DENGUE INFECTIONS IN HIV PATIENTS

Wong Chia Siong[1], Tan Huey Ching[1], Go Chi Jong[2], Chan Siew Pang[3], Lee Jian Ming Vernon[1] and Leo Yee Sin[2]

[1]Department of Clinical Epidemiology, [1]Department of Infectious Disease, [2]Clinical Research Unit, Tan Tock Seng Hospital, Singapore

Abstract. A retrospective review of hospital admission records was conducted on patients who were admitted to the Communicable Disease Center (CDC) / Tan Tock Seng Hospital, Singapore from 1 January 2004 to 31 December 2005. There were 5 HIV patients who were admitted with dengue infection during the study period. Their symptoms were generally mild and recovery was uneventful. None of the patients developed dengue hemorrhagic fever or dengue shock syndrome. The symptoms and signs of dengue infection in HIV patients are nonspecific. It is important for healthcare workers to maintain a high index of suspicion in order to make the diagnosis. Interactions between pathogenesis pathways or with antiviral treatments may have contributed to the apparently less severe dengue infections in HIV patients. This observation needs to be explored further.

INTRODUCTION

Human Immunodeficiency Virus (HIV) infection is an important condition in the tropics and the interaction between HIV infection and other endemic tropical diseases has been frequently described. For example, malaria (Whitworth *et al,* 2000) and HIV coinfections led to more severe manifestations of malaria. HIV-related immunosuppresion also increased the risk of acquiring leishmaniasis and the development of relapsing and eventually drug-resistant leishmaniasis (Anema and Ritmeijer, 2005).

However, there is little literature on the clinical presentations and outcomes of dengue infection in HIV infected persons. We are aware of only two other published case reports of similar coinfections. One case report documented an uncomplicated course and outcome of dengue infection in an HIV infected person (Watt *et al,* 2003) while another reported a case of dengue hemorrhagic fever in a patient with AIDS (Mendes Wda *et al,* 2006).

Singapore is a tropical country, and both HIV and dengue co-exist as important infectious diseases. There were 4,788 and 9,459 laboratory confirmed cases of dengue reported in Singapore in 2003 and 2004, respectively (MOH, 2005). In 2005, Singapore experienced a large increase in dengue infections with 14,209 laboratory-confirmed cases being reported (MOH, 2006). This represented an increase of 50.2% compared to the year before. In addition, there were cumulatively 2,703 Singapore residents who had been diagnosed with HIV/AIDS between 1985 and 2005 (MOH, 2006).

The objective of this study is to describe the clinical and laboratory features of dengue and HIV coinfection among hospitalized patients in Singapore.

MATERIALS AND METHODS

Tan Tock Seng Hospital is the second largest acute general hospital in Singapore and

Correspondence: Wong Chia Siong, Center for Molecular Epidemiology, Level 8, Matrix, 30 Biopolis Street S138671, Singapore.
Tel: +65 7738950
E-mail: cmewcs@nus.edu.sg

the Communicable Disease Center (CDC) is one of its specialty centers. The CDC is the National Referral Center for most infectious diseases, including HIV and dengue. While HIV testing is not routinely administered to all dengue patients in our hospital during the period of interest, this report is likely to cover most of the symptomatic dengue infections in known HIV patients in Singapore as close to 90% of patients with HIV/AIDS (Acquired Immunodeficiency Syndrome) in Singapore are managed in the Communicable Disease Center (Cutter *et al,* 2004).

This study was a retrospective review of hospital admission records of patients admitted to Tan Tock Seng Hospital from 1 January 2004 to 31 December 2005. The list of eligible patients with dengue and HIV coinfections was obtained through a review of hospitalization diagnoses within. We restricted our definition of dengue infection to dengue cases with laboratory confirmation, either with a positive polymerase chain reaction (PCR) or positive dengue serology, which is defined as a positive IgM or IgG antibody capture enzyme-linked immunosorbent assay (ELISA). For HIV diagnosis, each patient must have had a positive HIV ELISA and Western blot tests prior to their admission to Tan Tock Seng Hospital for dengue infections.

For each of the dengue and HIV coinfection cases, factors pertaining to their HIV status, dengue clinical presentation and severity of dengue infection were examined. These included days of illness, clinical symptoms, clinical signs, laboratory investigations and complications.

Ethical clearance

This study was approved by the research ethics committee of the affiliated institution.

RESULTS

Patients

A total of 5 HIV patients were admitted to our hospital with laboratory-confirmed dengue infections from 1 January 2004 to 31 December 2005. Their ages ranged between 33 and 59 years. There was one female patient, and all the patients were of Chinese race. Three of the patients had positive dengue immunoglobulin while the other two had positive dengue PCR. The patients were diagnosed to have HIV from 7 to 129 months prior to their dengue admission and two had AIDS. All patients were on HAART (Highly Active Antiretroviral Therapy) and had documented CD4 counts of more than 200 within 3 months prior to admission (Table 1).

Symptoms and signs

The commonest symptoms were fever (all 5 patients) and loss of appetite (4 patients). The other symptoms encountered included nausea, bodyache, headache, diarrhea, rash and vomiting. All patients reported fever as their first symptom and for one of the patients, fever was the only symptom. None of the five patients reported cough, sore throat, joint pain or retro-orbital pain; one had gum bleeding on admission. Patients presented to the hospital on Day2 to Day6 of symptoms. Fever and loss of appetite each lasted for 7.5 days on average.

Analyzing signs at presentation, fever was a consistent feature, ranging from 37.5ºC to 40.9ºC. Only one patient had petechial rash; the other 4 patients had a generalized flushing or a maculopapular rash documented. Vital signs were stable on admission for all patients. None of the patients had other signs of dengue infection such as detectable hepatomegaly, splenomegaly, pleural effusion, ascites or conjunctival suffusion.

Laboratory findings

Table 2 outlines the selected laboratory results. Four had leukopenia (white cell count equal or less than 4 $x10^9$/l) during their illness. All 5 patients had thrombocytopenia (platelet count less than 100 x 10^9/l) and the duration of thrombocytopenia ranged from 1 to 6 days

Table 1
Patient information.

Patient	1	2	3	4	5
Age at time of admission	55	33	59	59	40
Gender	Male	Male	Female	Male	Male
Laboratory diagnosis of dengue	Positive dengue PCR	Positive dengue IgM	Positive dengue IgM	Positive dengue PCR	Positive dengue IgM
Months of HIV diagnosis at time of admission	80	7	23	58	129
Most recent CD4 count (within 3 months prior to admission)	482	758	519	303	405
AIDS at time of admission	Yes	No	No	Yes	No
HAART at time of admission	Abacavir, Lopinavir, Ritonavir	Lamivudine, Zidovudine, Lopinavir, Ritonavir	Stavudine, Lamivudine, Efevirenz	Lamivudine, Zidovudine, Efevirenz	Saquinivir, Ritonavir, Nevirapine

Table 2
Laboratory findings.

	Laboratory reading		Number of days from onset of symptoms to reach this level of the respective laboratory test	
Laboratory test	Median	Range	Median	Range
Lowest white blood cell count ($x10^9$/l)	2.1	1.3 to 4.5	6	5 to 7
Lowest platelet count (cells/mm^3)	36,000	21,000 to 78,000	7	6 to 9
Highest hematocrit (%)	45.6	39.9 to 47.0	6	5 to 7

(median = 3 days). None of the patients had an increase in hematocrit of more than 20% above average levels or a drop in the hematocrit of 20% or more following volume-replacement therapy. However, one patient had documented hypoalbuminemia with an albumin level of less than 36 g/l.

Two patients had an elevated ALT and/or AST of more than 3 times the upper limit of the normal range. The highest AST and ALT values for Patient 1 and Patient 5 were 258 U/l and 364 U/l, and 152 U/l and 235 U/l, respectively. These peaks were recorded 5 to 6 days after the onset of symptoms.

Course of illness

All 5 patients had an uncomplicated course of illness and none of the patients fulfilled the case definition (WHO, 1997) for dengue hemorrhagic fever or dengue shock syndrome. The median length of hospital stay was 4 days, and all the patients were managed in the general medical ward with symptomatic therapy. None of the patients required blood or platelet transfusions.

DISCUSSION

There were a total of 5 HIV patients admitted with dengue infection to our hospital between 1 January 2004 and 31 December 2005. To our knowledge, this is the largest case series of dengue infections in HIV patients. As the Communicable Disease Center

follows up most of the HIV patients in Singapore and most HIV patients will turn to or be referred to their primary infectious disease physicians when they develop fever, this case series is likely to be inclusive and representative of such coinfection cases in Singapore.

It is known that HIV infection alters the natural history of other infections, often leading to more severe presentations and worse outcomes. For example, HIV infected individuals have twice as many episodes of symptomatic malarial parasitemia than non-infected persons.(Whitworth *et al,* 2000).Compared to uninfected persons, HIV infected persons are also more likely to have severe malaria and complications resulting from malaria (Cohen, *et al,* 2005). In contrast, the clinical progression among the 5 patients in our series was generally mild and recovery was uneventful. Three of the patients had a positive dengue IgM, which suggests they had primary dengue infection. None of the patients developed dengue hemorrhagic fever or dengue shock syndrome. To our knowledge, there have been no dengue deaths in HIV positive patients in Singapore to date.

Two thousand five hundred million people are now at risk for dengue and there may be 50 million cases of dengue infection worldwide every year (WHO, 2007). In 2006, there were 39.5 million people living with HIV (UNAIDS, 2006). Many of them live in dengue endemic regions. The sheer burden of these two conditions worldwide should make coinfections relatively frequent. If the mild clinical course of our cases is indeed true for these coinfections, this can help explain the unexpected lack of literature on this topic as mild cases are more likely to go undetected or unreported.

While the underlying nature of dengue and HIV infection differ, their pathogenesis pathways do involve common elements. For example, following re-infection with a dengue virus of a different serotype, severe dengue disease is linked to high levels of antibody-enhanced viral replication which is followed by a cascade of memory T-cell activation and release of inflammatory cytokines and other chemical mediators (Pang *et al,* 2007). Activation of CD4+ and CD8+ T cells is greater in patients with dengue hemorrhagic fever than those with milder dengue fever (Rothman, 2003). The hallmark of HIV-1 infection is the gradual weakening of the immune system, especially the destruction of naïve and memory CD4+ T-lymphocytes populations (Simon *et al,* 2006). Such interactions in pathogenesis pathways may result in fewer cases of severe dengue infection. There is a need to further explore this possibility.

The current treatment of dengue infection is largely supportive but recent improved understanding of the dengue virus biology has helped to identify new viral components that may be amenable to specific antiviral treatment. For example, the highly conserved nonstructural protein 5 (NS5) of the dengue virus, which is utilized by viral RNA dependent RNA polymerase (Rawlinson *et al,* 2006), and the protease domain of NS3 (Melino and Paci, 2007) are being studied as possible therapeutic targets. While there is no strong empirical evidence of activity by antivirals against dengue virus, it is interesting to note that all 5 patients were on HAART therapy at the time of dengue infection and interaction between antiviral agents and dengue virus remains to be studied.

One of the two earlier cited case reports showed a decrease in HIV viral load during dengue infection (Watt *et al,* 2003); this finding is of great interest because it has been shown that most acute coinfections are usually associated with increased HIV replication through *in vivo* immune activation (Sulkowski *et al,* 1998). As HIV viral load measurement was not routinely done for dengue admissions at our hospital, we did not have sufficient data

to make comparisons with the earlier case report. A future study with regular serial measurements of viral loads in HIV patients with detectable viral loads may help to clarify these observations.

Among our patients, the symptoms and signs of dengue infection in HIV patients were non-specific. Fever and loss of appetite were the common symptoms. These symptoms do not by themselves distinguish dengue from other viral infections. In addition, in HIV infected persons, there is always clinical concern about the presence of concurrent opportunistic infections. Hence, it is important for the clinicians to maintain a high level of suspicion, especially in countries where both HIV and dengue are prevalent, of the possibility of dengue infection in symptomatic HIV-infected persons.

The key constraint in our study is the small number of cases which does not provide sufficient power for comparison. This is unavoidable as HIV seroprevalence in Singapore remains low. The five cases in this case series were all on HAART and had CD4 counts above 200 at the time of dengue infection. Thus, conclusions drawn from this study should be interpreted with caution due to possible bias, and should be limited to this subgroup of HIV patients. In addition, it is possible that there is a lower clinical threshold to admit HIV patients with fever into our hospital than non-HIV patients such that our case series consists of a greater proportion of uncomplicated dengue infections. By comparing our findings with an earlier case series of hospitalized dengue patients in our hospital (Tai *et al,* 1999), we note that slightly more than half of all patients from that earlier case series had bleeding manifestations but among our cases, only one out of the five had bleeding.

In conclusion, while our study is constrained by the small number of cases, it suggests that dengue infections in HIV-infected persons may run a mild course. We did not see significant severe complications. Interactions between pathogenesis pathways of HIV and dengue infections, and between antiviral treatment and dengue infection remain to be further studied and may help to explain the mild nature of these coinfections. The symptoms and signs of dengue infection in HIV patients are nonspecific and it is advisable for healthcare workers to maintain a high index of suspicion to pursue the diagnosis.

REFERENCES

Anema A, Ritmeijer K. Treating HIV/AIDS and leishmaniasis coinfection in Ethiopia. *CMAJ* 2005; 172: 1434-5.

Cohen C, Karstaedt A, Frean J, *et al*. Increased prevalence of severe malaria in HIV-infected adults in South Africa. *Clin Infect Dis* 2005; 41: 1631-7.

Cutter JL, Lim WY, Ang LW, Tun Y, James L, Chew SK. HIV in Singapore – past, present, and future. *AIDS Educ Prev* 2004;16 (3 suppl A):110-8.

Melino S, Paci M. Progress for dengue virus diseases. Towards the NS2B-NS3pro inhibition for a therapeutic-based approach. *FEBS J* 2007; 274: 2986-3002.

Mendes Wda S, Branco Mdos R, Medeiros MN. Clinical case report: Dengue hemorrhagic fever in a patient with acquired immunodeficiency syndrome. *Am J Trop Med Hyg* 2006; 74: 905-7.

MOH. Communicable diseases surveillance in Singapore 2004. Singapore: Ministry of Health, 2005.

MOH. Communicable diseases surveillance in Singapore 2005. Singapore: Ministry Of Health, 2006.

Pang T, Cardosa MJ, Guzman MG. Of cascades and perfect storms: the immunopathogenesis of dengue haemorrhagic fever-dengue shock syndrome (DHF/DSS). *Immunol Cell Biol* 2007; 85: 43-5.

Rawlinson SM, Pryor MJ, Wright PJ, Jans DA. Dengue virus RNA polymerase NS5: a potential therapeutic target? *Curr Drug Targets* 2006; 7: 1623-38.

Rothman AL. Immunology and immunopathogenesis

of dengue disease. *Adv Virus Res* 2003; 60: 397-419.

Simon V, Ho DD, Abdool Karim Q. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. *Lancet* 2006; 368: 489-504.

Sulkowski MS, Chaisson RE, Karp CL, Moore RD, Margolick JB, Quinn TC. The effect of acute infectious illnesses on plasma human immunodeficiency virus (HIV) type 1 load and the expression of serologic markers of immune activation among HIV-infected adults. *J Infect Dis* 1998; 178: 1642-8.

Tai DY, Chee YC, Chan KW. The natural history of dengue illness based on a study of hospitalised patients in Singapore. *Singapore Med J* 1999; 40: 238-42.

UNAIDS. AIDS epidemic update. Geneva: UNAIDS, 2006.

Watt G, Kantipong P, Jongsakul K. Decrease in human immunodeficiency virus type 1 load during acute dengue fever. *Clin Infect Dis* 2003 36: 1067-9.

Whitworth J, Morgan D, Quigley M, *et al*. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet* 2000; 356: 1051-6.

WHO. Dengue and dengue haemorrhagic fever. Geneva: WHO, 2007.

WHO. Dengue haemorrhagic fever: diagnosis, treatment, prevention and control. 2nd ed. Geneva: WHO, 1997.