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"Clinical Profile and Pattern of Hemoglobinopathies and Thalassaemias: A Study in a Tertiary Care Hospital, Dhaka, Bangladesh"

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Abstract
Introduction: *Inherited hemoglobin disorders (hemoglobinopathies&Thalassaemias) constitute an importantcause of morbidity and mortality in children. They impose a heavy burden on the affected families and the health sector. This is a public health problem in Dhaka and others Districts. Data pertaining to the pattern of the Thalassaemias and hemoglobinopathies are lacking in our City.Hence, this study was undertaken to know the clinical profile and pattern of hemoglobinopathies and Thalassaemias cases admitted in pediatrics department.****Methods:*** *The present study was conducted in the department of Pediatrics,Tertiary Care Hospital in Dhaka, Bangladesh over a period of one year from January 2019 to December 2019. Total 75 children of inherited hemoglobin disorders (chronic hemolytic anemia) were included in this study. This was a retrospective study. We collected the bed head tickets (medical record files) of all children from medical record department of the hospital. Relevant data of the cases were collected, analyzed and interpreted accordingly.****Results:*** *The present study included total 75 children of Thalassaemia and hemoglobinopathies admitted duringthe study period. Total number of patients admitted in the pediatric ward, during the study period were 1883. Out of 75 studied cases, 58.6% patients were male and 41.3% were female. In the present study, most common hemoglobin disorder was HbE trait (HbAS) 26.6% followed by Beta Thalassaemia trait 21.3%, Sickle cell trait (18.7%), E beta Thalassaemia (9.3%) and HbE disease 8% and sickle cell disease (Hb SS) 8% respectively. The present study also showed that all cases of beta Thalassaemiamajor, E beta that and Sickle cell diseases had presented with pallor,generalized weakness and hepatosplenomegaly. It was also seen that all the beta Thalassaemia major, E beta Thalassaemia and Sickle cell diseases patients required blood transfusions. It was observed that 46.6% of cases were malnourished/stunted and 29.3% children had skeletal changes.****Conclusion:*** *The present study showed the pattern of Thalassaemias and hemoglobinopathies prevalent in Dhaka city, Bangladesh.Hence, mass education, genetic counselling, premarital counseling, neonatal screening and antenatal diagnosis are the mainstay for prevention and control of the disease. Further, Early diagnosis by (High-performance liquid chromatography)HPLC, adequate management of the cases with blood transfusion, chelation therapy, nutritional supplementation and splenectomy will decrease the associated complications and improve the quality of life.*

Key words: *Anemia, Hemoglobinopathies, Thalassaemia, Children, HPLC.*

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I. Introduction

Thalassaemias are a group of autosomal recessive disorder and the most common inherited disease worldwide with a wide geographical variation in incidence. Bangladesh, a developing country, having a population over 165.6 million people in Jun 2019. World Health Organization (WHO) has estimated that 3% of our population carries β- thalassaemia and 4% of population carries Hb-E in Bangladesh. But recently Khan WA showed that carrier status of Hb-E is 6.1% and as high as 41.7% in tribal school children in Bangladesh. Since Thalassaemia is a severe and incurable disease, it is only manageable when it is prevented. The WHO has advocated and promoted the programs for thalassaemia prevention from the early 1970s. Several countries have already set up comprehensive national thalassaemia prevention programs but in our country most of the

population is unware of this hereditary disease. The rapidly growing number of children diagnosed as thalassaemia in Bangladesh clearly indicate that thalassaemia will be an emerging health burden for our country. So, we need to prevent thalassaemia before it's too late by comprehensive national integrated prevention programs which include public awareness and education, carrier screening, genetic counseling, premarital screening and prenatal diagnosis. Hemoglobin is a tetramer consisting of 2 pairs of globin chains. Abnormalities in these proteins are referred to as hemoglobinopathies. More than 800 variant hemoglobins have been described. The hemoglobin gene clusters are involved in the production of hemoglobin and are located in the short arm of chromosome 16 and chromosome 11. During fetal life the major hemoglobin is Hb F. Though, Hb A first appears at 1 month of fetal life but it doesnot become dominant upto birth. The final hemoglobin distribution pattern that occurrs in childhood is not achieved until atleast 6 months of age and sometimes later. The normal hemoglobin pattern is > or equal to 95 % HbA, <or equal to 3.5 % HbA2, and <2.5 % HbF[1].Thalassaemia refers to a group of genetic disorders of globin chain production in which there is an imbalance between the alfa globin and beta globin chain production. Beta Thalassaemia syndrome result from a decrease in beta globin chains. Beta+Thalassaemiaindicate a mutation that makes decreased amount of beta globin chain. Beta 0 Thalassaemia refers to total absence of production of beta globin. Thalassaemia major refers to severe form of homozygous beta Thalassaemia who require early transfusion therapy. Carriers with a single beta globin mutation are generally asymptomatic except for microcytosis and anemia. The primary pathology in the Thalassaemia syndrome from the quantity of globin produced whereas the primary pathology in Hb variant is related to the quality of beta globin produced. There are > 200 different mutation resulting in absent or decreased globin production. Although most are rare, the 20 most common abnormal alleles constitute 80% of the Thalassaemia worldwide. 3% of world's population carries alleles for beta Thalassaemia[2].Inherited hemoglobin disorders (hemoglobinopathies and Thalassaemia) constitute an important cause of mobidity and mortality. They impose a heavy burden on the affected families and the health sector. They were originally characteristic of the tropics and sub tropics but are now common world wide due to migration. The figures of world health organization estimate that approximately 5% of world's population are being carriers for the genetic hemoglobin disorder. Every year, there are over 42 million carriers and more than 12000 infants born with a major and clinically significant hemoglobinopathy Jan3, 2018 [3]. There are almost 42 million carriers of beta Thalassaemia trait. While an average prevalence rate of 3-4 % has been established across the country, a higher frequency has been observed in certain communities. An estimated 10000 -15000 babies with Thalassaemia major are born every year. Hb E significantly contributes to the disease burden especially in Dhaka city. In certain communities in this region, the carrier frequency of Hb E is as high as 50%. The prevalence of sickle cell disease is variable with a very high frequency among many tribal communities and few states. However, it is not restricted to tribal community only due to inter marriage with Non tribals and migration of people, now found in all states [4]. Among the common Hb variant, Hb E and beta thalssemia are commonly found in Dhaka and other Districts. The ICMR study showed that Hb E was mainly seen in Assam (23.9 %) and in Kolkata (3.9%) in West Bengal [5]. It is well established that the incidence of HbE gene in the north Eastern region of India is one of the highest in the world [6]. Different states of the North Eastern region show a variable incidence of Hb E varing from 16.2 % to 47.3% [7 & 8]. The migrant tea garden population of Assam from central, eastern and southern India also shows a high incidence of Hb S [9, 10]. This inherited Hb disorder is a public health problem and a big burden to their families and even their communities. This genetic problem can be prevented by proper genetic counseling, premarital screening and by prenatal diagnosis. Very few studies were carried out in theDhaka City to find out the burden and patterns of this inherited disorder. In view of this, this study was conducted to know the clinical profile and pattern of hemoglobinopathy and Thalassaemia in our City.At present, several countries like Italy, Greece, Cyprus, UK, France, Iran, Thailand, Australia, Singapore, Taiwan, Hong Kong, Cuba and also in Northern Europe (Netherlands, Belgium and Germany)[22] have set up comprehensive national thalassaemia prevention program. Cyprus and Sardinia both are the unique examples for successful thalassaemia prevention. In Sardinia declination of birth rate of thalassaemia major from 1**:**250 live birth to 1**:**1660 has been reported in 2009 with an effective prevention of 85% of cases [23] and similar results have also been reported in Cyprus [24]. But in Bangladesh, there is no national thalassaemia prevention program yet.

II. Methods

The present study was carried out in the department of Pediatrics, Tertiary Care Hospital, Dhaka, Bangladesh over a period of one year from January 2019 to December 2019. This is a tertiary care hospital located in the city of Dhaka. This hospital provides health care services mainly to the people of rural and urban areas in the nearby districts Dhaka city. Most of the anemia cases from this tea garden hospital and rural hospital were referred to this hospital for proper investigations and diagnosis as there was lack of laboratory facilities in their hospital. This was a retrospective study. A total number of 75 hemolytic anemia (Inherited hemoglobin disorder) cases, admitted in pediatrics department were included in this study. We collected all bed

head tickets (medical record files) from medical record department after taking permission from the concern hospital authority. All 75 medical files were evaluated thoroughly and relevant data were recorded accordingly. Inclusion criteria: All the patients of inherited hemoglobin disorder up to age of 12 years of age. Exclusion criteria: Those patients with laboratory findings point to other causes of anemia like Iron deficiency anemia, aplastic anemia etc. were excluded from the study.

III. Results

Total number of patients admitted in the pediatric ward, during the study period from 1st January 2019 to 31st December 2019=1883. Thalassaemias and hemoglobinopathies cases admitted during this period =75. In this study, out of 75 hemoglobin disorder cases, 28% cases were 1 to 4 years age group and 72% cases above 4 years up to 12 years [Table 1].

Table 1: Showing age wise distribution of the cases (N=75)

Age	No. of cases	Percentage (%)
Less than 6 months	0	0
6 months to 1 year	0	0
1 year to 4 year	21	28 %
4 year to 12 year	54	72 %
Total Cases	75	100%

Table 2: Sex wise distribution of cases (N=75)

Sex	Number of cases	Percentage
Male	44	58.6 %
Female	31	41.3 %
Total	75	100%

This showed that 58.6% patients were male and 41.3% patients were female [Table 2].

Table 3: Showing distribution of cases according to different types of inherited hemoglobin disorders (N=75)

Type of hemoglobinopathy/Thalassaemia	Number of cases	Percentage
Beta Thalassaemia major	5	6.7%
Beta Thalassaemia trait	16	21.3%
E beta Thalassaemia	7	9.3%
Hb E trait	20	26.6%
Hb E disease	6	8%
Sickle cell trait	14	18.7%
Sickle cell disease	6	8%
Hb S beta thalssaemia	1	1.3%
Alpha thalssaemia	0	0
Total	75	100%

In the present study, most common hemoglobin disorder was HbE trait (HbAS) 26.6% followed by beta Thalassaemia trait 21.3%, Sickle cell trait (18.7%), E beta Thalassaemia (9.3%),and HbE disease 8% and,Hb SS 8% respectively [Table 3].

Table 4: Showing common clinical symptoms and signs of the admitted cases (N=75)

Symptoms & signs	B thal major (n=5)	B thal trait (n=16)	E beta thal(n=7)	HbE disease (n=6)	HbE trait (n=20)	HbS Dis (n=6)	HbS trait N=14
Pallor Present	5(100%)	9(56.2%)	7 (100%)	2(33%)	5(20%	100%	21%
Weakness/tiredness	5(100%)	8 (50%)	7(100%)	-----	----	100%	35%
Abdominal discomfort/ fullness	5(100%)	1(6.2%)	5(71%)	-----	-----	83%	----
Jaundice	1(20%)	Nil	2(28%)	------	-----	50%	----
Splenomegaly	----	2(12.5%)	7(100%)	1(16.6%	1(5%)	---	----
Hepatomegaly	----	--	--	-----	----	----	-----
Hepatosplenomegaly	5(100%)	---	7(100%)	------	----	100%	------

This [Table 4] showed that all cases of beta Thalassaemiamajor, E beta thal and Sickle cell diseases had pallor, generalised weakness and hepatosplenomegaly.

Table 5: Showing Hb% of the cases at the time of admission (N=75)

Anemia present	No of cases	Percentage
Mild anemia (> 9 gm%) or normal range	48	64%
Moderate anemia (6-9gm %)	15	20%
Severe anemia (below6 gm %)	12	16%
Total cases	75	100%

In this study, 16% cases had severe anemia, 20% cases moderate anemia and 64 % had mild anemia or Hb% level were within normal range [Table 5].

Table 6: Showing blood transfusion status of the cases (N=75)

Type of hemoglobin disorders	Transfused	Untransfused	Total
Beta thalassaemia major	5(100%)	0	5
Beta thalassaemia trait	0	16 (100%)	16
E beta thalassaemia	7(100 %)	0	7
Hb E trait	0	20 (100%)	20
Hb E disease	1(16.6%)	5 (83.3 %)	6
Sickle cell trait	0	14 (100%)	14
Sickle cell disease	6(100%)	0	6
Hb S beta thalssaemia	1(100%)	0	1
Alpha thalssaemia	0	0	0
Total	20	55	75

From [Table 6], it is seen that all the beta Thalassaemiamajor, E beta Thalassaemia and Sickle cell diseases patients required blood transfusion.

Table 7: Showing some morbidity status of the studied cases (N=75)

Morbidity	Number of cases	percentage
Malnorished/stunted	35	46.6%
Skeletal changes present	22	29.3%
Splenectomy done	1 beta thal major, 1 E beta thal.	
Iron overload /toxicity	2	2.6%

In this study, it is observed that 46.6% of cases were malnourished/stunted and 29.3% children had skeletal changes like frontal bossing, malar prominence, and malocclusion of teeth [Table 7].

IV. Discussion

The thalassaemias are a group of genetic disorder caused by reduction or absent production of one or more of the globin chain that make up the hemohlobin (Hb) tetramers. Worldwide thalassaemias are the commonest autosomal recessive disorders [14, 15, and 16]. About 60,000-70,000 children are born each year with severeform of Thalassaemia's [17], and unfortunately most affected children are born in low resource areas of the world [18]. Bangladesh, a developing country, has achieved appreciable reduction in infant and under-5 mortality [19] by combating against malnutrition, infectious disease and by improving health system but hereditary disorder receive little attention yet. It is presumed that approximately 6000 thalassaemic children are born each year in Bangladesh [20], but most of the population is unaware of this hereditary disease, only a few cases are diagnosed. It has also been estimated that, worldwide, 9 million carriers become pregnant annually and 1.33 million pregnancies are at risk for a thalassaemia major condition [14, 16]. Bangladesh, having population of over 160 million, there is no national data about the number of thalassaemia patient in the country, Khan et al [21] estimated that existing thalassaemic patient in Bangladesh is about 1 lac and suspected total number of β-thalassaemia major and Hb-E β-thalassaemia born around 1040 and 6443 per year respectively in our country. The present study included total 75 children of Thalassaemia and hemoglobinopathies admitted during the study period. Total number of patients admitted in the pediatric ward, during the study period was 1883. Out of 75 studied cases, 58.6% patients were male and 41.3% were female. In the present study, most common hemoglobin disorder was HbE trait (HbAS) 26.6% followed by Beta Thalassaemia trait 21.3%, Sickle cell trait (18.7%), E beta Thalassaemia (9.3%) and HbE disease 8% and sickle cell disease (Hb SS) 8% respectively. The incidence of Thalassaemia and hemoglobinopathies varies in different part of Bangladesh. HbE is mainly prevalent in Dhaka and others City. The ICMR studies (2013) also revealed that Hb E 23.9% in Assam [5]. Deka R, Reddy AP et al. in their study reported that HbE gene in Assam and N E region is highest in the world. [6]. Various Researchers in their study in North Eastern state reported variable incidence of HbE from 16.2% to47.3% [7, 8]. Whereas Manna AK et al (2009) observed beta Thalassaemia trait 44% is more

common than HbE 18% in Kolkata, West Bengal [12]. Another study done by Basu et al. (2002) in Kolkata also reported Beta Thalassaemia trait 68% as the most commonly seen hemoglobin disorder followed by Hb E trait 25%[11]. In our study, we observed 3 form of HbE variants namely Hb E homozygous/disease (Hb EE), Hb E heterozygous/trait (HbAE) and compound Hb E Beta Thalassaemia. This study showed that HbE detected across different ethnic groups in Dhakacity mainly among tribal population. Few cases were observed in Non tribal people may be due to intercaste marriages. 12 cases were seen among Muslim community. Beta thalssemia trait was detected in 21.3% of cases which is similar with the findings of different studies like ICMR study [5] and Baruah M K et al. in 2014 [13]. Another common variety of hemoglobinopathy in our study was Sickle cell trait (18.7%) and HbSS disease (8%). These observations were comparable with the findings of the various studies conducted by various workers like Balgiri R S et al [9], Sharma S K et al [10] and Baruah M K et al [13]. This sickle cell trait and disease were observed mainly among General communities. The present study showed that all cases of beta Thalassaemiamajor, E beta thal, and Sickle cell diseases had presented with pallor, generalized weakness and hepatosplenomegaly. It was also seen that all the beta Thalassaemia major, E beta Thalassaemia and Sickle cell diseases patients required blood transfusion. In this study, it was observed that 46.6% of cases were malnourished/stunted and 29.3% children had skeletal changes like frontal bossing, malar prominence and malocclusion of teeth etc.

V. Conclusion

The present study showed the pattern of Thalassaemias and hemoglobinopathies prevalent in Dhaka city, Bangladesh. Further, many children remain undiagnosed at the community level due to lack of knowledge, poverty and lack of laboratory facility at general population and rural hospital. We know that this inherited hemoglobin disorder is a major cause of morbidity and mortality in children. Hence, mass education, genetic counselling, premarital counseling, neonatal screening and antenatal diagnosis are the mainstay for prevention and control of the disease. Further, Early diagnosis by HPLC, adequate management with blood transfusion, chelation therapy, nutritional supplementation and splenectomy will decrease the associated complications and improve the quality of life.

VI. Limitation of the study

This was a hospital based study, hence the results inferred from this study was not thetrue reflection of the burden of the community. Many children are remaining undiagnosed in the rural area. Therefore, further studies are needed with large sample size at the community level to find out the exact burden.

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