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Determinants of infections among children with beta-thalassemia

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Abstract

Among the inherited disorders of blood, hemoglobinopathy and thalassemia constitute a major bulk of non-communicable genetic diseases in India. The carrier frequency of hemoglobinopathy varies between 3 and 17% in different population of India. The cumulative gene frequency of the three most predominant abnormal hemoglobin, i.e. Sickle cell, haemoglobin D and haemoglobin E has been found to be 5.35% in India. It has been estimated that with a population of 1000 million and a birth rate of 25 per thousand, there would be about 45 million carriers and about 15,000 infants born with hemoglobinopathies in India. Patients in our hospital were receiving triple saline washed packed red blood cells (RBCs) which is routinely screened for HIV, HbsAg, HCV, Syphilis and Malaria in the hospital blood bank. Some of the patients in our study also received blood transfusion from other hospitals at times whenever blood was not available in our hospital.

Results: UTI was the most common infection among both splenectomised and non splenectomised thalassemic patients followed by respiratory tract. Gram negative bacteria were the predominant organism causing infection among both splenectomised and non splenectomised patient.

Conclusion: In our study, Hypersplenism has no statistically significant correlation between hypersplenism and infections.

Keywords: hypersplenism, hemoglobinopathy, thalassemia

Introduction

Beta-thalassemia is prevalent in Mediterranean countries, the Middle East, Central Asia, India, Southern China, and the Far East as well as countries along the north coast of Africa and in South America. The highest carrier frequency is reported in Cyprus (14%), Sardinia (10.3%), and Southern Asia. The high gene frequency of Beta-thalassemia in this region is most likely related to the selective pressure from Plasmodium falciparum malaria [1].

Population migration and intermarriage between ethnic groups has introduced thalassemia in almost every country of the world, including Northern Europe where thalassemia was previously absent. It has been estimated that about 1.5% of the global population (80-90 million people) are carrier of Beta- thalassemia, with about 60,000 symptomatic individuals born annually, the great majority in the developing world. The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world and 1 in 10,000 people in the European Union. However, accurate data on carrier rates in many populations are lacking, particularly in areas of the world known or expected to be heavily affected. According to Thalassemia International Federation, only about 200,000 patients with thalassemia major are registered as receiving regular blood transfusion around the world [2].

The most common combination of beta-thalassemia with abnormal Hb or structural Hb variant with thalassemia properties is HbE/beta-thalassemia which is most prevalent in Southeast Asia where the carrier frequency is around 50% [3].

Among the inherited disorders of blood, hemoglobinopathy and thalassemia constitute a major bulk of non-communicable genetic diseases in India. The carrier frequency of hemoglobinopathy varies between 3 and 17% in different population of India. The cumulative gene frequency of the three most predominant abnormal hemoglobin, i.e. Sickle cell, haemoglobin D and haemoglobin E has been found to be 5.35% in India. It has been estimated that with a population of 1000 million and a birth rate of 25 per thousand, there would be about 45 million carriers and about 15,000 infants born with hemoglobinopathies in India [4].

Methodology

The thalassaemic child fulfilling the inclusion criteria was enrolled in the study after taking informed consent from the caretaker.

Patients in our hospital were receiving triple saline washed packed red blood cells (RBCs) which is routinely screened for HIV, HbsAg, HCV, Syphilis and Malaria in the hospital blood bank. Some of the patients in our study also received blood transfusion from other hospitals at times whenever blood was not available in our hospital.

Iron chelation was started in those patients who had received at least 20 blood transfusions or with serum ferritin levels > 1000 ng/ml. Patients were given subcutaneous iron chelation [inj. Deferoxamine- 50 mg/kg] at the time of blood transfusion and oral iron chelation on rest of the days. Detailed records were maintained on a pre designed proforma (appendix) incorporating symptoms, signs and investigation check list. Detailed history of chief complaints in a chronological order was taken. History of any of the risk factors such as splenectomy done or not, completely immunized or not, on antibiotic prophylaxis, special vaccinations like pneumococcal, meningococcal and Hib received or not as mentioned in the proforma were noted. Details regarding iron chelation therapy [oral or subcutaneous] and the compliance noted. Detailed family history highlighting any of the siblings with same complaints was noted. Details of previous infection episodes and admissions were elicited.

Results

Table 1: profile of patients with and without recurrent infections

	Recurrent infection		OR and P value
	Yes (n=32)	No (n=53)	
Age			
<2 years	0	8(15.09%)	OR=0.236* P=0.003
2-5 years	8(25%)	23(43.39%)	
5-12 years	24(75%)	22(41.50%)	
Sex			
Male	19(59.37%)	29(54.71%)	OR = 1.2 P= 0.676
Female	13(40.62%)	24(45.28%)	
Special vaccines taken			
Yes	11(34.37%)	10(18.86%)	OR = 2.2 P= 0.11
No	21(65.62%)	43(81.13%)	
Splenectomised			
Yes	8(25%)	9(16.98%)	OR = 1.62 P= 0.373
No	24(75%)	44(83.01%)	
Antibiotic prophylaxis			
Yes	8(25%)	9(16.98%)	OR = 1.62 P= 0.373
No	24(75%)	44(83.01%)	
Chelation			
Yes	31(96.87%)	36(67.92%)	OR=14.63 P=0.002
No	1(3.12%)	17(32.07%)	
Serum ferritin			
<2000	3(9.37%)	15(28.30%)	OR = 0.447** P= 0.084 OR=0.262*** P=0.0369
2000-5000	14(43.75%)	23(43.39%)	
>5000	15(46.87%)	15(28.30%)	

In our study recurrent infections were more common among patients aged less than 5 years of age compared to 5 to 12 years old. (p value 0.003).

There was no sex predilection for recurrent infections.

Splenectomy, antibiotic prophylaxis and special vaccination did not show them as statistically significant factors associated with recurrent infections.

In our study, it appears that thalassaemia patients on chelation have significant recurrent infections when

compared to those who were not on chelation therapy.

Children with serum ferritin more than 2000 ng/ml had recurrent infections compared to those below 2000 ng/ml. the difference was statistically significant.

Table 2: Patients profile in relation to splenectomy

	Splenectomised (n=17)	Not splenectomised (n=68)	OR and P Value
Age			
Mean(SD)	6.42(3.3)	6.36(3.15)	
Sex			
Male	12(70.58%)	36(52.94%)	OR = 2.13 P = 0.189
Female	5(29.41%)	32(47.05%)	
Type of infection			
Bacterial	8(47.05%)	27(39.70%)	OR = 1.44* P= 0.429
Viral	8(47.05%)	39(57.35%)	
Parasitic	0	2(2.94%)	
Antibiotic prophylaxis			
Yes	17(100%)	0	
No	0	68(100%)	
Chelation			
Yes	17(100%)	50(73.52%)	
No	0	18(26.47%)	
Serum ferritin			
<2000	2(11.76%)	16(23.52%)	OR = 0.73** P= 0.318
2000-5000	8(47.05%)	29(42.64%)	
>5000	7(41.17%)	23(33.82%)	OR = 0.433*** P= 0.291

All the patients who had splenectomy were on antibiotic prophylaxis. There was no statistically significant difference between the type of infection and splenectomy.

Table 3: Infection profile among patients who underwent splenectomy

Spectrum of infection	Splenectomised	
	yes	No
UTI	5(29.41%)	14(20.58%)
URTI	4(23.52%)	10(14.70%)
LRTI	4(23.52%)	11(16.17%)
TB	0	4(5.88%)
GIT with Hepato-biliary system	0	13(19.11%)
CNS	0	2(2.94%)
Sepsis	1(5.88%)	3(4.41%)
ENT	1(5.88%)	4(5.88%)
Malaria	0	2(2.94%)
Skin	1(5.88%)	2(2.94%)
Others	1(5.88%)	3(4.41%)
Spectrum of infectious agent		
Bacterial		
Gram negative		
K. pneumoniae	3	5
E. coli	2	8
Pseudomonas	1	2
Acinetobacter	0	1
Gram positive		
Staphylococcus	0	2
Streptococcus	1	0
Enterococcus	0	1
Parasitic	0	2
Viral	8	39

UTI was the most common infection among both splenectomised and non splenectomised thalassaemic patients followed by respiratory tract.

Gram negative bacteria were the predominant organism causing infection among both splenectomised and non splenectomised patient.

Table 4: Infection profile in relation to hypersplenism without splenectomy (n=68).

Hypersplenism	Bacterial	Viral	Parasitic	OR and P value
Yes	10	10	2	OR = 1.56
No	16	30	0	
Total	26	40	2	P= 0.400

In our study, Hypersplenism has no statistically significant correlation between hypersplenism and infections.

Table 5: Spectrum of micro-organisms according to age of the patient (n=25)

Causative agent	No. Of patients	Percentage
Age		
<2 years		
Klebsiella pneumoniae	1	4%
Escherichia coli	1	4%
2-5 years		
Klebsiella pneumoniae	3	12%
Escherichia coli	2	8%
Pseudomonas	1	4%
Staphylococcus	1	4%
>5 years		
Escherichia coli	7	28%
Klebsiella pneumoniae	4	16%
Pseudomonas	2	8%
Acinetobacter	1	4%
Enterococcus	1	4%
Staphylococcus	1	4%
Streptococcus	1	4%

In children aged less than 2 years, klebsiella and E.coli were 4% each.

Between 2 to 5 years, klebsiella was predominant (12%) followed by *E. coli* (8%).

Among children more than 5 years of age, *E. coli* was predominant (28%) followed by klebsiella (16%).

Discussion

The susceptibility to infections in thalassemia arises both from a large spectrum of immunological abnormalities and from the exposure to infectious agents. Excluding heart failure, infections are the predominant cause of death. It is directly responsible for 12-47% of patient's death.⁵

The four fundamental issues related to infections in thalassemia are,

- The disease itself, i.e. all those changes inherent to the pathological process which can interfere with the immune systems.
- Iron over load
- Transfusion therapy and
- The role of the spleen.

Transfusion therapy and iron chelation therapies represent the true progress in the management of the thalassemia patients and they dramatically changed the prognosis of thalassemia. Nevertheless, the advantage of blood transfusion is associated with the disadvantage of the high transfusion burden in terms of direct exposure to infection risk and to transfusion related immunomodulation and iron over load. Moreover, other therapeutic options like splenectomy, central venous catheterization, bone marrow transplantation or nutritional deficiency contributes to the infection risk.

The immune alteration concerns both innate and adoptive immunity. The CD4:CD8 cell ratio is lower than normal, neutrophil and macrophages phagocytosis, neutrophil

chemotaxis, natural killer (NK) function are compromised, C₃ and C₄ are reduced. High immunoglobulin levels were reported and B lymphocytes were found to be increased.

The pathogenesis of thalassemia is based on ineffective erythropoiesis, haemolysis and a tendency to increased iron absorption. Because of ineffective erythropoiesis and haemolysis, the monocytes and macrophages compartment undergoes gross hyperplasia and is hyperactive in phagocytizing all defective erythroid precursors and erythrocytes.

Severe anaemia itself is a risk factor for bacterial infections in thalassemia predominantly pneumonia.

Thalassemia patients who are well transfused and not properly chelated either because of difficulty in getting iron chelators or due to low compliance have increased risk of developing severe infections.

Iron may increase the severity of infections by

- Removing important chemicals called antioxidants that protect the body's cells against inflammation.
- Damaging certain types of cells that play an important role in the body's defense against infections.
- Serve as a nutrient for the growth of pathogens.
- Serve as a co enzyme for proteins that support the multiplication of infectious agents.

Many studies have demonstrated that immunological function is largely and negatively influenced by iron excess^[6].

Iron over load damage derives from disequilibrium between iron oxidation (through the Fenton reaction) and the effectiveness and availability of those systems able to counteract oxidative stress. In this sense, in addition to the antioxidant systems, ferritin and the monocyte/macrophage compartment also participate in cleaning up toxic iron. Indeed, lysosomes in these cells are able to endocytosis both free iron and ferritin and this contributes toward protection from iron. Additional oxidative stress can destabilize the secondary lysosomes of the macrophages, and their protective role is lost. Moreover, phagocytosis of micro-organisms, dyserythropoietic precursors and damaged red blood cells (intravascular and extravascular) causes oxidative stress. Finally, iron over load impairs phagocytosis and its negative effect on neutrophil function has been clearly demonstrated. Phagocytic function is the center of a vicious cycle, acting as a double edged sword: protective against oxidative stress while also generating oxidative stress on the one hand, on the other hand, having its own function impaired by the same oxidative stress.

Higher the iron load in the body more prone for infections because the micro-organisms thrive on the iron. The best documented infection is caused by a bacterium called *Yersinia enterocolitica* – a peculiar infectious agent that, unlike other bacteria, does not have a mechanism of its own for collecting and using iron from its own environment. In healthy individuals, these bacteria are harmless and of little or no clinical importance. However, in thalassemia major, where there is excess iron either free or bound to the iron chelator molecule, *Yersinia* grows and multiplies rapidly, causing serious, life threatening infections^[7, 8].

Although more work has been carried out on the role of iron in bacterial infections, there has also been considerable research into the role of iron in viral infections (such as Hepatitis and HIV), examining how iron may affect the progression of these infections and their response to their

treatment with recommended drugs ^[9]. The results of these investigations indicate that in thalassemia major, iron overload may be related to a worse prognosis for chronic viral hepatitis B and C and a poorer response to the treatment of chronic viral hepatitis. The effectiveness of iron chelation therapy thus seems to play an important role in the prognosis of chronic viral hepatitis in these patients. It has also been demonstrated that HIV infection in patients with thalassemia major becomes more severe ^[10].

Conclusion

- Recurrent infections were more when the serum ferritin levels was above 2000ng/ml .
- There was no association found between recurrent infections, age, sex, splenectomy, chelation and antibiotic prophylaxis.
- However, frequency of infections was less among patients who had undergone splenectomy and who were on antibiotic prophylaxis.

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