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Case Series

Internal Medicine Section

Dengue Co-infections-An Emerging Entity during the Outbreak

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ABSTRACT

Viral infections predispose a patient for super added infections and it is important to know the spectrum to suspect them. We analysed 98 cases of dengue fever who were presented at a tertiary care hospital; of which 12 were associated with co-infections. Bacterial infections were the most common type of co-infections (50%; n=6). Viral co-infections were present in 25% patients (n=3) and included hepatitis A, hepatitis B, and chikungunya. The remaining co-infections included parasitic and fungal co-infections. Severe dengue was seen in 83.3% cases (n=10). Amongst the organ involvement, the liver was maximally involved followed by deranged haematological parameters. Mortality was seen in 25% cases (n=3). Few unique co-infections caused by organisms like Ascaris and Aspergillus were identified. There is a possibility of bilateral increase in the severity of few co-infections. Prolonged fever (≥5 days) and severe organ dysfunction should alert the physician to actively look for co-infections.

Keywords: Ascariasis, Aspergillus pneumonia, Bacterial infections, Scrub typhus, Viral infections

Dengue, an arboviral disease, transmitted by the bite of Aedes mosquito, has seen resurgence in the past few decades. Data from WHO suggest that it has a prevalence of 390 million infections per year of which 96 million manifest with clinical disease each year [1]. Being a masquerader and a common aetiology of Acute Febrile Illness (AFI) during the outbreak, it causes significant delay in making the correct diagnosis, where suspicion for other diseases is very low [2]. Furthermore, co-infection is always a possibility when clinical course does not proceed as expected or when all clinical features cannot be explained by the dengue virus.

Dengue associated co-infections are rarely described and the evidence exists only in the form of few case reports and case series, that too individual co-infections (dengue with either bacterial infections, malaria, enteric fever, leptospirosis, scrub typhus, hepatitis A, chikungunya, or recently discovered Zika virus co-infection) [3-6]. To the best of our knowledge, there is no study describing overall co-infections associated with dengue, especially during an outbreak. This is important for public health point of view considering types of associated co-infections, severity of the diseases, management issues, and prognosis.

Therefore, we describe 12 dengue co-infected patients in one outbreak period (September 2014-February 2015), to describe the spectrum of co-infections, their hospital course, and to determine, if possible, some pointers which may indicate the co-infections.

CASE SERIES

During the outbreak, we analysed case files of 98 patients with dengue fever who were admitted in the Department of Medicine of the total 12 dengue cases were found to be having another infection, either single or multiple. Co-infection is defined as simultaneous infection by more than one pathogenic species in a host (Medical dictionary; Merriam-Webster). Therefore, all associated co-infections were included which may present as either acute or chronic course of the illness. These cases had been retrospectively analysed from the data repository after taking appropriate approval from the department/institute.

The laboratory evaluation performed in all patients were complete blood count, liver and kidney function tests, and prothrombin time by standard biochemical methods. Diagnostic test for dengue was performed for all cases; NS1 antigen (Panbio Dengue Early ELISA, Standard diagnostics Inc., Republic of Korea) if the patient presented within first five days of illness and IgM antibody (NIV DEN Immunoglobulin (IgM) Capture ELISA, National Institute of Virology, Pune, India) if presented later. According to the hospital policy, to rule out common alternative causes of AFI, all patients had also undergone chest X-ray, urine routine microscopy, peripheral smear for parasites, rapid-card test for malaria, Widal test if fever is more than a week duration, and blood culture. If patients had any specific pointers in history, physical examination, or laboratory findings, other tests were conducted. These included hepatitis virus serology (anti-hepatitis A IgM, HBsAg, Anti-hepatitis E IgM and anti-hepatitis C virus antibody), serology (IgM) for chikungunya, Leptospira, and scrub typhus, Cerebrospinal Fluid (CSF) analysis, sputum smear for bacterial and fungal staining, and bacterial culture of sputum, urine, CSF, and pus. In one suspected case of Haemophagocytic Lymphohistiocytosis (HLH), extensive evaluations including serum ferritin (chemiluminiscence), lipid profile (photometric method, Beckman counter), and bone marrow examination were also performed.

The demographic and clinical details of the co-infected patients showed in the [Table/Fig-1]. The mean age of patients was 35.6 years (SD=18.95) and with female predominance (male:female=5:7). Patients were divided into dengue without warning signs, dengue with warning signs, and severe dengue as per WHO-2009 classification system [7]. Dengue diagnosed with IgM positivity were in the majority (n=9), while 25% (n=3) had NS1 antigen positivity. Fever was a constant feature seen in all patients and average duration of fever was 6.3 days. Majority {n=8 (66.67%)} presented with ≥5 days of fever. Three (25%) had previously existing co-morbidities. Severe dengue was seen in 10 (83.33%) cases. These included plasma leakage leading to distributive shock (two patients), severe bleeding manifestations (two patients), and severe organ impairments (seven patients), which were marked transaminitis, Acute Kidney Injury (AKI), myocarditis, strokes and HLH.

Patient	Age (years)	Sex	Co-infection	Method of diagnosis of co-infection	Dengue classification (WHO-2009)	Duration of fever at presentation	Days of hospital stay	Co morbidities	Mortality	Special findings
1	15	M	Ascariasis	Vomitus containing adult worm	Severe	5	5	No	Yes	Myocarditis, distributive shock
2	14	F	Malaria (*Plasmodium vivax*)	Peripheral smear showing parasite	Severe	5	5	No	No	Haematemesis Haemoptysis
3	35	F	Leptospirosis	Serology IgM positive	Severe	4	4	No	No	Markedtransaminitis, AKI
4	48	F	Hepatitis B UTI (*Pseudomonas aeruginosa*)	HBsAg positive Urine culture positive	Severe	14	6	DM2/HTN	No	AKI Cholecystitis Encephalopathy Microangiopathic haemolytic anaemia MDR *Pseudomonas* in urine Culture (UTI) Septic Shock
5	56	F	Pneumonia (*Pseudomonas aeruginosa*)	Sputum culture positive	Severe	-	14	DM2/HTN/ Depression	Yes	CVA with haemorrhagic transformation Septic shock
6	28	F	SSSS (*Staphylococcus*)	Pus culture positive	Severe	8	9	No	No	Axillary folliculitis Distributive shock
7	52	F	Chikungunya	Serology IgM positive	Dengue without warning signs	3	7	No	No	Vitamin D deficiency
8	69	M	Pneumonia (*Aspergillus*)	Sputum fungal staining and culture positive	Severe	4	11	HTN/RA/CAD/ Old KOCH'S chest	No	Epistaxis/haemoptysis Moderate ascites/ capillary leak AKI
9	27	M	Enteric fever	Blood culture and Widal positive	Dengue without warning signs	8	14	No	No	Became afebrile after enteric treatment but again had fever with thrombocytopenia
10	18	M	Scrub Typhus	Serology IgM positive	Severe	6	13	No	No	Eschar positive Hepatosplenomegaly Focal myositis in left arm Mild ARDS
11	15	F	Hepatitis A	Anti-Hepatitis A IgM positive	Severe	6	2	No	No	Marked transaminitis
12	51	M	Hospital acquired pneumonia	No organism detected in short hospital stay (<24 hrs)	Severe	13	1	No	Yes	Orbital cellulitis with persistent fever, 5/8 criteria satisfied for HLH Marked transaminitis Septic shock

[Table/Fig-1]: . Demographic and clinical details of the dengue co-infected patients.
AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; CAD: Coronary artery disease; CVA: Cerebro-vascular accident; DM: Diabetes mellitus; HLH: Haemophagocytic lymphohistiocytic syndrome; HTN: Hypertension; MDR: Multidrug resistance; RA: Rheumatoid arthritis; UTI: Urinary tract infection; SSSS: Staphylococcal scalded skin syndrome

[Table/Fig-2] showed the trend of laboratory parameters in these patients. Thrombocytopenia (platelets <100×109/L) and anaemia {Hb<12 gm/dL (M) and <10 gm/dL (F)} were seen in 50% co-infected patients (n=6); whereas, leukopenia in two patients and pancytopenia in one. Transaminitis (raised AST or ALT >2 times upper limit of normal) was seen in 66.66% (n=8) patients. Three of them had marked (severe) transaminitis (>10 times upper limit of normal; Cases 3, 11 and 12). Raised bilirubin was present in four patients (33.3%) (Cases 1,5,11, 12). Acute kidney injury (serum creatinine >1.5 mg/dL) was seen in 25% (n=3), Cases 3, 4 and 8) of the patients; however, none of the patients required haemodialysis. Cardiac dysfunction was seen in one patient (Case 1). None of the patients had severe nervous system involvement except one who presented with haemorrhagic stroke after bleeding (Case 5).

Among categorical co-infections, bacterial infection was the most common and seen in 50% (n=6) of patients and included enteric fever, leptospirosis, scrub typhus, *Pseudomonas* pneumonia, staphylococcal skin infection, and *pseudomonas* urinary tract infection. Viral infections were present in 25% (n=3) of co-infected patients. They included hepatitis A, hepatitis B, and chikungunya. The remaining co-infections comprised of 16.6% parasites (n=2; malaria, ascariasis), 8.3% fungal (n=1; *Aspergillus* pneumonia) infection, and 8.3% unknown infection of hospital acquired pneumonia (n=1). Case 4 was having two infections simultaneously; Hepatitis B and UTI.

A young patient was found to have Ascaris adult worms in the vomitus. He presented with five days of fever with features of progressing capillary leak syndrome and subsequently diagnosed to have myocarditis. Another patient having pneumonia with sputum culture positive for Aspergillus presented with bleeding manifestations, ascites-capillary leak phenomenon, AKI, bilateral lower lobes pneumonia, and improved with antifungal treatment. One of other patients was found to have orbital cellulitis and presented with prolonged fever. On further evaluation he was found to have bicytopenia, hyperferritinemia, splenomegaly, hepatic dysfunction, and haemophagocytosis on bone marrow examination, therefore diagnosed to have HLH syndrome, later on developed hospital acquired pneumonia with an unknown infection. Here HLH was considered as one of the severe organ manifestations of dengue fever.

Apart from supportive treatments for dengue fever, associated co-infections were treated with specific antimicrobial therapy. Other

Patient	Hb (g/dL)	WBC (x109/L)	Minimum platelets (x109/L)	Serum Urea/Creatinine (mg/dL)	AST (IU/L)	ALT (IU/L)	Total Bilirubin (mg/dL)
1	10.5	500	13	61/1.1	108	45	2.5
2	4.3	4600	111	85/1.4	19	13	0.5
3	11.1	5200	176	71/1.7	783	581	0.7
4	6.8	16000	70	30/1.0	115	25	0.6
5	6.1	12700	107	69/1.0	90	45	2.8
6	11.3	8300	245	68/0.9	31	41	1.1
7	14.4	2300	140	31/0.9	72	65	0.5
8	11.1	7500	43	73/2.0	54	36	0.3
9	12.5	6200	18	12/1.1	319	421	0.5
10	10.7	10500	100	39/0.8	138	126	0.7
11	12.3	5000	124	17/0.5	593	1965	4.9
12	10.0	14800	60	20/4.5	1228	2175	2.1

[Table/Fig-2]: Laboratory parameters of the dengue co-infected patients.
ALT: Alanine transaminase; AST: Aspartate transaminase; Hb-Haemoglobin; WBC: White blood cell count

viral co-infected patients (hepatitis A and B, chikungunya) had also received supportive treatments only. Bacterial co-infected patients received ceftriaxone for enteric fever and leptospirosis, doxycycline for scrub typhus, linezolid for *staphylococcus* infection, and piperacillin-tazobactum and amikacin for *pseudomonas* infections. Broad spectrum antibiotics (meropenam, levofloxacin, and vancomycin) were used for hospital-acquired pneumonia patient. Artisunate combination therapy and albendazole were used for malaria and ascariasis co-infected patients, respectively. Dexamethasone was used for HLH patient. Mortality was seen in 25% (n=3) of the co-infected patients. Ascaris co-infected dengue patient died because of distributive/cardiogenic shock; while the other two due to septicaemic shock due to *Pseudomonas* pneumonia after stroke and an unknown hospital acquired pneumonia after HLH.

DISCUSSION

In the last few decades, dengue co-infections, whether true or due to serological cross-reactivity, have been emerging as a separate entity as far as presentation and morbidity are concerned [8]. However, to best of our knowledge, there is no study describing all co-infections during an outbreak except few describing simultaneous presence of two or three co-infections. This case series has brought a comparative analysis of all co-infected patients during one outbreak.

Among types of co-infections, more number of dengue patients are infected with bacterial infection followed by viral, parasite, and then fungal. The isolated bacteria are Salmonella, Leptospira, *Staphylococcus*, *Pseudomonas*, and *Rickettsia*. Most of these organisms have been reported individually with dengue fever. *Klebsiella* is one of the important isolated organism in a study, however, not seen in present case series [3]. Same study also postulates that maximum mortality is due to the Gram negative bacteraemia, disseminated after the breakdown of mucosal barrier (e.g., gut) induced by dengue. Important pointers towards suspecting the bacterial co-infection are prolonged fever and AKI, as suggested by the previous study. Most of present patients have prolonged fever of >5 days duration and AKI. There is also a dengue dual infection score to predict the risk of bacterial co-infection which includes pulse rate ≥90 beats/minute, total white cell count ≥6×109/L, haematocrit<40%, serum sodium <135 mmol/L, and serum urea ≥5 mmol/L [2]. However, this score is yet to be validated.

One-fourth patients have co-infections with viruses. Two of them presents as an acute illness (hepatitis A and chikungunya) and third one as a chronic carrier (hepatitis B). Acute infections with these hepatotropic viruses have been described earlier in the case reports but generally do not change the course of illness [6]. In case of hepatitis A, co-infection should be suspected when patient has deranged coagulation parameters, jaundice, or highly elevated liver enzymes; although these features may be seen in isolated dengue infection. Chikungunya co-infection has also been described and generally does not change the course of illness and is a self-limiting disease [9-11]. Future studies are necessary to characterise the pointers to know the possibilities of other viral co-infections.

One-sixth patients have parasite co-infections. As per Epelboin L et al., study, concurrent malaria-dengue infection increases the severity of both infections; however few studies disprove this [12,13]. One study even says co-infection favours presentation of dengue features more than malaria while another points the opposite [14,15]. This complexity requires a larger well balanced study to answer. Jaundice (in dengue patients) and spontaneous bleeding (in malaria patients) should raise the suspicion of other co-infection and also increase the severity [4]. Present case favours the dengue severity. In Ascaris co-infected patient, the parasite must be present before the inoculation of dengue virus, however, few questions remain unanswered; does dengue severity helps in growth and migration of adult worm leading to hyperparasitemia? Does ascariasis makes dengue more severe? This is the first case of co-infection of ascaris with dengue as per present literature search. Therefore, future studies can answer these vital questions.

One patient was having fungal pneumonia, confirmed to be an *Aspergillus*. This patient had past history of tuberculosis and few lung parenchymal fibrotic strands which may have nodus for aspergillosis. However, what aggravated it to be presented as lower lobes infiltrates needs to be answered. Does capillary leak help it? Because this is the first case report having dengue-aspergillus co-infection, future studies may clarify it.

The last patient of the series was having an unknown chest infection. The suspected infection may have developed either simultaneous to or after the patient developed secondary HLH. Dengue fever is known to be associated with HLH, mostly in the children [16]. Prolonged fever with cytopenia and organomegaly should raise the possibility and further hyperferritinemia confirms HLH. But its association with orbital cellulitis is not documented, which can be consequence of hyperinflammation of HLH or a trigger factor leading to HLH. Since, patient had come to us after the diagnosis of dengue, cellulitis, HLH, hospital-acquired pneumonia of unknown organism from outside hospital and stayed <24 hours before the death, we couldn't investigate much.

Among co-infected patients, death rate was 25%, however, severe dengue was seen in more than 75% cases. Henceforth, co-infection increases the severity of dengue. In contrast, one cannot confidently say dengue increases the severity of other co-infections. This needs a large trial to establish. In this small case series, one

may say dengue increases the spread of *Aspergillus*, dissemination of *Ascaris*, and severity of scrub typhus (mild ARDS).

CONCLUSION

To summarise the findings, the bacterial infections are the most common category of dengue associated co-infections. There is probable bilateral increase in the severity of the associated infections and lead to higher mortality and morbidity. Hence, high index of suspicion is required at time of the epidemic for early identification. This is also important because definite treatment is available for many co-infections. Few unique infections like *Ascaris* and *Aspergillus* are identified which iterates the possibility of all types of co-infections during the dengue outbreak. Lastly, prolonged fever (≥5 days) and any major organ involvement are possibly criterias to suspect the co-infections and accordingly one should approach.

REFERENCES

[1] World Health Organization. Dengue and severe dengue. Fact sheet. Updated July 2016. http://www.who.int/mediacentre/factsheets/fs117/en/Accessed on 10 April 2017.

[2] See KC, Phua J, Yip HS, Yeo LL, Lim TK. Identification of concurrent bacterial infection in adult patients with dengue. Am J Trop Med Hyg. 2013;89(4):804-10.

[3] Lee IK, Liu JW, Yang KD. Clinical characteristics and risk factors for concurrent bacteremia in adults with dengue haemorrhagic fever. Am J Trop Med Hyg. 2005;72(2):221-26.

[4] Magalhães BML, Siqueira AM, Alexandre MAA, Souza MS, Gimaque JB, Bastos MS, et al. P. vivax malaria and dengue fever co-infection: a cross-sectional study in the Brazilian Amazon. PLoS Negl Trop Dis. 2014;8(10):e3239.

[5] Bansal R, Bansal P, Tomar LR. Typhoid and dengue coinfection: case reports. Trop Doct. 2015;45(1):52-53.

[6] Shah I, Dey A. Hepatitis A and dengue coinfection. J Vector Borne Dis. 2015;52(3):265-66.

[7] World Health Organization and the Special Programme for Research and Training in Tropical Diseases (TDR). Dengue guidelines for diagnosis, treatment, prevention and control: new edition. http://apps.who.int/iris/bitstream/10665/44188/1/9789241547871_eng.pdf/Accessed on 10 April 2017.

[8] Ahmad S, Dhar M, Mittal G, Bhat NK, Shirazi N, Kalra V, et al. A comparative hospital-based observational study of mono- and co-infections of malaria, dengue virus and scrub typhus causing acute undifferentiated fever. Eur J Clin Microbiol Infect Dis. 2016;35(4):705-11.

[9] Kalawat U, Sharma KK, Reddy SG. Prevalence of dengue and chickungunya fever and their co-infection. Indian J Pathol Microbiol. 2011;54(4):844-46.

[10] Rezza G, El-Sawaf G, Faggioni G, Vescio F, Al Ameri R, De Santis R, et al. Co-circulation of Dengue and Chikungunya Viruses, Al Hudaydah, Yemen, 2012. Emerg Infect Dis. 2014;20(8):1351-54.

[11] Pessôa R, Patriota JV, Lourdes de Souza M de, Felix AC, Mamede N, Sanabani SS. Investigation into an outbreak of dengue-like illness in Pernambuco, Brazil, revealed a co-circulation of Zika, Chikungunya, and Dengue Virus type 1. Medicine (Baltimore). 2016;95(12):e3201.

[12] Wiwanitkit V. Concurrent malaria and dengue infection: a brief summary and comment. Asian Pac J Trop Biomed. 2011;1(4):326-27.

[13] Epelboin L, Hanf M, Dussart P, Ouar-Epelboin S, Djossou F, Nacher M, et al. Is dengue and malaria co-infection more severe than single infections? A retrospective matched-pair study in French Guiana. Malar J. 2012;11:142.

[14] Mohapatra MK, Patra P, Agrawala R. Manifestation and outcome of concurrent malaria and dengue infection. J Vector Borne Dis. 2012;49(4):262-65.

[15] Magalhães BML, Alexandre MAA, Siqueira AM, Melo GC, Gimaque JBL, Bastos MS, et al. Clinical profile of concurrent dengue fever and Plasmodium vivax malaria in the Brazilian Amazon: case series of 11 hospitalized patients. Am J Trop Med Hyg. 2012;87(6):1119-24.

[16] Hein N, Bergara GH, Moura NBV, Cardoso DM, Hirose M, Ferronato AE, et al. Dengue fever as a cause of haemophagocytic lymphohistiocytosis. Autopsy Case Rep. 2015;5(3):33-36.

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