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Undifferentiated tropical febrile illness in Cordoba, Colombia: Not everything is dengue

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SUMMARY

In Colombia, undifferentiated tropical febrile illness (UTFI) are frequent and of considerable concern. They also share many clinical features. Between 2012 and 2013 in an endemic tropical area of Cordoba, Colombia, we conducted a prospective study to establish an etiological diagnosis of UTFI. Using diagnostic tests for dengue, leptospirosis, hantavirus, malaria, rickettsia, brucellosis, hepatitis A and B on 100 patients recruited for the study. We identified 69 patients with presumed UTFI: leptospirosis ($n=27$), dengue ($n=26$), hantavirus infection ($n=4$), malaria ($n=4$), rickettsial infection ($n=2$), hepatitis A ($n=1$), and brucellosis ($n=1$); no hepatitis B cases were detected. Co-infections with malaria and leptospirosis ($n=1$), hepatitis A and dengue ($n=1$), hantavirus and dengue ($n=1$), hantavirus, dengue, and leptospirosis ($n=1$) were also identified. No etiologic agent was identified for 31 patients. We conclude that other etiologic agents besides dengue virus deserve greater attention by physicians and public health authorities in tropical area of Colombia.

Introduction

During the past 20 years, there has been a dramatic emergence and re-emergence of UTFI caused by viruses, bacteria and parasites previously believed to be under control. These include dengue, Chikungunya, yellow fever, Venezuelan equine encephalitis, Saint Louis encephalitis, mayarovirus, arenavirus and hantavirus diseases, and other diseases caused by bacteria and parasites that have extended their geographic distribution, such as *Leptospira*, *Rickettsia* and *Plasmodium* [1]. The epidemiology and even the definition syndrome of many of these diseases is changing in the tropics and globally. Population growth, urbanization, unplanned human activities, displacement of people by internal violence, and even climate variability contribute, sometimes synergistically to the changing epidemiology of UTFI in the Colombian tropics.

Some UTFI, are caused by arthropod-borne agents transmitted by mosquitoes or ticks. For others, person-to-person transmission may occur through direct contact with infected blood or secretions. Animal reservoirs are often wild rodents; however, pets, domestic livestock, urban mice, monkeys, and other primates may also serve as intermediate hosts [1].

The definition of viral hemorrhagic fevers describes a potentially fatal clinical syndrome characterized by an insidious onset of nonspecific signs followed by bleeding manifestations and shock. The hemorrhagic fever syndrome is also characterized by capillary leak and bleeding diathesis. The clinical manifestations and even histopathological findings are similar among the diseases and differential diagnosis may be difficult [1]. Because, the undifferentiated febrile illnesses can be caused by bacteria, virus and parasites and they show very similar clinical features, the definition of viral hemorrhagic fevers can be extended to them.

In Colombia endemic UTFIs are frequent and of considerable concern. Because dengue is endemic in tropical Colombia, the disease is often over-diagnosed, while other UTFIs such as leptospirosis, hantavirus and arenavirus infections, rickettsioses, Venezuelan equine encephalitis, chikungunya virus infection, Zika virus infection and malaria are misdiagnosed as dengue. Those diseases are clinically indistinguishable from dengue and other vector-borne diseases and confirmatory diagnosis requires specific laboratory tests that are often unavailable or too expensive in developing countries [2]. Consequently, many of the endemic diseases mentioned above remain mostly undiagnosed in Colombia. Recent surveillance suggests that Venezuelan equine encephalitis may represent up to 10% of the 'dengue' burden in neotropical cities,

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or tens of thousands of cases per year throughout Latin America [2]. In addition, co-infections are common in the tropics [3]. Tropical fevers diseases are defined as diseases that are prevalent in, or unique to tropical and subtropical regions. The diseases are less prevalent in temperate climates, due in part to the occurrence of a cold season, which controls the insect population by forcing hibernation. Most often disease is transmitted by an insect "bite", which causes transmission of the infectious agent [4].

Because, clinical manifestations and even histopathological findings are comparable and challenging to make a differential diagnosis, we conducted a study to establish the diagnosis of UTFI patients at a hospital in the Caribbean area of Colombia.

Materials and methods

Patients and data collection

Between 2012 and 2013, we conducted active surveillance at the main hospital in an endemic tropical area of Cordoba (Colombia), to establish the etiologic diagnoses of UTFI cases. The undifferentiated febrile illnesses are defined as a fever without a focus of infection on initial physical examination or in basic laboratory tests [5]. In Colombia as a tropical country, tropical fevers are defined as infections that are prevalent in, or are unique to tropical and subtropical regions. Some of these occur throughout the year and some especially in rainy and post-rainy season [4]. During our study, there was no "fenomeno del niño" nor floods, distribution of rainy was normal during the year of the study. The studied area is not endemic for yellow fever and West Nile virus disease.

Patients with acute phase were admitted to the emergency ward with febrile illnesses accompanied by prodromal symptoms typical of UTFI infection, including myalgia, arthralgia, headache, asthenia, chills, icterus, dyspnea, abdominal pain, rash, and nausea. Patients were enrolled in a clinical trial for UTFI at the University of Cordoba. Serum samples were collected on admission and at discharge. Clinical data collected for each patient during their hospital stay included name, age, sex, history of illness (date of onset of disease and date of admission), symptoms, physical findings, and laboratory findings, including blood cell counts, prothrombin time, platelet counts, liver function (bilirubin, ASAT, ALAT), and renal function (creatinine). Clinical tests such as chest X-ray, electrocardiogram, and pulse oximetry were done depending on patient clinical condition. We included 100 consecutive clinically suspected UTFI cases according to the Centers for Disease Control and Prevention (CDC) case definition of viral hemorrhagic fevers [6]. For leptospira, rickettsia and malaria we followed the protocols of National Health Institute of Colombia [7,8].

Exclusion criteria

We excluded patients with upper urinary tract infections, bronchitis, tonsillitis, otitis media, tuberculosis, liver abscesses, diarrhea as initial and primary symptom, chronic liver disease, hemorrhagic syndrome of non-infectious etiology, acute poisoning, tumors, hematological diseases, autoimmune diseases, snake-bites, diseases of the biliary tract, patients under a year old, and those with possible confusion with physiological jaundice.

Sampling and diagnostic tests

From each patient we collected one acute phase and one convalescent phase (15–30 days after illness) peripheral venous blood sample. Seroconversion was defined as negative serology with becomes positive in a convalescent serum sample, hence the increase of detectable antibodies (usually four times titers increase) between the first sample and second one was used as a definition in the present study. Diagnostic tests performed included: Duo quick test dengue NS1 Ag; ELISA IgM/IgG Ad-BIO®; Leptospirosis MAT using 19 serovars and ELISA IgM Panbio® diagnostics (Queensland, Australia); hantavirus IgG and IGM DxSelect™ (Focus Technologies, California, USA); Malaria thick smear; Rickettsia spotted fever group IgG IFI antigens from *Rickettsia rickettsii* (a strain Taiaçu) donated by M. Labruna of University of Sao Paulo (Brazil); Brucellosis Rose Bengal antigen (Pourquier Institute, Montpellier, France); hepatitis A rapid test for IgG/IgM Bio LINE Standard Diagnostics and surface antigen hepatitis B and hepatitis B anticore IgM LINE Standard Diagnostics (Republic of Korea).

Statistical analysis

The Chi-squared test to compare proportions was used, analyses were performed with EPI-INFO (Version 7.2, CDC, USA) software for Windows, with a probability (p) value <0.05 as statistically significant.

Ethical aspects

The research committee of the Institute of Tropical Biological Research of the University of Cordoba and hospital San Jeronimo of Monteria approved the ethics protocol, and informed consent was obtained from all patients. Patients were anonymized using a numeric code. The study incorporated procedures, management and conservation of samples, and technical-administrative procedures for health research required by resolution 8430 of the Ministry of Health of Colombia, in 1993 [9] and declaration of Helsinki for ethical and medical research in human subjects [10].

Results

Etiologic agents of undifferentiated tropical fevers

IgG or IgM seroconversion allowed the demonstration of UTFI infection in 69 of the 100 patients in the study. The pathologies diagnosed were: leptospirosis ($n=27$), dengue ($n=26$), hantavirus infection ($n=4$), malaria ($n=4$), rickettsiosis ($n=2$), hepatitis A ($n=1$) and brucellosis ($n=1$). No hepatitis B cases were detected (Table 1). Co-infections of malaria and leptospira ($n=1$), hepatitis A and dengue ($n=1$), hantavirus and dengue ($n=1$), hantavirus, dengue, and leptospirosis ($n=1$) were identified. In 31 (31%) of the patients no etiology agent was identified (Table 1).

The patient's age range was 1–79 years, mean = 27 years; 40 pediatric patients (range 1–17 years, mean = 10.6 years) and 60 adults patients (>18 years, mean = 39.2 years) were included. The 30% (15/40) of pediatric patients were affected by dengue and 20% (10/40) by leptospira; 20% (17/60) of adult patients were affected by leptospira and 10% (11/60) by dengue, the majority of the population involved in the trial was male (62/100) (Table 1).

Eighteen patients died and the analysis of mortality was guided by serology, post-mortem pathological anatomy and clinical analysis. Six patients died from dengue virus infection and three died from leptospirosis (one of which had both malaria and leptospirosis), one died from hantavirus infection and one died from malaria. The remaining six patients had negative serologic results and no specific post-mortem findings (Table 1).

Clinical characteristics of patients diagnosed with UTFI

The most relevant clinical findings were: cephalea (69%), myalgia (64%), abdominal pain (61%), arthralgia (58%) vomiting (53%), nausea (52%), and chills (36%). All of these symptoms were common to leptospirosis, dengue, hantavirus infection,