International Journal of Infectious Diseases 39 (2015) 53–56

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Severe bacterial infections in patients with non-transfusion-dependent thalassemia: prevalence and clinical risk factors

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ARTICLE INFO

Article history:
Received 12 November 2014
Received in revised form 30 August 2015
Accepted 1 September 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

Keywords:
Clinical risk factor
Bacterial infection
Non-transfusion-dependent thalassemia

SUMMARY

Introduction: Bacterial infection is one of the major causes of death in patients with thalassemia. Clinical predictive factors for severe bacterial infection were evaluated in patients with non-transfusion-dependent thalassemia (NTDT).
Methods: A retrospective study was conducted of patients with NTDT aged ≥10 years at Srinagarind Hospital, Khon Kaen University, Thailand. Clinical characteristics and potential clinical risk factors for bacterial infection were collected. Risk factors for bacterial infection were evaluated by multivariate logistic regression analysis.
Results: A severe bacterial infection was found in 11 of the total 211 patients with NTDT (5.2%). None of the clinical factors assessed was shown to be statistically associated with severe bacterial infection in patients with NTDT. However, three factors were demonstrated to be potential predictive factors for severe bacterial infection: time after splenectomy >10 years, deferoxamine therapy, and serum ferritin >1000 ng/ml. None of the patients died from infection.
Conclusion: The prevalence of bacterial infection in patients with NTDT was found to be moderate. Time after splenectomy >10 years, deferoxamine therapy, and iron overload may be clinical risk factors for severe bacterial infection in patients with NTDT. Bacterial infection should be recognized in splenectomized patients with NTDT, particularly those who have an iron overload.

1. Introduction

Thalassemia is the most common genetic disorder worldwide. The prevalence is high among populations in the Mediterranean region, Africa, and Southeast Asia. Thalassemia syndrome can be classified into three subgroups according to the severity of clinical presentation: thalassemia major, thalassemia intermedia, and thalassemia minor. Non-transfusion-dependent thalassemia (NTDT) is a term used to describe the group of patients with thalassemia who do not require lifelong regular blood transfusions for survival, but who may need an occasional blood transfusion in some situations, e.g., pregnancy, an operation, or infection.[1]

Infection is one of the major causes of death in patients with thalassemia.[2–4] The prevalence of infection in patients with thalassemia varies from 22.5% to 66%.[5–9] The mechanisms resulting in the increase in susceptibility to infection in these patients[10] include (1) impaired chemotaxis and phagocytosis of macrophages and neutrophils,[11,12] (2) alteration in T-lymphocyte subsets,[13,14] (3) decreased numbers and activity of natural killer cells,[15] (4) increased numbers and activity of B lymphocytes,[14,16] and (5) impaired immunoglobulin secretion and the suppression of complement system function.[17] Many clinical risk factors for bacterial infection in patients with thalassemia have been reported in the literature, including splenectomy, iron overload, severe anemia, facial deformities, and gallstones.[5,8,9,18,19]

Most of the studies on bacterial infections in patients with thalassemia have focused on those patients with thalassemia major. Information on the prevalence of infection and clinical risk factors in patients with NTDT remains limited. The aim of this study was to determine the prevalence and associated factors for severe bacterial infection in patients with NTDT.

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http://dx.doi.org/10.1016/j.ijid.2015.09.001

2. Patients and methods

A retrospective study was conducted of patients with NTDT in the thalassemia registry of the "Epidemiologic Study of Major Complications in Adult and Adolescent Patients with Thalassemia in Northeastern Thailand" study (E-SAAN study). Eligible participants were thalassemic patients aged ≥10 years. Severe bacterial infection was defined as a bacterial infection necessitating hospitalization and intravenous antibiotic administration. The clinical presentations and laboratory data, including those of potential risk factors for bacterial infection indicated in the literature, were collected. Bacterial infection was confirmed by the isolation of pathogens from blood, pus, stool, cerebrospinal fluid (CSF), and other body fluids. Serum ferritin levels were the mean serum ferritin levels from the last 6 months of data.

The research protocol was approved by the Ethics Review Board of the Faculty of Medicine, Khon Kaen University.

2.1. Statistical analysis

Continuous parameters were reported as the mean and standard deviation (SD). Categorical parameters were reported as the number and percentage. Clinical predictive factors for bacterial infection were analyzed by univariate and multivariate logistic regression methods. All statistical analyses were performed using STATA program version 10 (StataCorp, College Station, TX, USA). A probability value of less than 0.05 was considered statistically significant.

3. Results

The records of a total of 211 patients (119 females, 92 males) were reviewed. Severe bacterial infections were found in 11 patients (5.2%). The baseline clinical characteristics of the 211 patients are summarized in Table 1. The mean age at the time of enrollment was 25.9 years. Seventy-seven patients (36.5%) had undergone a splenectomy, with the mean duration of time since the splenectomy of 4.2 years. None of the splenectomized patients in this study had received prophylactic antibiotics after the splenectomy. One hundred and thirty-three patients had received and were receiving iron chelation therapy. Deferiprone was the most common iron chelation treatment (n = 79, 37.4%), followed by a combination of deferoxamine and deferiprone (n = 29, 13.8%) and deferoxamine alone (n = 22, 10.4%). None of the patients in this cohort had experienced neutropenia due to the use of deferiprone. The schedule for monitoring neutropenia was every week for the first month, followed by every 4–6 weeks, in accordance with the local practice at the Khon Kaen University hospital. The mean hemoglobin level was 7.9 g/dl and the mean serum ferritin was 1692.3 ng/ml.

Table 2 shows a summary of the causative organisms and sites of infection in the 11 infected patients. Of these 11 patients with 12 episodes of infection, *Klebsiella* species were the most common causative organisms (n = 4, 36.4%), followed by *Burkholderia pseudomallei* (n = 3, 27.2%). Septicemia was the most common site of infection (n = 7, 63.6%), followed by abscesses of the spleen and lymph nodes (n = 3, 27.3%). One patient had two episodes of infection, which were abscesses of the parotid gland and lymph nodes; the causative organisms were *Klebsiella* species in both episodes. One splenectomized patient had group B streptococcal meningitis. This patient received the pneumococcal vaccine before undergoing splenectomy, however she did not receive any further vaccinations after the splenectomy. Of the 11 infected patients, only one (9.1%) received prophylaxis vaccinations prior to splenectomy. None of the patients in this cohort died from infection. A summary of the clinical characteristics of the 11 infected patients with NTDT is shown in Table 3.

The univariate analysis of risk factors for bacterial infection in patients with thalassemia is shown in Table 4. Serum ferritin >1000 ng/ml (odds ratio (OR) 8.3, 95% confidence interval (95% CI) 1.1–69; p = 0.04), time after splenectomy >10 years (OR 4.0, 95% CI 1.1–14; p = 0.02), and deferoxamine therapy (OR 4.1, 95% CI 1.2–14; p = 0.02) were statistically significant for bacterial infection. The multivariate analysis of risk factors for bacterial infection in patients with thalassemia is shown in Table 5. None of the clinical

Table 1
Demographic and clinical characteristics of the 211 patients with non-transfusion-dependent thalassemia

Characteristics	Patients (N = 211)
Age at enrollment, years, mean ± SD	25.9 ± 13.3
Age at first diagnosis, years, mean ± SD	8.2 ± 12.6
Age at first transfusion, years, mean ± SD	9.5 ± 13.5
Transfusion index, ml/kg/6 months, mean ± SD	19.1 ± 19
Hemoglobin, g/dl, mean ± SD	7.9 ± 1.2
Platelet count, $\times 10^9$/l, mean ± SD	383.5 ± 242.7
Serum ferritin, ng/ml, mean ± SD	1692.3 ± 1759
Time after splenectomy, years, mean ± SD	4.2 ± 7.5
Gender, n (%)	
Female	119 (63.5)
Male	92 (36.5)
Splenectomy, n (%)	
No	134 (61.1)
Yes	77 (38.9)
Previous bacterial infection, n (%)	
No	200 (94.8)
Yes	11 (5.2)
Current iron chelation, n (%)	
No	78 (37)
Deferoxamine	22 (10.4)
Deferiprone	79 (37.4)
Deferasirox	3 (1.4)
Combined deferoxamine + deferiprone	29 (13.8)
Genotype group, n (%)	
β-thalassemia/Hb E	127 (60.2)
Hb H disease	10 (4.7)
Hb H disease with Hb CS	24 (11.5)
Hb H disease with Hb Paksé	4 (1.9)
EABart's disease[a]	14 (6.6)
EABart's disease with Hb CS[b]	26 (12.4)
EFBart's disease with Hb CS[c]	2 (0.9)
EABart's disease with Hb Paksé[d]	2 (0.9)
EFBart's disease[e]	2 (0.9)

SD, standard deviation; Hb CS, hemoglobin constant spring; Hb Paksé, hemoglobin Paksé.
[a] Compound heterozygous Hb H and heterozygous Hb E.
[b] Compound heterozygous Hb H with Hb CS and heterozygous Hb E.
[c] Compound heterozygous Hb H with Hb CS and homozygous Hb E.
[d] Compound heterozygous Hb H with Hb Paksé and heterozygous Hb E.
[e] Compound heterozygous Hb H and homozygous Hb E.

Table 2
Characteristics of bacterial infections in 11 patients with non-transfusion-dependent thalassemia

Bacterial infections	Patients (n = 11)
Organisms, n (%)	
Klebsiella species	4 (36.4)
Burkholderia pseudomallei	3 (27.2)
Escherichia coli	1 (9.1)
Aeromonas sobria	1 (9.1)
Stenotrophomonas maltophilia	1 (9.1)
Group B Streptococcus	1 (9.1)
Site of infection, n (%)	
Septicemia	7 (63.6)
Meningitis	1 (9.1)
Abscess (spleen, lymph node)	3 (27.3)

Table 3
Clinical characteristics of 11 infected patients with non-transfusion-dependent thalassemia

No.	Age (years)/ sex	Hb (g/dl)	Ferritin (ng/ml)	Splenectomy (time after splenectomy)	Organism	Site of infection
1.	36/F	8.2	1128	No	*Burkholderia pseudomallei*	Septicemia
2.	33/M	10.8	1250	No	*Burkholderia pseudomallei*	Splenic abscess
3.	23/M	6.8	8020	Yes (14 years)	*Aeromonas sobria*	Septicemia
4.	27/M	6.1	400	Yes (21 years)	Group B Streptococcus	Meningitis
5.	30/F	6.7	1410	Yes (24 years)	*Klebsiella* species	Lymph node abscess
6.	52/M	6.9	1965	No	*Escherichia coli*	Septicemia
7.	30/F	6.6	7883	No	*Klebsiella* species	Septicemia
8.	22/M	8.4	9999	Yes (15 years)	*Stenotrophomonas maltophilia*	Septicemia
9.	22/F	8.1	1646	Yes (13 years)	*Burkholderia pseudomallei*	Septicemia
10.	16/F	8.2	1959	No	*Klebsiella* species	Septicemia
11.	16/F	8.1	1756	Yes (11 years)	*Klebsiella* species	Lymph node abscess

F, female; M, male.

factors showed statistical significance for bacterial infection in the multivariate logistic regression analysis.

4. Discussion

The prevalence of severe bacterial infection was found to be moderate in patients with NTDT (5.2%). Time after splenectomy >10 years, deferoxamine therapy, and serum ferritin >1000 ng/ml may be clinical risk factors for severe bacterial infection in patients with NTDT.

It is well established that iron overload is an important predisposing factor for bacterial infection. The mechanism for this might be an impairment of phagocytic activity of macrophages and neutrophils and alteration of T-lymphocyte cell subsets resulting in immune system abnormalities.[20,21] Moreover, iron overload also increases the apparent virulence of some bacteria, for example *Yersinia enterocolitica*, *Klebsiella* species, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus pneumoniae*, *Listeria monocytogenes*, and *Legionella pneumophila*. This study also demonstrated that serum ferritin >1000 ng/ml may be a significant clinical risk factor for bacterial infection in patients with NTDT.

Splenectomized patients are known to have an increased susceptibility to infection, particularly from encapsulated bacteria. The duration of time since the splenectomy is a strong risk factor for bacterial infection. Supporting this, Rahav et al. showed that time after splenectomy >10 years had an adjusted rate of infection as high as 15.6 per 100 patient-years ($p = 0.0052$).[9] In the present cohort, it was found that time after splenectomy >10 years increased the risk of bacterial infection with an OR of 4.0 (95% CI 1.1–14; $p = 0.02$); however on multivariate analysis, time after splenectomy did not show a statistically significant association with bacterial infection. This finding might be due to the small number of events and sample size.

Vaccination prior to splenectomy surgery was noted in 38 patients (49.3%). There are two main possible reasons for the low percentage of vaccination prior to splenectomy in this study: (1) the patients' healthcare insurance did not cover the vaccine cost, so the patients would have had to pay for themselves, and (2) the vaccines only became available in the Khon Kaen University hospital in 2005, therefore patients who underwent splenectomy before 2005 did not receive vaccinations. Nevertheless, vaccination was not associated with a decreased risk of bacterial infection in patients with NTDT. The infections seen in this patient population were not preventable with vaccinations given prior to splenectomy.

Klebsiella species were the most common causative organisms in this study. This finding is in agreement with those of previous studies in Asian patients with thalassemia.[5,22] However, the result is different from those of studies performed in Western countries, where *Yersinia* species have been identified as the most common causative organisms in patients with thalassemia.[23–25] Previous in

Table 4
Univariate analysis of risk factors for bacterial infection in 211 patients with non-transfusion-dependent thalassemia

Variables	Number ($N = 211$)	% of infection ($n = 11$)	OR	95% CI	*p*-Value
Age (every increase in 1 year)	-	-	0.9	0.9–1.1	0.9
Gender					
Female	119	46.1	0.6	0.2–1.9	0.4
Male	92	53.9	1	-	-
Splenectomy					
No	134	45.5	1	-	-
Yes	77	54.5	2.2	0.6–7.4	0.2
Time after splenectomy >10 years					
No	172	54.5	1	-	
Yes	39	45.5	4.0	1.1–14	0.02
Hemoglobin ≤7 g/dl					
No	159	63.6	1	-	-
Yes	52	36.4	1.8	0.5–6.4	0.3
Thalassemic facies					
No	151	54.5	1	-	-
Yes	60	45.5	0.4	0.1–1.5	0.2
Serum ferritin >1000 ng/ml					
No	92	9.1	1	-	-
Yes	119	90.9	8.3	1.1–66	0.04
Deferoxamine therapy					
No	160	45.5	1	-	-
Yes	51	54.5	4.1	1.2–14	0.02
Deferiprone therapy					
No	132	54.5	1	-	-
Yes	79	45.5	1.4	0.4–4.8	0.5
β-thalassemia					
No	84	27.2	1	-	-
Yes	127	72.8	1.8	0.4–7.0	0.38
Vaccination					
No	163	90.9	1	-	-
Yes	37	9.1	0.4	0.05–3.5	0.4

OR, odds ratio; 95% CI, 95% confidence interval.

Table 5
Multivariate analysis of risk factors for bacterial infection in 211 patients with non-transfusion-dependent thalassemia

Variables	AOR	95% CI	*p*-Value
Serum ferritin >1000 ng/ml	5.6	0.6–51.5	0.1
Deferoxamine therapy	1.8	0.4–7.7	0.4
Time after splenectomy >10 years	2.5	0.5–11.1	0.2
Hemoglobin ≤7 g/dl	1.1	0.2–4.3	0.9
Thalassemic facies	0.6	0.2–2.5	0.5
β-thalassemia	0.6	0.1–3.2	0.5

AOR, adjusted odds ratio; 95% CI, 95% confidence interval.

vitro studies have found that the growth of Klebsiella is enhanced by deferoxamine therapy.[23]

Deferoxamine therapy is one of the clinical factors for severe bacterial infection, especially due to *Yersinia enterocolitica*, in Western countries.[23–26] This study also demonstrated that deferoxamine therapy is one of the clinical factors that is potentially associated with severe bacterial infection. On multivariate analysis, however, deferoxamine therapy did not show a statistically significant association with bacterial infection, which might be due to the small number of events. Deferiprone, the most common iron chelating agent in this study, was not associated with bacterial infection. This finding is in agreement with those of previous studies that have found deferiprone not to enhance the growth of pathogenic organisms in patients with thalassemia.[23,26]

Northeastern Thailand is an area endemic for *B. pseudomallei*. A previous study has shown that thalassemia is one of the significant clinical risk factors for *B. pseudomallei* infection.[27] The mechanism of the increased susceptibility to this infection in patients with thalassemia remains unclear.

A limitation of this study is that serum ferritin was used to evaluate iron overload instead of liver iron concentrations by magnetic resonance imaging technology. Serum ferritin may not reflect the true iron excess in these patients; however, recent studies have shown a good correlation between serum ferritin >800 ng/ml and liver iron concentration (LIC) ≥5 mg Fe/g dw, the level used to initiate chelation therapy, with a positive predictive value of 91.7%.[28]

In conclusion, iron overload, a time after splenectomy >10 years, and deferoxamine therapy may be risk factors for severe bacterial infection in patients with NTDT. Evaluation for iron excess should be performed regularly in patients with NTDT. Early recognition of bacterial infection in patients with NTDT may reduce morbidity and mortality, especially in those splenectomized patients with iron overload.

Acknowledgement

The Thailand Research Fund is acknowledged for assistance in this project (number IRG5780016). The authors would like to thank Emeritus Professor James A. Will, University of Wisconsin-Madison, for his help in preparing the manuscript.

Conflict of interest: The authors report no conflicts of interest.

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