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

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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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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)