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Dengue infection in sickle cell patients in French Guiana

Emilie Mosnier[1,2]*, Magalie Demar[1], Emmanuelle Bernit[3], Dominique Rousset[4], Loic Epelboin[1,2], Mathieu Nacher[2,5], Philippe Abboud[1], Vincent Vantilke[6] and Felix Djossou[1]

[1]Unit of Infectious and Tropical Diseases, Hospital of Cayenne , Cayenne, French Guiana, France
[2]EA3593 , Amazonian ecosystems and Tropical Pathology , University of Guyana, Cayenne , French Guiana, Cayenne, France
[3]Department of Internal Medicine , Hospital of the Conception, Marseille, France
[4]Virology Laboratory, Pasteur Institute of French Guiana, Cayenne, French Guiana, France
[5]CIC 1424 INSERM , Infectious Diseases, Genetic and emerging in the tropics, Centre Hospitalier de Cayenne, Cayenne, France
[6]Service Medicine, Hospital of Saint Laurent du Maroni, Saint Laurent du Maroni, French Guiana, France

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***Corresponding author:** Mosnier Emilie, Unit of Infectious and Tropical Diseases, Hospital of Cayenne Andrée Rosemon, Rue des Flamboyants 97306 Cayenne, French Guiana, France, Tel: +594-395-040; Fax: +594-395-041; E-mail: emilie.mosnier@gmail.com*

Abstract

Reports on dengue morbidity in patients with Sickle Cell Disease (SCD) are scarce. Dengue is arthropod-borne viroses due to dengue virus (DENV) and affects populations with a high prevalence of SCD; therefore, the risk of morbidity may be increased.

To determine the impact of dengue infection in SCD patients, we reviewed medical records during a vast outbreak of dengue virus serotype-2 (DENV-2) in French Guiana in 2012-2013.

We identified 10 cases of laboratory-confirmed dengue infection; these were classified into A, B and C categories based on levels of severity of dengue according to World Health Organisation (WHO).

The average age of SCD patients was 18.2 years. 1, 6 and 3 cases were classified as A, B and C WHO severity criteria, respectively. All patients had an important decrease in haematocrit (while one of the WHO severity criteria is the increase of haematocrit). Only one patient had decreased platelet count. Seven cases had Vaso-Occlusive Crisis (VOC), six patients developed acute hepatitis and eight had a simultaneous bacterial infection. Six of them needed a blood transfusion.

The results suggested that the WHO severity laboratory criteria of hemoconcentration and platelet counts were not helpful in the management of SCD patients. The morbidity was mainly caused by specific complications of SCD, especially VOC, likely facilitated by vascular endothelial damages consecutive to dengue fever, severe haemolysis, hepatitis and bacterial co-infections.

Keywords: Dengue infection; Sickle cell disease; French Guiana

Introduction

Dengue fever is an increasing global health threat with an estimated 50-100 million new cases each year [1]. It is an endemo-epidemic disease in French Guiana in relation to the circulation of 4 serotypes of dengue virus (DENV-1, DENV-2, DENV-3 and DENV-4). During the last outbreak in 2012-2013, there were 5473 serologically confirmed cases and six deaths which were mainly caused by DENV-2 serotype (92%) [2]. In the WHO guidelines on dengue fever, Sickle Cell Disease (SCD) is considered to be a risk factor for development of severe dengue fever [3]. This genetic disease is frequent in French Guiana, with an estimated incidence at birth of 1/227 [4]. There are approximately 2,000 patients with SCD (0.8% of the total population) in French Guiana, all of whom are managed within the French Guianese health system [4]. Previously, few cases of dengue had been reported in patients with SCD and all the reports have included fatalities [5-8]. Among the few described cases, the report by Moesker et al. [8] which included two fatal cases in young individuals, is the only one that has suggested treatment options or case management [8]. To date, the physiopathology patterns and mechanisms between these two diseases have not been described.

Our study represents the first, to date, to evaluate the morbi-mortality of acute dengue on SCD patients.

Methods

The study was performed in hospitals in French Guiana, which is a French overseas territory of 260,000 inhabitants, neighbouring Brazil and Suriname in the Amazonian region. We studied all patients with SCD that were admitted to the French Guianese hospitals and presented a positive diagnosis of dengue infection, from January 1, 2012 to October 31, 2013. We categorised dengue infection cases into probable and confirmed. Probable cases showed a definite presence of dengue-specific IgM (IgM positive) associated with the WHO criteria of acute dengue fever (fever and two or more clinical signs such as: headache, eye pain, myalgia, arthralgia, leukopenia, rash, and bleeding). The confirmed cases presented positive NS1 antigen detection, associated or not with dengue-specific IgM.

All cases were classified into A, B, C categories according to the WHO severity criteria of dengue infection (Table 1) [3]. A medical chart review was undertaken to extract demographic, clinical, laboratory, treatment and outcome data. These data was used to determine the incidence, the type of medical complications and the severity of dengue infection in SCD patients.

The retrospective use of anonymous patient files on the

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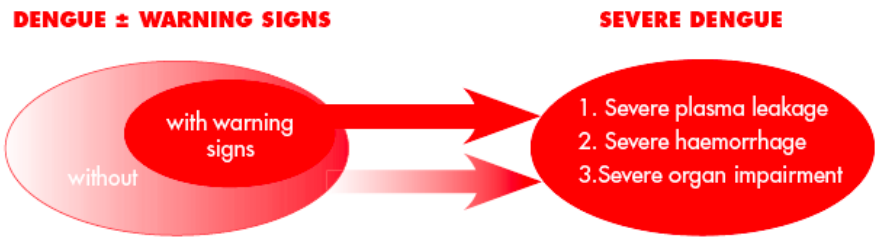
Table 1: Total of patients hospitalized with a diagnosis of dengue.



Criteria for dengue +/- warning signs		Criteria for severe dengue
Group A **(May be sent home)**	**Group B** **(Referred for in-hospital care)**	**Group C** **(Require emergency treatment)**
Probable dengue Live in or travel to dengue endemic area. Fever and 2 of the following criteria: - Nausea, vomiting - Rash - Aches and pain - Tourniquet test positive - Leukopenia - Any warning sign **Laboratory-confirmed dengue** (Important when no sign of plasma leakage)	**Warning signs** - Abdominal pain or tenderness - Persitent vomiting - Clinical fluid accumulation - Mucosal bleed - Lethargy, restlessness - Liver enlargement > 2cm - Laboratory: increase in HCT concurrent with rapid decrease in platelet count	**Severe plasma leakage** Leading to: - Shock (DSS) - Fluid accumulation with respiratory distress **Severe bleeding** As evaluated by clinician **Severe organ involvement** - Liver: AST or ALT > = 1000 - CNS: Impaired consciousness - Heart and other organs
	Group criteria Patients with any of the following features: - Co-existing condition such as pregnancy, infancy, old age, diabetes mellitus, renal failure - Social circumstances such as living alone, living far from hospital	

HCT, hematocrit; DSS, dengue shock syndrome; CNS, central nervous system
Dengue case definition and diagram displayed in this table were extracted from the WHO guidelines and were combined and summarized [3].

site of patient care was authorized by the French National Commission on Informatics and Liberties. All the data collected retrospectively were anonymised in a standardised case report form and in the database.

Results and Discussion

Epidemiology

A total of 678 hospitalised or inpatients with a diagnosis of dengue were examined with 546 cases positive for IgM, and 241 patients with positive NS1 Ag detection (Table 2). Ten patients (1.5%) had SCD co-morbidity Homozygote Sickle Cell Anemia (HbSS), Heterozygote Sickle Cell Disease (HbSC) or Sickle Cell Beta-Thalassemia (HbSβ), including six probable cases and four confirmed cases of acute dengue infection. The prevalence of SCD in general population in French Guiana is about 0.8% [4]. According to these results, in our study the prevalence of SCD among patients hospitalized due to dengue fever complications was higher than in the general population (1.47% vs 0.8%, respectively) A large proportion of the patients (n = 8) were HbSS SCD. Table 3 shows the detailed results of demographical, clinical, laboratory, treatment and outcome data. Most patients were women (60%) and had a mean age of 18.2 years (range 2 to 39). Five patients (50%) were < 15 years old.

Clinical features

Fever, myalgia, arthralgia, anorexia and abdominal pain were the most frequent clinical features reported. All patients had tachycardia and half of them presented abdominal tenderness.

The laboratory results did not show any increase of haematocrit. On the contrary, all patients presented a low haematocrit (< 30%) with a drop < 20% from the basal level for eight patients.

There was only one case of severe thrombocytopenia. This is

Table 2: Total of patients hospitalized with a diagnosis of dengue .

WHO criteria Percentage of total patient (%)	NS1 Ag positive *n* = 214 *(n* SCD patients = *4)*	IgM positive, *n* = 546 (*n* SCD patients = 7)
A (8.8)	29 **(0)**	31 **(1)**
B (87.6)	159 **(2)**	435 **(5)**
C (15.6)	26 **(2)**	80 **(1)**

Laboratory and clinical feature of acute dengue = 678, of whom 82 (n SCD patient =1) have both positive NS1 and IgM serology.

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probably due to the fact that thrombocytosis is a common finding in patients with SCD, even in steady states or in the absence of any infection. Thrombocytosis in SCD patients was attributed to the background haemolytic anaemia and autosplenectomy [9]. Thrombocytosis is also higher in SCD patients with infections associated with platelets activation. Because of this, endothelial damage leads to an increased risk of vascular occlusion [10,11]. A large proportion of our cases presented severe haemolysis leading to blood transfusion support. SCD is usually associated with chronic haemolysis, which can increase with infection [11]. However, dengue is generally not known to induce haematocrit disease, but it has been demonstrated to aggravate anemia while in patients with malaria attacks, compared to malaria alone [12].

There were also frequent complications of dengue such as VOC, severe haemolysis and bacterial co-infection. The latter included pneumonia, pyelonephritis and cholangitis and in 4 cases antibiotic therapy without documented infection (Table 3). It is well-known that patients with SCD present a higher susceptibility to infections, which is partly due to the autosplenectomy resulting from recurrent vaso-occlusive splenic infarcts. Several other factors that predispose SCD patients to infections have also

Table 3: Demographic, clinical, laboratory, treatment and outcome data of the 10 SCD patients according to the 2009 WHO dengue case classification.

	General characteristics of patients	**WHO 2009 criteria**		
	(*n* = 10)	A (*n* = 1)	B (*n* = 6)	C (*n* = 3)
Demographic details				
Median age, years,* (range)	18.02 (2,39)	36	15.3 (2,39)	18 (13,22)
Male gender, *n* (%)	4 (40)	0	1 (10)	3 (100)
Comorbidity (other than SCD), *n*	2	0	1	1
epilepsy	1	0	1	0
hypertension	1	0	0	1
SCD type				
HbSC, *n*	1	0	1	0
HbSS, *n*	8	1	5	2
HbSβthal, *n*	1	0	0	1
Laboratory diagnosis				
Serology (IgM positive), *n*	7	1	5	1
NS1 positive, *n*	4	0	2	2
Dengue virus serotype, *n*	1			
DENV-2	1			
Dengue probable, *n*	6	1	4	1
Dengue confirmed, *n*	4		2	2
duration of symptom before admission, days*	5	4	4,3	6,6
duration of hospitalisation, days*	6.6	3	5. 6	9.6
Clinical feature				
fever > 38° at admission, *n*	9	1	6	2
Headache, *n*	1	1	0	0
Impaired consciousness, *n*	1	0	0	1
Lethargy, restlessness, *n*	4	0	3	2
Eye pain, *n*	1	1	0	0
Myalgia, *n*	10	1	6	3
Arthralgia, *n*	6	0	4	2
Rash, *n*	0	0	0	0
Anorexia, *n*	6	0	4	2
Nausea/vomiting, *n*	3	0	2	1
Abdominal pain, *n*	5	0	3	2
Diarrhea, *n*	0	0	0	0

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Cough, *n*	2	0	1	1
Bleeding, *n*	0	0	0	0
Clinical signs				
Blood pressure < 90 mm Hg, *n*	3	0	2	1
Pulse>100/min, *n*	10	1	6	3
Abdominal tenderness, *n*	5	0	3	2
Pleural effusion or ascites, *n*	0	0	0	0
Hepatomegaly > 2 cm, *n*	3	0	1	2
Splenomegaly, *n*	4	1	1	2
Laboratory results				
Leucopenia < 4×109/l, *n*	2	0	2	0
Hematocrit (normal 42-51), *n*				
Hematocrit > 50%, *n*	0	0	0	0
Hematocrit < 30%, *n*	10	1	6	3
Lost > 20% of hematocrit from basal, *n*	8	1	4	3
Platelet count < 50×109/l, *n*	1	0	1	0
Anormal increase of serum creatinine > 100 mol/l, *n*	2	0	1	1
Increase of aspartate transaminase > 40 UI/l, *n*	6	0	4	2
Increase of alanine transaminase > 40 UI/l, *n*	6	0	4	2
Raised prothrombin time, *n*	2	0	0	2
Median level of CRP mg/l at admission*	20 (0,24)	35	21 (0,54)	14 (0,26)
Management and outcome				
Intraveinous fluid, *n*	10	1	6	3
Platelet transfusion, *n*	0	0	0	0
Blood transfusion, *n*	7	1	3	3
Vaso-oclusion crisis, *n*	7	0	5	2
Acute chest syndrom, *n*	1	0	1	0
Liver failure, *n*	2	0	0	2
Renal failure, *n*	0	0	0	0
Bacterial infection associated, *n*	8	0	6	2
Pneumonia, *n*	2	0	1	1
Pyelonephritis, *n*	1	0	1	0
Cholangitis and pancreatitis, *n*	1	0	1	0
Antibiotherapy without documented infection, *n*	4	0	3	1
Morphine analgesia, *n*	4	0	4	0
Intensive care unit admission, *n*	0	0	0	0
Death, *n*	0	0	0	0

been reported, such as abnormalities of opsonisation, antibody productions, activation of the complement system alternative pathway, leukocyte functions and cell immunity [13,14]. The physiopathological interaction(s) between dengue virus, endothelial cell and immune cells in SCD patients remain unclear. However, dengue infection impacts immune response, capillary permeability and viremia due to the ability of the virus to infect endothelium cell [15]. By damaging the endothelium the dengue virus may increase the abnormal adhesion of erythrocyte in SCD and promote vaso-occlusive complications [16]. This could be one of the explanations of the importance of vaso-occlusive syndromes in our cases.

Another important aspect is the impact of dengue infection on the liver function. Six patients had hepatitis, two of them also had decreased prothrombin time. It has been well established that patients with dengue fever have some degree of hepatic abnormalities involving a dengue virus-induced liver apoptosis [17,18]. Considering that SCD patients have a high risk of hepatic dysfunction mediated by possible secondary hemochromatosis,

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vaso-occlusive hepatic crises and consumption of non-steroid anti-inflammatory drugs, they may be particularly at risk of hepatic dysfunction during acute dengue infection.

Treatment and outcome

The average duration of symptoms before admission and during hospitalisation was 5 and 6.6 days, respectively, and increased with the severity of dengue infection. Fortunately, there was no report of any death and no admission to the intensive care unit. However patients had a relatively prolonged hospitalisation. These results are rather reassuring compared with previous reports of systematic fatal cases [5,6,8]. Nevertheless, all patients required intravenous fluid rehydration and for most of them (n = 7) a blood transfusion was necessary. Dengue infection was complicated with VOC and bacterial co-infection in the majority of cases.

WHO criteria which are considered as a measure of disease severity were not helpful in the medical management of the SCD. For example, the patient classified as category A had severe haemolysis requiring a blood transfusion and intensive treatment and monitoring.

More generally, all our cases showed a drop of haematocrit, 80% of whom had severe haemolysis leading to blood transfusion. This suggests that it is the decrease rather than the increase in haematocrit that should be used as a marker of severity in patients with SCD. Similarly, platelet counts may be not a good severity marker in dengue infection of SCD patients.

In conclusion, SCD patients with acute dengue infection present an exacerbation of their disease with an increase of VOC and severe haemolysis. Our data suggest that there is an increased risk for hospitalisation as well as specific complications, such as haemolysis in dengue infected SCD patients. These results suggest that clinical signs and laboratory results need to be carefully monitored to identify and manage the risk of severe haemolysis, vaso- occlusive crisis, hepatitis and bacterial co-infections as soon as possible.

References

1. World Health Organization. Dengue and severe dengue. 2015.
2. Surveillance de la dengue. Institut de Veille Sanitaire. 2013 Oct 21. Available from URL: http://www.invs.sante.fr/Publications-et-outils/Points-epidemiologiques/Tous-les-numeros/Antilles-Guyane/2013/Situation-epidemiologique-de-la-dengue-en-Guyane.-Point-au-4-octobre-2013
3. Dengue guidelines for diagnosis, treatment, prevention and control. World Health Organization. 2009.
4. Etienne-Julan M, Elana G, Loko G, Elenga N, Vaz T, Muszlak M. La drépanocytose dans les départements français d'outre-mer (Antilles, Guyane, la Réunion, Mayotte). Données descriptives et organisation de la prise en charge. INVS BEH 2012; 27-28.
5. Andrianarisoa AC, Rakotoson J, Randretsa M, Rakotondravelo S, Rakotoarimanana RD, Rakotomizao J, et al. Madagascar: public health situation on the "Big Island" at the beginning of the 21st century. Med Trop (Mars). 2007; 67(1): 19-29.
6. Limonta D, González D, Capó V, Torres G, Pérez AB, Rosario D, et al. Fatal severe dengue and cell death in sickle cell disease during the 2001-2002 Havana dengue epidemic. Int J Infect Dis 2009; 13(2):77-78.
7. Bravo JR, Guzmán MG, Kouri GP. Why dengue haemorrhagic fever in Cuba? 1. Individual risk factors for dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS). Trans R Soc Trop Med Hyg. 1987; 81(5):816-20.
8. Moesker FM, Muskiet FD, Koeijers JJ, Fraaij PL, Gerstenbluth I, van Gorp EC. et al. Fatal dengue in patients with sickle cell disease or sickle cell anemia in Curaçao: two case reports. PLoS Negl Trop Dis. 2013; 8;7(8):e2203. doi: 10.1371/journal.pntd.0002203.
9. Anwar F, Abdelaal M, Albaiti A, Felimban S. Transfusion medicine illustrated. Sickle cell disease: splenectomy and thrombocytosis. Transfusion. 2008; 48(1): 10-1. doi: 10.1111/j.1537-2995.2007.01500.x.
10. Ahmed SG, Bukar AA, Jolayemi B. Hematological indices of sickle cell anaemia patients with pulmonary tuberculosis in northern Nigeria. Mediterr J Hematol Infect Dis. 2010; 7;2(1):e2010014. doi: 10.4084/MJHID.2010.014.
11. Ahmed SG. The role of infection in the pathogenesis of vaso-occlusive crisis in patients with sickle cell disease. Mediterr J Hematol Infect Dis. 2011; 3(1):e2011028. doi: 10.4084/MJHID.2011.028.
12. Epelboin L, Hanf M, Dussart P, Ouar-Epelboin S, Djossou F, Nacher M, et al. Is dengue and malaria co-infection more severe than single infections? A retrospective matched-pair study in French Guiana. Malar J. 2012; 11:142. doi: 10.1186/1475-2875-11-142.
13. Overturf GD. Infections and immunizations of children with sickle cell disease. Adv Pediatr Infect Dis. 1999; 14:191-218.
14. Falcão RP, Donadi EA. Infection and immunity in sickle cell disease. AMB Rev Assoc Med Bras. 1989; 35(2): 70-4.
15. Dalrymple NA, Mackow ER. Roles for Endothelial Cells in Dengue Virus Infection. Advances in Virology Volume2012; 2012:840654.
16. Odièvre MH, Verger E, Silva-Pinto AC, Elion J. Pathophysiological insights in sickle cell disease. Indian J Med Res. 2011; 134: 532-7.
17. Seneviratne SL, Malavige GN, de Silva HJ. Pathogenesis of liver involvement during dengue viral infections. Trans R Soc Trop Med Hyg. 2006; 100(7): 608-14.
18. Tristão-Sá R, Kubelka CF, Zandonade E, Zagne SM, Rocha Nde S, Zagne LO, et al. Clinical and hepatic evaluation in adult dengue patients: a prospective two-month cohort study. Rev Soc Bras Med Trop. 2012 Dec;45(6): 675-81.