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Study of prevalence of haemoglobin subtypes/variants in the ethnic population of Manipur

Dr. Ratan Konjengbam[1], Dr. Abena Hidangmayum[2], Dr. Rajkumari Jayshree Devi[3], Dr. Mary Apang[4], Dr. Davina Hijam[5], Dr. Priyanka Maisnam[6]

[1] Professor, Department of Pathology, Regional Institute of Medical Sciences, Imphal, Manipur, India.
[2,3] Senior Resident, Department of Pathology, Regional Institute of Medical Sciences, Imphal, Manipur, India.
[4] Post Graduate Trainee, Department of Pathology, Regional Institute of Medical Sciences, Imphal, Manipur, India.
[5] Professor, Department of Biochemistry, Regional Institute of Medical Sciences, Imphal, Manipur, India.
[6] Senior Resident, Department of Biochemistry, Regional Institute of Medical Sciences, Imphal, Manipur, India.

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Corresponding Author:

Dr. Priyanka Maisnam
Senior Resident, Department of Biochemistry, Regional Institute of Medical Sciences, Imphal, Manipur, India.

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ABSTRACT

This present study was undertaken to see the prevalence of haemoglobin (Hb) variants in the ethnic population of Manipur. An estimated 7% of the world population carries an abnormal haemoglobin gene, resulting in various haemoglobin subtypes. Inherited abnormalities of haemoglobin synthesis include a spectrum of disorders ranging from thalassemia syndromes to structurally abnormal haemoglobin variants. A total of 2840 subjects were studied in Manipur of whom 1313 (0.46%) had haemoglobinopathies. The plethora of Hb variants ranged from haemoglobin E (HbE) (66.4%), β thalassemia carrier/homozygous β0/β+ (28.2%), heterogeneous d/β thalassemia (3.2%), β thalassemia carrier (1.9%) and Hereditary Persistence of Fetal Haemoglobin (HPFH) heterozygous (0.3%). The Meitei population accounted for 730 cases (0.55%) of haemoglobinopathies, followed by the Naga tribe with 306 cases (0.23%), Kuki with 214 cases (0.16%) and others with 63 (0.04%) cases. Females were observed to have a higher propensity than males.

Keywords: *Haemoglobin variants, Haemoglobinopathies, Electrophoresis, HbE.*

INTRODUCTION

An estimated 7% of the world population carries an abnormal haemoglobin (Hb) gene, while about 300,000-500,000 individuals are born each year with significant haemoglobin disorders (1). Haemoglobinopathies are the most common inherited genetic disorders in India, characterised by abnormal production or structure of the haemoglobin molecule. It is grouped into two major groups: (i) thalassaemia syndromes consisting of β and α-thalassaemia and (ii) structural variants of Hb consisting of sickle cell disease (HbS), haemoglobin E disease (HbE), haemoglobin C disease (HbC), haemoglobin D disease (HbD) and rare haemoglobin Constant Spring disease (HbCS) (2). According to the World Health Organisation (WHO), approximately 5% of the world's population carries trait genes for haemoglobin disorders, primarily sickle cell disease and thalassaemia (3). WHO reports that India shows marked diversity in the distribution of haemoglobin disorders. The expected annual number of affected births, estimated at 0.5/1000 live births for an average annual birth cohort of 25 million, was predicted to be 12,500 thalassaemia major births per year (2). The 2011 Census of India states that there are 1.38 billion people, with the tribal population accounting for 8% of the total. Many multicentric studies have been conducted by various organisations or as part of state thalassaemia control programmes, as well as numerous Tribal surveys across different states of India (4). The literature on the prevalence of haemoglobin E in North-eastern India primarily comes from Assam and Meghalaya, with minimal literature from the rest of the north-eastern states (5). According to a recent meta-analysis, the prevalence of thalassemia carriers in India is estimated at 4% (6). From Manipur, there are a few reports on the prevalence of haemoglobin variants among its ethnic groups. However, research specific to the ethnic tribal population of Manipur, one of the North-eastern states of India, is rare. The clinical spectrum of the disorders varies from asymptomatic conditions to serious disorders like thalassemia major that require regular blood transfusions and extensive

medical care. Identification of these disorders is of immense epidemiological importance and helps prevent more serious haemoglobin disorders.

MATERIAL AND METHODS

This was a cross-sectional, observational study conducted for a period of 5 years from May 2014 to June 2019 at the Regional Institute of Medical Sciences, Manipur, funded by the Department of Biotechnology (DBT), Delhi. The study was approved by the Research Ethical Board, RIMS, Imphal. A total of 2840 volunteers from Manipur, representing different ethnic groups, participated in the study. The study population was grouped into four major classes based on their ethnicity as Meitei, Naga, Kuki and others. The "others" group consisted of subjects of ethnicities other than the three major groups mentioned above. Neonates and individuals who had received a recent blood transfusion were excluded from the study. Voluntary informed consent was taken from all the individuals and three mL of blood was collected from each subject in an EDTA vacutainer. The sample was run on an Inter Lab Genio electrophoresis instrument using a commercially available InterLab Master Kit at pH 8.6. For Hb electrophoresis, hemolysate of each sample was prepared on the same day of performing the electrophoresis and the hemolysate was run on cellulose acetate strips. Haemoglobin is a negatively charged protein and migrates towards the anode at an alkaline pH. Also, the structural variants of Hb deflect a change on the surface of the molecule that separates from HbA. Haemoglobin variants that have an amino acid substitution that is internally sited may not separate and those that have an amino acid substitution that has no effect on overall charge will not be separated by electrophoresis. This kit provides the electrophoresis separation of haemoglobin on a cellulose acetate strip. After electrophoresis, different haemoglobin types form different bands on a cellulose acetate strip. These bands are then read by a densitometer automatically by the electrophoretic apparatus.

RESULTS

Of all the 2840 subjects, abnormal Hb variants were observed in 1313 cases accounting for 0.46%. Five haemoglobin variants were observed amongst the study population. The plethora of Hb variants ranged from HbE (66.4%) as the most common Hb variant, followed by β thalassemia carrier/homozygous $\beta^0/\beta+$ (28.2%), heterogeneous d/β thalassemia (3.2%), β thalassemia carrier (1.9%) and Hereditary Persistence of Fetal Haemoglobin (HPFH) heterozygous (0.3%). The Meitei tribe accounted for 730 cases (0.55%) for hemoglobinopathies, followed by Naga tribe with 306 cases (0.23%), Kuki with 214 cases (0.16%) and others with 63 (0.04%) cases. (Table 1). The least Hb variant, HPFH heterozygous was observed to be prevalent among the Meitei population (75%).

Table 1: Prevalence of Hb variants among the ethnic population:

Hb variants	**Meitei**	**Naga**	**Kuki**	**Others**	**Total (%)**
HbE	477	204	148	43	872 (66.4)
β thalassemia carrier/ homozygous β0/β+,	213	85	56	16	370 (28.2)
Heterogeneous d/β thalassemia,	22	12	6	2	42(3.2)
β thalassemia carrier	15	5	3	2	25 (1.9)
HPFH heterozygous	3	-	1	-	4 (0.3)
Total	730	306	214	63	1313

In this study, Haemoglobinopathy was observed more frequently amongst females than amongst males, irrespective of ethnicity. The Male (M): female (F) ratio was 1:1.2. However, heterogeneous d/β thalassemia was observed twice more common in males than females. The most common Hb variant, HbE, showed a greater female preponderance than the male population, M: F was 0.8:1. Also, β-thalassemia carrier/ homozygous β0/β+ had a M: F of 0.7:1; β-thalassemia carrier of 0.5:1, HPFH heterozygous of 1:3. Table 2 depicts the sex prevalence of Hb variants amongst the study population.

Table 2: Sex prevalence of Hb variants amongst the study population:

Hb variants	**Male**	**Female**
Hb E	393	479
β thalassemia carrier/ homozygous β^0/β^+,	156	214
β heterogenous δ /β thalassemia	28	14
Thalassemia carrier	8	17
HPFH heterozygous	1	3
Total	**586**	**727**

DISCUSSION

Haemoglobinopathies are autosomal recessive genetic disorders caused by abnormal synthesis of the globin chain of haemoglobin. It is known to be distributed to certain tribes, religions, and geographical areas. However, this trend of distribution of haemoglobinopathies has been evolving gradually, dispersed over places, possibly due to migration of people and interracial marriages (5). HbE is prevalent in Southeast Asia (7). In India, HbE is prevalent in the north-eastern states (8,9), mainly in West Bengal, Assam, Nagaland, Manipur, Tripura, and Meghalaya, with an average allele frequency

of 10.9% (10). The present study also conforms with HbE as the most common Hb variant among the study groups. This result is consistent with studies conducted in other north-eastern states (11,12). The diagnosis of haemoglobinopathy, including thalassaemia, can be made on clinical suspicion or from follow-up of an abnormality detected during screening. In this study, β thalassemia trait was the second most common abnormal haemoglobin variant found in the np (1.99%). India has nearly 30 million carriers of β thalassemia (13,14) with varying distribution rates. Southern India has a 1-3% carrier rate, compared with 3-15% in Northern India (15,16). A high incidence of β thalassemia and abnormal HbE in the general population of Eastern India, including the heterogeneous population of West Bengal, has been reported (17). The high prevalence of HbE and β thalassemia trait among the diversified ethnic population of Manipur reflects the paramount importance of screening of haemoglobin variants for carrier detection to reduce the burden of haemoglobinopathies in this region and India as a whole; HPFH is an infrequent, asymptomatic inherited haemoglobin variant where there is persistence of HbF into adult life (18). Based on the distribution pattern, it can be either pan-cellular/homocellular or heterocellular. The level of HbF can range from 10–40 % in pancellular HPFH, whereas only a decent elevation in HbF levels is observed in heterocellular HPFH. Variable increase in HbF may be associated with drugs, chromosomal disorders, hemoglobinopathies, and malignancies. Elevated levels of HbF production are known to be associated with drugs like hydroxyurea and thalidomide analog, Pomalidomide. Chromosomal disorder like trisomy 13 is associated with the delayed switch of HbF to HbA and persistently elevated HbF levels (19,20).

CONCLUSION

A plethora of abnormal haemoglobin variants exists among the ethnic population of Manipur. A simple electrophoresis test in an EDTA sample easily detects the abnormal variant of haemoglobin in seemingly healthy subjects. This observation is especially important considering the high prevalence of beta-thalassemia trait in the Indian subcontinent. Prompt detection of traits prevents the inheritance of thalassemia major in progeny. Recognition and detection of other abnormal Hb variants becomes significant due to complex interactions in cases with double heterozygous and homozygous states, which may result in severe inadvertent haematological abnormalities.

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DECLARATION

Conflicts of interests: The authors declare no conflicts of interest.
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