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Spectrum of infections in children with beta-thalassemia

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Abstract
At present, as an effect of hyper transfusion regimen, fewer thalassemia patients undergo splenectomy. However, when transfusional need rises, splenic enlargement or hypersplenism occurs, splenectomy is indicated. In splenectomised patients antibody production in response to new antigens is impaired. Phagocytosis, chemotaxis is also impaired. For all these reasons, splenectomised patients are at increased risk of sepsis from any pathogen. However, encapsulated pathogens like Streptococcus pneumoniae, Haemophilus influenza type B, Neisseria meningitidis, E.coli are the most common. Risk of infection is very high if the patient is below the age of 5 years. Splenectomised patients must receive routine vaccinations, including both live attenuated and killed vaccination. The thalassemic child fulfilling the inclusion criteria was enrolled in the study after taking informed consent from the caretaker. Total of 85 patients below 12 years of age were studied which included patients who were receiving blood transfusion regularly in our hospital and also patients referred from other centers were included in the study. In our study, one patient is positive for HIV and HbsAg [1.17%], two are positive for HCV [2.35%] and 2 patients were diagnosed to have possibly transfusion transmitted Malaria [2.35%].

Keywords: Infections, Children, Beta-Thalassemia

Introduction
Blood has long been recognized as a major source of infectious agents that can be transmitted to patients through transfusion. Hepatitis C virus (HCV), Hepatitis B virus (HBV), Human Immunodeficiency virus (HIV) and Syphilis are the most common infectious agents transmitted via transfusions. In Europe and North America, improved blood transfusion services, vaccination programmes, donor screening and high quality public health services have made transmission of these infections very rare. However, in developing countries these infections are still a major concern because of poor transfusion services. Additional infectious agents which can be transmitted by transfusion include Parvovirus B19, HGV, Human T-cell Lymphotropic virus (HTLV), West Nile virus (WNV), Trypanosoma cruzi, Cytomegalovirus (CMV), Dengue fever virus (DFV),Malaria, Chagas disease, Babesia microti, Plasmodia species, Leishmania, Brucella etc [1].

At present, as an effect of hyper transfusion regimen, fewer thalassemia patients undergo splenectomy. However, when transfusional need rises, splenic enlargement or hypersplenism occurs, splenectomy is indicated. In splenectomised patients antibody production in response to new antigens is impaired. Phagocytosis, chemotaxis is also impaired. For all these reasons, splenectomised patients are at increased risk of sepsis from any pathogen. However, encapsulated pathogens like Streptococcus pneumoniae, Haemophilus influenza type B, Neisseria meningitidis, *E. coli* are the most common[2]. Risk of infection is very high if the patient is below the age of 5 years. Splenectomised patients must receive routine vaccinations, including both live attenuated and killed vaccination. And also against Streptococcus pneumoniae, Haemophilus influenza type B and Neisseria meningitides. In case of elective splenectomy, vaccinations should be completed at least 2-4 weeks prior to the date of surgery. However, vaccination does not completely protect against infection with encapsulated bacterias and prophylactic antibiotics have a role as well [3].

For the optimal management of thalassemia, a multidisciplinary approach is essential, involving Paediatrician, Haematologist, Geneticist, Transfusion specialist, Endocrinologist, Child psychiatrist, Transplantation experts and many others. Even in the best of centers the management of this disease is far from satisfactory.

The only curative treatment for this disease at present is bone marrow transplantation or stem cell transplantation. Without this curative therapy what remains as a back bone for the management of thalassemia is lifelong blood transfusion and iron chelation therapy. Even this conventional treatment is often unavailable to patients in remote areas [4]

So far the Government or the non- governmental organizations, have not regarded thalassemia and other hemoglobinopathies as an important public health problem. With limited treatment facilities, children with thalassemia are not treated properly and the social and economic constrains limit the treatment further.

The thalassemia patients due to various above mentioned factors are thus susceptible to various infections. The present study was planned to study the profile of various types of infections seen in multi transfused thalassemic children which can help plan preventive measures to reduce the morbidity and mortality among these children, especially associated with Infections.

Methodology

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

Total of 85 patients below 12 years of age were studied which included patients who were receiving blood transfusion regularly in our hospital and also patients referred from other centers were included in the study.

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.

Patients were examined in detail with special attention to the growth and development (WHO growth charts were used to identify wasting and stunting) and specific system involved. Skin, ophthalmologic, orthopaedic, and ENT examination was also performed. Detailed neurological examination was done with special attention to signs of meningitis.

Appropriate laboratory investigations were carried out to evaluate fever etiology their baseline investigations like CBC was done by cellaneous cell counter, RFT was done by Biochemistry auto analyser, PBS, CXR, Serum iron and TIBC were carried out at the time of admission. Serum Ferritin assay was done at end of one week of fever. HIV testing was done by an immunochromatographic rapid test for the detection of antibodies of all isotypes (IgG, IgM, IgA) specific to HIV 1 and 2 and confirmed in case of any doubt by ELISA test, HbsAg, HCV, HAV were done by ELISA during admission or on follow up for patients who were admitted. Urine was sent for microscopy, collected by midstream collection or by catheter collection, supra pubic aspiration was not done as it was an invasive procedure. Urine was sent for culture. Blood was sent for bacterial culture and other appropriate body fluids were sent for bacterial cultures in BACTEC and routine culture media as per the clinical diagnosis, preferably before the antibiotics were started. In suspected cases of TB early morning sputum/gastric aspirate on 2 consecutive days was sent for ZN staining for AFB identification and also for TB culture by BACTEC MIGIT technique and also on LJ media. USG Abdomen, 2D Echo, CT scan, MRI was done depending on the clinical diagnosis.

Results

Table 1: Bacterial and viral infections associated with thalassemia patients (n=85)

Causative agent	No. Of patients	Percentage
Bacterial causes (n=35)		
Blood culture positive (n=5)		
Klebsiella pneumoniae	2	2.35%
Staphylococcus aureus	1	1.17%
Streptococcus pneumoniae	1	1.17%
Acinetobacter	1	1.17%
Urine culture positive (n=17)		
Klebsiella pneumoniae	5	5.88%
Escherichia coli	10	11.7%
Pseudomonas aeruginosa	1	1.17%
Staphylococcus aureus	1	1.17%
CSF culture positive (n=1)		
Enterococcus	1	1.17%
Pus culture positive (ear discharge) (n=2)		
Klebsiella pneumoniae	1	1.17%
Pseudomonas aeruginosa	1	1.17%
Culture negative but features suggestive of bacterial infections*	10	15.05%

Table 2: Viral and Parasitic infections

Causative agent	No. Of patients	Percentage
Viral causes (n=47)		
HBV**	1	1.17%
HCV	2	2.35%
HIV	1	1.17%
HAV	1	1.17%
Other virus	43*****	48.34%
Parasitic infections (n=2)		
Malaria***	2	2.35%
Etiology not certain		
Synovitis of right hip joint with AVN****	1	

Table 3: Clinical characteristics of patients with bacterial infections (n=35)

Serial no.	Age in years	Sex	Infections	Pathogens	Culture specimen
1	8	M	UTI	Escherichia coli	Urine
2	7	F	UTI	E.coli	Urine
3	5.5	M	UTI	E.coli	Urine
4	8	F	UTI	E.coli	Urine
5	10	F	UTI	E.coli	Urine
6	5.5	M	UTI	E.coli	Urine
7	4	M	UTI	E.coli	Urine
8	2	M	UTI	E.coli	Urine
9	11	M	UTI	E.coli	Urine
10	9	M	UTI with cystitis	E.coli	Urine
11	12	F	UTI	K. pneumoniae	Urine
12	12	F	LRTI with severe PHT with UTI	K. pneumoniae	Urine
13	1	M	UTI	K. pneumoniae	Urine
14	9	F	UTI	K. pneumoniae	Urine
15	5	F	UTI with cystitis	K. pneumoniae	Urine
16	5	M	UTI	Staphylococcus aureus	Urine
17	2.5	F	UTI	Pseudomonas	Urine
18	3	M	Sepsis	K. pneumoniae	Blood
19	6	M	Sepsis	Streptococcus pneumoniae	Blood
20	5.5	F	Sepsis	Staphylococcus aureus	Blood
21*	12	M	Sepsis	Acinetobacter	Blood
22	4	F	ASOM	Klebsiella pneumoniae, Pseudomonas aeruginosa	Pus
23	6	M	ASOM	Pseudomonas aeruginosa	Pus
24	5	F	ASOM	NG	NA
25	9	F	ASOM	NG	NA
26	7	F	Bacterial meningitis	Enterococcus	CSF
27	12	M	Splenic abscess	K. pneumoniae	Blood
28	6	F	Right hip joint abscess	NG	NA
29	12	M	Dental abscess	NG	NA
30	4.5	M	Dysentery	NG	NA
31	10	M	Seborrheic dermatitis with secondary infection	NG	NA
32	9	F	SNTB	NG	NA
33	7	F	SNTB	NG	NA
34	12	M	SNTB	NG	NA
35	11	M	SPTB	NG	NA

Table 4: Distribution according to gram positive and gram negative organisms

Infectious agents	No. Of patients	Percentage
Bacteria		
Gram negative		
Escherichia coli	10	11.76%
Klebsiella pneumoniae	8	9.41%
Pseudomonas	3	3.52%
Acinetobacter	1	1.17%
Gram positive		
Staphylococcus	2	2.35%
Streptococcus	1	1.17%
Enterococcus	1	1.17%

Gram negative bacterial infections accounted for 25.88% and gram positive for 4.7%.

Discussion

In our study, one patient is positive for HIV and HbsAg [1.17%], two are positive for HCV [2.35%] and 2 patients were diagnosed to have possibly transfusion transmitted Malaria [2.35%].

In a study conducted in Iran[5], it was found that 19.3% patients were HCV positive while 1.5% were HbsAg positive and no one was HIV positive.

Similar study conducted in Australia [6] found that the infection with HCV was higher than others and the epidemic of HCV infection continue to escalate in Australia predominantly through transmission related to injecting drug use.

In a study conducted at PGIMER Chandigarh in 1989-90 [7], no thalassemic patient was positive for HIV, HbsAg or HCV and in 2002, 6% were positive for HbsAg and 54.4% for HCV. In a study conducted at AIIMS Delhi in 1997-98 showed 18% were positive for HbsAg, 30% for HCV and 18% for HIV and in 2002, 20% were HbsAg positive, 30% HCV positive and 10% is HIV positive.

In a study conducted in Mumbai BYL Nair children hospital. [8] showed 2.5% of patients were HIV positive, 45% were Hbs Ag positive and 17.5% HCV positive. In LTMC TMG hospital, Mumbai, 3.97% were found to be HIV positive, 2.38% HbsAg positive and 43.63% were HCV positive.

The prevalence of HIV infection in thalassemia patient was reported to be 8.9% in India, while it was 1.6% in multitransfused subjects in Bahrain. Our blood bank screens all voluntary donated blood bags for HIV, HbsAg and HCV routinely as mandated by the FDA.

Bacterial infections represented by E. coli (n=10), Klebsiella (n=8), pseudomonas (n=3), acinetobacter (n=1), staphylococcus (n=2), Streptococcus (n=1), and enterococcus (n=1). Viral infection HIV (n=1), HCV (n=2), HbsAg (n=1), HAV (n=1) and other unidentified viruses (n=43). Parasitic infection like Malaria (n=2).

Gram negative infections accounted for 25.88% and gram positive infections which accounts for 9.41%.

These results were in accordance with other studies where the percentage of gram negative bacilli especially K. Pneumoniae was the main causative organism and only 10% of the causative agents were gram positive bacteria.

Another study conducted in Thailand, according to review by Wanachiwanawin [9], one-half of the major organisms responsible for severe infection in patients with thalassemia in Thailand were gram negative bacilli such as E. coli (26%) and K. Pneumoniae (23%).

In contrast, in a study conducted in Hillah city, where gram positive organism like staphylococcus aureus, streptococcus were the main causative organisms. This study was in accordance with the study conducted in Israel [10].

Yersinia enterocolitica organism was not isolated in our study. This is in accordance with study conducted in Taiwan. In contrast, studies did in western countries showed Y.enterocolitica as one of the major causative organism especially among those on regular iron chelation therapy.

In our study, 4 of our patients had tuberculosis, one patient was sputum positive, one was sputum negative but montoux positive (TST) and the other two were sputum negative and montoux negative.

Four of our patients had life threatening sepsis, eventually one of the patient died due to sepsis caused by Acinetobacter. This patient had relatively low levels of

serum ferritin but had recurrent infections and was not on any antibiotic prophylaxis, was HIV negative with no other underlying disorder.

The major long term risk after splenectomy is overwhelming sepsis. In older studies, the risk of post splenectomy sepsis in thalassemia major is increased more than 30 folds in comparison to the normal population.

Infection with gram negative rod shaped bacteria, notably E.coli, K. Pneumoniae and pseudomonas occur with increased frequency in asplenic patients and are often associated with high mortality.

Malaria is repeatedly reported as more severe in asplenic people with an increased risk of death.

In our study, infection with gram negative organisms was more than gram positive organisms among splenectomised patients. The frequency of infection among splenectomised patients appears to be less compared to those patients who were not splenectomised. This difference is mainly because more number of patients who were not splenectomised were under 5 years in whom splenectomy is contraindicated but they were more prone for recurrent infections.

As compared to patients more than 5 years age, the infection frequency is slightly less among splenectomised patients in our study. This difference is mainly because the patients who are splenectomised in our study are vaccinated against pneumococcus, meningococcus and Hib prior to splenectomy and they are all on penicillin prophylaxis every month.

In our study, presence of hypersplenism had no relation to increased risk of infections. After splenectomy, patients are at increased risk of life-threatening infections, prevention and treatment of infections is very important particularly in thalassemia patients. In our study, invasive bacterial infections were less frequent among the patients who received immunization than patients who were not immunized with routine vaccination and special vaccines.

However even vaccination does not completely protect against infection with encapsulated organisms and prophylactic antibiotics have a role as well.

There was no statistically significant correlation among patients having recurrent infections, immunization and special vaccinations.

Our study is in agreement with the above study. Our patients who are on antibiotic prophylaxis had less frequent invasive bacterial infection among splenectomised patients, and also patients had fewer episodes of infections requiring hospital admission than compared to those who were not on any antibiotic prophylaxis and also recurrent infections were less among patients who were on prophylactic antibiotics post splenectomy.

In our study 16.47% cases had upper respiratory tract infections although due to non availability of viral infection testing at the hospital confirmatory evidence of viral etiology was not possible. Immunization against influenza virus should be considered in thalassemia patients. This is also supported by various other studies.

In our study, iron overload was noted among patients with infections. The adverse effect of iron overload was noted as physical growth retardation, and recurrent infections among patients who had increased iron overload. The mean serum ferritin level among patients with recurrent infection was 4095.43 ng/ml, and among patients not having recurrent infections was 4052.24 ng/ml which was statistically significant [P value=0.037].

There was also a significant relationship with iron overload and recurrent infections, when serum iron exceeded 2000ng/ml [P value=0.0369]. Iron overload was more among patients with bacterial infections than with viral infections, serum ferritin levels were 3997.30ng/ml and 3971.61ng/ml, respectively.

The one patient who died of sepsis had relatively less iron overload serum ferritin levels being 2972ng/ml. Patients condition was complicated by recurrent infections and cardiomyopathy due to iron overload.

Iron chelation in this group of patients was insufficient mainly because of non affordability of adequate iron chelation therapy and also the issue of non-compliance to therapy.

In the study conducted in Taiwan [11], iron overload was noted in the infection group. It is clear that many organisms such as Y. Enterocolitica, Klebsiella, E. coli, Streptococcus, Pseudomonas and others have been shown to increase in virulence in the presence of excess iron in vitro [12].

Conclusion

- Respiratory and urinary tract infections were common necessitating the need to send appropriate investigations to confirm the diagnosis and initiate early appropriate treatment to reduce morbidity and mortality.
- Gram negative bacteria were the predominant organism causing bacterial infections.
- Transfusion transmitted infections like HIV, HBV, HCV and Malaria are associated with repeated blood transfusion among thalassemia patients. Although the prevalence was low in the present study, it highlights the need to regularly investigate them for these infections so as to treat appropriately.

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