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Distribution of Hemoglobinopathy in Nepalese Population

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ABSTRACT

Background: Sickle cell and thalassemia are the inherited disorders of globin chain synthesis, and are the most common monogenic disease worldwide. This study aims to find the distribution of hemoglobinopathies (sickle cell and thalassemia) cases in Nepal using laboratory based data.

Methods: A retrospective study was carried out at five different sites of Nepal Government that uses capillary electrophoresis for screening of hemoglobin disorders from January 2019 to March 2019. All the cases diagnosed positive for hemoglobinopathy till December 2018 were collected from laboratory record at each sites, and analyzed using Statistical Package for Social Sciences (SPSS version 20.0).

Results: Out of total 4018 patients tested during the period in all five different sites, 1470 were diagnosed positive for hemoglobinopathy. Sickling disorder was the most predominant hemoglobinopathy followed by β-thalassemia. Province 5, province 6 and province 7 were mostly affected by sickling disorder while the other provinces by β-thalassemia.

Conclusions: Sickle cell is the commonest cause of hemoglobinopathy followed by B thallesmias in Nepalese population. Sickle cell is more concentrated towards western part of Nepal and especially in Tharu ethnic population. In contrast, the distribution of β-thalassemia is found throughout the country and among all ethnic groups of population.

Keywords: Hemoglobinopathy; Nepal; sickle cell; thalassemia

INTRODUCTION

Hemoglobinopathies refers to the inherited disorders of globin chain synthesis that include both reduced rate of globin chain synthesis (thalassemia), and synthesis of structurally abnormal hemoglobin molecule (variant hemoglobin) such as sickle cell.[1] Approximately 7% of the world's populations are careers of hemoglobinopathies making it as one of the major health problems globally.[2] About 3.5% of the death in children below 5 years is due to hemoglobin disorders and, over 330000 infants born with this disorders annually.[3]

Thalassemia is a condition in which production of normal hemoglobin is partly or completely suppressed due to defective synthesis of one or more globin chains while in sickle cell, normal round shape of the red blood cells becomes crescent like moon which interconnect to form blood clot.[4,5] Nepal is expected to have large number of hemoglobinopathy cases, however the data is still lacking. In this context, we aimed to find the distribution of hemoglobinopathy in five different sites of Nepal.

METHODS

A retrospective study was performed at five different sites of Nepal Government that uses Capillary electrophoresis for screening of hemoglobin disorders from January 2019 to March 2019. Data were collected from laboratory records of those sites from the beginning of hemoglobinopathy testing (July 2016) till

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December 2018. The different sites included in the study were National Public Health Laboratory, Kathmandu, Bharatpur Hospital, Chitwan, Lumbini Zonal Hospital, Butwal, Bheri Zonal Hospital, Nepalgunj and Seti Zonal Hospital, Dhangadhi. All the subjects visiting those sites for hemoglobinopathy screening upon doctor's request or voluntarily were included in the study. Ethical approval was taken from NHRC before carrying out this study.

The samples were analyzed using SEBIA Minicap Flex piercing that uses the principle of capillary electrophoresis to separate different hemoglobin variants. All the samples were processed within a week from the date of collection following instructions manual of SEBIA Minicap Flex piercing and the diagnosis of cases were made based on electrophoretogram generated by the instrument and complete blood count parameters. The data collected from all sites was entered into excel. It was then transferred to Statistical Package for Social Sciences [SPSS] version 20.0 [IBM, Armonk, NY, USA] and analyzed using the SPSS.

RESULTS

Among the 4018 cases recorded from all the five sickle cell and thalassemia testing sites, 1470 cases were found diagnosed of hemoglobinopathy related disorders. The highest number of case was recorded from Bheri Zonal Hospital, Nepalgunj and the least from Bharatpur Hospital, Chitwan. Out of the total 1470 cases, 668 (45.45%) were male and 802 (54.55%) were female. Sickling disorder and ß-thalassemia were the most common hemoglobinopathy in all the sites. The highest incidence rate (41.0%) for positive cases of hemoglobinopathy was found at Bheri Zonal Hospital, Nepalgunj where sickling disorder was more common (24.8%). However, the cases for ß-thalassemia were found more common (20.5%) at NPHL, Kathmandu (Table 1).

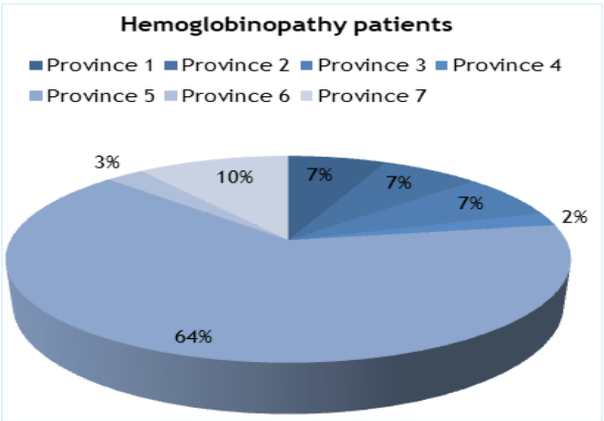

Figure 1. Distribution of hemoglobinopathy cases in different provinces (N = 1145).

Out of total 1470 cases recorded positive for hemoglobinopathies, address of 325 cases were missing while 1145 cases had valid address. Those 1145 cases were segregated based on their permanent address as mentioned in the laboratory records which shows that the highest number of cases (64%) were from province 5 followed by province 7(10%) that comprises of majority of indigenous Tharu population living in western Terai of Nepal. The least number of cases were recorded from province 4 (2%) (Figure 1).

The bar chart compares the percentage of major hemoglobinopathy types prevailing in different provinces of Nepal. Overall, it was observed that the types of disease were not uniformly distributed in different geographical areas. Sickle cell was more prevalent in Province 5, Province 6 and Province 7 while ß-thalassemia in Province 2, Province 3 and Province 4. In Province 1, HbE was more common than sickle cell or ß-thalassemia. The highest proportion of sickle cell cases were recorded in Province 6 (70.0%) while not a single case was recorded from Province 3 (0.0%). Likewise, the highest proportion of ß-thalassemia was recorded in Province 3 (86.3%) followed by Province 2 (74.0%) and Province 4 (62.5%). Rest of the other provinces had comparable proportion of ß-thalassemia cases (Figure 2). The chart also depicts that sickle cell and ß-thalassemia is common in all the seven provinces however, their frequency and proportion vary as we move from eastern part to the western part of the country. Beta-thalassemia seems to be more concentrated to the eastern part of the country while sickle cell towards western part of Nepal.

Table 2 illustrates the frequency distribution of different hemoglobinopathy types in seven provinces of Nepal. Unlike other provinces, a very different data has been observed in Province 1 which is the eastern most part of the country. Almost half the total cases of hemoglobinopathy in this province seem affected by HbE disorder which is very less common in other provinces. Beside sickle cell and thalassemia, a large number of populations were also found affected with compound heterozygous state of sickle cell/ß-thalassemia 125(10.9%). Similarly, higher number of cases 36 (3.1%) showed decreased HbA2 level with features suggestive of α-thalassemia. Few rare hemoglobin variants were also reported from different provinces.

Nepal has a diverse ethnic group of population. Though most of the geographical places of the country share mixed ethnicity, some ethnic group seems predominant in particular geographical locations of the country. Among the total 1470 cases of hemoglobinopathy recorded

from different sites of Nepal, ethnicity of 42 cases were missing. Table 3 shows that more than three-fourth of the total hemoglobinopathy cases (1162) comprises only of Tharu ethnic population who live mostly in western terai part of Nepal. Besides Tharu, cases of hemoglobinopathy were also reported from other ethnic group of populations residing in Nepal. More than half (58.3%) of the Tharu population was affected by sickling disorder while major portion of other ethnic group was found troubled with ß-thalassemia. Unlike other ethnic group, Rajbanshi group of population shows a distinct pattern of hemoglobinopathy diseases. Out of total 47 recorded cases of hemoglobinopathy in Rajbanshi, highest proportion (87.2%) was found troubled with HbE disorder. Beta-thalassemia was found completely absent however, few case of sickle cell was reported from this group of population. Despite the fact that sickling disorder is present only in Tharu population in Nepal, it was also found in other ethnic group as well. Few cases of sickling disorder were also recorded from Newar, Chhetri, Rajbanshi, Janjati and other inhabitants of Terai (Table 3).

Table 1. Number of cases recorded from different testing sites (N = 4018)

Sites	Sickling disorder (%)	ß-thalassemia (%)	Others (%)	Negative (%)	Total (%)
Nepalgunj	516(24.8)	148 (7.1)	190 (9.1)	1228 (59.0)	2082 (100)
NPHL	94 (8.8)	218 (20.5)	111 (10.4)	640 (60.3)	1063 (100)
Dhangadhi	82 (11.8)	33 (4.7)	64 (9.2)	518 (74.3)	697 (100)
Lumbini	7 (4.7)	2 (1.3)	2 (1.3)	139 (92.7)	150 (100)
Chitwan	2 (7.7)	0 (0.0)	1 (3.8)	23 (88.5)	26 (100)
Total	701 (17.4)	401 (10.0)	368 (9.2)	2548 (63.4)	4018 (100)

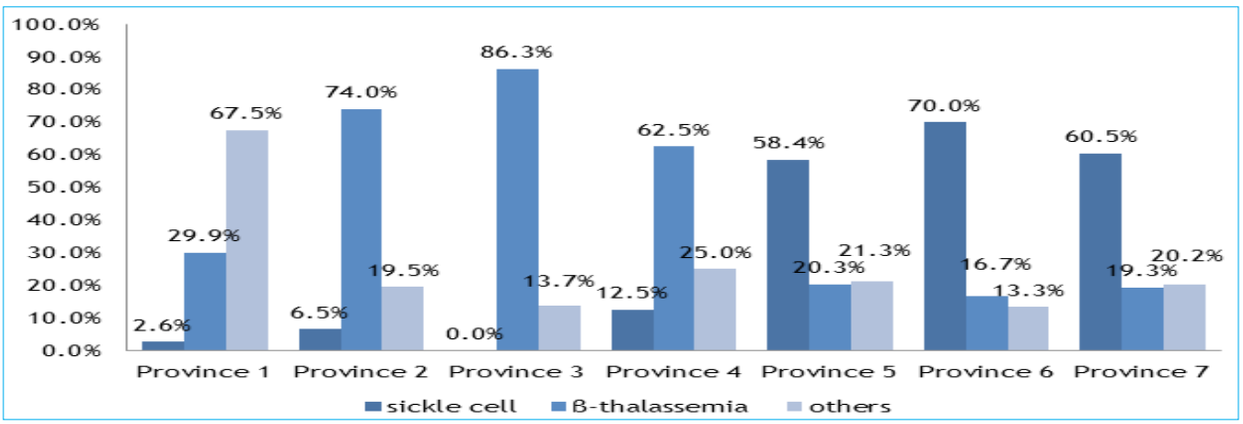

Figure 2. Province wise distribution of hemoglobinopathy types.

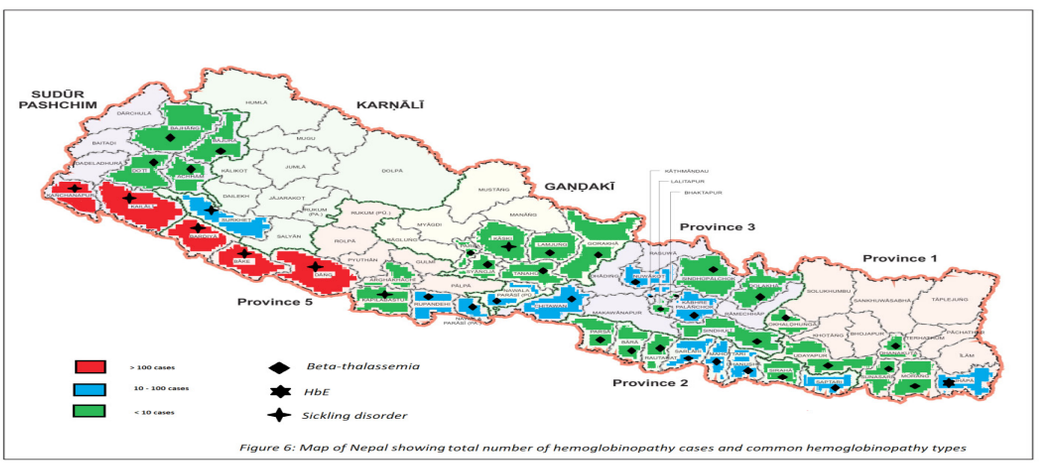

Figure 3. Map of Nepal showing total number of hemoglobinopathy cases and common hemoglobinopathy types.

Table 2. Type of hemoglobinopathies in different provinces.

Diagnosis	Provinces No.							Total (%)
	1	2	3	4	5	6	7	
Homozygous sickle cell	1	1	0	1	81	1	11	96 (8.4)
Heterozygous sickle cell	1	4	0	2	350	20	61	438 (38.3)
Compound heterozygous HbS/ß-thalassemia	0	2	0	3	98	4	18	125 (10.9)
Compound heterozygous HbS/HPFH	0	0	0	0	6	0	1	7 (0.6)
Homozygous ß-thalassemia	1	2	1	1	9	0	0	14 (1.2)
Heterozygous ß-thalassemia	22	55	68	14	141	5	23	328 (28.7)
HbH disease	0	0	3	1	6	0	0	10 (0.9)
Hb Barts	1	0	0	0	0	0	0	1 (0.1)
HbE trait	37	7	4	1	6	0	2	57 (5.0)
Decreased HbA2	0	0	1	0	33	0	2	36 (3.1)
Compound heterozygous ß-thalassemia/HbE	6	3	2	1	3	0	0	15 (1.3)
HPFH	0	1	0	0	4	0	1	6 (0.5)
HbD trait	0	0	1	0	0	0	0	1 (0.1)
Homozygous HbE	7	2	0	0	0	0	0	9 (0.8)
Compound heterozygous HbE/HbD	1	0	0	0	1	0	0	2 (0.2)
Total	77	77	80	24	738	30	119	1145 (100)

Table 3. Major hemoglobinopathy types in different ethnic groups.

Ethnicity	Sickling disorder (%)	ß-thalassemia (%)	HbE (%)	Others (%)	Total (%)
Tharu	677 (58.3)	212 (18.2)	13 (1.1)	260 (22.4)	1162 (100)
Newar	1 (9.1)	8 (72.7)	1 (9.1)	1 (9.1)	11 (100)
Chhetri	7 (23.3)	20 (66.7)	2 (6.7)	1 (3.3)	30 (100)
Brahmin	0 (0.0)	78 (92.8)	1 (1.2)	5 (6.0)	84 (100)
Muslim	0 (0.0)	3 (33.3)	4 (44.4)	2 (22.3)	9 (100)
Rajbanshi	2 (4.3)	0 (0.0)	41 (87.2)	4 (8.5)	47 (100)
Janjati	1 (5.8)	8 (47.1)	0 (0.0)	8 (47.1)	17 (100)
Dalit	0 (0.0)	8 (88.9)	0 (0.0)	1 (11.1)	9 (100)
Other(terai inhabitants)	7 (9.6)	51 (69.9)	5 (6.8)	10 (13.7)	73 (100)
Total	695 (48.2)	388 (26.9)	67 (4.6)	292 (20.2)	1442 (100)

DISCUSSION

Hemoglobinopathies are the common monogenic diseases causing one of the world's major health problems which were initially present in Mediterranean region and, parts of Asia and Africa but now has spread globally.[2] It is believed that the global spread of these inheritable diseases might be due to international migration occurring in different locations of the world. One of the reasons for increasing number of hemoglobinopathy related diseases is high number of consanguineous marriage in some countries and poor public health measures to control this issue.[6] Nepal being located in the south east part of Asia is suspected

to have higher number of hemoglobinopathies cases which is also supported by some of the previous studies in different districts of Nepal.[7,8] Though few studies have been carried out in some districts, probably this is the first study of its kind to accompany maximum number of districts as a part of surveillance which aims to find the distribution of hemoglobinopathy related diseases, and is also expected to fill the gap in policy making for control and prevention of these diseases.[8] Overall, the findings from this study suggest that there are high prevalence of sickle cell and ß-thalassemia in Nepal, especially in western part.

Our findings suggested that sickle cell is predominant in Tharu ethnic group while ß-thalassemia among other ethnic group of population residing in Nepal. Since western terai part of Nepal (Province 5, Province 6 and Province 7) is densely populated with Tharu ethnic group of population, the prevalence of sickle cell is higher in those provinces. A recent study by Marchand et al. in Dang district of Nepal also supports high prevalence of sickle cell (9.3%) in Tharu population which is in correspondence to the finding of this surveillance.[8] Likewise, a study conducted at Tribhuvan University Teaching Hospital by Shrestha A et al. presents all the cases of sickle cell from Tharu communities only which is also in support of our finding that sickle cell is more concentrated to Tharu ethnic population.[9] According to WHO report, more than 330000 infants born with hemoglobin disorders annually among which 89 % have sickle cell disorder and 17% have thalassemia, which further portrays that the global epidemiology of sickle cell is also high.[3]

There are several reasons for high prevalence of sickle cell among inhabitants of south-western part of Nepal, especially among Tharus living in the districts linked to boundaries of India. Firstly, these districts were endemic for malaria in the past years.[10] Sickle hemoglobin (HbS) is believed to have incorporate into their genes as a result of natural selection to prevent the multiplication of malarial parasite and thus, preventing development into a clinical malaria infection.[6] Study suggests that 3 to 40% of the individuals living in malaria endemic area carry one of the hemoglobin variant genes which has risen the prevalence rate of hemoglobin disorders from 0.3 to 25 per 1000 live births.[3] Secondly, the intra-caste marriage among Tharu, the result of which has limited the spread of this disease to other caste and finally, the poor attitude and economic conditions to prevent the disease.[11] Furthermore, lack of facilities for diagnosis of hemoglobin disorders in that area might also be the cause of higher prevalence of sickle cell. In absence of diagnostic facilities, people affected by heterozygous form of the disease lives a normal life and are no longer conscious about what they have in their hemoglobin genes. This doesn't affect much to them but to their children to whom they have passed affected genes.

Province 1, Province 2, Province 3 and Province 4 comprises of mixed ethnicity of population besides Tharu.[12] For this reason the prevalence rate of sickle cell might be lesser in these provinces as compared to the provinces of western Nepal. Our finding shows that ß-thalassemia is more predominant in these provinces. A study carried out by Jha R. also claims for the predominance of ß-thalassemia in Nepal which is in support to our findings.[13] Our findings are also in correspondence to the findings of Mondal et al. (ß-thalassemia trait 4.60%) and Warghade et al. (ß-thalassemia trait 11.21%) ; a study from West Bengal and Mumbai, India, respectively.[14,15] Most part of India share common climatic condition and lifestyle to Nepal, so, it is more likely to have common disorders to the people living in Nepal and India. In addition a study from China also reports thalassemia (16.45%) as the major cause of hemoglobin disorder but, somewhat surprisingly noticed was α-thalassemia (12.03%) more common despite of ß-thalassemia (3.80%).[16] It is possible that geographical structure, genetic status, socio-economic status and lifestyle of people in China might be different from those of Nepal due to which hemoglobin disorders seem to vary.

Apart from Tharu population, sickle cell was found in other ethnic group of population as well. Furthermore, Tharu population was not found affected by sickle cell disease only but also with variety of hemoglobinopathy diseases. Some rare hemoglobinopathies such as HbH disease were also reported from this group of population. Studies from various parts of the world reports that sickle cell is prevalent in variety of ethnic group and tribal population living across the world. A study by Colah et al.(India) reported HbS (sickle hemoglobin) common in more than 15 tribal population living in different states of India who seem to belong from socio-economically disadvantaged ethnic groups namely scheduled tribes and scheduled castes.[17] A study by William TN and Weatherall DJ also suggests distribution of sickle cell anemia throughout Sub-Saharan Africa and in small cluster in the Mediterranean region, the Middle East and the Indian subcontinent.[6] It is likely that other ethnic group might share disadvantaged socio-economic conditions besides Tharu, or belong to malaria endemic area in the past, or have married with Tharu due to which sickle hemoglobin have imparted in their normal

hemoglobin genes.

Province 1 shows a different picture of hemoglobin disorders in comparison to other provinces. Report shows high prevalence of HbE especially among Rajbanshi group of populations. A previous study in Nepal by Adams et al. also reports high prevalence of HbE (4%) in southeast part of Nepal which is comparable to the finding of this study.[7] One of the reasons for high prevalence of HbE in Rajbanshi population of Jhapa districts might be, they belong to a distinct tribe of population who have imparted HbE gene once as a result of mutation, and that has spread among them due to intra-caste marriage.

The finding shows that overall proportion of the population affected by sickle cell is far higher than the proportion of people affected by other hemoglobinopathies besides sickle cell. One of the reasons for higher number of cases of sickle cell in this study might be due to testing sites more concentrated towards Tharu community of western Nepal and less testing sites towards eastern part of the country. Moreover, free sickle cell testing services among public at Nepalgunj site, public awareness towards sickle cell and a lot more screening camps for sickle cell among Tharu communities might be the other reasons for the higher prevalence rate of sickle cell in this study. This finding may not be the data supporting the scenario of whole Nepal since the higher number of cases recorded in this study were from the western part of Nepal, most of which were Tharu populations. Therefore, it is possible that the scenario for hemoglobinopathy could be change if more number of testing sites and screening camps be established especially in eastern part of the country.

Thus, in future community based screening for hemoglobinopathies throughout the country need to be carried out to find the actual prevalence rate of different hemoglobinopathies. Moreover, public awareness and thalassemia screening program also seems necessary in the eastern part of the country as well to reveal out the actual burden of hemoglobinopathy related cases. It is also more important to focus on screening camps for hemoglobin disorders in Terai region of the country since it was endemic for malaria in the past and is expected to have more hemoglobinopathy related cases.

CONCLUSIONS

Sickle cell is more prevalent among Tharu communities of western Nepal while ß-thalassemia towards eastern part of Nepal among different ethnic groups. Beta-thalassemia is not only limited to the eastern part of the country but has distributed throughout the country among different ethnic population including Tharu. Likewise, sickle cell is also not only limited to Tharu but has been reported from other ethnic group of population as well. Some rare hemoglobinopathies such as HbC, HbD, HbH, reported supports the evidence that other variety of disorders might be present among patients which have gone undiagnosed by electrophoresis testing. This provides hallmarks for further implication of genetic testing at government level. Similarly, higher number of cases having decreased HbA2 level and suspect of α-thalassemia further supports the genetic test to be made mandatory for further confirmation of diagnosis.

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