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Research Article

Does Clinical-Laboratory Workup in COVID-19 Cases Misdiagnosed as Dengue Fever in Tropical Setting or These are Two Sides of Same Coin?

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Abstract

Objectives: Dengue-covid-19 overlap is mixture of both diseases sharing few similarities in pulmonary and extrapulmonary involvement.

Methods: Prospective, multicentric, and observational study conducted during May 2021-September 2021, included 200 Covid-19 cases with dengue NS1 or Dengue IgM positive, with lung involvement documented and categorized on HRCT thorax at entry point. All cases were subjected to dengue IgG antibody titers and dengue IgM/IgG antibody titer analysis after 12 weeks of discharge form hospital after clinical recovery. Statistical analysis is done by using Chi square test.

Results: Dengue-Covid-19 overlap was documented in 16.33% (49/300) cases. CT severity has documented significant correlation with Dengue-Covid-19 overlap cases. [p<0.00001] Hematological parameters as white blood cell count & platelet count were having significant association with Dengue-Covid-19 overlap [p<0.0076] & [p<0.00001] respectively. Clinical parameters as hypoxia have significant association with dengue-covid-19 overlap. [p<0.00001] Inflammatory markers as IL-6, CRP and LDH has significant association in dengue-covid-19 overlap [p<0.00001] respectively. In study of 49 cases of 'Dengue-covid-19', post covid lung fibrosis [p<0.004] and serological assessment in dengue IgM/IgG and covid antibody titers has significant association [p<0.00001].

Conclusion: 'Dengue-covid-19' is disease of concern in ongoing pandemic in critical care setting, high index of suspicion is must as natural trend of this entity is different and it behaves like 'two sides of same coin'.

Keywords: Antigenic mimicry, COVID-19, dengue-covid-19 overlap, post covid lung fibrosis

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Coronavirus disease 2019 (Covid-19) is caused by novel severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) and resulted in rapid surge of cases with increase in hospitalizations due to pneumonia globally. In March 2020, the World Health Organization (WHO) publicly announced that Covid-19 had become a pandemic.[1] Dengue, a mosquito-borne viral infection caused by four dengue virus, and according to WHO's report, the global incidence of dengue has grown dramatically in the past few decades. There are an estimated 100–400 million infections each year, and approximately half of the world's population is now at risk of contracting the disease.[2]

The pandemic is still ongoing in Asian countries in which dengue, caused by dengue virus, has been endemic for

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decades. Some countries in the region are facing dengue outbreaks amid the Covid-19 pandemic creating a double-burden on resources and health systems.[3]

In the near future, the overlap of Covid-19 and dengue epidemics is a concrete threat in tropical regions.[4,5] Covid-19 and dengue share several features of clinical and laboratory presentation, and differential diagnosis should rely on specific diagnostic tests.[6] Recently, two cases of false-positive results[7] and If serological cross-reactivity between patients with Covid-19 and dengue will be confirmed, it may result in a high number of misdiagnoses, with dangerous consequences both from the patients and from public health point of view.[8] The Covid-19 pandemic in dengue-endemic areas is a public health concern because of the overlapping clinical and laboratory features of these diseases. This causes challenges in the correct diagnosis and management of both diseases.[9,10,11] Further, infection with the dengue virus has been reported in SARS-CoV-2 infected patients during the pandemic.[12,13] Co-infection with these diseases has been associated with higher morbidity than single infections.[14,15] Dengue Fever and Covid-19 share many pathogenic and clinical features which might make it very difficult to differentiate the two infections. The phenomenon of ADE (Antibody Dependent Enhancement) has been described for both dengue virus as well as for SARS-CoV-2 virus resulting in escalation in degree of infection and number of complications. Both being RNA viruses they share certain common features in pathogenesis, eventually leading to subsequent cytokines and chemokine release and also affecting the integrity of the vascular endothelium leading to vasculopathy, coagulopathy and capillary leak.[16]

In present study, we have documented Covid-19 pneumonia cases with concurrent dengue like manifestations with dengue serology positivity i.e., either NS1 or IgM antibody positive; and we have followed these cases for 12 weeks to exactly confirm dengue-covid overlap.

Methods

Prospective, observational study conducted in Venkatesh chest hospital, and Pulmonary Medicine, MIMSR medical college Latur during May 2021 to September 2021, to find out 'covid-dengue overlap' in diagnosed covid-19 pneumonia cases admitted in critical care unit. Total 300 cases were enrolled in study after IRB approval and written informed consent of patient (Fig. 1).

Inclusion criteria: Covid-19 patients, confirmed with RT-PCR, above the age of 18 years, hospitalized in the study centers, including those with comorbidities and irrespective of severity and oxygen saturation were included in the study.

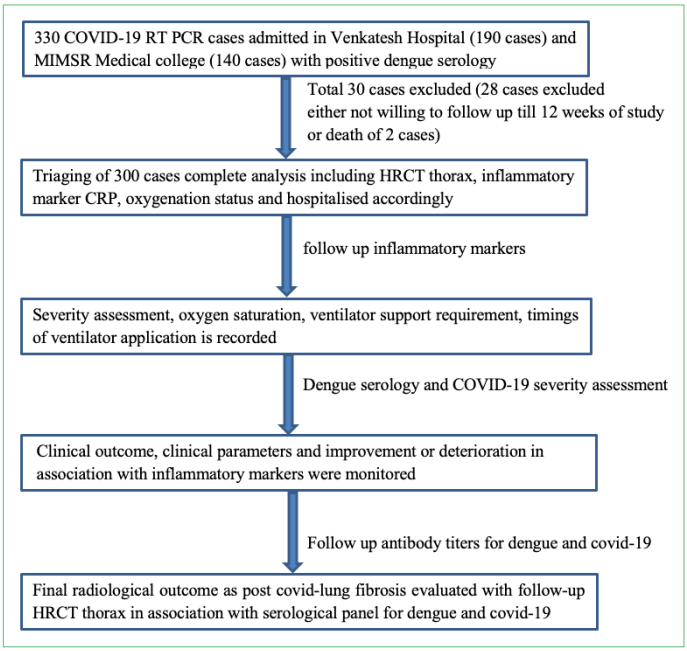

Figure 1. Flow of the study.

Exclusion criteria: Those not willing to give consent, not able to perform follow-up dengue and covid-19 antibody titers and patients less than 18 years of age were excluded

All study cases were undergone following assessment before enrolling in study:

1. Covid-19 RT PCR test performed in all cases, if first test results were negative and radiological features clearly documenting pneumonia, we have repeated RT PCR test and enrolled all cases with positive Covid-19 RT-PCR test.
2. HRCT Thorax to assess severity of lung involvement, and categorized as Mild if score <7, moderated if score 8-15 and severe if score >15 or 15-25.
3. Clinical assessment as- vital parameters like heart rate, respiratory rate, blood pressure and documentation of respiratory adventitious sounds
4. Laboratory parameters- hemoglobin, renal functions, blood sugar level, liver functions, ECG
5. Viral inflammatory markers like CRP, LDH, IL-6 assessed at entry point and repeated whenever required during course of illness as for monitoring the covid-dengue overlap cases for necessary interventions. Normal and abnormal parameter readings were considered as per pathological laboratory standard.
6. Covid-19 antibody titers and Dengue IgM and IgG titers and follow-up HRCT thorax done at twelve weeks or 3 months of discharge from hospital.

Case definition used in this study:

1. *Dengue-covid-19 overlap:* covid-19 RT PCR positive cases with Dengue serology positive for NS1 with or without IgM antibody with clinical and laboratory parameters corelated with concurrent possibility of both illnesses.
2. *False dengue or antigenic mimicry:* Initially presented with Dengue-covid-19 overlap, and later on in course of illness during follow up analysis of these cases at 12 weeks shown dengue IgM or Dengue IgG antibody negative
3. *Concurrent covid-dengue illness:* Initially presented with Dengue-covid-19 overlap, and later on in course of illness during follow up analysis of these cases at 12 weeks shown dengue IgM or Dengue IgG antibody positive
4. *Covid-dengue immune senescence:* Initially presented with Dengue-covid-19 overlap, and later on in course of illness during follow up analysis of these cases at 12 weeks shown dengue IgM or Dengue IgG antibody negative and covid antibody test negative or weakly positive.

Diagnosis of dengue infection

1. *Dengue NS1 antigen:* Qualitative screening test of dengue infection which uses nonstructural protein NS1 antigen which is secreted in dengue infected patient sample. This is a rapid detection method based on immune-chromatographic technique and performed on plasma or serum sample on SD Dengue Duo test kit (SD Dengue Duo, Standard Diagnostics, Germany)
2. *Dengue IgG and IgM:* qualitative IgM and IgG antibody assays were performed by immune- chromatography strip method (SD Dengue Duo, Standard Diagnostics, Germany). SD Dengue Duo test kit has greater sensitivity and specificity 94.2% and 96.4% for the classification of dengue cases into primary and secondary dengue infection respectively.
3. *Diagnosis of SARS-CoV-2 infection by RT-PCR:* Qualitative screening of the SARS-CoV-2 virus, performed on nasopharyngeal swab samples as fully automated RT PCR on Cobas 6800 instrument (Roche Molecular Diagnostics, USA). Interpretation of results was done on amplification of target genes as COVID-19 positive or negative.

The statistical analysis was done using chi-squared test. Significant values of χ^2 were seen from probability table for different degree of freedom required. P value was considered significant if it was below 0.05 and highly significant in case if it was less than 0.001.

Observations and Analysis

In this study, total 300 Covid-19 pneumonia cases, Dengue-covid-19 overlap was documented in 16.33% (49/300) cases, cases enrolled between age group 18-95 years of age; age above 50 years were 60% (180/300) and age below 50 were 40% (120/300). In gender distribution in study group, male population was 70.33 % (211/300) and females were 29.66% (89/300). Main symptoms in study group were shortness of breath in 79% cases, fever in 71%, cough especially dry in 48% cases, and fatigability in 79% cases, Tachycardia in 72% cases, Tachypnea in 24% cases and oxygen desaturation on 6 min walk in 29% cases. 'Dengue-covid-19 overlap' as per CT severity scoring was documented as- 26/42 in mild CT severity cases, 16/92 in moderate CT severity cases and 7/166 in severe CT severity cases. [p<0.00001] (Table 1) Hematological parameters were having significant association in covid-19 cases with and without dengue overlap as like abnormal white blood cell count [p<0.0076] and abnormal platelet count [p<0.00001]. (Table 2) Clinical parameters like hypoxia have significant association in covid-19 cases with and without dengue overlap. [p<0.00001] (Table 2) Inflammatory markers analysis was documented significant association in covid-19 cases with and without dengue overlap as abnormal IL-6 [p<0.00001], abnormal CRP [p<0.00001] and abnormal LDH [p<0.00001] (Table 2) In study of 49 cases of 'Dengue-covid-19 overlap', post covid lung fibrosis was documented in one case while in 251 covid patients with negative dengue serology documented post covid lung fibrosis in 45 cases. [p<0.004] (Table 3) In study of 49 cases of 'Covid-Dengue Overlap', serological assessment in dengue IgM/IgG and covid antibody titers was documented in significant association. [p<0.00001] (Table 4)

Table 1. Pattern of COVID-19 disease in study cases (n=300)

CT severity and COVID-19 RT PCR positive (n=300)	Dengue NS1/IgM positive (n=49)	Dengue NS1/IgM negative (n=251)
Mild (n=42) (score <8)	26	16
Moderate (n=92) (score 9-15)	16	76
Severe (n=166) (score 16-25)	07	159

χ^2=81.71; p<0.00001.

Table 2. Other variables in 'COVID-Dengue overlap' cases

COVID-19 RT PCR positive (n=300)	Dengue NS1/IgM positive (n=49)	Dengue NS1/IgM negative (n=251)	Analysis
Normal Platelets level (n=110)	3	107	χ^2=23.52 p<0.00001
Abnormal Platelets level (n=190)	46	144	
Normal White blood counts (n=105)	9	96	χ^2=7.12 p<0.0076
Abnormal White blood counts (n=195)	40	155	
Normal CRP level (n=28)	22	6	χ^2=87.53 p<0.00001
Abnormal CRP level (n=272)	27	245	
Normal LDH level (n=58)	12	46	χ^2=66.98 p<0.00001
Abnormal LDH level (n=242)	37	205	
Normal IL-6 level (n=58)	46	12	χ^2=208.67 p<0.00001
Abnormal IL-6 level (n=242)	3	239	
Required BIPAP/NIV (n=96)	6	90	χ^2=10.50 p<0.0011
Not Required BIPAP/NIV (n=204)	43	161	
Cases with hypoxia (n=239)	12	227	χ^2=110.07 p<0.00001
Cases without hypoxia (n=61)	37		24

Table 3. Radiological outcome in 'COVID-Dengue overlap' cases

Covid-19 RT PCR (n=300)	Lung Fibrosis Present (n=46)	Lung fibrosis absent (n=254)
Dengue NS1/IgM positive (n=49)	1	48
Dengue NS1/IgM negative (n=251)	45	206

χ^2=7.97 p<0.004.

Table 4. Actual serological assessment in covid-dengue overlap and covid-19 with dengue coexistent pathology (n=490) follow up at 12 weeks

Covid-dengue overlap cases (n=49)	COVID antibody titers raised (n=29)	Covid antibody titers negative (n=20)
Dengue IgM/IgG positive (n=33)	27	6
Dengue IgM/IgG negative (n=16)	2	14

χ^2=21.43 p<0.00001.

Discussion

Prevalence of 'Dengue-covid-19 overlap' in present study:

In this study, of total 300 Covid-19 pneumonia cases confirmed by Covid-19 RT PCR test, 'Covid-dengue overlap' was documented in 16.33% (49/300) cases after positive dengue NS1/IgM antibody analysis. This will be first study enrolling and analyzing a greater number of cases having covid-dengue overlap. Dengue became endemic in Asian countries due to trading industry and transportation services in last century due to movement of people.[17,18] Presently, most of the countries in this region are affected with Covid-19 pandemic and resulted in socioeconomic crisis due significant disease burden in compromised health sector.[19-23] India

is one of the most affected country due to Covid-19 with ranked second and third in number of affected cumulative cases and deaths due to Covid-19 respectively.[24] Now, South East Asia region has documented widespread distribution of cases and deaths due to Covid-19.[25-27]

In present study, we have observed many cases were initiated treatment in consideration of dengue fever due to overlap of common symptom of fever and later on during course of illness when these patients started cough and or shortness of breath, were evaluated for Covid-19 and documented positive serology with lung parenchymal involvement on HRCT thorax. Authors, Tsheten T et al.[28], Chen N et [9] & Kembuan GJ et al.[14] documented similar findings. We have also observed that clinical worsening or requirement of oxygen supplementation due to fall in oxygen saturation was reason to investigate for underlying covid-19 in primary dengue hospitalizations, and vice versa. Authors, Estofolete CF et al.[15], Mahajan NN et al.[29], Bicudo N et al.[30] & Rodriguez-Morales AJ et al.[31], Tsheten T et al.[28], Pontes RL et al.[32] and Ratnarathon AC et al.[33] documented similar observation. As both the disease involves similar pathophysiological pathways[16], and thrombocytopenia in these diseases results from depressed platelet synthesis due to virus-induced bone marrow suppression and immune-mediated clearance of platelets.[34, 35] Further, autoantibodies and immune complexes produced in response to SARS-CoV-2 and dengue virus infection destroy platelets.[35, 36]

'Dengue-Covid-19 Overlap': Is it an 'Antigenic Mimicry'?

In study of 49 cases of 'Dengue-covid-19 overlap', actual serological assessment in dengue IgM/IgG and covid antibody titers were documented in 33/49 and 29/49 cases respectively, while cases with antibody titers negative at follow up at three weeks for dengue and covid were negative in 16/49 and 20/49 cases respectively. ($p<0.00001$). In present study of these 49 cases with covid-dengue overlap antigenic cross reactivity has been documented initially in 16 cases i.e., false positive Dengue NS1 without dengue antibody titer documentation at 3 weeks follow up. Few studies have documented similar observation.[49,50]

'Dengue-covid-19 overlap' documentation needs high index of suspicion due to overlapping clinical and laboratory markers and concurrent double infection complicates either disease clinical outcome. All cases with dengue NS1 and or IgM positive needs Covid-19 to be ruled out as many cases are having underlying OCVID-19, we specially recommend in scenario with abnormal chest radiograph or cases with adventitious sounds on auscultation clinically. few studies[38,39] have similar observations collaborating with our study.

'Dengue-Covid-19 Overlap': Is it a Coexistent Two Different Viral Genotypic Disease?

In study of 49 cases of 'Dengue-covid-19 overlap', actual serological assessment in dengue IgM/IgG antibody and covid IgG antibody titers at 3 weeks was documented in significant association ($p<0.00001$) i.e. 33 cases with dengue overlap syndrome were having coexistent dengue and Covid-19 diseases. Initially Dengue-covid-19 overlap was considered important health issue in ongoing covid pandemic in high dengue burden setting in tropical countries in South East Asia region and as pandemic grown across globe irrespective of Dengue trends, now it is considered as global health issue. Various studies[41,42] and author Epelboin L et al.[13], Saavedra-Velasco M et al.[40] documented similar observation.

'Covid-Dengue Immune Senescence'- is it a Natural Trend or Worrisome Pattern in Ongoing Pandemic?

In study of 49 cases of 'Dengue-covid-19 overlap', actual serological assessment in dengue IgM/IgG antibody and covid IgG antibody titers at 12 weeks of illness were negative 16 and 20 cases respectively ($p<0.00001$) In study of these cases in follow up, 14 cases were showing negative both covid and dengue antibody titers. Negative Antibody titer is really a concern and it would suggest 'weak antigen-antibody memory link' and issue of great research being all such cases again become virgin to catch infection due to covid-19. Author Nalbandian, A et al.[51] documented that Acute Covid-19 usually lasts until 4 weeks from the onset of symptoms, beyond which replication-competent SARS-CoV-2 has not been isolated.

In Covid-19 cases viral load is highest in respiratory system in first to second week or initial phases of infection and documented maximum in second week of illness. Then viral load decreases over four weeks and become undetectable in respiratory secretions after four weeks. In few cases with severe disease, the viral load in respiratory fluids is highest at approximately the third and fourth weeks. [51] The factors that cause the viral load to persist more in some individuals than in others remain to be clarified.[44] Synthesis of antibodies against SARS-CoV-2 is a primary immune response to infection.[45] IgM levels increase during the first week after infection, peaking after 2 weeks; they then tend to disappear in most individuals. IgG is detectable after the first week and remains elevated for approximately 90 days. However, it is not yet clear whether these antibodies can protect against reinfection during that time.[46] Raafat N et al.[47] documented that in primary dengue infection in acute phase, both nonstructural protein 1 (NS1) and viral RNA can be detected in first week of illness till five days. In acute phase IgM documented at 3-5

days and remains detectable for several months. Towards end of acute phase, IgG antibody start rising which last for 10 days, and confers immunological memory for many years. In secondary dengue infection, IgG antibody rises earlier than IgM.[47] Recent studies[52-54] have shown that neutralizing antibodies may disappear after 3 months. Long et al.[52] observed that Forty percent of asymptomatic individuals became seronegative and 12.9% of the symptomatic group became negative for IgG in the early convalescent phase. Wu F et al.[54] mentioned that, the relationship between detectable antibodies to SARS-CoV-2 and protective immunity against future infection is not known.

We have further analyzed these 14 cases, and documented that all these 6 cases were having mild lung involvement on CT thorax imaging, means that more immunological behavior of Corona virus leading to short lasting immunity and of 'short lasting immune memory' or viral escape from immune restoration leading to 'immune escape' from presenting and sensing covid antigens to memory T cells and developing protective antibodies for same.

Other important observations in present study:

Hematological parameters were having significant association in covid-19 cases with and without dengue overlap, especially normal and abnormal white blood cell count [p<0.0076] and normal or abnormal platelet count [p<0.00001] Rational for similar observations were more immunological nature of Dengue-covid-19 overlap' syndrome.

Clinical parameters like oxygen saturation at entry point i.e with or without hypoxia have significant association in covid-19 cases with and without dengue overlap. [p<0.00001] Rational for similar observation in Dengue-covid overlap as compared to isolated covid illness, where lung involvement was predominant pathological nature of covid and hypoxia was predominantly documented in these cases due to more pulmonary involvement.[48]

Inflammatory markers analysis was documented significant association in covid-19 cases with and without dengue overlap as abnormal IL-6 [p<0.00001], abnormal CRP [p<0.00001] and abnormal LDH [p<0.00001] Rational for same findings were more immune nature of overlap cases as compared to isolated covid cases, and predominant pattern of involvement is pulmonary, leading to direct pulmonary alveolar and vasculature involvement and correlated with raised inflammatory markers IL-6, CRP and LDH. We used LDH as marker of assessment of oxygen status and hypoxia, and observed grossly raised it with predominant lung involvement as documented in previous study.[48]

In study of 300 covid-19 pneumonia cases, 'Covid-Dengue Overlap' as per CT severity scoring was documented as- 26/42 in mild CT severity cases, 16/92 in moderate CT severity cases and 7/166 in severe CT severity cases. [p<0.00001] Rational for these observations may be antigenic cross-reactivity or mimicry is feature of early course of covid illness and as disease evolves over period of time and enters in second to third week of illness this cross-reactivity decreases, CT radiological features progresses and presented with advanced stage or more CT severity. CT documented mild lung involvement in cases with prolonged fever and these cases were initially documented as Dengue and later on diagnosed as concurrent COVID-19 coinfection in many cases and few cases were shown antigenic cross reactivity. While in majority of moderate to severe COVID-19 cases on HRCT thorax, proportionately high number of cases were having antigenic cross reactivity and only small proportion of cases were having concurrent covid-dengue coinfection.

In study of 49 cases of 'Covid-Dengue Overlap', post covid lung fibrosis was documented in one case while 251 covid patients with negative dengue serology documented post covid lung fibrosis in 45 cases. [p<0.004] Rational for same findings may be immunological nature of disease which has resolved over period of 12 weeks and usually these cases may have lesser lung parenchymal necrosis and more extrapulmonary features or manifestations. As disease progressed to 12 weeks of illness and chances of antigenic cross-reactivity decreased and isolated covid cases were predominant category showing lung fibrosis and we have confirmed these cases with antibody titer analysis.

Issues needs to analyze further are:

1. Dengue-covid-19 overlap' and antigenic mimicry scenario was documented in second wave i.e., Delta variant of corona virus and less frequently documented with Wuhan variant corona virus of first wave. Is there any antigenic cross-reactivity with genetic makeup of corona virus is behaving selectively, really, we don't know, and further workup is required?
2. Is Immunological phenomenon documented in Dengue-covid-19 overlap reversible? or is it persists longer? and or pre-requisite for certain autoimmune rheumatological syndromes in post-covid illness cases which has been documented in all clinical settings, needs further work up.
3. It is necessary to prepare for dengue outbreaks immediately under the premise of controlling the Covid-19 pandemic. Co-infection of SARS-CoV-2 and dengue has become a hot research topic, mentioned by com-

missioners of Lancet Commission[39], and the common pathogenesis and biological pathways of the two can be used as resection points for project research.

Conclusion

Dengue-covid-19 overlap is clinical syndrome with overlapping clinical and laboratory workup of both the illnesses. High index of suspicion is must in all covid cases in tropical setting where dengue is endemic; and all cases with leucopenia and thrombocytopenia with fever should be screened for dengue serology. False positive dengue serology or dengue antigen cross-reactivity is known to occur in underlying covid-19 illness, and have impact on clinical outcome as it will result in delay in covid appropriate treatment initiation and many cases require intensive care unit treatment due to progressed covid pneumonia.

Covid-dengue antigenic cross-reactivity has significant association with lung fibrosis as resultant pathophysiological effect of immune activation pathway; and these cases were required longer oxygen supplementation and anti-fibrotics in follow up. 'Dengue-covid-19 overlap' is very frequently documented in tropical setting and disease of concern in critical care setting; as natural trend of this entity is different and having impact on clinical outcome if diagnosis is delayed. Both diseases may behave like 'two sides of same coin', and rational for coexistent pathology were still undetermined.

Disclosures

Ethics Committee Approval: Venkatesh Chest Hospital & MIMSR Medical college Latur India, 21/05/2021, number: VCC/58/2021.

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