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Original Article

Dengue infection in North India: An experience of a tertiary care center from 2012 to 2017

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Abstract

Objective: Recently, an alarming rise of dengue has been seen in India which remains a major public health concern. This study has been designed for a comprehensive overview of the epidemiology, gender, age, area distribution, symptomology, and seasonal variability. **Materials and Methods:** Retrospective analysis of 900 suspected dengue cases of all age groups of either sex from 2012 to 2017 at a North Indian tertiary care hospital revealed 461 (51.22%) cases seropositive for dengue. **Results:** The age group of 20–30 years was the most affected group with male predominance. The urban population was more affected as 75.05%, and maximum cases were detected in October month followed by November. Common abnormal laboratory parameters were thrombocytopenia (99.1%), hepatic dysfunction (59%), and leukopenia (26.68%). Two uncommon findings, pancytopenia and pancreatic dysfunction were reported in 7 and 3 cases respectively. **Conclusion:** Dengue infection in India has evolved rapidly, and regular outbreaks have been observed with a changing epidemiology, as the disease is rapidly spreading from urban to rural areas with increasing atypical manifestations.

Keywords: *Atypical presentation, Dengue virus, Pancytopenia, Platelet transfusion, Vector-borne disease*

Introduction

Today, dengue is the most important mosquito-borne, a human viral disease in terms of both the number of cases and the number of deaths. Therefore, dengue is considered a major global health threat by the World Health Organization. Dengue infection in humans is caused by one of the four dengue virus (DENV) serotypes (DENV1, DENV2, DENV3, and DENV4) through the bite of infected mosquitoes [1,2]. In recent years, it has changed its course of the presentation by a range of variety of manifestations and outcome from self-limiting to severe illness and fatal outcomes with increasing frequency of outbreaks [3]. Around 100 million new cases are estimated in 100–125 countries per year while in the year 2010, 96 million apparent and 293 million unapparent cases of the dengue were estimated [2,4]. India is one of the dengue prevalent countries. Studies had described dengue in terms of occurrence of these epidemics in India, annual numbers of reported cases with serotypes, and mechanism of pathogenicity, clinical presentation, and the role of the vectors [5]. Many times, the real number of cases could not be identified due to the under/over-reporting or misdiagnosis of cases. Due to lack of awareness, effective and early management, unavailability of the vaccine, dengue remains a challenge for public health authorities in India [2]. The purpose of the present paper is to provide a comprehensive overview of the epidemiology of gender, age distribution, spread, and seasonality from January to December 2012–2017.

Materials and methods

It is a retrospective (record based) study. Serum samples from clinically dengue suspected cases (n = 900) of all age groups and either sex were collected from various departments of Institute of Medical Science, Banaras Hindu University (IMS, BHU), Heritage IMSs, district hospitals of Varanasi and nearby districts such as Chandauli and Jaunpur from 2012 to 2017. BHU is a tertiary care center serving patients of whole eastern Uttar Pradesh and other nearby states (Bihar and Madhya Pradesh). A whole blood sample of 5 mL along with detailed clinical history was collected from the suspected dengue patients and transported by the staff to the department of microbiology in an ice box maintained at 2°C–8°C within 24–48 h. All samples were tested for dengue using IgM

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antibody capture ELISA kit produced by the National Institute of Virology (Arbovirus Diagnostic NIV, Pune, Maharashtra, India). The sensitivity and specificity for dengue IgM antibody capture ELISA were 98.53% and 98.84%, respectively. The tests were carried out following the manufacturer instructions. The study was approved by the Local Ethics Committee of the institute. Informed written consent was waived because the study was a retrospective data analysis.

Results

Dengue suspected cases (n = 900) were studied for 6 years from 2012 to 2017, in which, 461 (51.22%) cases were sero-positive. Distributions of suspected and confirmed cases are represented in Figure 1. More of the cases in 2012, 2014, 2016, and 2017 were found in the age group of 20–30 years while in 2013 and 2015, most cases were of age <20 years. Throughout the study, 595 males were suspected, in which 337 (56.63%) were found positive. Male gender was dominant as male and female ratio was (2.7:1). The Urban population (75.05%) was more affected than rural (24.95%). In collected data, Varanasi district was found most affected throughout the years as suspected cases (S) from Varanasi were 650, in which 338 cases were found positive (P), followed by Jaunpur and Chandauli districts [Table 1]. Maximum dengue confirmed cases 218 (47.29%) were found in October month followed by 111 (24.08%) in November and 109 (23.64%) cases in September Figure 2].

The clinical presentation of DENV infection revealed in study as the sudden onset of fever (100%) accompanied by headache (77%), myalgia (58.78%), abdominal discomfort/pain (46.64%), nausea (38.83%), backache (32.97%), fatigue (29.07%), rashes (17.14%), and arthralgia (3.47%). The common abnormal laboratory parameters were thrombocytopenia (99.1%), hepatic dysfunction (59%), and leukopenia (26.68%) [Table 2].

Discussion

First of all, DENV was isolated by inoculation of serum of patients in suckling mice in Japan in 1943 while in India,from serum samples of the US soldiers in Kolkata in 1944 [6]. In India, the first epidemic of clinical dengue-like illness was reported in Madras (now Chennai) in 1780 [7]. The first large epidemic of dengue began in Calcutta (now Kolkata) and Eastern Coast of India in 1963–1964 [7]. In the epidemic of Kolkata, 200 deaths were reported, in which 30% of cases were having hemorrhagic manifestations. After this epidemic, many outbreaks of dengue fever (DF) occurred from different parts of the country [8,9].

Regular and gradually larger outbreaks have been observed with an increase in atypical manifestation. Although there had been persisting of multiple DENV serotypes, considered as a risk factor for dengue hemorrhagic fever (DHF) [8]. In India, the earliest virologically proved outbreak occurred in Vellore, Tamil Nadu, in 1956 and the first-time isolated DENV was established as serotype 1 virus in 1945 in Calcutta, followed by DENV-2 in 1956, DENV-4 in 1960, and DENV-3 in 1965. In 1963, DENV-1, DENV-2, and DENV-4 were isolated during a DF outbreak in an outbreak of 1968 in Vellore [8,10]. Delhi remained a hyperendemic region for dengue throughout, and all four DENV serotypes were found to co-circulate in Delhi for the first time in 2003, followed by in 2006 [8,11].

In general, all age groups are affected by dengue infections in India [1,5]. Younger age group is more commonly affected by DF while children of age under 15 years are more prone

Table 1: Demographic characteristics of cases

Characteristics	2012		2013		2014		2015		2016		2017		Total	
	S	P	S	P	S	P	S	P	S	P	S	P	S	P
Age (years)														
<20	11	5	34	28	9	3	135	72	43	5	38	21	270	134
20-30	18	12	31	25	25	8	105	48	65	34	72	49	316	176
30-40	7	3	21	18	3	0	49	21	27	17	26	13	133	72
40-50	8	3	7	6	10	3	36	15	33	20	17	9	111	56
>50	1	0	5	2	7	1	20	5	18	9	19	6	70	23
Sex														
Male	31	18	69	52	31	11	237	118	112	66	115	72	595	337
Female	14	5	29	27	23	4	108	43	74	19	57	26	305	124
Locality														
Urban	40	21	58	41	39	11	297	143	97	46	122	84	653	346
Rural	5	2	40	38	15	4	48	18	89	39	50	14	247	115
District														
Varanasi	43	22	50	42	48	12	305	149	96	48	108	65	650	338
Chandauli	0	0	10	8	0	0	18	6	49	8	14	9	91	31
Jaunpur	0	0	18	12	0	0	10	2	31	27	45	23	104	64
Others	2	1	20	17	6	3	12	4	10	2	5	1	55	28
Total	45	23	98	79	54	15	345	161	186	85	172	98	900	461

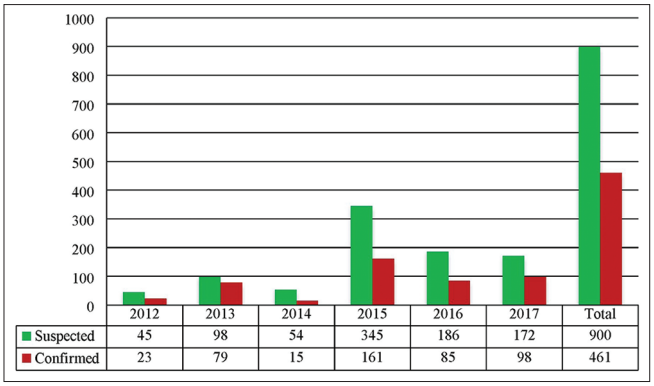

Figure 1: Dengue cases during the study period from 2012 to 2017

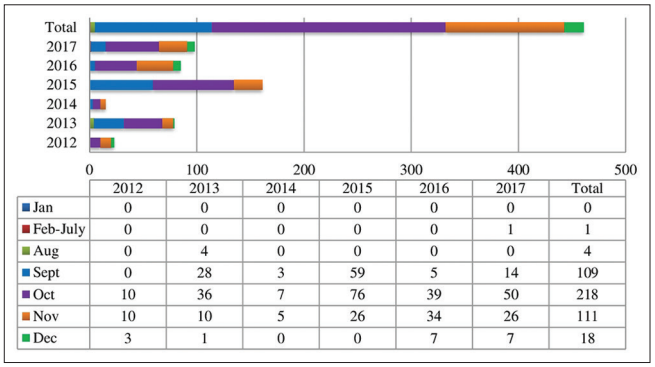

Figure 2: Seasonal distribution of dengue confirmed cases

Table 2: Clinical features and laboratory parameters of dengue positive cases (*n*=461)

Clinical features/lab parameters	Patients, *n* (%)
Fever	461 (100)
Headache	355 (77.00)
Nausea/vomiting	179 (38.83)
Backache	152 (32.97)
Muscle pain	271 (58.78)
Joint pain	16 (3.47)
Retro-orbital pain	36 (7.81)
Generalized weakness	134 (29.07)
Abdominal discomfort	215 (46.64)
Rash	79 (17.14)
Itching	41 (8.89)
Loose stool	9 (1.95)
Bleeding manifestations	47 (10.19)
Altered behavior	5 (1.08)
Thrombocytopenia	457 (99.13)
Leukopenia	123 (26.68)
Pancytopenia	7 (1.52)
Leukocytosis	42 (9.11)
Ascites	23 (4.99)
Pleural effusion	9 (1.95)
Hepatic dysfunction	272 (59.00)
Renal dysfunction	13 (2.82)
Pancreatic dysfunction	3 (0.65)

to DHF [8]. The present study revealed that the age group (20–30 years) was more affected. Studies supporting young adults as predominantly affected are during epidemics in Delhi of period 1999–2006, Chandigarh, Haryana, Maharashtra, Punjab, and Uttar Pradesh [8,9,11]. On the other hand, the highest numbers of cases in the 5–12-year-old age group were reported from epidemic in Delhi in 1996, West Bengal in 1990 and 2005, Tamil Nadu in 1998 and 2003, Madhya Pradesh in 2001 and 2003, Uttar Pradesh in 2003–2006, and Puducherry in 2003–2004 [7,8,12,13]. The lack of immunity among children could be the possible role of the high fatality rate. Although reviewing literature does not differentiate age groups for DF and DHF [5].

It is very inconclusive to say which gender is prone to dengue infection. This study found the high male to female (2.7:1) ratio as shown in most of the outbreaks in India [8,9,14]. In contrast, a study observed females are more commonly infected than males [15]. Although many studies showed no difference in the gender distribution of dengue cases [16]. This difference in gender may be due to social and cultural biasing as India is male predominant country.

In tropical areas, transmission is maintained throughout the year and intensifies at the start of the rainy season, when infected vector mosquitoes are more abundant as high humidity lengthens their lifespan and increased temperatures shorten the extrinsic incubation period. Most studies reported bulk of dengue cases during and subsequent to monsoon months in India as observed in this study, dengue was on peak in October month followed by November. In contrast, some outbreaks occurred during the dry summer months as outbreaks during April and May 1985 in Rajasthan, March–May 1989 in Maharashtra, January–March 1998 in Tamil Nadu [8,17]. Exceptionally, long-epidemic period (July–March) was recorded in Calcutta and recently, throughout the year in Lucknow [9].

In the past, it is no doubt that most of the outbreaks were reported from large cities of India that suggestive of dengue is an urban disease. Multiple outbreaks of DF/DHF in Delhi, Chandigarh, Puducherry, Bengaluru, and Mangalore in Karnataka, Gwalior in Madhya Pradesh, Amalner in Maharashtra, Ludhiana in Punjab, Jalore and Ajmer in Rajasthan, Vellore and Chennai in Tamil Nadu, Lucknow in Uttar Pradesh, and Calcutta in West Bengal are occurred in urban areas [10-12,18]. The mosquitoes flourish vigorously in urban and semi-urban localities congested with human population usually during rains [5]. The rapid urban growth creating poor water supply and wastewater management systems, human-made water logged provides an ideal environment for vector proliferation. In contrast, currently, dengue is spreading progressively to rural areas rapidly, and cases are distributed dominantly in rural areas, as observed from Northern India (Haryana) in 1996, Tamil Nadu and Maharashtra, also observed in our study [9,11,16].

Recently, apart from classical presentation, the clinical profile of dengue is changing, and atypical manifestations are reported frequently [Table 3] [1,7,9,19-25]. The frequent laboratory-detected abnormalities found in the present study were leukopenia and thrombocytopenia, though the deranged liver function was not also uncommon as observed in previous studies [9,26]. Pancytopenia and pancreatic dysfunction were uncommon findings observed during the course of illness which were improved fully subsequently on the recovery of dengue infection. Thrombocytopenia in DF was typical and prominent laboratory finding. Patients receiving multiple platelets transfusions or use of other blood products may be alloimmunized to many human leukocyte antigen and platelet-specific antigens [20,26,27]. Hence, single-donor apheresis platelets transfusion should be promoted as compared to random donor platelets to decrease the risk of alloimmunization.

Factors influencing the clinical outcome of dengue

(A) It is widely reported that susceptibility to DHF/dengue shock syndrome lowers considerably after 12 years of age [28]. It may be related to immunological status and serotype of dengue. (B) It is well observed that severe dengue is more likely to occur with a second DENV infection than with the first DENV infection [28]. Further, serotype 1 followed by serotype 2 seems to be more dangerous than serotype 4 followed by serotype 2. Besides this, serotype 2 is considered more dangerous than other serotypes [28]. Therefore, during secondary infections, serotype 2, severe illness and unusual presentations are considered as determinants [29]. (C) To be a determinant, it may relate to socioeconomic status, cultural behaviors, climatic changes, and adaptive immunity. It has a protective role for African ancestry/"Blacks," while risk factor for Caucasian/"Whites" [2,28]. (D) Gender differentiation in dengue is variable in different studies, but no study described significant sex differentiation as a determinant of mortality. Studies have been reported the majority of dengue mortalities in men [2,23] and women [26]. (E)

Table 3: Atypical manifestations of expanded dengue syndrome

System	Manifestations
Neurological involvement	Neurological involvement seizures, encephalopathy, Encephalitis/aseptic meningitis, intracranial hemorrhages/thrombosis, subdural effusions, Mononeuropathies/polyneuropathies/Guillain-Barre syndrome, transverse myelitis, papilledema, myoclonus, pyramidal signs, myelitis, acute motor weakness, neuritis, hypokalemic paralysis, cranial nerve palsy
Gastrointestinal/hepatic involvement	Hepatomegaly, hepatitis/fulminant hepatic failure, hepatic encephalopathy, acalculous cholecystitis, acute pancreatitis, hyperplasia of Peyer's patches, acute parotitis, moderate ascites, acute inflammatory colitis and gastric hemorrhage
Renal involvement	Hematuria. Acute renal failure, Hemolytic uremic syndrome
Cardiac involvement	Myocarditis, pericarditis, cardiogenic shock, pulmonary edema, bradyarrhythmia (severe sinus bradycardia), heart block, tachyarrhythmia - atrial fibrillation, acute reversible cardiac insult, sinoatrial block, and atrioventricular dissociation
Respiratory involvement	Acute respiratory distress syndrome, pulmonary hemorrhage
Musculoskeletal involvement	Myositis, rhabdomyolysis, polyarthritis, postinfectious fatigue syndrome
Lymphoreticular/bone marrow involvement	IAHS or HLH, ITP, spontaneous splenic rupture, lymph node infarction
Ophthalmic involvement	Impaired visual acuity, Macular hemorrhage, Optic neuritis, uveitis
Psychological involvement	Depression, hallucinations, psychosis
Vasculitis/immunological involvement	Systemic lupus erythematosus, Kawasaki disease in the young child
Dermatological involvement	Maculopapular/morbilliform eruption followed by ecchymotic, petechial, and macular/scarlatiniform eruption, confluent erythema, morbilliform eruptions, and hemorrhagic lesions, alopecia
Hematological/coagulation disorder	Bone marrow hemophagocytosis associated with nasal bleeding (epistaxis), pancytopenia, DIC
Oxidative stress	Increase in oxidative stress significantly elevated PCOS and low PBSH group levels

HLH: Hemophagocytic lymphohistiocytosis, IAHS: Infection associated hemophagocytic syndrome, DIC: Disseminated intravascular coagulation, PBSH: Protein-bound sulfhydryl group, PCOS: Protein carbonyls, ITP: Idiopathic thrombocytopenic purpura

There is no study describing comorbidities directly related to fatal outcomes. However, an association of comorbidities such as Type 2 DM, HTN, Pulmonary, and Cardiac diseases is described to worsen dengue [20]. Further, more studies are needed for a clear conclusion. (F) Occupation is not describing directly as the determinant of mortality in the literature [2]. (G) Socioeconomic status is not related to mortality, but education is described to relate to mortality. It was analyzed on the basis of knowledge of patients and health staff [2]. (H) No study to show direct correlation mortality with nutrition but malnutrition is described to protect from induction of vascular permeability and shock [28].

Co-infection

The situation of simultaneous cocirculation of dengue, chikungunya, and zika is an interesting issue in the current scenario. Recently, many studies had shown increased incidences of coinfection with chikungunya [26]. Both diseases (chikungunya and dengue) are transmitted by the bite of infected *Aedes* species mosquitoes and share similar clinical signs and symptoms becoming difficult to differentiate clinically [30]. It is controversial, but more studies favor no clinical outcomes were exacerbated by coinfection [26]. The studies showing coinfection of dengue and zika virus is a very curious topic nowadays. Similar to chikungunya, *Aedes aegypti* is capable of cotransmission of dengue with zika virus [31]. Fortunately, studies did not observe increased severity with dengue with zika virus coinfection [32]. Furthermore, one study had demonstrated simultaneous cocirculation of dengue, chikungunya, and zika virus [33]. However, in India, a study in the year 2016 from Jammu (a Sub-Himalayan Region of India) analyzed 808 samples and showed seroprevalence of DENV, chikungunya virus, and coinfection but no positive case of zika virus [34].

Conclusion

Increasing circulation of multiple DENV serotypes is reported from all over India, particularly in large urban areas. As soon as clinical features are an indicator of a possible etiological agent, newer molecular diagnostic techniques, such as reverse transcription-polymerase chain reaction, is needed to detect rapid increment of viral circulation or changes in predominant serotypes. Besides early recognition and prompt management, one has to concentrate on vector surveillance and control strategies. In the absence of a vaccine, dengue prevention currently relies on public health and community-based *A. aegypti* control programs to remove and destroy mosquito breeding sites. Future vaccination, public awareness, and a better understanding of the role of the mortality determinants in disease severity would definitely helpful to implicate the planning and implementation of effective public health measures.

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Conflicts of interest

There are no conflicts of interest.

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