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ORIGINAL RESEARCH ARTICLE

Hemoglobinopathies Among Patients Referred to Single Centre in Central India: An Observational Study

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Abstract Sickle cell disease (SCD) and thalassemia are the most common hereditary disorders encountered in Central India. Timely identification of these disorders is critical to reduction in severe clinical manifestations and for identifying disease burden. Present study reports spectrum of hemoglobinopathies among the referred anemia patients to single centre in central India. All individuals referred to the institute from 1st January 2012 to 31st August 2020 for diagnosis were included in the study. Demographic details, clinical and transfusion history were obtained. Hemoglobin electrophoresis or High-Performance Liquid Chromatography (Variant II, Bio-Rad) was performed to identify the type of hemoglobinopathy. Molecular characterization of unknown or rare variants was performed wherever necessary. During the study period 13,587 individuals were screened. Homozygous beta thalassemia was observed in 0.6% of the patients, whereas SCD was observed in 12% of the patients. Seventy-four individuals have either hereditary persistence of fetal hemoglobin (HPFH) or delta beta thalassemia. More than 50% of SCD patients referred were over the age of 12 years. SCD disease was more common among Pradhan, Gond and Baiga tribes whereas HPFH and delta beta thalassemia was found among Other socially and educationally backward classes. High occurrence of hemoglobinopathies in central India warrants the need of large scale screening in highly prevalent communities for its prevention.

Keywords Hemoglobinopathies · Sickle cell disease · Tribes · Ethnicity

Introduction

Sickle cell disease (SCD) and thalassemia syndromes are the commonest inherited monogenic disorders of hemoglobin that are widely distributed throughout sub-Saharan Africa, the Mediterranean region, South-East Asia, parts of the Indian sub-continent and some parts of south and central America [1]. World Health Organization has estimated that 5% of world population carries a mutation in beta globin gene and globally around 3,00,000–5,00,000 babies are born with severe form of diseases (thalassemia (30%) or sickle cell disease (70%)) annually [2]. Both sickle cell disease and thalassemia cause life threatening crisis and poses psychosocial and economic burden on the families besides economic drain on the national resources.

In India, the prevalence of sickle cell trait (SCT) varies from 0 to 40% among different communities [3–5] and it is present in high frequencies among scheduled caste and scheduled tribes of Gujarat, Madhya Pradesh, Chhattisgarh, Odisha, Maharashtra, Andhra Pradesh, Karnataka and Kerala. The prevalence of β thalassemia traits ranges from 1 to 17% in different geographical areas and ethnic groups in India. It is estimated that more than 1,50,000 transfusion dependent thalassemia major patients are living in India and 10,000 to 12,000 patients are born annually [6].

With the recent advances, the prognosis and health related quality of life of both thalassemia and SCD have improved. Nonetheless, factors like (i) lack of diagnostic and specialised health care facilities in rural/ tribal areas (ii) awareness about the disease among affected population and medical workers and (iii) absence of the national burden,

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drastically affects disease outcome. Moreover, factors that notably affect disease outcome include broad distribution of types of hemoglobinopathies in different geographical areas and ethnic groups and migration of affected communities from one state to another for livelihood. Therefore, for the formulation of diagnostic, preventive and management strategies, it is imperative to study the distribution and types of hemoglobinopathies in different geographical areas and ethnic groups from time to time. Being a referral centre for diagnosis of hemoglobinopathies, anemic patients are referred to the Institute for diagnosis from Jabalpur and surrounding districts. Here, we report the frequency and types of hemoglobinopathies and their ethnic distribution.

Material and Methods

Subjects

All individuals having any symptoms of SCD or thalassemia such as anemia, joint pain, splenomegaly or requirement of blood transfusion and individuals requiring volunteer screening for hemoglobinopathies were referred to the Division of Genetic Disorders, ICMR-National Institute of Research in Tribal Health, Jabalpur. A total of 13,587 individuals were recruited between 1st January 2012 to 31st August 2020. Brief detail of individuals such as age, gender, caste and sub caste, category (General, other socially and educationally backward classes, scheduled castes and scheduled tribes) were obtained. Clinical symptoms and history of blood transfusion were also recorded to clinically correlate with laboratory findings.

Laboratory Investigations

Two mL of peripheral blood was drawn in EDTA vials under aseptic conditions after obtaining written informed consents. Cellulose acetate hemoglobin gel electrophoresis (Cellas Gel; Cleaver Scientific, Rugby, Warwickshire, UK) at alkaline pH was run on all samples to determine the hemoglobin pattern. Level of hemoglobin variants was quantified using cation exchange- high performance liquid chromatography technique on variant II (Bio-Rad laboratories (India) Pvt Ltd).

Individuals showing HB pattern of SS, SF, SFA_2, SD, SE and compound heterozygous of HbS with HPFH and delta beta thalassemia were classified as SCD. Individuals showing pattern of F and no sign and symptoms of beta thalassemia were classified as delta beta thalassemia or hereditary persistence of fetal hemoglobin. Parental and family screening was done wherever necessary. Sanger sequencing of alpha and beta globin gene was performed to characterise the rare or unknown alpha and beta globin variants (Applied Biosystem 3130, Thermo Fisher Scientific). Diagnosis was provided based on the corroboration of laboratory findings, clinical symptoms and transfusion history. The study was approved by the Institutional Ethics and Scientific Advisory committees.

Results

In all 13,587 subjects (7547 female and 6040 male) were referred by the Government Medical College and Hospital, Jabalpur for testing of various hemoglobinopathies during the study period.

The median age of the referred individuals was 22 year (25th to 75th centile: 9 to 30 years). Table 1 shows the type of hemoglobinopathies identified in different age groups. Sickle cell disease (SCD) (homozygous sickle cell anemia, sickle beta thalassemia, SD disease, SE disease and compound heterozygous of HbS and HPFH/delta beta thalassemia) was observed in 1630 (12.0%) of studied subjects whereas homozygous beta-thalassemia disease was found in 87 (0.6%) individuals. Sickle cell trait (SCT) and beta thalassemia trait was observed in 19.1% and 3.8% individuals respectively. Homozygous HbE disease was observed in 7 cases and homozygous hereditary persistence of fetal hemoglobin (HPFH) and delta beta thalassemia was observed in 22 cases. Out of the 1630 SCD diagnosed patients, 544 were registered in sickle cell clinic of the institute and are being routinely followed up.

More than 50% of SCD patients were referred after the age of 12 years, while all homozygous beta thalassemia patients were below 6 years at the time of referral. Only eight percent of SCD patients were referred before the age of 2 years for diagnosis. In case of SCD, among 2393 patients in the age group of 18 to 24 years, 1817 (75.9%) were females and majority of them were referred for screening during antenatal testing. Spouse of the carriers were also tested, and 22 couples were identified as high-risk and referred to our sister institute for prenatal diagnosis.

Out of 13,587 studied individuals, 18.3% belonged to tribal communities whereas 30.5% individuals were from schedule caste community. Distribution of hemoglobinopathies was highest among scheduled caste communities followed by the schedule tribes. Heterozygous beta thalassemia was about 2.5-fold higher in general community as compared to the scheduled tribe communities. On the other hand, SCT was two-fold higher in scheduled tribes as compared to general communities (Table 2). Strikingly, 50% of HPFH and delta beta thalassemia cases were observed in other socially and educationally backward classes (SEBCs).

Variation in the age of diagnosis of homozygous hereditary persistence of fetal hemoglobin and delta beta thalassemia cases were also noted. Rare hemoglobin variants such

Table 1 Age wise distribution of hemoglobinopathies identified at referral. Rows represent the various haemoglobin variants and columns represent the age distribution. Rare haemoglobin variants have been represented under others

Hemoglobinopathies	Age groups (in years)						Total
	< 2	2.1–6	6.1–12	12.1–18	18.1–24	> 24	
Homozygous beta thalassemia	70(80.5)	14(16.1)	3(3.4)	0 (0.0)	0 (0.0)	0 (0.0)	87
Heterozygous beta thalassemia	26 (5.1)	22 (4.3)	28 (5.5)	18 (3.5)	81 (15.9)	335 (65.7)	510
Sickle cell disease	124 (7.6)	295 (18.1)	389 (23.9)	237 (14.6)	274 (16.8)	309 (19.0)	1628
Sickle cell trait	153 (5.9)	154 (5.9)	206 (7.9)	197 (7.6)	348 (13.4)	1536 (59.2)	2594
Homozygous HPFH and delta beta thalassemia	03 (13.6)	04 (18.2)	05 (22.7)	01 (4.5)	08 (36.4)	01 (4.5)	22
Compound heterozygous of thalassemia and HPFH	02 (6.7)	09 (30.0)	08 (26.7)	03 (10.0)	02 (6.7)	06 (20.0)	30
Heterozygous HPFH and delta beta thalassemia	11 (21.6)	04 (7.8)	03 (5.9)	02 (3.9)	05 (9.8)	26 (51.0)	51
E-Beta thalassemia	03 (30.0)	02 (20.0)	02 (20.0)	03 (30.0)	0 (0.0)	0 (0.0)	10
Other (HbD-Punjab, HbEHb-O Indonesia, Lepore, HbH, HbJ and Hb Q India)	08 (10.5)	05 (6.6)	08 (10.5)	06 (7.9)	09 (11.8)	40 (52.6)	76
Normal	1234 (14.4)	660 (7.7)	782 (9.1)	1051 (12.3)	1666 (19.5)	3167 (37.0)	8560
Total	1634 (12.0)	1169 (8.6)	1434 (10.6)	1518 (11.2)	2393 (17.6)	5420 (39.9)	13,568

*Figures in parenthesis indicate percent value of each of the variant respective to its total number given in last column

Table 2 Community wise distribution of hemoglobinopathies—shows the hemoglobin variants identified among scheduled tribe, scheduled caste, other socially and economically backward classes and general communities. Rows represent the various haemoglobin variants and columns represent the communities

	Community				Total
	General	SEBC	SC	ST	
Homozygous beta thalassemia	30 (35.3)	31 (36.5)	13 (15.3)	11 (12.9)	85
Heterozygous beta thalassemia	159 (31.2)	204 (40.1)	85 (16.7)	61 (12.0)	509
Sickle cell disease	182 (11.2)	410 (25.3)	716 (44.1)	315 (19.4)	1623
Sickle cell trait	276 (10.7)	660 (25.6)	1104 (42.9)	536 (20.8)	2576
Homozygous HPFH and delta beta thalassemia	04 (18.2)	11 (50.0)	03 (13.6)	04 (18.2)	22
Compound heterozygous of thalassemia and HPFH	6 (20.7)	12 (41.4)	02 (6.9)	09 (31.0)	38
Heterozygous HPFH and delta beta thalassemia	12 (24.0)	23 (43.0)	12 (24.0)	03 (6.0)	50
E-Beta thalassemia	5 (50.0)	5 (50.0)	0 (0.0)	0 (0.0)	10
Other (HbD-Punjab, HbE, Hb-O Indonesia, Lepore, HbH, HbJ and Hb Q India)	22 (28.9)	29 (38.2)	20 (26.3)	05 (6.0)	76
Normal	1832 (21.6)	2981 (35.2)	2150 (25.4)	1514 (17.9)	8477
Total	2528 (18.8)	4366 (32.4)	4105 (30.5)	2458 (18.3)	13457*

SEBC: socially and educationally backward class; SC: Scheduled Caste; ST: Scheduled Tribe. * community details of 130 individuals were missing

#Figures in parenthesis indicate percent value of each of the variant respective to its total number given in last column

as Hb-O Indonesia (n = 6), Lepore (n = 5), HbH (n = 1), HbJ (n = 5), and Hb Q India (n = 1) were also observed. In a case of HbH, homozygous deletion of two adenosine nucleotides in the poly A sequence in the 3′ untranslated region (AAT AAA > AATA–) of the α2-globin gene was also observed (Fig. 1).

Table 3 shows the tribe wise distribution of hemoglobinopathies. Frequency of SCT was highest among Pradhan tribe (34.6%) followed by the Gond (23.7%) and the Baiga tribe (17.5%). In general, Gond, Pradhan, Kol, Baiga and Bhumia constituted the major fraction of tribes tested in the current studies.

Discussion

Sickle cell disease and thalassemia are highly prevalent in India with distinct variation in spatial distribution linked to

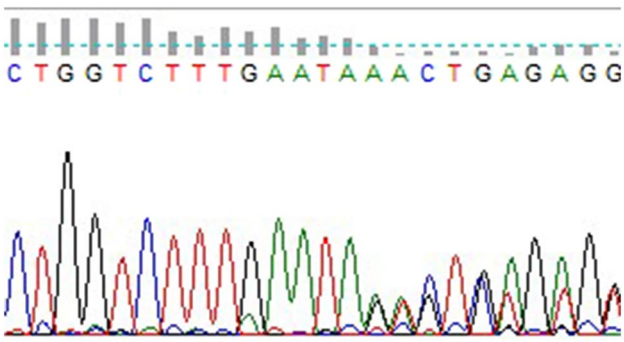

Fig. 1 Electropherogram showing AATAAA > AATA– mutation in α2 globin gene of a parent of HbH disease

ethnicity and geographical location. Population screening and burden estimation are paramount to control, prevention and management. Several small and large hospital-based studies carried out relate to Northern, Western Eastern and North-eastern states or regions only [7–15]. Data from Central or Southern India is scarce. Tripathi et al. [7] reported 11% beta-thalassemia trait in Northern India with relatively lower proportion of sickle cell. Similarly, Gupta et al. reported high incidence of beta-thalassemia and HbE-beta thalassemia in Eastern Uttar Pradesh [13]. In western India, Shrivastava et al. [12] reported 11.5% prevalence of thalassemia trait in hospital settings. HbE variant was predominantly encountered in North-Eastern States of India [8, 10] whereas HbD Punjab was found in North-Western India [15].

Madhya Pradesh in central India is home to the largest tribal population in India and carries the highest sickle cell load in India [3]. Sickle cell carrier prevalence has been estimated to vary from 10–33% in different communities of Madhya Pradesh [16]. High occurrence of sickle cell in referred cases in present study, mirrors the estimated prevalence in community. Presence of HbE thalassemia, HbD Punjab could be due to migration of workers/population from these regions to central India.

Early diagnosis and necessary therapeutic intervention are crucial to improve the prognosis and quality of life. In the present studies majority of SCD patients (50%) were referred after twelve years of age for diagnosis. Globally, new-born screening for common metabolic and preventable genetic disorders like SCD is advocated as early therapeutic intervention, prevents physical and mental deformities besides life threatening illnesses. The chronic morbidity associated with SCD results in increased catastrophic expenditure [17], further aggravating the socioeconomic constraints on most individuals with the disease in low-income countries. Delayed diagnosis results in failure to receiving appropriate treatment resulting in varying levels of organ damage, thereby affecting their quality of life and increased mortality. It is now well accepted that use of hydroxyurea, prophylactic antibiotics and specific vaccines, folic acid supplementation, adequate nutrition, hydration, continuous medical follow-up, and management of complications prevent organ damage and increases the health-related quality of life [18, 19].

However, in India due to lack of comprehensive sickle disease burden, it is essential that large-scale community wide screening (all age groups) be undertaken to identify the SCD patients having mild symptoms. Many SCD patients with mild to moderate severity remain undiagnosed in the community which indirectly or directly increases the disease burden. Furthermore, this underscores the need for raising the awareness among affected communities, healthcare workers, establishing public health facilities and access to improve the quality of life. Absence of an organised referral

Table 3 Tribes wise distribution of Hemoglobinopathies among referred individuals—shows the hemoglobin variants identified among various tribes. Rows represent the various haemoglobin variants and columns represent the communities

	Tribe					
	Pradhan	Kol	Gond	Bhumia	Baiga	Other
Homozygous beta thalassemia	0 (0.0)	05 (2.0)	05 (0.3)	01 (1.1)	0 (0.0)	0 (0.0)
Heterozygous beta thalassemia	4 (2.9)	11 (4.3)	42 (2.3)	01 (1.1)	0 (0.0)	03 (4.5)
Sickle cell disease	39 (28.7)	05 (2.0)	256 (13.8)	06 (6.9)	03 (4.8)	06 (9.1)
Sickle cell trait	47 (34.6)	17 (6.7)	439 (23.7)	10 (11.5)	11 (17.5)	12 (18.2)
Homozygous HPFH and delta beta thalassemia	0 (0.0)	02 (0.8)	02 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Compound heterozygous of thalassemia and HPFH	02 (1.5)	01 (0.4)	06 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Heterozygous HPFH and delta beta thalassemia	0 (0.0)	0 (0.0)	03 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other (HbD-Punjab, HbE, Hb-O Indonesia, Lepore, HbH, HbJ and Hb Q India)	0 (0.0)	01 (0.4)	03 (0.2)	0 (0.0)	0 (0.0)	01 (1.5)
Normal	44 (32.4)	211 (83.4)	1095 (59.2)	69 (79.3)	49 (77.8)	44 (66.7)
Total	136 (100)	253 (100)	1851 (100)	87 (100)	63 (100)	66 (100)

*Figures in parenthesis indicate percent value of each of the variant respective to its total number given in the respective totals in last the row

system, non-existence of interlinks between data/outcomes of the screening programs carried out sporadically by the government or private institutions etc. have failed to achieve their goals. As majority of these programs were limited to screening with no awareness campaigns, counselling of carriers and patients in affected communities, they failed to achieve desired outcomes. In this context, government of India issued guidelines in 2016 and prepared a policy draft in 2018 and launched a mission in 2023 for the elimination of SCD by 2047 that advocates the training to healthcare workers, strengthening of diagnostic facilities at district levels, community wide screening and free treatment to the affected individuals[20–22].

In the present study, it was observed that SCD is common among Pradhan, Gond and Baiga tribes as reported earlier [23, 24]. High frequency of HPFH and delta beta thalassemia cases among other socially and educationally backward class (SEBC) has not been reported earlier. Observed high frequency of beta thalassemia among general communities than the other communities is similar to that reported earlier [5].

In the current studies a few limitations exist. Firstly, there is a bias in sample selection as only referred individuals were included and the data does not provide the prevalence of different hemoglobinopathies in the communities. As a result, it only shows the distribution and hence cannot be applied to the community at large. Secondly, molecular analysis for distinguishing homozygous Sickle cell anemia with sickle beta thalassemia and delta beta thalassemia with hereditary persistence of fetal hemoglobin could not done on all samples. Many a times only samples are received with a minimal description of clinical symptoms and transfusion history. Furthermore, extended family and parental testing could not be done in all the referred cases.

In view of the study findings, it would be beneficial to undertake community specific screening programs with extended family member screening and prenatal diagnosis of high-risk couples to reduce the disease burden in a cost-effective manner [25]. However, it may be noted that due to social stigma and fear of boycott from the community, many of the affected families fail to inform the disease status to relatives and therefore a large number of disease carriers among families remain undetected or hidden. Consequently, more affected children could be born in the next generation. To counter this behaviour, extensive awareness campaigns, regular genetic and family counselling are essential for trust build up among ethnic and socio-economically deprived communities.

In conclusion, wide heterogeneity in the spectrum of inherited hemoglobin disorder in different communities of central India was observed. Strengthening community specific locally appropriate screening programs and organised referral system are required to lower the disease burden and improve the health-related quality of life especially in resource poor settings.

Informed Consent

Written Informed consent was obtained from all individual participants included in the study.

Human Rights

All procedures performed in this study involving human participants were in accordance with the standards of the institution and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the ICMR-NIRTH Institutional Ethical Committee (IEC ref no 201501).

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Authors Contribution MS did the literature search and execute the study. RK and RS designed the study. RK did the literature search, data analysis and wrote the manuscript. MS and RK contributed equally. PP, RU and AM did the laboratory work. RS wrote and revised the manuscript. All authors approved the final version of manuscript.

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Declarations

Conflict of Interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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