature over time. Lastly, while key complications were examined, other important outcomes such as organ damage and overall mortality were not assessed. Future studies addressing these limitations would strengthen our understanding of HbF's role in modulating SCA severity across different ethnic groups in India.

Conclusion

The present study highlights significant variations in HbF levels and SCA clinical manifestations between Tribal and non-Tribal communities. These findings contribute to our understanding of SCA heterogeneity and may inform more targeted, population-specific approaches to SCA management and treatment.

Declarations

Acknowledgement.

The authors declare no acknowledgements for this study.

Conflict of interest

The authors declare no conflicts of interest relevant to this research study.

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