



RESEARCH ARTICLE

First reported cases of *Borrelia* and dengue co-infection: A case series

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ABSTRACT

Dengue fever is one of the most common diagnoses in patients presenting with acute febrile illness in tropical countries. *Borrelia*, on the other hand, is the cause of vector-borne infections of relapsing fever and Lyme disease. While co-infections of dengue with chikungunya, Zika, malaria, influenza and typhoid have been reported, clinical cases of *Borrelia* infections have never been reported in Malaysia. Based on available evidence, this is the first case series to report dengue fever and *Borrelia* spp. co-infection. All three patients in this report were admitted to medical wards on day 3 to day 8 of illness for dengue fever as evidenced by a positive dengue NS1 antigen test. The clinical manifestations were typical of dengue fever, with all patients having high grade fever, myalgia, and arthralgia. All patients also had thrombocytopenia. Features of severe dengue, such as shock, hemorrhage and impaired consciousness were absent. *Borrelia* DNA were detected in the blood samples of the patients. However, all the patients denied having skin lesions and a history of insect bites. All the patients were given intravenous fluid therapy and were discharged after 3 to 5 days of hospitalization.

Keywords: *Borrelia*; dengue; co-infection; Malaysia.

INTRODUCTION

Dengue fever is, by far, the most common diagnosis of acute febrile illness in Malaysia, especially in areas of hyperendemicity. The incidence of dengue in Malaysia ranges from 69.9 to 93.4 per 1000 population, with 55% of the total population being infected by dengue in a year (Chew *et al.*, 2016; Woon *et al.*, 2018). In Kota Bharu, Kelantan, 7504 dengue cases were recorded between 2018 and 2022 (Kamaruzaman *et al.*, 2023). *Borrelia* spp. is the causative agent of relapsing fever and Lyme disease and is transmitted through arthropod vectors such as *Ornithodoros* and *Ixodes* ticks and *Pediculus* louse. Co-infections of *Borrelia* spp. have been reported with malaria (Neves *et al.*, 2017), babesiosis, anaplasmosis, and deer tick virus infection, mainly in the Americas and Africa. We report a case series of three patients with dengue fever and *Borrelia* spp. co-infection at our hospital (Hospital Universiti Sains Malaysia, Kelantan). Based on available evidence, these are the first reported cases of dengue and *Borrelia* spp. co-infection.

CASE SERIES

Three cases of dengue fever and *Borrelia* spp. co-infection were diagnosed in our hospital. The patients, who were between 24 and 64 years old, all stayed in dengue endemic areas, and were admitted to the hospital for febrile illnesses associated with arthralgia and myalgia. At the time of presentation, the patients were at day 3 to day 8 of illness. Two of the patients had gastrointestinal symptoms such as vomiting and diarrhea. All of them had thrombocytopenia at presentation, but their total leukocyte counts were normal. One of the patients had deranged liver enzymes and hemoconcentration and was treated as dengue fever with warning signs (persistent vomiting, reduced platelet counts with raised hematocrit). The patient also had acute kidney injury, as evidenced by raised urea and creatinine. All three patients denied having skin lesions or rashes, denied history of tick or insect bites, had no clinical symptoms and signs suggestive of severe dengue infection, such as shock, hemorrhage, and impaired consciousness.

Table 1. Clinical manifestation of patients with dengue and *Borrelia* co-infection

Case	Clinical Presentations	Provisional diagnosis at presentation	Relevant clinical and laboratory findings	Laboratory diagnosis	Treatment	
1	24 years old female Student	Fever, arthralgia, myalgia, cough and vomiting for 4 days No significant travel history and contact history for <i>Borrelia</i>	Dengue fever with warning signs	Thrombocytopenia (platelet count on admission: 61×10^9 /L) Hemoconcentration (HCT (%): 39.8) Acute kidney injury Elevated liver enzyme (AST: 135 U/L, ALT: 89 U/L) No hypotensive episodes/bleeding tendency	Dengue NS1 antigen and IgM positive <i>Borrelia</i> spp. DNA detected	IV fluid therapy
2	64 years old male Unemployed	Fever, myalgia and arthralgia for 3 days Underlying hypertension No significant travel history and contact history for <i>Borrelia</i>	Dengue fever with no warning signs	Thrombocytopenia (platelet count on admission: 68×10^9 /L) Elevated liver enzyme (AST: 106 U/L, ALT : 40 U/L) No hypotensive episodes/bleeding tendency	Dengue NS1 antigen positive <i>Borrelia</i> spp. DNA detected	IV fluid therapy
3	31 years old female Housewife	Fever, arthralgia and myalgia for 5 days Loss of appetite and diarrhea for 2 days No significant travel history and contact history for <i>Borrelia</i>	Dengue fever without warning signs	Thrombocytopenia (platelet count on admission: 77×10^9 /L) No hypotensive episodes/bleeding tendency	Dengue NS1 antigen positive <i>Borrelia</i> spp. DNA detected	IV fluid therapy

The rapid point of care immunochromatographic test (ICT) done using the dengue duo test kit (SD Biosensor, Korea) at the emergency department revealed that all three patients were positive for dengue NS1 antigen. One of the patients, who presented at day 4 of fever, also had a positive dengue IgM antibody, suggesting a recent dengue infection. Blood samples were also sent for a multiplex panel polymerase chain reaction (PCR) for etiological agents of tropical fever, namely *Salmonella* Typhi, *Salmonella* Paratyphi, *Rickettsia* spp. and *Borrelia* spp. The test was conducted using the GenoAmp Real-Time PCR Tropical Fever II kit (MEDIVEN, Malaysia). *Borrelia* DNA were detected in all three patients. All three patients were given intravenous fluid therapy and were discharged after 3 to 5 days of hospitalization. The patients' clinical findings are summarized in Table 1.

DISCUSSION

The diagnosis of acute febrile illnesses in tropical countries is challenging, as the clinical manifestations are non-specific, and there is a wide array of etiological agents to consider for the differential diagnoses, including dengue, leptospirosis, malaria, brucellosis, scrub typhus and typhoid fever. Although dengue is common in Malaysia, the detection of *B. yangtzensis* and *B. miyamotoi* in Sarawak, Malaysia, and *B. miyamotoi* in neighboring Thailand, from tick and rodent samples, provides the evidence that *Borrelia* spp. is circulating in the region (Lau et al., 2020; Takhampunya et al., 2023). Relapsing fever in human has never been reported to date in Malaysia. Lyme disease, on the other hand, was reported in a serological study conducted by Tay et al. who detected

Lyme borreliosis antibodies in 121 patients with febrile illnesses. Around 19.8% and 4.1% were positive for IgM and IgG antibodies, respectively. However, only 6 patients (4.95%) were positive for the confirmatory Western blot test (Tay et al., 2002). Screening for IgG antibody using ELISA performed in the indigenous community showed a seroprevalence of 8.1% (Khor et al., 2019). However, clinical cases of Lyme disease have never been reported in Malaysia. Given the presence of evidence of circulating *Borrelia* in tick vectors in Malaysia, and the serological evidence of exposure and/or infections among the population, it is likely that *Borrelia* infections in Malaysia are under-recognized and underreported, particularly in the rural or semi-rural areas.

The three cases reported in our case series demonstrated clinical manifestations which are typical for dengue: non-specific febrile illness with arthralgia, myalgia, and two cases of gastrointestinal symptoms. The clinical picture may be similar to relapsing fever. However, the recurrent episodes of fever were absent. The patients also denied tick or insect bites prior to presentation. All three patients did not have hemorrhagic diathesis. Nevertheless, if present, this may cause confusion in clinical diagnosis, as such, clinical picture may occur both in dengue fever and relapsing fever. The three patients also denied having rashes or skin lesion, which if present, the typical erythematous expanding erythema migrans may lead to the clinical diagnosis of Lyme disease. The presence of thrombocytopenia may provide a clue for diagnosis of relapsing fever (Keller et al., 2016).

In Malaysia, the widespread availability of the point of care testing of dengue at various health facilities aids the rapid diagnosis of dengue. Similarly, the availability of testing for leptospirosis,

enteric fever and malaria also allows for the diagnosis of the common causes of tropical fever. In contrast, the laboratory testing for *Borrelia* spp. is less widely available. The lack of awareness and recognition for *Borrelia* infections among clinicians may also hinder the diagnosis. Confirmatory testing for Lyme disease and relapsing fever is difficult, as it requires a high index of clinical suspicion, highly specialized testing and expert interpretation of the results (e.g., the two tier testing algorithm and the complex interpretation of immunoblot for Lyme disease) (Mead et al., 2019). In Malaysia, these tests are only available in national reference laboratories. The cases reported were investigated using a multiplex PCR assay for the detection of agents of undifferentiated tropical fever. This was done as part of evaluation study for the PCR assay. The assay has the advantage of being highly sensitive and specific with reduced turnaround time to result, coupled with the ability to detect multipathogen infections. This may suggest a role of multiplex PCR as an effective diagnostic tool in febrile patients with non-specific and atypical clinical presentations.

The clinical significance of co-infection of dengue and *Borrelia* is unknown, as the patients in our case series were all diagnosed with dengue and improved with intravenous fluid therapy alone without the administration of antimicrobials. Given that the overall mortality of tickborne relapsing fever is about 6.5% (Jakab et al., 2022), more studies are warranted to determine the potential fatalities in cases of co-infection.

CONCLUSION

In conclusion, in tropical countries with dengue endemicity and circulating *Borrelia* in vectors such as tick, the co-infection of dengue and *Borrelia* spp. may have similar clinical presentations with other common causes of acute febrile illness and may be underrecognized and unreported. The role of syndromic laboratory testing for undifferentiated febrile illness and the clinical significance of this co-infection may warrant further investigation.

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Competing Interests

None declared. The funder of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Ethical approval

Ethical approval was received from the Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/KK/23010113 and USM/JEPeM/22080520). The authors certify that they have obtained all appropriate patient consent forms.

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