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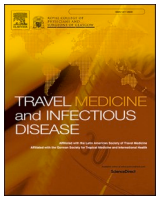

Unusual coinfection of Malaria and Hantavirus in the Colombian Caribbean Region

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Viruses, parasites, and bacteria may cause nonspecific acute tropical febrile illnesses (NEATFI). They describe a life-threatening clinical syndrome characterized by an insidious onset of nonspecific signs, sometimes followed by hemorrhagic manifestations and shock. The similar histopathological findings and clinical manifestations of NEATFIs make diagnosis and clinical management problematic, especially concerning infections of Hantavirus pulmonary syndrome (HPS) and malaria. Dengue, Chikungunya, Zika, Mayaro, Hantavirus, arenavirus, equine encephalitis virus, and leptospirosis, among others, can also coexist in endemic areas. In the prodromal phase, NEATFIs present clinical manifestations such as fever, myalgia, malaise, headache, abdominal discomfort, chills, nausea, and vomiting [1].

Hantavirus Pulmonary Syndrome (HPS) is a severe and often fatal disease in the Americas. In the Colombian Caribbean area, in the department of Córdoba, infections and human cases due to Hantavirus have been reported [2]. On the other hand, Córdoba is an endemic area for Malaria; between 2021 and 2022, there were 8663 and 9486 cases, respectively. The mortality rate is 0.10 cases/1000/inhabitants [3]. Publications on malaria and hantavirus coinfections are scarce and have not been reported in Colombia. The symptoms of Malaria and Hantavirus are common with fever, myalgia, malaise, headache, chills, nausea, and vomiting. The diagnosis is complicated when patients with malaria present respiratory complications that mimic HPS in the cardiopulmonary stage. In this phase, the patient presents dry cough, tachycardia, dyspnea, and hypoxemia, followed by rapid progression to pulmonary disease, edema, hypotension, and circulatory collapse [4]. In Florida, seven cases of autochthone Malaria in the USA in 2023 have been notified. In Texas, one case, the cases in both states were unrelated, and the patients had no history of travel to tropical endemic areas of Malaria [5]. With climate change, the tropics seem to rise to the Northern Hemisphere, and the southern states of the US have become atypical subtropical areas. That is why it is essential to surveil mosquitoes to establish with certainty the activity of parasites and viruses. Public health measures include epidemiological surveillance of suspected acute febrile syndromes in humans [6]. This study aims to describe the first cases of hantavirus and malaria coinfection in Colombia.

During 2021 and 2022, a prospective descriptive study of patients with NEATFI was done at the San Jeronimo third-level public hospital (HSJ) in Monteria, the capital of Córdoba. The hospital cares for the entire population (1.556.000 inhabitants) of the Department of Córdoba and other neighboring departments. Informed consent was obtained from all registered patients with an anonymous code. The study was approved by the research committee of the Institute of Tropical Biological Research of the University of Cordoba, following resolution 8430 of the Ministry of Health of Colombia and the Declaration of Helsinki [7]. The study included 75 patients with persistent fever (>48 hours), headache, myalgia, gastrointestinal manifestations (abdominal pain, vomiting, and diarrhea), and a marked decrease in platelet count and manifestations of respiratory compromise. Córdoba is endemic for Dengue, Zika, Chikungunya, malaria and leptospira. The patients underwent serological tests to detect Dengue (NS1, IgG, IgM), Zika, Chikungunya, leptospira, and COVID-19. The malaria diagnosis was made using a thick smear technique of blood samples. To detect the infection of Hantavirus, an ELISA Hantavirus Pool 2 America to detect Andes (ANDV) and Sin Nombre Virus (SNV)-IgG- (Euroimune, Ge) was carried out. Hantavirus genome detection by total RNA extraction using Gene Jet RNA Purification Kit (Thermo Scientific™) was done from whole blood after an RT-qPCR.

Four of 75 patients had malaria and hantavirus coinfection. Two were diagnosed with Plasmodium vivax, two with Plasmodium falciparum, and coinfected with Hantavirus (Table 1). Of the four malaria patients, all had IgG antibodies against Hantavirus, and two cases had IgM antibodies. All four patients were PCR-negative for Hantavirus (Table 1). Patients admitted due to acute febrile syndrome, who presented nonspecific systemic manifestations, did not present respiratory

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Table 1
Demographic description, clinical and laboratory findings of four patients with coinfection with malaria and hantavirus.

Age (years)/ gender	Initial clinical presentation	Radiological findings	Malaria thick smear	ELISA Hantavirus Ratio[b] RU[c]	Treatment
44/M	Fever, headache, myalgias, arthralgia, retroocular pain, Hemoglobin (g/l): 13,6 Hematocrit (%): 43,2 White Cells: 3850/mm Platelet count: 81000/mm	CT scan: Normal	*Plasmodium falciparum*	IgM+ (Ratio: 1,34)[b] IgG+ (RU:287) [c]	Acetaminophen, Artemetere/lumefantrine
21/M	Fever, headache, myalgias, arthralgia, retroocular pain, gingivorrhagia Hemoglobin (g/l): 11.8 Hematocrit (%): 35.3% White Cells: 6550/mm Platelet count: 12000/mm	CT scan: Normal	*Plasmodium vivax*	IgM+ (Ratio: 3,34) IgG+ (RU: 108)	Acetaminophen, Chloraquine and Primaquine
26/F	Fever, headache, myalgias, vomiting and diarrhea, gingivorrhagia Hemoglobin (g/l): 12.8 Hematocrit (%): 36.7% White Cells: 1700/mm Platelet count: 69000/mm	CT scan: Normal	*Plasmodium falciparum*	IgG+ (RU:138)[a]	Artemether and lumefantrine Primaquine metoclopramide
20/F	Fever, headache, myalgias, vomiting and diarrhea. Hemoglobin (g/l): 8,2 Hematocrit (%): 25% White Cells: 6270/mm Platelet count: 37000/mm	CT scan: Normal	*Plasmodium vivax*	IgG+ (RU:106)[a]	Acetaminophen, Chloroquine + Primaquine

[a] High hantavirus IgG titers.
[b] Ratio: 0–0,8: Negative, ≥0,8 – <1,1: Borderline, ≥1,1: Positive.
[c] RU: 0–18: Negative, 19–20: Borderline, ≥21: Positive.

or renal complications, with similar laboratory abnormalities. The patients had a clinical improvement at the beginning of the malaria treatment and survived without additional complications. Hantavirus infection confirms the hypothesis that infection by Hantavirus genotypes circulating in this area of the Caribbean might not produce severe clinical manifestations, in contrast to Hantavirus infections in Argentina, Chile, and Brazil [2,4]. In Brazil, in four people engaged in mining, two seropositive for Hantavirus had concomitant *P. falciparum* infection. Two patients died from HPS; molecular analysis detected the presence of the Castelo dos Sonhos virus genome exclusive to Brazil [4]. In the present study, due to the clinical improvement with the antimalarial treatment, it is presumed that the underlying pathology was malaria, and the hantavirus infection could have been in the recent past in two of the four patients. Undifferentiated tropical febrile illness becomes complicated due to the coinfections affecting the patients [1,4]. The unique Dengue panorama has changed; doctors now face complex challenges, such as treating a patient with malaria parasitemia, an arbovirus, and concomitant Leptospirosis or Rickettsiosis [1].

In conclusion, under the concept of One health, it is essential to study the findings of the present work. The coinfection results of the present work receive special attention due to the appearance of recent autochthonous malaria in the United States [5]. The transmission, diagnostic, and treatment guidelines for fever of unknown origin become more complex due to coinfections, including malaria, regardless of international travel history to endemic areas. Our results can help the medical community in countries with tropical diseases and are helpful for public health policies.

Author contributions

All authors participated equally in the manuscript's design, analysis, and edition.

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Declaration of competing interest

On behalf of the authors, I declare that this paper's disclosure will not generate or constitute any conflict of interest. I also declare that this material has not been and will not be submitted for publication elsewhere as long as it stays under consideration by Travel Medicine and Infectious Diseases. Furthermore, we affirm that this is an original study, and the manuscript has not been published elsewhere.

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