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Short Communication **Open Access**

COVID-19 and Dengue co-infection in paediatric patients: An endemic in a pandemic

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Abstract:

Background: The clinical presentation and outcome of COVID-19 are likely to be complicated by co-infection with other endemic viruses such as Dengue. This study aimed to investigate the occurrence of co-infections of SARS-CoV-2 and Dengue viruses in paediatric patients from Osmania General Hospital, Hyderabad, Telangana, during the COVID-19 pandemic.
Methodology: This was a cross-sectional study of 420 paediatric patients (aged 5-17 years) with febrile illness, consecutively recruited from the hospital from June to November 2021. Serum samples were collected and tested for SARS-CoV-2 antibodies, and COVID-19 positive samples were further analysed for Dengue IgM antibodies by enzyme linked immunosorbent assay (ELISA).
Results: Of the 420 patients, serum samples of 109 (26.0%) were reactive for SARS-CoV-2 antibodies. Of these, 13 were reactive for Dengue IgM antibodies, giving a co-infection rate of 3.1% (1.9% females and 1.2% males). The three most common symptoms in the co-infected patients were joint ache (myalgia) in 53.8% (75.0% in females, 20.0% in males, p=0.1026), fever in 46.2% (50.0% in females, 40.0% in males, p=1.000), and rash in 46.2% (62.5% in females, 20.0% in males, p=0.2657).
Conclusion: These findings suggest that paediatric patients with COVID-19 may be susceptible to Dengue. Understanding the presence of multiple viral infections in paediatric patients is crucial for accurate diagnosis, management, and prognosis. Further research is needed to explore the potential synergistic mechanisms of these co-infections.

Keywords: SARS-CoV-2, COVID-19, Dengue, co-infection, paediatrics, antibodies, ELISA.

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Co-infection COVID-19 et dengue chez les patients pédiatriques: une endémie dans une pandémie

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Résumé:

Contexte: La présentation clinique et l'issue de la COVID-19 sont susceptibles d'être compliquées par une co-infection avec d'autres virus endémiques tels que la dengue. Cette étude visait à étudier la survenue de co-infections par les virus du SRAS-CoV-2 et de la Dengue chez des patients pédiatriques de l'Hôpital Général d'Osmania, Hyderabad, Telangana, pendant la pandémie de COVID-19.
Méthodologie: Il s'agissait d'une étude transversale de 420 patients pédiatriques (âgés de 5 à 17 ans) atteints de maladie fébrile, recrutés consécutivement à l'hôpital de Juin à Novembre 2021. Des échantillons de sérum ont été prélevés et testés pour les anticorps anti-SARS-CoV-2, et Les échantillons positifs au COVID-19 ont été analysés plus en détail pour les anticorps IgM de la dengue par dosage immuno-enzymatique (ELISA).
Résultats: Sur les 420 patients, des échantillons de sérum de 109 (26,0%) étaient réactifs pour les anticorps SARS-CoV-2. Parmi ceux-ci, 13 étaient réactifs aux anticorps IgM de la dengue, soit un taux de co-infection de 3,1% (1,9% de femmes et 1,2% d'hommes). Les trois symptômes les plus fréquents chez les patients co-infectés étaient les douleurs articulaires (myalgies) chez 53,8% (75,0% chez les femmes, 20,0% chez les hommes,

p=0,1026), la fièvre chez 46,2% (50,0% chez les femmes, 40,0% chez les hommes, *p*=1,000) et éruption cutanée chez 46,2% (62,5% chez les femmes, 20,0% chez les hommes, *p*=0,2657).
Conclusion: Ces résultats suggèrent que les patients pédiatriques atteints de COVID-19 peuvent être sensibles à la dengue. Comprendre la présence d'infections virales multiples chez les patients pédiatriques est crucial pour un diagnostic, une prise en charge et un pronostic précis. Des recherches supplémentaires sont nécessaires pour explorer les mécanismes synergiques potentiels de ces co-infections.

Mots clés: SARS-CoV-2, COVID-19, Dengue, co-infection, pédiatrie, anticorps, ELISA

Introduction:

The COVID-19 pandemic highlighted the significance of understanding the clinical implications and dynamics of co-infections, particularly in the paediatric age group. Paediatric patients with SARS-CoV-2 infections often present with acute sickness and hyperinflammatory syndrome that can lead to severe outcomes such as multiorgan failure and shock (1). Simultaneously, Dengue virus infections continue to pose a major public health challenge, with millions of annual cases reported worldwide (2).

The coexistence of Dengue epidemics in tropical regions with the SARS-CoV-2 pandemic raises concerns due to the shared clinical features and potential for missed cases, which can have fatal consequences (3). The range of clinical symptoms associated with SARS-CoV-2 infections varies from mild respiratory symptoms resembling a common cold to life-threatening conditions such as bronchiolitis, pneumonia, acute respiratory distress syndrome (ARDS), inflammatory syndrome, and multi-organ failure. In this context, it becomes crucial to understand the dynamics of co-infection between Dengue and COVID-19 to accurately assess the clinical impact and enable early interventions (4,5).

However, differentiating Dengue and COVID-19 in endemic regions during the pandemic poses' challenges, particularly in the early stages of infection when symptoms may overlap (6,7). The simultaneous peak in Dengue and SARS-CoV-2 infections observed in the year 2020 further strained healthcare systems, with the implementation of lockdowns and social segregation policies exacerbating the spread of Dengue (1,8). Therefore, there is a pressing need to identify clinical and laboratory factors that can predict co-infection in paediatric COVID-19 patients.

Early identification of co-infections is essential to guide appropriate antibiotic selection and provide timely supportive care. This study aims to address this gap by analysing the range of co-infections in paediatric COVID-19 patients and identifying factors that can aid in the prediction of co-infection, ultimately facilitating early interventions and improved patient management.

Materials and method:

Study design and ethical approval:

A cross sectional study was conducted at the Osmania General Hospital, Hyderabad, Telangana, from June to November 2021. The study protocol was approved by the ethical committee (IEC/OMC/M.N.49(Acad)/60), and informed consent was obtained from the parents of all participating paediatric patients.

Study participants and data/sample collection:

Patients aged 5-17 years presenting with symptoms of COVID-19 were consecutively recruited and included in the study. A structured questionnaire was used to collect demographic details and record clinical symptoms. Blood samples were collected from each participant, serum was separated and stored at -20 ºC until further processing.

Serological testing:

The serum samples were tested for presence of SARS-CoV-2 antibodies using the Wantai SARS-CoV-2 Ab ELISA kit (Beijing Wantai Biological Pharmacy Enterprise Co., Ltd., Beijing, China). Subsequently, positive samples were tested for Dengue IgM antibodies using the ICMR-NIV MAC ELISA kit (ICMR-National Institute of Virology, Pune, India).

For SARS-CoV-2 antibody detection, the assay was performed by adding negative and positive controls, as well as the serum samples, to microwells coated with SARS-CoV-2 antigen. HRP conjugate was added, followed by the addition of TMB substrate, which was then incubated in a dark room. The reaction was stopped by the addition of H_2SO_4, and the absorbance value at 450nm was measured to interpret the results. An absorbance value above the cut-off was considered positive, indicating the presence of antibodies to SARS-CoV-2.

For Dengue IgM detection, the assay utilized a capture ELISA approach. During incubation, IgM in the patient's serum were captured by anti-human IgM. After washing, DEN antigen was added and incubated. Any unbound antigen was removed by further washing, followed by the addition of DEN monoclonal antibody and Avidin HRP. Chromogenic substrate was added and the reaction was stopped using 1N H_2SO_4. The intensity of the resulting

color was measured at 450nm. The results of the serological testing were analysed based on absorbance values and interpreted according to predetermined cut-off values for each assay.

Statistical analysis of data:

Descriptive statistics were used to summarize the demographic and clinical data. Chi-Square (or Fisher Exact) test was used to compare categorical variables and the level of significance was $p<0.05$.

Results:

During the study period, serum samples were collected from 420 paediatric patients with symptoms of COVID-19 out of which 109 (26.0%) were reactive to SARS-CoV-2 antibodies. Out of the 109 seropositive patients, 54 (49.5%) were males and 55 (50.5%) were females. The age range of the seropositive patients was 5-17 years. Twenty three of 55 (41.8%) female and 24 of 54 (44.4%) male patients had fever of more than 38ºC.

A total of 13 among the 109 seropositive samples were reactive to Dengue IgM, giving co-infection of Dengue and SARS-CoV2 rate of 3.1% (13/420), with 8 (1.9%) females and 5 (1.2%) males. The clinical presentations of the 13 patients with co-infection of SARS-COV-2 and Dengue are shown in Table 1, with the three most common symptoms being joint ache (myalgia) in 53.8% (75.0% in females, 20.0% in males, p=0.1026), fever in 46.2% (50.0% in females, 40.0% in males, p= 1.000), and rash in 46.2% (62.5% in females, 20.0% in males, p=0.2657).

Discussion:

The co-infection of SARS-CoV-2 and Dengue in paediatric patients is a matter of concern due to the overlapping clinical features and potential complications associated with both viral infections. Our study, which included 420 symptomatic paediatric patients, showed 26.0% SARS-CoV-2 seropositivity and 3.1% co-infection of COVID-19 and Dengue. The clinical similarities between COVID-19 and Dengue pose a challenge in distinguishing between the two infections. There is significant overlap in the clinical symptoms of Dengue and COVID-19 including fever, myalgia, headache, cough, dyspnoea, vomiting, abdominal pain, and skin rashes (9-11). In our study, we observed similar symptoms in the co-infected patients.

There was a slightly higher prevalence of co-infection in females, with 8 (1.9%) females and 5 males (1.2%) showing co-infection. The presence of high-grade fever was more frequent in females (50.0%, 4/8) compared to males (40.0%, 2/5), indicating a potential gender difference in symptom severity, although the small sample size here makes this observation of little importance, but this finding is consistent with previous studies reporting mild to moderate illness in children with COVID-19 (12).

Table 1: Clinical manifestations of COVID-19 and Dengue co-infection in paediatric patients in Osmania General Hospital, Hyderabad, Telangana, India

Clinical symptoms	Female (%) (n=8)	Male (%) (n=5)	Total (%) (n=13)	OR (95% CI)	*p* value
Fever (≥38°C)	4 (50.0)	2 (40.0)	6 (46.2)	1.50 (0.1559-14.428)	1.000
Sore throat	3 (37.5)	0	3 (23.1)		
Runny nose (rhinorrhea)	2 (25.0)	1 (20.0)	3 (23.1)		
Cough	3 (37.5)	1 (20.0)	4 (30.8)		
Shortness of breath (dyspnea)	0	0	0		
Chills	2 (25.0)	2 (40.0)	4 (30.8)		
Vomiting	2 (25.0)	1 (20.0)	3 (23.1)		
Nausea	1 (12.5)	1 (20.0)	2 (15.4)		
Diarrhea	1 ((12.5)	3 (60.0)	4 (30.8)		
Headache	1 (12.5)	4 (80.0)	5 (38.5)		
Rash	5 (62.5)	1 (20.0)	6 (46.2)	6.667 (0.4863-91.39)	0.2657
Conjunctivitis	2 (25.0)	0	2 (15.2)		
Muscle aches	1 (12.5)	0	1 (7.7)		
Joint ache (myalgia)	6 (75.0)	1 (20.0)	7 (53.8)	12.00 (0.7952-181.1)	0.1026
Loss of appetite	1 (12.5)	0	1 (7.7)		

Interestingly, the co-infected patients did not exhibit symptoms of shortness of breath, which is commonly associated with severe COVID-19 cases. This suggests that the presence of Dengue antibodies might have a mitigating effect on the severity of Dengue symptoms, as hypothesized by Namita Ravikumar et al., (7). Studies by Ratageri et al., (11) and Khalil et al., (12) reported cases of co-infection between Dengue and SARS-CoV-2, with varying symptom severity and outcomes in paediatric patients. Additionally, Ghosh et al., (4) documented multiple cases of co-infection of COVID-19 with various diseases in the paediatric population, highlighting the need for vigilance in diagnosing and managing co-infections. Co-epidemics of Dengue and COVID-19 have been reported in Brazil and other regions, indicating the potential for simultaneous outbreaks and increased burden on healthcare systems (13-17). However, studies in adults, such as the one by Joubert et al., (14) suggest that severe dengue cases may not be more symptomatic than mild to moderate COVID-19 cases.

The limitations of our study include the relatively small sample size and its single-centre nature (18-20). However, the study highlights the co-infection of SARS-CoV-2 and Dengue in paediatric patients, emphasizing the need for awareness and early detection of these dual infections. The overlapping clinical features and potential complications necessitate careful evaluation and management of co-infected cases.

Further research with larger sample size and multi-centre collaborations are needed to validate our findings and gain better understanding of the clinical impact and outcomes associated with co-infection of SARS-CoV-2 and Dengue in paediatric patients. There is also the need to explore the mechanisms underlying the interaction between the two viruses and to develop effective strategies for diagnosis, treatment, and prevention of co-infection in paediatric populations.

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Contributions of authors:

PS was involved in the concept and design of the study; SW and RV were involved with data collection and serological testing; SW, SM and MSF prepared the first draft of the manuscript; RVS reviewed and edited the manuscript. All the authors read and approved the final manuscript.

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Conflict of interest:

Authors declare no conflict of interest.

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