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Emerging Co-Infections in Dengue: A Hospital Based Study

Authors
**Srikant Kumar Dhar[1], Uday Bhanu Rout[2*], Suse Naqash Nadar[3], K Sruthi[3],
Nalini Kanta Sahoo[3], Saptaswa Nayak[3]**
[1]Professor,PG Department of Medicine, IMS and SUM hospital, Siksha "O" Anusandhan University, K8,
Kalinganagar, Bhubaneswar-751003, Odisha, India
[2*]Assistant Professor, PG Department of Medicine, IMS and SUM hospital, Siksha "O" Anusandhan
University, K8, Kalinganagar, Bhubaneswar-751003, Odisha, India
[3]Junior Resident, PG Department of Medicine , IMS and SUM hospital, Siksha "O" Anusandhan University,
K8, Kalinganagar, Bhubaneswar-751003, Odisha, India
*Corresponding Author
Uday Bhanu Rout
Department of Medicine, IMS & SUM Hospital, Siksha "O" Anusandhan, K8, Kalinganagar Bhubaneswar,
Odisha, India

Abstract
Background: *Concurrent infection with two agents can result in an illness having overlapping symptoms creating a diagnostic confusion for the treating physician. This study attempts to find the current co-infections rates in dengue patients in a tertiary care hospital Eastern Odisha.*
Method: *Study conducted from July 2018 to June 2019 comprising of 100 dengue seropositive (NS1/IgM/IgG) patients of age >15 years in IMS & SUM Hospital.*
Result: *In our study 57% were NS1 positive and 28% had IgM positive for Dengue. NS1 and IgM positive in 8% patients, IgM and IgG positive in 3 % of case which indicated secondary cases and 2 cases with all NS1, IgM,IgG for Dengue positive. Out of 100 dengue patients, 39 % patients had co-infections. In which 12% were ICT positive for malaria, 9% salmonella IgM reactive, 8% Scrub typhus IgM reactive, 8% chikungunya IgM reactive, 2% Hepatitis B positive. We have found 2% mixed co-infections in dengue IgM positive patients. In our series in clinical manifestations all case (100%) presented with fever, mylagia (70%), headache (52%), rashes (22%), vomiting (17%), retro orbital pain (12%), abdominal pain (10%), yellowish sclera (4%), oliguria (2%), alter sensorium (2%) and bleeding manifestations (46%) cases. Complications detected hepatopathy (52%), ascites (10%), pleural effusion (8%), pneumonia (7%), splenomegaly (7%) nephropathy (5%), DSS (4%), MODS (4%) and DHS in 20 % of cases.*
Conclusion: *Co-infection should always be kept in mind while dealing with cases of dengue fever.This study brings out the incidence of dengue and co-infections and also differentiate concurrent infections.*
Keywords: *Coinfections, Dengue, malaria, salmonella, Scrub Typhus, chikungunya.*

Introduction and Background
Dengue fever had been a health care problem in 1950. In 1980s, there was second expansion of dengue epidemic in Asian countries. In 1996 and thereafter, there have been outbreaks of dengue in different parts of India. Again, of late, from 2013

dengue fever has become an epidemic in the whole country of India and it has been a huge health hazard.

Dengue is the emerging mosquito-borne viral disease of mankind with public health importance, with a 30- fold increase in global incidence over the last five decades. According to World Health Organization (WHO), about 50–100 million new dengue infections are suspected to occur annually in more than 100 endemic countries, with a progressively increase in the number of countries reporting the disease[1].

Worldwide

For dengue infection, approximately 2.5 billion (more than 70%) of the population at risk worldwide live in Member States of the WHO South-East Asia Region (SEAR) and Western Pacific Region, which bear nearly 75% of the current global disease burden due to dengue[2]. 3 Of the 11 countries of SEAR, 10 countries including India are endemic for dengue. The only exception is the Democratic People's Republic of Korea.

In India

For the first time in 1945 Dengue virus was isolated in India .occurrence of dengue fever in the country was reported in 1956 from Vellore district in Tamil Nadu that was the first evidence. The first dengue hemorrhagic fever (DHF) outbreak occurred in Calcutta (West Bengal) in 1963[2]. mid-1990s, epidemics of dengue in India have become frequent, especially in urban zones, and have quickly spread to regions, such as Arunachal Pradesh, Mizoram and Odisha.10 Recently it had spread uniformly to a number of states and union territories.10 It has also spread from urban to rural regions.

Dengue Virus

A positive-strand RNA virus of the Flaviviridae family with 4 distinct serotypes (DENV1–4), is transmitted to humans by several species of the Aedes mosquito, These viruses contain single stranded RNA and are small in size (50 nm)[3]. Etiology for dengue viral infections are viral replication, primarily in macrophages and immunological and chemical-mediated mechanism induced by host–viral interaction[4]. Humoral, cellular, and innate immunity of host are implicated in the progression of the illness. Dengue is clinically characterized by acute onset of high-grade fever lasting for 5 days to 6 days, associated with symptoms of malaise, vomiting, cough, headache (retro-orbital), muscle ache, joint pain, vomiting and stomach-ache[5]. Of patients with DF, 50-80% report with a peculiar cutaneous rash. Dengue infection is diagnosed clinically but confirmed by laboratory test. Virus detection in cell cultures, nucleic acid demonstration by using polymerase chain reaction (PCR), and viral antigens detection by serology (such as NS1) or particular antibodies are the preferred microbiological assays. During early phase of infections (febrile period), dengue PCR is performed. After febrile illness dengue IgG and Ig M is preferred tests.

Co-infections

Mixed infection with two agents can result in an illness having overlapping symptoms creating a diagnostic dilemma for the treating physician.

Co-infectionsin dengue patients (Fig.1) are underest-imated most of time. Co-infection has atypical presentation in dengue patients. Co-infections detected are malaria, chikunguniya, scrub typhus, salmonella typhi and hepatitis B infection.

Dengue is one such disease which usually presents with symptoms of flu-like illness with high-grade fever, generalized body ache, nausea, and vomiting as well as peculiar rashes. The symptoms of dengue may mimic other diseases such as malaria, influenza A, *Salmonella* Typhi, Japanese encephalitis, chikungunya and scrub typhus which are also prevalent in areas where dengue is endemic[6]. The similarity in symptoms and differential diagnoses of these diseases often mimick those of dengue and thereby makes

accurate clinical diagnosis and treatment difficult for physician without laboratory confirmation[7]. In India, potential dengue fever is generally ascribed to all febrile illnesses during the monsoon period (July to November) unless confirmed through laboratory testing.

Dengue co- infection with malaria, scrub typhus and other arboviral illnesses has been studied in many parts of the world[8]. Epidemiology, disease course and complications have been studied and reported for co-infections, both in India and abroad. This study attempts to find the current co-infections rates ina tertiary care hospital Eastern Odisha.
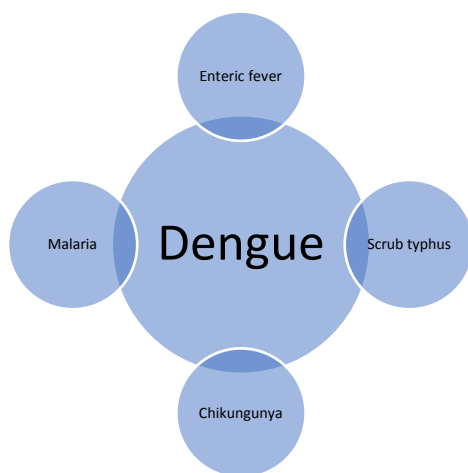

Fig 1. Co-infections in dengue.

Method

This study was a prospective, observational study conducted in department of Medicine comprising of 100 patients suffering from dengue selected from Indoor of Department of Medicine of IMS and SUM Hospital, a tertiary care hospital, Bhubaneswar, during the period from July 2018-June 2019.

Inclusion Criteria

Patients of more than 15years of age who had fever and who were found to be positive for NS1 antigen (Micro ELISA) or dengue IgM (antibody) with or without IgG positive for Dengue were included in study.

Exclusion criteria

Any pediatrics patients less than 15 years, outdoor patients of dengue, known case of CLD and known case of CKD.

Total of 100 patients (age>15years) were enrolled during the outbreak of disease. A detail clinical history, systemic examination routine haematological examination i.e. haemoglobin (Hb), total leukocyte count(TLC), platelet count(PC), Liver Function Test(LFT), Renal Function Test(Serum Urea, Creatinine),Fasting Blood Sugar(FBS), PT, INR, Stool for Ocult Blood, Urine Routine and Microscopy, malarial antigen Test(MP ICT), slide test for malaria parasite, IgM antibodies for typhoid and Widal test for typhoid ,Chest X ray PA View , Ultrasonography of Abdomen and Pelvis was performed. Special investigations done to detect co-infections like chikungunya IgM (ELISA), scrub typhus IgM (ELISA) and hepatitis B antigen (HbsAg). Patients who were suffering from diabetes, hypertension and other correlated disease were excluded from our study. All subjects were classified according to WHO guidelines. Thrombocypopenia was taken as platelet count less than 1 lakh/mm3 and leuopenia as white blood cells (WBC) <5000 cells/mm3.

Data were entered and analysed in SPSS version 12 statistical software.

Table 1: Antigenic/ Antibody presentations of dengue cases.

Antigen/Antibodies detected	No.of patients (out of 100)
NS 1 antigen	57
IgM antibody	28
NS1 Antigen + IgM Antibody	8
IgM Antibody + IgG Antibody	3
NS1 Antigen + IgM Antibody+IgGAntibody	2

In our study 57% were NS1 positive and 28% had IgM positive for Dengue. NS1 and IgM positive in 8% patients, IgM and IgG positive in 3 % of case which indicated secondary cases and 2 cases with all NS1,IgM,IgG for Dengue positive (Table 1)

Table 2: Co-infections in dengue patients

Co-infections detected in dengue seropositive (NS1/IgM/IgG) patients	No.of patients (out of 100)
Malaria (MP ICT +ve)	12
Enteric fever (Salmonella IgM +ve)	9
Scrub typhus (IgM reactive)	8
Chikungunya(IgM reactive)	8
Hepatitis B +ve	2

Out of 100 dengue patients, 39 % patients had co-infections. In which 12% were MP-ICT.
positive, 9% salmonella IgM reactive, 8% Scrub typhus IgM reactive, 8% chikungunya IgM reactive, 2% Hepatitis B positive (Table 2).

Table 3: Mixed co-infections

Mixed co-infections	No.of patients (out of 100)
Scrub typhus IgM +chikungunya IgM+ Dengue IgM positive	1
Scrub typhus IgM + hepatitis B + Dengue IgM positive	1

We have found 2% mixed co-infections in dengue IgM positive patients. Scrub typhus IgM +chikungunya IgM+ Dengue IgM positive and Scrub typhus IgM + hepatitis B + Dengue IgM positive (Table 3).

Table 4: Clinical manifestations

Symptoms	Number of cases	Percentage (%)
Fever	100	100
Myalgiaandbackache	70	70
Headache	52	52
rashes	22	22
Vomiting	17	17
Retro orbital pain	12	12
Abdominal pain	10	10
Yellowish sclera	4	4
Oliguria	2	2
Alter sensorium	2	2
Bleeding manifestions	46	46

In our series in clinical manifestations all case(100%) presented with fever, mylagia (70%), headache (52%), rashes (22%), vomiting (17%), retro orbital pain (12%), abdominal pain (10%), yellowish sclera (4%), oliguria (2%), alter sensorium (2%) and bleeding manifestations in (46%) cases (Table 4).

Table 5: Complications

Complications	Number of cases	Percentage (%)
Hepatopathy	52	52
Ascites	10	10
Pleural effusion	8	8
Splenomegaly	7	7
Pneumonia	7	7
Nephropathy	5	5
DSS	4	4
MODS	4	4
DHF	20	20

Complications detected like hepatopathy (52%), ascites (10%), pleural effusion (8%), pneumonia (7%), splenomegaly (7%) nephropathy (5%), DSS (4%), MODS (4%) and DHS in 20 % of cases (Table 5).

Results
In our study 57% were NS1 positive and 28% had IgM positive for Dengue. NS1 and IgM positive in 8% patients, IgM and IgG positive in 3 % of case which indicated secondary cases and 2 cases with all NS1, IgM,IgG for Dengue positive (Table 1).Out of 100 dengue patients , 39 % patients had co-infections. In which 12% were MP-ICT positive, 9% salmonella IgM reactive, 8% Scrub typhus IgM reactive, 8% chikungunya IgM reactive, 2% Hepatitis B positive(Table 2).We have found 2% mixed co-infections in dengue IgM positive patients. Scrub typhus IgM +chikungunya IgM+ Dengue IgM positive and Scrub typhus IgM + hepatitis B + Dengue IgM positive (Table 3). In our series in clinical manifestations all case(100%) presented with fever, mylagia (70%), headache (52%), rashes (22%), vomiting (17%), retro orbital pain (12%), abdominal pain (10%), yellowish sclera (4%), oliguria (2%), alter sensorium (2%) and bleeding manifestations in (46%) cases (Table 4). Complications detected like hepatopathy (52%), ascites (10%), pleural effusion (8%), pneumonia (7%), splenomegaly (7%) nephropathy (5%), DSS (4%), MODS (4%) and DHS in 20 % of cases (Table 5).

Discussion

The top three causes of fever in Odisha during the rainy season (July- October) are dengue fever, *scrub typhus* and malaria other viral illnesses (hepatitis A, influenza A, chikungunya etc).

Arboviral diseases are very important emerging infectious diseases in India. The changing Indian scenario in terms of mass migration to urban states,global climate changes, deforestation, etc has possibly made a marked difference in terms of infectious diseases.

Malaria is the mostcommonest co-infection has been seen in dengue. Co-infection rate has been documented 8.3% in a Brazilian series to 26% in an Indian seriesmaghada et al[9]. We found 12% malaria case in our series may be because of our series is smaller than the other studies. According to indian studies Pl. falciparum is most commonly associated; however, Pl. vivax is frequently reported in foreign literature[9]. Typical fever paroxysms were absent. Yellowish sclera and bleeding manifestations were common presentation along with headache, myalgias and backache. Hypotension and hepato-splenomegaly noted. Laboratory-wise, anemia, leucopenia and thrombocytopenia are more severe in co-infection. Hematocrit is not that useful to guide to treatment in the presence of malaria.

Enteric fever

IgM salmonella detected in 9% cases with dengue our study. Some of Indian studies found 7.8% cases like in Sharma Y et al[10]. Enteric fever is usually caused by *S*. typhi and by *S*. paratyphi and *S*. choleraesuis. The onset of symptoms is insidious with an incubation of 10-14 days. The fever is unremittent; there are spikes in temperature without getting back to normal temperature (saddle back fever)[10]. In contrast, dengue fever presents as spectrum of illness ranging from mild febrile illness to severe and fatal hemorrhagic disease. In a typical case of dengue fever, the patient experiences high fever lasting for 5 to 6days. Concomitantly, myalgias (70%), especially lower back, arm, and leg pains, malaise, arthralgia and anorexia may accompany[10]. In Enteric fever, a dull, continuous frontal headache begins during the initial days of fever; mild arthralgia is seen involving multiple joints and vague, poorly localized back pain may occur[10]. Constipation is more occur than diarrhea in Enteric fever however In dengue fever, constipation is occasionally occured; diarrhea and respiratory symptoms are frequently reported and may be due to concurrent infections.

Scrub typhus

We have detected 8% of scrub typhus cases in dengue patients. Most of the scrub typhus patients presented with pneumonia which was comparatively less in dengue patients. It is diffuct to differentiate with dengue but CMC Vellore has done some studies and given clinical score to differentiate scrub typhus and dengue. Scoreless then13 favors scrub typhus and more than 13 favors dengue, the sensitivity and specificity to diagnose dengue was 85% and 77% respectively[11]. So we used this scoring system in our case series.

Chikungunya

Aedesaegypti is the common Vector for both Chikungunya and Dengue .We have detected 8% chikungunya in dengue patients. Dengue patients also experience arthralgias. So diagnosing Chikungunya in the setting of dengue fever is a difficult[12]. Evidence of thrombocytopenia, serositis, shock and point towards dengue. Arthralgia in dengue was subsiding, whereas; Chikungunya leads to disabling arthritis which may last for several months[13].

Early recognition along with meticulous monitoring and targeted supportive care is the cornerstone of a successful outcome in dengue co-infections.

Conclusion

With the rise in incidence of co-infections in dengue fever, there is necessity to understand co-infections, now more than ever, and this study brings out the incidence of dengue and co-

infections and also differentiate concurrent infections. Dengue and co-infections, may lead to multi-organ involvement and further undesired consequences so that early diagnosis of co-infections in dengue is very much essential for better clinical outcome. However, further studies are required for more evaluation of clinical and laboratorial spectrum of co-infections in dengue.

Conflict of interest: Nil
Ethical committee clearance: taken from Hospital Ethical Committee
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