

Differential diagnosis between dengue and COVID-19

Diagnóstico diferencial entre dengue y COVID-19

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ABSTRACT

Introduction: at the end of 2019, the existence of SARS-CoV-2, which causes COVID-19, was reported for the first time. In this context of global public health alarm, it is essential to remember that countries in the tropical and subtropical world may be affected by other pathogens with an impact on health, such as dengue viruses. Objective: to synthesize the key elements to make a correct differential diagnosis between dengue and COVID-19. Method: a review of articles published in the databases PubMed, MEDLINE, SciELO, Scopus, Lilacs and BVS, in the period 2012-2021, was carried out. The following descriptors were used: "COVID-19", "dengue" and "differential diagnosis". Twenty-eight articles were included in the review. Development: from a clinical point of view, dengue and COVID-19 share some characteristics that make their differential diagnosis difficult. Both diseases present a great similarity in relation to physiopathological events, as well as signs and symptoms. In the initial phases of their clinical picture it is difficult to differentiate them. Conclusions: it is essential to make a rapid and accurate differential diagnosis between these two entities. In epidemiological terms, the delay in the detection of cases leads to a late implementation of preventive measures, which can generate a workload for health services.

Keywords: COVID-19; Dengue; Differential Diagnosis; Signs and Symptoms.

RESUMEN

Introducción: a fines de 2019, se informó por primera vez sobre la existencia del SARS-CoV-2, causante de la COVID-19. En este contexto de alarma para la salud pública mundial, es indispensable recordar que países del mundo tropical y subtropical pueden verse afectados por otros agentes patógenos de impacto para la salud, como los virus del dengue. Objetivo: sintetizar los elementos claves para realizar un correcto diagnóstico deferencial entre el dengue y la COVID-19. Método: se realizó una revisión de artículos publicados en las bases de datos PubMed, MEDLINE, SciELO, Scopus, Lilacs y Biblioteca Virtual de Salud (BVS) en el periodo 2012-2021. Se emplearon los descriptores: "COVID-19", "dengue" y "diagnóstico diferencial". Se incluyeron en la revisión 28 artículos. Desarrollo: desde el punto de vista clínico, el dengue y la COVID-19 comparten algunas características que dificultan su diagnóstico diferencial. Ambas enfermedades presentan una gran similitud con relación a los eventos fisiopatológicos, así como signos y síntomas. En las fases iniciales del cuadro que producen es difícil su diferenciación. Conclusiones: es imprescindible realizar un diagnóstico diferencial, rápido y certero, entre estas dos entidades. En términos epidemiológicos, el retraso en la detección de casos lleva a una tardía implementación de las medidas preventivas, lo cual puede generar una carga de trabajo para los servicios de salud.

Palabras clave: COVID-19; Dengue; Diagnóstico Diferencial; Signos y Síntomas.

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INTRODUCTION

fln late 2019, the existence of the new coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), causing the so-called coronavirus disease of 2019 (COVID-19), was first reported from a group of patients with pneumonia of unknown cause who were epidemiologically linked to a wholesale seafood market in Wuhan City, People's Republic of China^{1,2}. Currently, COVID-19 has been declared a pandemic by the World Health Organization (WHO) as of March 11, 2020, and has become a threat as an emerging and re-emerging disease worldwide³.

In this context of alarm for global public health, it is essential to remember that countries in the tropical and subtropical world may be affected by other pathogens of health impact, such as the arboviruses that cause Zika (ZIKV), chikungunya (CHIKV) and dengue (DENV), known for their ability to cause outbreaks and spread to new areas, as well as to cause diseases that, in some cases, can be fatal⁴.

Simultaneous circulation of SARS-CoV-2 and dengue viruses has been observed in Cuba. Both present a great pathophysiological and clinical similarity⁵.

From the clinical point of view, dengue and COVID-19 share some characteristics that make their differential diagnosis difficult. Both diseases present great similarity in terms of pathophysiological events, as well as signs and symptoms, including the maculopapular rash, characteristic of dengue, already reported in cases of patients with COVID-19⁶. The problem is increased by the possibility of co-infection already reported in several studies^{7,8,9}.

However, in the case of coinfection, some researchers argue that it does not necessarily lead to clinical worsening, compared to when each infection is suffered separately. This may be explained by the opposing coagulant and anticoagulant actions of SARS-CoV-2 and dengue viruses, or by other potential causes such as viral interference. In addition, some computational studies have shown that human antibodies against dengue are able to bind to receptors for the SARS-CoV-2 spike protein and reduce the severity of the disease. These and other hypotheses attempt to explain how the interaction between the two viruses may modulate disease progression¹⁰.

The present review aims to synthesize the key elements for a correct differential diagnosis between dengue and COVID-19.

METHOD

A review was made of articles published in the databases PubMed, MEDLINE, SciELO, Scopus, Lilacs and Virtual Health Library (VHL), on the clinical and complementary elements for the diagnosis of dengue and COVID-19. The descriptors: "COVID-19", "dengue" and "differential diagnosis", in English and Spanish, were used and combined using the Boolean operators AND and OR.

The search for information focused on articles published in the period from 2012 to December 2021. Systemic reviews, meta-analyses, clinical trials, clinical practice guidelines and literature reviews were included. Any article that had not been published in a peer-reviewed journal, did not show the full text or had an insufficiently explained methodology was excluded. Twenty-eight articles were finally selected.

DEVELOPMENT

Dengue and COVID-19 are two diseases that currently have a strong incidence in our region. It is a real diagnostic challenge to differentiate between the two, given their many similarities, mainly in the initial stages of the disease that each one produces.

Dengue, a disease caused by any of the four dengue viruses, is transmitted to humans mainly through the bites of Aedes species mosquitoes (especially Ae. aegypti or Ae. albopictus species). After primary infection by one dengue serotype, there is temporary cross immunity against the other serotypes, but in the long term immunity is only protective against the infecting serotype¹¹.

Although the etymology of the term "dengue" is not entirely clear, it is thought that it may come from dinga or dyenga, which in Swahili - an East African language - means "sudden attack resembling a cramp or shudder caused by an evil spirit", describing the patient's suffering with severe bone pain¹¹.

The incubation period varies from 3 to 10 days; it is usually between 5 and 7 days¹².

The clinical picture of dengue fever and the presentation of the various manifestations and complications varies from patient to patient. Typically, individuals infected with dengue virus are asymptomatic (80%). After an incubation period, a viral picture appears, characterized by fever of over 38 °C, headaches, retroocular pain, severe joint and muscle pain - hence the name "breakbone fever" - and swollen lymph nodes¹³.

In dengue, dermatological manifestations occur in about 40% of cases and consist of erythematous or

erythematopapular lesions, which subsequently leave a lot of itching. A petechial rash may sometimes appear, with or without associated thrombocytopenia¹⁰.

Although dengue is not a respiratory virus, it can cause cough and pharyngitis. Studies report that 25% of patients with confirmed dengue have cough and 20% have upper respiratory tract symptoms¹⁰.

Warning signs may appear and rapid clinical deterioration may occur within 48 h after defervescence (3 to 7 days after the onset of fever). Warning signs of severe disease include abdominal pain or tenderness, persistent vomiting, hydrops, hemorrhage, defervescence, lipothymia, hepatomegaly, lethargy, restlessness, and rising hematocrit¹⁴.

Severe dengue fever presents with any of these symptoms and signs: plasma extravasation causing shock, severe bleeding with thrombocytopenia, and organ failure¹⁵.

Laboratory findings classically associated with dengue are hemoconcentration, leukopenia, thrombocytopenia and hypoalbuminemia. During an acute primary infection, dengue virus is detectable in serum during the first 5-6 days after the onset of symptoms by culture (available in specialized laboratories), the commonly used real-time polymerase chain reaction (RT-PCR) or detection of NS1 antigen by ELISA (Enzyme-Linked ImmunoSorbent Assay). Due to the short viraemia period, many diagnoses are made by serology. IgM antibodies are often detectable within 3-5 days of onset; they are positive by the end of the first week in almost all cases. After 2-3 months they are usually undetectable in most cases. IgG antibodies are detected at the end of the first week and are positive for years. Detection of virus in serum in the presence of IgG is diagnostic of secondary infection¹⁶.

Dengue is not treated with a specific drug or an effective vaccine. Its management is symptomatic and supportive, consisting of oral fluid replacement at the onset of the disease and intravenous fluids when the warning signs of shock appear, usually when the fever subsides¹⁷.

COVID-19 is a respiratory disease caused by SARS-CoV-2. It is transmitted mainly from person to person by respiratory droplets that are spread when an infected person coughs, sneezes or speaks¹⁷.

There are five variants¹⁸:

• The alpha variant (also known as Kent variant or B.1.1.7), which was first discovered in southeast England in September 2020.

- The beta variant (also known as the South African variant or B.1.351).
- The gamma variant (also known as the Brazilian variant or P.2).
- The delta variant (also known as Indian variant or P.1).

• The omicron variant, detected at the end of November 2021, which appears to be milder in vaccines. Caution remains necessary for vulnerable and at-risk groups, for whom this variant remains dangerous¹⁸.

The incubation period for COVID-19 is believed to extend to 14 days, with a median of 4 to 5 days from exposure to onset of symptoms. Symptoms associated with the disease include fever, cough, fatigue, shortness of breath, anorexia, myalgia, headache, anosmia or ageusia, nausea or vomiting, diarrhea¹⁹.

In coronavirus infection, the first week is the week of infectious signs, the second week is the week of aggravation and the third week is the week of recovery. Although COVID-19 is primarily an acute respiratory illness, it can present with fever and muscle and joint pain without respiratory manifestations, as well as anorexia and headache²⁰.

The omicron variant tends to affect mainly the upper respiratory tract and also causes sore throat, runny nose and night sweats, without many alterations in taste or smell²⁰.

About 20% of patients with COVID-19 develop cutaneous manifestations; recognition and classification of these is necessary during the physical evaluation. Therefore, an algorithm has recently been formulated to facilitate the classification of COVID-19 skin lesions that can be applied during the care of patients with COVID-19 and associated skin manifestations. It proposes the division of lesions into three main groups: lesions that do not disappear with pressure, which include rash with petechiae, acral ischemic lesions and livedo reticularis; lesions that disappear with pressure, such as urticarial rash and rash erythematosus; and vesicle or crusting/erosion pattern²¹.

Patients with COVID-19 are at high risk for arterial and venous thrombotic occlusions. Pulmonary histopathology often reveals fibrin-based occlusions in the small blood vessels of patients who succumb to the disease²². A study conducted in the Netherlands and published in Thrombosis Research²³ noted that 31 % of 184 patients suffered thrombotic complications, a figure the investigators described as remarkably high, although extreme consequences such as amputation are rare.

Among patients who became critically ill, the median time to dyspnea ranged from 5 to 8 days, the median time to acute respiratory distress syndrome ranged from 8 to 12 days, and the median time to intensive care unit admission ranged from 10 to 12 days. Signs and symptoms of severe illness may include dyspnea, hypoxia, respiratory failure, shock and systemic multiorgan failure^{24, 25}.

Risk factors for severe disease from COVID-19 include: being 65 years of age or older and conditions such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, previous stroke, liver disease, obesity, chronic respiratory disease, chronic kidney disease for which dialysis treatment is being received, or immunosuppression^{26,27}.

For laboratory confirmation, molecular diagnosis by PCR is the diagnosis of certainty, since viral culture is cumbersome and time-consuming. Serological diagnosis has also been extended for coronavirus, for the identification of IgG-positive cases by the so-called "rapid techniques", but more for epidemiological purposes, or to confirm patients in their third week of illness²⁶.

For the new coronavirus, several antiviral drugs have been tested, some of which were promising at one time. Plasma from convalescents, monoclonal antibodies, antimalarial drugs and various treatments have been used. Combinations of some form of interferon with antiviral drugs have also been used²⁵.

The summary shown in Table 1 may be very useful in establishing a differential diagnosis between these two entities.

Table 1. Similar and differential aspects between dengue fever and COVID-19		
Indicator	Dengue	COVID-19
Etiology	It is produced by four RNA virus serotypes of the flavivirus genus that are transmitted by <i>Ae. aegypti</i> and <i>Ae. albopictus</i> mosquitoes. A fifth serotype has been described but has not been associated with disease or epidemics.	It is caused by the SARS-CoV-2 virus, a coronavirus, an RNA virus that is easily transmitted from person to person by saliva droplets. Fecal-oral transmission occurs in patients with diarrhea. The virus has been identified in semen and tears.
Clinical manifestations	High fever, rash, headache, retro-orbital pain, nausea, vomiting, rash, myalgia, arthralgia, petechiae. Cardiac, renal, neurological and hepatic manifestations may occur. In general, it defines its course in one week. Most patients improve and recover, but in others plasma extravasation occurs, with fluid accumulation in serous cavities and with the possibility of hypovolemic shock, pulmonary edema, massive hemorrhages with or without disseminated intravascular coagulation, multiorgan failure and death.	It almost always begins with fever, particularly in the pediatric age group, associated with dry cough and dyspnea, sore throat, diarrhea, anosmia, dysgeusia and around the sixth day pulmonary lesions are present, of progressive severity, and multiorgan failure occurs. Various cutaneous manifestations: maculopapular and vesicular rashes, inflammation of the artifacts, livedo reticularis. The first week is that of infectious signs, the second week is that of aggravation and the third week is that of recovery.
Warning signs	They announce the likelihood of the patient's aggravation due to plasma extravasation: intense and sustained abdo- minal pain in the epigastrium, persistent vomiting, ascites, pleural or pericardial effusion, mucosal bleeding, altered state of consciousness, hepatomegaly, progressive increa- se in hematocrit, among others.	These warning signs are not well defined, although the fo- llowing are noted: being on the sixth day of illness, increa- sed fever, onset of vomiting
Clinical laboratory	Leukopenia and neutropenia are common.	Lymphopenia is more common.
Source: Díaz Trujillo E y Batista Cuenca M ²⁸ .		

CONCLUSIONS

It will not always be an easy task to make the diagnosis between dengue and COVID-19, but it is possible if the epidemiological criteria, the sequence of appearance of symptoms and signs, and the main laboratory results are taken into consideration.

A rapid and accurate differential diagnosis between these two entities is essential. In epidemiological terms, the delay in case detection leads to late implementation of preventive measures, which can generate a workload for health services.

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CONFLICT OF INTERESTS

Authors declare there was no conflict of interests.

AUTHORSHIP

Damián Valladares Reyes: conceptualization, data curation, formal analysis, visualization, writing-original draft, writing-revision and editing. Antonio Belaunde Clausell: conceptualization, data curation, formal analysis, validation, visualization, writing-revision and editing. Alicia Morales Díaz: conceptualization, data curation, formal analysis, validation, visualization, writing-revision and editing.

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