Dengue Hemorrhagic Fever in Patients with Thalassemia

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Dengue hemorrhagic fever (DHF) causing by dengue viral infection is endemic in Thailand and Southeast Asian countries where thalassemias are prevalent. Thalassemic patients are also at risk to acquire dengue viral infections and to develop DHF. However, they can have different clinical manifestations and complications as well as more severity than general population requiring special awareness for proper diagnosis and management. We reported 20 thalassemic patients (10 boys and 10 girls) with DHF admitted to Department of Pediatrics, Siriraj Hospital during 1977 to 2001. Their ages ranged from 2-16 years (average 9.5 years). These cases included 5 cases of Hb H disease, 5 cases of Hb H with Hb Constant Spring (CS), 9 cases of β-thalassemia/Hb E disease and 1 case of β-thalassemia major. Two cases were in Grade I, 10 cases in grade II, 7 cases in Grade III and one case in grade IV severity of DHF. Though there were evidences of plasma leakage, instead of hemoconcentration, eighteen patients (90 percent) had hematocrit dropped at the range of 11-66% of the initial level. Fifteen patients (75 percent) required at least one packed red cell transfusion. Nine patients (45 percent) had mild bleeding symptoms, one of them had upper gastrointestinal hemorrhage requiring platelet concentrate transfusion. Two patients (10 percent) had serious complications including one with infection-associated hemophagocytic syndrome (IAHS) requiring intravenous immunoglobulin (IVIG) and packed red cell transfusion and the other had generalized seizure due to hyponatremia and hypotension. No mortality was observed among this group of patients. Early recognition of the DHF in thalassemic patients and appropriate packed red cell transfusion in patients with anemic symptoms is warranted to reduce morbidity and mortality in these patients.

Keywords : *Dengue hemorrhagic fever, Thalassemia, Anemia, Complications*

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Dengue virus infection is endemic in Thailand and Southeast Asian countries. Infection by dengue viruses may result in the mild clinical symptoms of dengue fever or in serious manifestations of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). The morbidity and mortality of this disease is high if no appropriate managements are given especially in cases with complications or unusual manifestations. These include shock, severe bleeding, hepatic failure, encephalopathy, renal failure, acute intravascular hemolysis and secondary infections[1-7].

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Thalassemia is the most common inherited genetic disease in the world and highly prevalent in Thailand and Southeast Asian countries[8]. Thalassemic patients are also at risk to acquire dengue virus infections and can have different clinical manifestations and more complications than general population which pose the problems of early recognition for diagnosis and proper managements. The purpose of this study is to report clinical manifestations, laboratory findings, complications, management and outcome in thalassemic patients with DHF.

Material and Method

We review the medical records of all patients with thalassemia and dengue hemorrhagic fever (DHF)/

dengue shock syndrome (DSS) who were admitted to department of Pediatrics, Siriraj Hospital from January 1977 to December 2001.

Criteria for diagnosis of dengue virus infection

Cases of DHF are characterized by four clinical manifestations and laboratory findings. All of which must be present[1].

1. Fever or recent history of acute fever.

2. Hemorrhagic phenomena (presence of at least one of the followings: positive tourniquet test, petechiae, ecchymoses or purpura or bleeding from mucosa, gastrointestinal tract, etc.)

3. Thrombocytopenia (platelet count less than 100,000/mm^3)

4. Hemoconcentration from plasma leakage due to increased capillary permeability (defined as increased level of hematocrit more than 20% of baseline). Dengue shock syndrome (DSS) is characterized by the presence of all four DHF manifestations as well as circulatory failure. All three manifestations of circulatory failure must be present: rapid and weak pulse, narrow pulse pressure or hypotension for age of the patients and cold, clammy skin and altered mental state.

Dengue fever (DF) is characterized by the same clinical manifestations of DHF but has mild clinical symptoms and has no evidence of hemoconcentration from plasma leakage.

The severity of DHF was classified into 4 grades as previously described[9]. The diagnosis of dengue virus infection was based on clinical, hematological and serological study.

Serological testing for confirmation of dengue virus infection

Paired samples were obtained from patients for serological testing by hemagglutination inhibition test to dengue type 1, 2, 3 and 4 and by enzyme-linked immunoassay (ELISA) for IgM[1]. The acute dengue titers over 1:1,280 or 4-fold rising of antibody titer to all four dengue types were considered as secondary dengue infection. The acute dengue titer of less than 1:1,280 or 4-fold rising of antibody titer to only one dengue type were considered as primary dengue infection[1,3]. IgM antibody to dengue virus was determined by enzyme-linked immunosorbent assay (ELISA) to confirm dengue virus infection[10,11].

Management of patients with DHF/DSS

Patients with DHF/DSS received management according to the WHO guidelines[1]. Those with DHF grade I or II with history of vomiting and exhibited dehydration, received fluid replacement therapy. Those with grade III or IV DHF received half or full strength normal saline in 5% dextrose solution at a rapid rate of 10 to 20 ml/kg/hour for 1 to 2 hours. In severe cases of DSS with circulatory failure, other volume expanders such as plasma or dextran must be added. Packed red cells were transfused in patients who manifested a rapid drop in the hematocrit either due to hemolysis or excessive bleeding. In cases of active bleeding or bleeding in vital organs, platelet concentrate, prepared from either single donor or multiple donors, were given in the dose of 0.2 to 0.4 unit per kg body weight.

Results

There were 20 thalassemic patients with dengue hemorrhage fever (DHF) admitted to Department of Pediatrics, Siriraj Hospital for proper management. Their ages ranged from 2 to 16 years (average 9.5 years). Nine cases were β-thalassemia/Hb E disease, 5 cases were Hb H disease, 5 cases were Hb H with Hb Constant Spring (CS), and 1 case was β-thalassemia major. All except one case were previously diagnosed as thalassemias and were followed regularly at the Hematology clinic. Six cases (4 Hb H disease and 2 Hb H with Hb CS) required no blood transfusions while the rest had previous packed red cell transfusions ranging from 1 to 30 times per year. Four patients enrolled in hypertransfusion programme (packed red cell transfusion every 2-3 weeks) and iron chelation with subcutaneous desferrioxamine. Splenectomy had been done in 4 cases who had hypersplenism. Most of the thalassemic patients with DHF were hospitalized in the febrile stage with mean duration of fever for 4.6 days. The severity of DHF was classified into 4 grades; 2 cases with grade I, 10 cases with grade II, 7 cases with grade III, and one case with grade IV DHF. The clinical and laboratory data are shown in Table 1. The serological results were confirmed in 13 tested patients which revealed secondary dengue infection in 11 cases and primary dengue infection in 2 cases. Nine patients had mild bleeding symptoms such as petechiae and epistaxis. There was only one patient who had upper gastrointestinal bleeding. There were 17 patients (85 percent) with platelet count less than 100,000/mL, the other 3 cases, however, had clinical picture of thrombocytopenia with mild bleeding. It was surprising that among 20 thalassemic patients with DHF, only one patient had hemoconcentration. Besides, eighteen patients (90 percent) had hematocrit dropped and 15 patients (75 percent) needed packed red cell transfusion at least one time.

Among 15 patients who required packed red cell transfusion, 6 patients were transfused once, 7 patients were transfused twice, 1 patient was transfused three times and 1 patient was transfused four times (Table 1.) All patients recovered completely and none died.

There were two patients with serious complications. The first case (patient No. 4) was a 9-year-old boy with grade II DHF who had progressive pancytopenia. Bone marrow aspiration was performed at day 5 of fever and demonstrated hemophagocytic syndrome. Infection- associated hemophagocytic syndrome (IAHS) was diagnosed in this patient. The patient was treated with intravenous immunoglobulin (IVIG) and packed red cell transfusions. Pancytopenia gradually resolved and he was discharged from the hospital 8 days after admission. The second case (patient No. 19) was a 13-year-old girl with grade IV DHF with generalized tonic clonic seizure on day 5 of fever. The investigation showed hyponatremia (serum sodium 122 mEq/L). She also had hypotension and hematocrit dropped rapidly (grade IV DHF). She was transfused with packed red cell and fresh frozen plasma as well as correction of hyponatremia. She was hospitalized for 10 days and had full recovery without any sequlae.

Discussion

Dengue virus infection produce a spectrum of clinical illness ranging from undifferentiated fever, dengue fever (DF), dengue hemorrhagic fever (DHF)

Table 1. Clinical and laboratory data of thalassemic patients with dengue hemorrhagic fever

Patient No.	Sex	Age (yrs)	Type of thalassemia	Serology**	Severity of DHF	Bleeding	Hct (%)		Platelet (/mL)	Blood component requirement
							Pre	Post		
1.	M	11	Hb H	1 DEN	Gr. I	Petechiae	35	31	143,000	No
2.	F	16	Hb H/CS	2 DEN	Gr. II	No	34	15	56,000	PRC x 2
3.	M	5	β-Thal/Hb E	2 DEN	Gr. III	Epistaxis	21	11	12,000	PRC x 2
4.	M	9	Hb H/CS	1 DEN	Gr. II	No	35	12	72,000	PRC x 3
5.	M	10	Hb H #	2 DEN	Gr. II	No	39	29	44,000	No
6.	M	12	β-Thal/Hb E, PS #	2 DEN	Gr. II	No	26	18	44,000	PRC x 4
7.	F	15	Hb H/CS, PS	2 DEN	Gr. II	Epistaxis	37	22	68,000	PRC x 1
8.	F	10	β-Thal/Hb E +	2 DEN	Gr. III	Petechiae	24	19	50,000	PRC x 2
9.	F	14	β-Thal/Hb E, PS	ND	Gr. III	Epistaxis UGI bleeding	22	17	16,000	PRC x 2 Plt conc x 1
10.	M	12	β-Thal/Hb E PS	ND	Gr. III	No	24	19	75,000	PRC x 1
11.	M	8	Hb H	2 DEN	Gr. II	No	29	15	64,000	PRC x 1
12.	M	10	β-Thal/Hb E	2 DEN	Gr. III	No	20	17	38,000	PRC x 2
13.	F	9	β-Thal/hb E	ND	Gr. II	No	30	25	40,000	PRC x 2
14.	F	5	β-Thal/Hb E +	2 DEN	Gr. III	Epistaxis	30	25	21,000	PRC x 1
15.	M	9	β-Thal major +	ND	Gr. II	No	29	35	78,000	No
16.	F	5	Hb H/CS	ND	Gr. II	Epistaxis		28	184,000	No
17.	F	6	Hb H	ND	Gr. II	Petechiae	29	24	48,000	PRC x 1
18.	M	2	β-Thal/Hb E +	ND	Gr. III	No	24	19	66,000	PRC x 1
19.	F	13	Hb H/CS	2 DEN	Gr. IV	No	25	15	71,000	PRC x 4 FFP x 2
20.	F	9	Hb H	2 DEN	Gr. I	Petechiae	-	30	120,000	No

ND = not done
DEN = Dengue infection
+ on regular blood transfusion with pre transfusion hematocrit ~ 30%
PS = post splenectomy
* with infection associated hemophagocytic syndrome (IAHS)
** 1 = primary, 2 = secondary
# presence of pleural effusion from chest X-ray
Pre = Hct before dengue infection
Post = Hct during dengue infection

and dengue shock syndrome (DSS) which may be fatal[1]. Several factors determine the severity of DHF; these include nutritional status[12], immune status of the patients as well as the underlying disease of the patients. Thalassemia disease is one of the chronic illness highly prevalent in Southeast Asian countries including Thailand which is also an endemic area of dengue virus infection. Several aspects about the susceptibity to infections in thalassemia had been studied. The study of immune status including phagocytic activity, cell mediated immune response, humoral antibody and compliment system in pediatric thalassemic patients were not different from the general population and also there was no difference between splenectomized and non-splenectomized thalassemic patients[13-15]. The secondary dengue infection is more severe in clinical symptoms than the primary dengue infection. The secondary dengue infection depends on the ability of enhancing antibody production of the patients[16,17] and the development of immunopathogenesis of the disease[18-21]. Since the immunological response in thalassemic patients are normal, they can also have severe clinical symptoms similar to normal individual. In this study, we found that the clinical manifestations and complications in thalassemic patients are different from those of normal children. Though our patients had general symptoms as others who suffered from DHF, all patients except one (patient No.15) did not have hemoconcentration as should be expected. This was observed despite evidences of plasma leakage such as presence of pleural effusion seen in the cases that chest X-ray s were taken. Lack of hemoconcentration not only make the diagnosis of DHF difficult but also could not be used as guideline for fluid replacement therapy. On the contrary, most patients (90%) had hematocrit dropped significantly ranging from 11 to 66% of the initial level and 1-4 blood transfusions were required in 15 cases (75 percent) of our patients. Only one patient required platelet concentrate transfusion. This observation was seen both in the patients with Hb H diseases and in β-thalassemia patients (Table 1.) In thalassemic patients after febrile illness, anemic crisis may occur especially in Hb H disease who usually have only mild or no anemia[22]. This episode is usually acute, serious and require blood transfusion. Dengue virus infection, thus, is one infection that cause anemic crisis in thalassemic children. This is very important because it could overshadow the hemoconcentration typically seen in DHF. Acute anemia in patients with DHF was also observed in patients with other underlying conditions such as glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. We found 3 out of 17 G-6-PD deficient males with DHF had acute anemia from acute intravascular hemolysis while the rest of the patients still had hemoconcentration[7]. However, in this study only one out of 20 thalassemic patients had hemoconcentration where most of the patients had anemia which was likely due to extravascular hemolysis, suppression of hematopoiesis and possible hemophagocytosis caused by dengue virus. Thus the main problem for thalassemic patients with dengue viral infection is severe anemic symptom which may need blood component therapy as packed red cell transfusion rather than platelet transfusion for bleeding problems as in general population [23]. Severe anemia can cause hemodynamic compromised and lead to hypoxemia, hypotension and shock. Prolonged shock further results in organ damage and poor outcome. Thus, in thalassemic patient with DHF, not only early diagnosis but also proper management is required; this includes all supportive measures and good monitoring. Appropriate blood component should be prepared in advance and the packed red cell should be promptly transfused in patients with anemic symptoms.

Conclusion

The thalassemic patients with dengue viral infection have distinct clinical manifestations. Dengue infection should be aware of in thalassemic patients having sustained fever, progressive anemia and thrombocytopenia. The main problem of them is anemia due to hemolysis rather than hemoconcentration. Awareness of this clinical features and recognition for early diagnosis and appropriate management including packed red cell transfusion in severe anemic patients can reduce morbidity and mortality in these patients.

References

1. World Health Organization. Dengue hemorrhagic fever, diagnosis, treatment, prevention and control. 2nd ed Geneva 1997.
2. Nimmanitya S, Thisyakorn U, Hemsrichart V. Dengue hemorrhagic fever with unusual manifestations. Southeast Asian J Trop Med Public Health 1987;18:398-406.
3. Lam SK. Rapid dengue diagnosis and interpretation. Malay J Path 1993;15:9-12.
4. Thisyakorn U, Thisyakorn C. Dengue hemorrhagic fever: unusual manifestations and problems in management. JAMA SEA 1994;10:102-3.

5. Thisyakorn U, Thisyakorn C, Limpitikul W, Nisalak A. Dengue infection with central nervous system manifestations. Southeast Asian J Trop Med Public Health 1999;30:504-6.
6. Sirivichayakul C, Sabcharoen A, Chanthavanich P, Pengsaa K, Chokejindachi W, Prarinyanupharb V. Dengue infection with unusual manifestation; a case report. J Med Assoc Thai 2000;83:325-9.
7. Tanphaichitr VS, Cholasin R, Suwantol L, Pungamritt P, Tachavanich K, Yoksan S, et al. Effect of red blood cell glucose-6-phosphate dehydrogenase deficiency on patients with dengue hemorrhagic fever. J Med Assoc Thai 2002;85(Suppl 2): S521-9.
8. Galanello R, Eleftheriou A, Traegen Synodinos J, Old J, Petrou M, Angastiniotis M. Prevention of thalassemias and other hemoglobin disorders. Vol. I. Nicosia: Thalassemia International Federation, 2003.
9. Nimmanitya S, Halstead SB, Cohen S, Margiotta MR. Dengue and Chickungunya virus infection in man in Thailand 1962-1964. I. Observations in hospitalized patients with hemorrhagic fever. Am J Trop Med Hyg 1969;18:954-71.
10. Lam SK, Devi S, Pang T. Detection of specific IgM in dengue infections. Southeast Asian J Trop Med Public Health 1987;18:532-8.
11. Innis BL, Nisalak A, Nimmanitya S, Kusalerdchariya S, Choongswasdi V, Suntayakorn S, et al. An enzyme-linked immunosorbent assay to characterized dengue infections where dengue and Japanese encephalitis co-circulate. Am J Trop Med Hyg 1989;40:418-27.
12. Thisyakorn U, Nimmanitya S. Nutritional status of children with dengue hemorrhagic fever. Clin Infect Dis 1993;16:295-7.
13. Tuchinda S, Suvatte V, Moongkarndi P. Host defense in thalassemia and the effect of splenectomy: NBT test. J Med Assoc Thai 1978;61:74.
14. Suvatte V, Tuchinda M, Tuchinda S. Cell-mediated immunity in thalassemia and the effect of splenectomy. Thai Med J 1978;2:26-30.
15. Suvatte V, Tuchinda M, Pongpipat D, Assateerawat A, Tuchinda S. Host defense in thalassemia and the effect of splenectomy. 3. Humoral and cell-mediated immunities. J Med Assoc Thai 1978;61:73.
16. Halstead SB. Observation related to pathogenesis of dengue hemorrhagic fever. VI Hypothesis and discussion. Yale J Bio Med 1970;42:350-62.
17. Halstead SB. Pathogenesis of dengue: challenges to molecular biology. Science 1988;239:476-87.
18. Suvatte V, Malasit P, Sarasombath S, Wasi C. Immunopathogenesis of dengue hemorrhagic fever/dengue shock syndrome. Proceeding of the first International Congress of Tropical Pediatrics 1987;206-14.
19. Bhakdi S, Kazatchkine MD. Pathogenesis of dengue: an alternative hypothesis. Southeast Asian J Trop Med Public Health 1990;21:652-7.
20. Kurane I, Innis BL, Nimmanitya S, Nisalak A, Rothman AL, Livingston PG, et al. Human immune response to dengue viruses. Southeast Asian J Trop Med Public Health 1990;21:658-62.
21. Malasit P, Mongkotsapaya J, Kalayanarvooj S, Nimmanitya S. Complement and dengue hemorrhagic fever/dengue shock syndrome. Southeast Asian J Trop Med Public Health 1987;18:316-20.
22. Wasi P. Thalassemia: clinical aspects and screening. In: McArthur JR, Lee SM, Wong JEL, Ong YW, editors. Hematology 1996. Education programme of the 26th Congress of the International Society of Hematology, Singapore: Panache Design 1996:226-33.
23. Chuansumrit A, Phimolthares V, Tardton P, Tapaneya-Olarn C, Tapaneya-Olarn W, Kowsathit P, et al. Transfusion requirements in patients with Dengue hemorrhagic fever. Southeast Asian J Trop Med Public Health 2000;31:10-4.

โรคไข้เลือดออกในผู้ป่วยธาลัสซีเมีย

บุญชู พงศ์ธนากุล, นัทธี นาคบุญนำ, กวิวัณณ์ วีรกุล, กลีบสไบ สรรพกิจ, วิปร วิประกษิต, วรวรรณ ตันไพจิตร, วินัย สุวัตถี

โรคไข้เลือดออกเป็นโรคที่เกิดจากการติดเชื้อไวรัสเด็งกี่ พบมากในประเทศแถบภาคพื้นเอเชียอาคเนย์ รวมทั้งประเทศไทย ซึ่งเป็นภูมิภาคที่พบผู้ป่วยโรคธาลัสซีเมียมากเช่นกัน ผู้ป่วยธาลัสซีเมียจึงมีอัตราเสี่ยงที่จะติดเชื้อไวรัสนี้ และเป็นโรคไข้เลือดออกได้ คณะผู้รายงานได้รวบรวมข้อมูลผู้ป่วย ธาลัสซีเมีย 20 รายที่เป็นโรคนี้ที่มารับการรักษาที่ภาควิชากุมารเวชศาสตร์ โรงพยาบาลศิริราช ในระหว่างปีพ.ศ. 2520-2544 เป็นเพศชาย 10 ราย และหญิง 10 ราย อายุ 2-16 ปี (เฉลี่ย 9.5 ปี) เป็นโรคฮีโมโกลบินเอ็ช 5 ราย ฮีโมโกลบิน เอ็ช คอนแสตนท์สปริง 5 ราย เบต้าธาลัสซีเมีย/ฮีโมโกลบิน อี 9 ราย และเบต้าธาลัสซีเมีย เมเจอร์ 1 ราย เป็นโรคไข้เลือดออกในระดับความรุนแรง I-IV จำนวน 1, 10, 7 และ 1 ราย ตามลำดับ พบว่าผู้ป่วยธาลัสซีเมียเหล่านี้แม้จะมีภาวะรั่วซึมของน้ำจากหลอดเลือดพบผู้ป่วยเพียงรายเดียวที่มีภาวะเลือดข้น ซึ่งเป็นลักษณะอาการสำคัญอย่างหนึ่งของโรคไข้เลือดออก กลับพบว่ามีผู้ป่วย 18 ราย (ร้อยละ 90) มีฮีมาโตคริตลดลงถึงร้อยละ 11-66 ของระดับเดิม 15 ราย (ร้อยละ 75) มีอาการชีดจนต้องให้เลือด 1-4 ครั้ง มีผู้ป่วย 9 รายที่มีปัญหาเลือดออกเล็กน้อย 1 รายมีเลือดออกจากระบบ ทางเดินอาหารตอนบน และได้รับเกล็ดเลือดเข้มข้น มีผู้ป่วยที่มีภาวะแทรกซ้อนรุนแรง 2 ราย 1 รายมีภาวะ infection-associated hemophagocytic syndrome ต้องได้รับ IVIG และ 1 รายมีอาการชักจาก ภาวะโซเดียม และความดันโลหิตต่ำ ทุกรายได้รับการรักษาอย่างรวดเร็ว ผู้ป่วยที่ชีดลงได้รับเม็ดเลือดแดงเข้มข้น และทุกรายมีอาการดีขึ้น โดยไม่มีผู้ใดเสียชีวิต ผู้ป่วยธาลัสซีเมียที่เป็นโรคไข้เลือดออก นอกจากจะไม่มีภาวะเลือดข้นแล้ว ยังมีภาวะชีดร่วมด้วย จนต้องให้เลือดเพื่อแก้ไขภาวะชีดโดยเร็วที่สุด