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Short Communication

Serological cross-reactivity using a SARS-CoV-2 ELISA test in acute Zika virus infection, Colombia

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ABSTRACT

Objectives: We investigated seroreactivity by using a commercial SARS-CoV-2 ELISA test in samples collected from different groups of individuals, including patients diagnosed to have Dengue, Zika, and Chikungunya infection between 2015 and 2019, from an endemic area in the Caribbean Colombian region.
Methods: A total of 127 sera samples obtained from six different groups of individuals were included in this study: Group A: patients with confirmed SARS-CoV-2 infection; Group B: patients with symptoms suggestive of COVID-19 or asymptomatic contacts with confirmed patients; Group C: patients with acute or recent dengue virus infection; Group D: patients with acute Zika virus infection; Group E: patients with previous Chikungunya virus infection; and Group F: individuals with exposure to spotted fever group rickettsiae.
Results: Overall, group A, group B, and group D showed seroreactivity to SARS-CoV-2 in 92%, 75%, and 26% of samples, respectively; furthermore, group C, group E, and group F showed 100% seronegativity.
Conclusions: We found 26% of serological cross-reactivity in patients with acute Zika virus infection by using a commercial SARS-CoV-2 ELISA test. Further studies are needed to evaluate whether serological cross-reaction is maintained with time in nonacute patients with previous exposure to the Zika virus and its effect in SARS-CoV-2 serosurveys in endemic areas for this arbovirus.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the etiological agent of coronavirus disease-2019 (COVID-19), an emerging zoonotic viral disease responsible for an ongoing pandemic (Chams et al., 2020). The infection has spread globally, with 31,167,374 confirmed cases and 962,046 related deaths as on September 21, 2020 (https://coronavirus.jhu.edu/map.html). Clinically, according to a recent systematic review with meta-analysis, in patients with COVID-19, fever was the most prevalent clinical manifestations (88.7%, 95% CI 84.5–92.9%), followed by respiratory symptoms such as cough and dyspnea, which could be present in less than 60% of the patients (Rodriguez-Morales et al., 2020). Thus, in tropical areas, it is recommended to include COVID-19 in the differential diagnosis of the acute undifferentiated febrile syndrome (AUFS), along with arboviral diseases. This is because failure to differentiate common causes of AUFS from COVID-19 could lead to delay in appropriate management and potentially overestimate SARS-CoV-2 epidemiological burden (Nunthavichitra et al., 2020).

During the 2013–2016 period, Dengue, Chikungunya, and Zika have affected more than 1 million people in Colombia, and presently, Colombia is considered as an endemic country for these arboviruses (Mora-Salamanca et al., 2020). Colombia is also part of the SARS-CoV-2 ongoing pandemic, with a total of 765,076 confirmed COVID-19 cases as on September 21, 2020

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(https://coronavirus.jhu.edu/map.html). Thus, overlapping clinical pictures and co-epidemics of SARS-CoV-2 with other tropical etiologies such as arboviral diseases is a matter for concern in many tropical countries, including Colombia (Nunthavichitra et al., 2020).

We investigated seroreactivity by using a commercial SARS-CoV-2 ELISA test in samples collected from groups from different individuals, including patients diagnosed to have Dengue, Zika, and Chikungunya virus infection, between 2015 and 2019, from the Córdoba Department, an endemic area for these arboviruses in the Caribbean Colombian region (Arrieta et al., 2019).

Materials and methods

A total of 127 anonymized sera samples obtained from six different groups of individuals were included in this study (Table 1). The groups were as follows: Group A: patients with confirmed SARS-CoV-2 infection diagnosed as positive by RT-qPCR on a nasopharyngeal swab during June-July, 2020 (n = 63); Group B: patients with symptoms suggestive of COVID-19 (n = 6) or asymptomatic contacts with confirmed patients (n = 2), diagnosed during July 2020; Group C: patients with acute or recent dengue virus infection, diagnosed by positive RT-qPCR or NS1 antigen on a blood sample (n = 8), or ELISA IgM (n = 15), during April-December, 2019; Group D: patients with acute Zika virus infection, diagnosed by positive RT-qPCR on blood samples during November 2015–February, 2016 (n = 19); Group E: patients with previous Chikungunya virus infection, diagnosed by positive ELISA IgG during November 2015–April 2016 (n = 9); Group F: individuals with exposure to spotted fever group rickettsiae, diagnosed by positive IgG immunofluorescence assay during February 2013 (n = 5). These sera were collected from native individuals from the Córdoba Department, with no travel history, and tested at the Instituto de Investigaciones Biológicas del Trópico using INgezim® COVID 19 DR test (Ingenasa, Eurofins Madrid, Spain), a dual recognition ELISA detecting semi-quantitatively total SARS-CoV-2 virus N-protein-specific antibodies (IgG, IgM, and IgA).

Results and discussion

Overall, among the six groups, group A, group B, and group D showed seroreactivity to SARS-CoV-2 N-protein in 92%, 75%, and 26% of samples, respectively, using INgezim® COVID 19 DR test (Table 1). Group C, group E, and group F showed 100% seronegativity using the same ELISA test (Table 1). Assuming group B patients (n = 8) and group A patients (n = 63) as true positives, we found a sensitivity of 90.1% for the INgezim® COVID 19 DR test, which agrees with the reported percentage by the assay manufacturers (85–100% according to the period of sample collection). It is worth mentioning that 46% of A and B group samples were collected in the first two weeks since symptom onset or obtaining a positive result in RT-qPCR for nasopharyngeal swab, which may explain the sensitivity found in our study. This fact reinforces the recommendation for performing SARS-CoV-2 serologic tests at least two weeks after symptom onset to obtain accurate results (Hanson et al., 2020).

Recently, two research groups from Israel and Italy used a semiquantitative ELISA (anti-SARS-CoV-2 ELISA IgG, Euroimmun, Germany) and COVID-19 IgG/IgM Rapid Test Cassette (Orient Gene, Zhejiang, China) and showed 22% and 2% of serological cross-reactivity, respectively, in dengue-infected travelers before SARS-CoV-2 emergence (Lustig et al., 2020; Spinicci et al., 2020). By using a SARS-CoV-2 dual recognition ELISA test, we did not find cross-reactivity either in patients with acute or recent dengue infection or in patients with previous Chikungunya infection or recent exposure to spotted fever group rickettsiae. Interestingly, through bioinformatics analyses, the Israeli research group identified structure similarities between chains of the SARS-CoV-2 spike protein and chains of the envelope protein of both dengue and Zika, predicting potential cross-reactivity, in addition to dengue, with the Zika virus (Lustig et al., 2020). Thus, according to this prediction, we found 26% of serological cross-reactivity in patients with acute Zika virus infection. Curiously, although we used a SARS-CoV-2 ELISA test, such as the Israeli group (Lustig et al.,

Table 1
Seroreactivity using SARS-CoV-2 dual recognition ELISA test (INgezim® COVID 19 DR) in different groups of native individuals from Córdoba department, Colombia.

Group (No. of serum samples)	Diagnosis period	Sex (n)	Age, y (median)	No. of positive samples by INgezim® COVID 19 DR test[a] (%)	No. of negative samples by INgezim® COVID 19 DR test[a] (%)
Group A[b] Confirmed SARS-CoV-2 infection (63)	June–July, 2020	F (22) M (41)	31–64 (35)	58 (92)	5 (8)
Group B[c] COVID-19 clinically diagnosed (6) Asymptomatic contacts (2)	July, 2020	F (6) M (3)	21–57 (36)	6 (75)	2 (25)
Group C[d] Acute dengue infection (8) Recent dengue infection (15)	April–December, 2019	F (9) M (14)	2–67 (13)	0 (0)	23 (100)
Group D[e] Acute Zika infection (19)	November, 2015–February, 2016	F (15) M (4)	14–78 (31)	5 (26)	14 (74)
Group E[f] Previous Chikungunya infection (9)	November, 2015–April, 2016	F (4) M (5)	16–22 (17)	0 (0)	9 (100)
Group F[g] Recent exposure to spotted fever group rickettsiae (5)	February, 2013	F (4) M (1)	24–49 (39)	0 (0)	5 (100)

[a] According to assay manufacturers: sensitivity of 100% from day 17 after symptoms onset (85% between days 7 and 16), and specificity of 99.2% (no cross-reactivity with respiratory coronaviruses 229E, NL63, OC43 and HKU1, and other respiratory viruses such as Influenza or RSV) (https://www.eurofins-technologies.com/ingezim-covid-19-dr.html).
[b] Serum samples were collected before two weeks in 32 patients and after two weeks in 31 patients, since the date of positive result for SARS-CoV-2 in RT-qPCR for the collected swab sample.
[c] Serum samples of symptomatic patients were collected at the first two weeks of symptoms in 1 patient, and after two weeks symptoms in 5 patients.
[d] Serum samples were collected on the same day of dengue tests (RT-qPCR, NS1 antigen, ELISA IgM) positive samples.
[e] Serum samples were collected on the same day of Zika RT-qPCR-positive samples.
[f] Serum samples were collected on the same day of Chikungunya ELISA IgG-positive samples.
[g] Serum samples were collected on the same day of spotted fever group rickettsiae-IFA IgG-positive samples.

2020), we did not find cross-reactivity in patients with dengue infection. The used antigen could explain the above results of these ELISA tests. Hence, while the Euroimmun test uses S1 domain of the SARS-CoV-2 spike protein as antigen (Lustig et al., 2020), the Ingenasa test uses the nucleocapsid protein (our study). Nonetheless, this hypothesis must be confirmed.

Finally, we tested the INgezim® COVID 19 DR test in three of our research group members who had a history of confirmed Zika infection during the 2015 epidemic and were found to be seronegative (data not shown). Thus, further studies should evaluate whether serological cross-reaction is maintained with time in nonacute patients with previous exposure to the Zika virus and its effect in SARS-CoV-2 serosurveys in endemic areas for this arbovirus, such as Colombia and other countries of Latin America (Rodriguez-Morales, 2015).

Conflicts of interest

The authors declare no conflict of interest applicable to this research.

Ethical Approval

The research committee of the Instituto de Investigaciones Biológicas del Trópico of the University of Cordoba approved the ethics protocol. Patients were registered using an anonymous 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 and Declaration of Helsinki for ethical and medical research in human subjects. The study was considered as minimal risk.

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