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DENV and SARS-CoV-2 and their coexistence in an endemic area in Mexico, 2020-2021

DENV y SARS-CoV-2 y su coexistencia en un área endémica en México, 2020-2021

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Abstract:

The circulation of SARS-CoV-2 in endemic regions of dengue fever and its confluence with the dengue virus DENV has been a reason for study. The objective of this study was to determine the epidemiological characteristics of the simultaneous circulation of both viruses in an endemic region and estimate the prevalence of SARS-CoV-2 in patients with dengue fever. A retrospective search on epidemiological databases was performed for both diseases The records in both databases were classified as Co-infection, non-simultaneous infection, and initial dengue diagnosis. The estimated prevalence of SARS-CoV-2 infection in individuals with dengue fever was 2%. No significant differences were observed concerning the frequency of symptoms in patients with co-infection versus those with SARS-CoV-2 infection. SARS-CoV-2 was more frequent in non-simultaneous infections as a first infection followed by dengue fever acquired during the COVID-19 lockdown. Co-infections with both viruses occur in populations from dengue fever - endemic regions and given the similarity of the symptoms during the first days of infection, it is imperative to study the clinical and epidemiological characteristics in order to provide a timely diagnosis.

Keywords:

Dengue fever, COVID-19, co-infection, coexistence, endemic region.

Resumen:

La circulación del virus SARS-CoV-2 en regiones endémicas a fiebre por dengue y su confluencia con el virus del dengue DENV ha sido motivo de estudio. El objetivo del trabajo fue determinar las características epidemiológicas de la circulación simultánea de ambos virus en una región endémica y estimar la prevalencia de SARS-CoV-2 en pacientes con fiebre por dengue. Se llevó a cabo una búsqueda retrospectiva en bases de datos epidemiológicas de ambos padecimientos. Los registros localizados en ambas bases de datos fueron clasificados en: Coinfección, Infección no simultanea y Fiebre por dengue diagnóstico inicial. La prevalencia estimada de infección por SARS-CoV-2 en personas que padecieron fiebre por dengue fue del 2%. No se observó diferencias significativas en la frecuencia de síntomas para pacientes con coinfección vs. infección por SARS-CoV-2. En infecciones no simultaneas se presentó SARS-CoV-2 en mayor frecuencia como primera infección seguida de fiebre por dengue, esta última probablemente adquirida durante el resguardo por COVID-19. En regiones endémicas a fiebre por dengue, el número de coinfecciones por ambos virus ocurre en la población y ante la similitud de los síntomas durante los primeros días de infección, es imperante el estudio de las características clínicas y epidemiológicas a fin proporcionar un diagnóstico oportuno.

Palabras Clave:

Fiebre por *dengue, COVID-19, coinfección, coexistencia, región endémica*

INTRODUCTION

Dengue virus (DENV) is transmitted through bites of infected Aedes species mosquitoes, *Aedes aegypti*, and to a lesser degree,

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Ae. albopictus.[1] It is estimated that each year, there are 390 million dengue fever worldwide; of these, 96 million present mild clinical manifestations.[2] In Mexico, according to the Directorate of Epidemiological Surveillance of Communicable Diseases of the Ministry of Health, as of November 7, 2023, a total of 42,203 confirmed cases are reported, of which 583 belong to the state of Hidalgo.[3] Dengue fever, according to the severity of the symptoms, is classified into three categories, which go from a) Non-Severe Dengue, b) Dengue with warning signs, and c) Severe Dengue. Non-Severe Dengue is operationally defined as a disease with the following symptoms or characteristics: Individual of any age who resides or comes from a region where there is transmission of the disease in the 14 days before the onset of signs and symptoms and who presents fever and two or more symptoms such as nausea and/or vomiting, rash, myalgia and/or arthralgia, headache and/or retroocular pain, petechiae or leukopenia. While dengue with Warning Signs, in addition to complying with the characteristics of Non-Severe Dengue, presents one or more of the following warning signs such as intense and continuous abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy or irritability, hypotension postural, hepatomegaly, progressive increase in hematocrit and decrease in platelets and hemoglobin. Finally, Severe Dengue is classified as any probable case of dengue that presents one or more of the following findings, such as shock due to severe extravasation of plasma evidenced by tachycardia, cold extremities and capillary refill equal to or greater than three seconds, weak or undetectable pulse, convergent differential pressure, ≤ 20 mm arterial hypotension in the late phase, fluid accumulation leading to respiratory failure, severe hemorrhage, and severe compromise of organs such as liver, heart, kidneys, among others. [4]

The disease is characterized by a pattern of infrequent epidemics with presence in inter-epidemic periods (endemism) in mainly urban tropical regions.[5]

On the other hand, Coronavirus disease (COVID 19) is caused by SARS-CoV-2 virus, which is transmitted mainly by respiratory droplets or nasal secretions that cause an infected person to cough or sneeze.[6] In this context and derived from its high contagion rate, a total of 7,633,355 confirmed cases have been reported nationwide, while a total of 130,505 confirmed cases have been reported for the state of Hidalgo.[7]

Both viruses, DENV and SARS-CoV-2, can cause similar symptoms in the initial stage of the disease.[8] COVID-19 symptoms, including fever, cough, myalgia, fatigue, and dyspnea, can vary widely.[9,10] Dengue fever is characterized by an initial phase with a body temperature of ≥38.5°C, accompanied by headache, vomiting, myalgia, joint pain, a transitory macular rash, and mild bleeding manifested by petechiae and bruises, and an enlarged liver. After a few days, most patients will recover without complications.[11] Given the similarity of their symptoms, especially in the first hours, errors in the diagnosis of both conditions were reported.[12] The progressive appearance of symptoms in patients with COVID-19 occurred more slowly compared to subjects affected by non-severe dengue. While fever dengue symptoms appear on an average of 4.2 days from the onset of the first symptoms and the first symptoms of SARS-CoV-2 infection appear on an average of 7.5 days, the presentation of symptoms is more abrupt in the non-severe dengue fever.[13] In Mexico, the General Directorate of Epidemiology established that laboratory confirmation of cases must be carried out through the RT-PCR methodology for arboviruses including DENV and COVID-19.[4, 14]

The simultaneous presence of both epidemics has been identified as a syndemic that can collapse health systems, particularly given the complicated epidemiological panorama that prevails. [15] The circulation of SARS-CoV-2 in dengue fever endemic regions has represented an additional burden on health systems,[16] particularly given the increase in mortality rates, admission to intensive care units, and prolonged hospital stays.[17] Coinfection of SARS-CoV-2 and dengue virus has been associated with an increase in mortality and morbidity, particularly in patients with comorbidities such as diabetes and cardiovascular diseases.[18]

Currently, both viruses coexist in dengue fever endemic regions, and co-infection with DENV virus and SARS-CoV-2 has been documented, as in Brazil,[19, 20] Thailand,[21] Colombia,[22] Ecuador,[23] Peru,[24] Mexico,[25] Argentina,[26] Maldives,[27] Indonesia,[28] and Reunion Island in the Indian Ocean.[29]

Because of the simultaneous circulation of DENV and SARS-CoV-2, we carried out a retrospective study to collect information on the simultaneous circulation of both viruses in a dengue fever-endemic region in Mexico.

MATERIALS AND METHODS

The records contained in the Arbovirosis case study and Epidemiological Study of Suspected Case of Viral Respiratory Disease databases of the Hidalgo Health Services (SSH) was evaluated, with prior institutional authorization. The inclusion criteria of the research included the municipalities of Huejutla, Jaltocan, San Felipe Orizatlán, Atlapexco, Huautla, Yahualica, Xochiatipan y Huehuetla considered endemic to dengue fever in the state of Hidalgo by SSH. The research was carried out in the period from March 2020 to March 2021. Matching records by name in both databases were corroborated using CURP (Unique Population Registry Code), age and address. The resulting records were contacted by telephone for the application of the questionnaire. The questionnaire included the following sections: 1) Identification data; 2) history of vaccination against COVID-19; 3) presence of comorbidities; 4) signs and symptoms for COVID-19 and dengue fever in the last year; 5) date of onset of symptoms; 6) COVID-19 confirmation method

and date; 7) performing chest x-ray; 8) time it took to receive medical attention and 9) evolution of the disease.

The project adhered to the precepts of the Declaration of Helsinki and has approvals from the ethics and research committees of Servicios de Salud de Hidalgo with identification number FSSA2021100. In addition, verbal consent was obtained from the participants surveyed via telephone.

RESULTS

During the study period, 1,263 cases of SARS-CoV-2 infection were recorded from eight municipalities considered endemic for dengue fever in the state of Hidalgo. All cases were confirmed by laboratory test using the polymerase chain reaction (PCR) assay. Of the total cases, 43% were women, and 57% were men. Treatment for SARS-CoV-2 infection was ambulatory in 69%, and 31% required hospitalization. Patient evolution was favorable in 83%, but 17% died. Regarding the number of infections caused by the dengue virus in the same period, a total of 581 cases were confirmed by PCR. Of the patients infected with the dengue fever, 59.2% were women, and 40.8% were men; 95% of cases were classified as non-severe dengue, 4.5% as dengue fever with warning signs, and 0.5% as severe dengue fever. In 92.8% of cases, patient management was ambulatory, and 7.2% were hospitalized.

As a result of the intentional search in both databases, 37 records were located by name. Thirty-three percent of the 37 records were located and accepted to answer the questionnaire; however, it was impossible to contact 67% of this population by phone. A total of 12 records had SARS-CoV-2 and DENV infection during the study. The clinical and epidemiological characteristics of the people who suffered dengue fever and COVID-19 in endemic regions were classified into three groups: 1) co-infection, 2) non-simultaneous infection by both viruses, and 3) initial dengue fever diagnosis (Table 1). The coinfection group included the simultaneous presence of both infections confirmed through PCR; the non-simultaneous infection group included the presence of both non-simultaneous infections confirmed by PCR, and in the group with initial dengue fever diagnosis, the records with initial diagnosis of Non-Severe Dengue fever and confirmation of COVID-19 by PCR were present.

TABLE 1. Dengue fever and COVID-19 diagnoses March 2020 - March 2021

No	Sex	Age	Occupation	Group
1	Female	43	Health professional	Initial dengue diagnosis
2	Female	39	Health professional	Initial dengue diagnosis‡
3	Female	32	Employee	Initial dengue diagnosis‡
4	Male	39	Health professional	Non-simultaneous infection
5	Male	28	Employee	Non-simultaneous infection
6	Female*	30	Other	Initial dengue diagnosis
7	Female	45	Other	Initial dengue diagnosis‡
8	Male	44	Health professional	Non-simultaneous infection
9	Male	37	Health professional	Initial dengue diagnosis‡
10	Female	24	Health professional	Initial dengue diagnosis‡
11	Male	34	Health professional	Initial dengue diagnosis‡
12	Male	36	Other	Initial dengue diagnosis‡
13	Female	41	Homemaker/ House wife	Non-simultaneous infection
14	Male	24	Student	Co-infection
15	Female	41	Health professional	Initial dengue diagnosis
16	Male	70	Other	Initial dengue diagnosis
17	Male	38	Health professional	Initial dengue diagnosis
18	Female	49	Health professional	Initial dengue diagnosis
19	Male	52	Health professional	Initial dengue diagnosis
20	Female	37	Health professional	Non-simultaneous infection
21	Male	32	Employee	Initial dengue diagnosis‡
22	Male	47	Other	Initial dengue diagnosis
23	Male	35	Other	Initial dengue diagnosis‡
24	Female*	22	Homemaker	Initial dengue diagnosis‡
25	Female	42	Health professional	Initial dengue diagnosis‡
26	Female†	63	Homemaker	Initial dengue diagnosis‡
27	Male	36	Health professional	Non-simultaneous infection
28	Male	75	Homemaker	Initial dengue diagnosis
29	Female	24	Other	Non-simultaneous infection

No	Sex	Age	Occupation	Group
30	Female	7	Student	Initial dengue diagnosis‡
31	Female*	24	Homemaker	Non-simultaneous infection
32	Male	59	Other	Initial dengue diagnosis‡
33	Male	39	Employee	Co-infection
34	Male	30	Homemaker	Co-infection
35	Male	22	Student	Non-simultaneous infection
36	Female	31	Health professional	Initial dengue diagnosis‡
37	Female	23	Student	Initial dengue diagnosis‡

* Pregnancy; †Decease; ‡ a confirmation of COVID-19 in a period of 15 days after the diagnosis of dengue fever. Databases: Case Study of Arbovirosis and Epidemiological Study of a Suspected Case of Viral Respiratory Disease of the Health Services of Hidalgo Own elaboration

In the first group, three cases of co-infection by both viruses were registered. The three male patients were diagnosed with severe dengue fever with address in the municipality of Huejutla de Reyes. All recorded patients had fever greater than 38°C, severe headache, and retro-orbital pain. Symptoms such as petechiae and exanthema occurred in 33% of the co-infection cases. None of the patients had comorbidities at the time of infection. Infection management for SARS-CoV-2 was ambulatory in two patients, and only one required hospitalization with a stay of 12 days. The three cases had a favorable evolution. The co-infection cases occurred during July (1), August (1), and October (1) 2020. One of the notable cases was a 30-year-old male patient who, during the first week of October, had both infections and 119 days later was reinfected by SARS-CoV-2 with a favorable evolution.

A total of nine cases of non-simultaneous infection with both viruses were found in the second group; in this group, 55% of patients were men and 45% women. In 80% of cases, SARS-CoV-2 occurred as a first infection with a median of 26 days between each infection. The most frequent symptoms during SARS-CoV-2 infection were odynophagia (78%), rhinorrhea (78%), fever greater than 38°C (67%), intense headache (67%), and myalgia (56%). Ambulatory management was reported in 90% of the records during infection with SARS-CoV-2. There was a five-day difference in the appearance of dengue as a second infection.

The third group consisted of 24 cases with the initial diagnosis of dengue fever followed by confirmation of infection with SARS-CoV-2; of these, 16 cases were confirmed positive in a period of 15 days. The median time between the start of symptoms and the time it took to receive medical attention oriented toward SARS-CoV-2 infection was two days. Of the total cases, 67% were women, and 33% were men. Of the cases in this group, 50% reported not having been in previous contact with a COVID-19 patient, 35% knew they had been in contact, and 15% were unaware of any contact with a COVID-19 patient. In 36% of the records, patients had an occupation related to health. Homemakers, students, and employees had the same percentage (13%) for the three categories, and 20% worked in an occupation different from the previous ones. A favorable evolution occurred in 93% of patients, and 7% died. The most frequent symptoms were myalgia (100%), fever higher than 38°C (93%), severe headache (86%), arthralgia (87%) and chills (73%); retro-orbital pain (60%), rash (6.7%) and petechiae (8.3%) were less frequent.

No significant differences were found in the 18 symptoms in patients with SARS-CoV-2 infection and patients with simultaneous DENV and SARS-CoV-2 infection (Table 2). Finally, the prevalence of SARS-CoV-2 infection in people who suffered from dengue fever from March 2020 to March 2021 was 2.0%.

Table 2. Comparison of symptoms

Symptom	Co-infection (n=3)		Non-simultaneous infection (n=9)		*P*
	Yes %(n)	No %(n)	Yes %(n)	No %(n)	
Age (mean)	31±7		32±8		
Fever > 38ºc	100(3)	0	67(6)	33(3)	0.511
Cough	67(2)	33(1)	56(5)	44(4)	0.696
Headache	100(3)	0	67(6)	33(3)	0.393
Dyspnoea	33(1)	67(2)	11(1)	89(8)	0.35
Odynophagia	33(1)	67(2)	78(7)	22(2)	0.136
Irritability	0	100(3)	22(2)	78(7)	0.393
Diarrhea	33(1)	67(2)	11(1)	89(8)	0.607
Chest pain	0	100(3)	22(2)	78(7)	0.511
Chills	67(2)	33(1)	22(2)	78(7)	0.214
Myalgia	100(3)	0	56(5)	44(4)	0.214
Arthralgia	67(2)	33(1)	44(4)	56(5)	0.6
Rhinorrhea	0	100(3)	78(7)	22(2)	0.063
Conjunctivitis	33(1)	67(2)	22(2)	78(7)	0.607
Anosmia	0	100(3)	22(2)	78(7)	0.295
Dysgeusia	0	100(3)	22(2)	78(7)	0.511
Retro-orbital pain	100(3)	0	44(4)	56(5)	0.122
Erythema	33(1)	67(2)	22(2)	78(7)	0.58

Symptom	Co-infection (n=3)		Non-simultaneous infection (n=9)		*P*
	Yes %(n)	No %(n)	Yes %(n)	No %(n)	
Petechiae	67(2)	33(1)	11(1)	89(8)	0.423

Co-infection*:* DENV + SARS-CoV-2; Non-simultaneous infection: SARS-CoV-2. Database: Epidemiological Study of a Suspected Case of Viral Respiratory Disease of the SSH. Own elaboration

DISCUSSION

Virus co-infections that cause dengue fever with diverse pathogens can have complex and unpredictable consequences on severity, as documented with the influenza virus.[30] This work reports the presence of three cases of co-infection, all confirmed by PCR. The co-infection cases had a favorable evolution, and the main symptoms registered were fever higher than 38°C, intense headache, and retro-orbital pain. The symptoms coincide with what was previously reported in systematic reviews carried out on coinfections.[18] The presence of a maculopapular rash or erythema is a common symptom of dengue fever that has also been reported in patients with COVID-19[31] and co-infection. In the case of dengue fever and COVID-19 co-infection, the appearance of an erythematous rash has been reported days after the start of symptoms, such as fever, intense headache, and retro-ocular pain.[20] In this work/the present work, the presence of an erythematous rash was recorded in three patients with co-infection. The presence of symptoms is hardly a differential criterion when faced with diagnosing dengue fever and COVID-19 or co-infection with both conditions. Although reports of clinical and laboratory manifestations of co-infections caused by COVID-19 and dengue fever are scarce, studying the dynamics of both infections in the presence of comorbidities, conditions that could favor fatal outcomes, is essential.[19,22]

Co-infection with both viruses occurs in dengue-endemic areas; therefore, timely detection and confirmation of both infections through PCR are meaningful. This finding means that the number of co-infections by SARS-CoV-2 and DENV could be more frequent than reported, particularly in regions where circulation of the DENV is recurrent, coupled with the difficulty in the differential diagnosis of COVID-19 infection.[32]

Ninety percent of the cases of SARS-CoV-2 infection that underwent outpatient treatment had a median of 39 days between SARS-CoV-2 infection and subsequent acquisition of dengue fever. This fact confirms that dengue fever was acquired during home care as a containment measure against SARS-CoV-2 infection. Physical distancing and shelter-at-home orders with mild symptoms of SARS-CoV-2 infection until recovery were among the protection measures established by the World Health Organization and adopted by the Mexican government to prevent the spread of the virus. This phenomenon was first documented in Thailand, where an increase in the number of dengue fever cases was observed due to social distancing measures implemented in that country. The authors attributed the increase to period of time people spent in their homes during COVID-19 recovery.[33] This scenario coincides with the fact that the most productive *Ae. aegypti* egg nests are located in the home and surrounding areas.[34,35] Therefore, it is essential to maintain active entomological surveillance and control with the measures proposed to reduce the increase in dengue fever cases during recovery in the face of SARS-CoV-2 infection in dengue-endemic regions. At the community level, these measures are the promotion of personal protection to reduce mosquito bite exposure and the elimination of breeding sites of immature forms of the vector, mainly in homes.[12] Information should also be provided to the community in the endemic region regarding symptoms and signs of both infections and possible co-infection with both diseases.

From the beginning of the COVID-19 pandemic, early diagnosis of dengue fever has been a matter of concern, especially in endemic areas, because both diseases share similar clinical and laboratory characteristics at early stages. A maculopapular rash is a characteristic symptom of dengue fever that has also been reported in patients with SARS-CoV-2 infection.[31] Therefore, its presence is not conclusive for a diagnosis of non-severe dengue.

Chest X-rays can reveal pneumonia or an infectious process.[9] This outcome does not happen with COVID-19. Due to the low sensitivity of chest X-rays (69%) compared to RT-PCR (91%)[36], chest radiography is not indicated as a diagnostic method in patients with suspected COVID-19 and mild clinical features unless they are at risk of disease progression.[37,38]

Aminotransferase values, the blood cell count, particularly platelets, and the neutrophil/lymphocyte ratio (NLR) have been proposed as convenient criteria for the differential diagnosis of COVID-19 and dengue fever[27] during the first week of the onset of symptoms; the NLR index is significantly higher in patients with COVID-19 than patients with dengue fever.[39] In this review, two cases had complete blood counts and one aminotransferase levels; therefore, they were not considered for the analysis. In addition to the presence of symptoms, the history of contact and the patient´s profession could guide the doctor toward an accurate diagnosis, considering that 39% of the records had a health-related profession among these nurses who worked in health centers and hospitals where COVID-19 patients were treated and with reference to contacts who had suffered COVID-19.

Some of the limitations of this work are that the records were retrieved from two disease databases with different epidemiological notifications, and only two records had

laboratory test parameters, so it was not feasible to analyze the clinical parameters. Also, success in locating cases by telephone was low. Despite the limitations of this work, we highlight the finding of co-infections in the population from endemic regions in the state, which had not been previously registered. Because of this finding, the number of co-infections in dengue-endemic regions in Mexico could be higher than reported.

CONCLUSIONS

The circulation of SARS-CoV-2 in regions endemic to dengue fever has constituted a challenge for medical care by health systems. Given the similarity of symptoms, errors in diagnosis occurred, particularly during the first days of both infections. In the present work, the presence of coinfection by SARS-CoV-2 and DENV in the state of Hidalgo was reported, and it is estimated that the occurrence is higher than reported, particularly in the period before vaccination for SARS-CoV-2. Although the coinfections had a favorable evolution, it is important to know the dynamics of two viruses that circulate for the first time in time and space, with the aim of implementing approaches in medical care and epidemiological surveillance of both conditions.

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