

**Clinical Presentations of Dengue Fever: Is there a Paradigm Shift? Experience in a Teaching Institution in Delhi**Dr. Balvinder Singh Arora,<sup>1</sup> Dr. Deepti Kiran,<sup>2</sup> Dr. Ritin Mohindra,<sup>3</sup> Dr. Arun Gogna,<sup>4</sup> Dr. K.C. Aggarwal<sup>5</sup><sup>1</sup>Director – Professor, Department of Microbiology, VMMC & Safdarjung Hospital, New Delhi.<sup>2</sup>Dr. Deepti Kiran, Senior Resident - Department of Microbiology, VMMC & Safdarjung Hospital, New Delhi.<sup>3</sup>Dr. Ritin Mohindra, Assistant Professor, Department of Emergency Medicine, A.I.I.M.S. New Delhi.<sup>4</sup>Dr. Arun Gogna, Consultant, Department of Medicine, VMMC & Safdarjung Hospital, New Delhi.<sup>5</sup>Dr. K.C. Aggarwal, Consultant, Department of Paediatrics, VMMC & Safdarjung Hospital, New Delhi.**Correspondence Author: Dr. Balvinder Singh Arora**, Director – Professor, Department of Microbiology, VMMC & Safdarjung Hospital, New Delhi.**Conflicts of Interest:** Nil**Abstract**

Dengue, a Flavi virus causes disease that may vary from subclinical infection to self-limiting disease, the Dengue Fever (DF), or 'Dengue Hemorrhagic Fever (DHF/DSS)' that may prove fatal. Dengue illness usually presents as asymptomatic or mild Acute Undifferentiated Fever (AUF).

Although, it is usually diagnosed on the basis of its clinical presentations but changes in trends of clinical presentations have been witnessed in recent times. Such shifts in 'clinical presentations paradigms' tends to cloud the index of clinical suspicion especially during outbreak periods. The present hospital based observational study, retrospective in nature, was to understand current trends in clinical pictures of acute dengue infection in serologically confirmed IgM positive cases reporting in our tertiary care hospital in Delhi. The study enrolled a total of 500 cases clinically suspected of DF/DHF/DSS that either reported directly or were referred to Safdarjang hospital for treatment.

All patients underwent routine investigations but only 'clinical picture presentations of IgM seropositive cases' are discussed in the present study. Of total 500 serum samples tested, 169 i.e. 33.8% were found to be sero

positive for presence of IgM antibody. Fever was recorded in all cases (100%). Retro orbital pain (61.22% cases) emerged as the next most important symptom. It was followed by calf tenderness in 55.71% cases. Rashes and bleeding manifestations were seen equivocally to the extent of nearly 39%. Organomegaly in 43% and serositis in 25% cases were a significant finding. p value of less than 0.05 was considered as significant.

A shift from DHF/DSS cases to atypical presentations with organ dysfunctions is becoming more common as seen in the study. Since every case does not buildup evidence for IgM seropositivity, this paradigm shift in clinical presentations with increasing organ dysfunctions and atypical presentations pose a diagnostic challenge, especially during epidemic outbreaks.

**Keywords:** Dengue infection, IgM seropositivity, epidemics, clinical presentations paradigm shifts.

**I. Introduction**

Dengue has shown 30-fold increase globally over the past five decades.<sup>1</sup> About 50 to 100 million people are infected annually leading to approximately 5,00,000 hospitalizations every year.<sup>2</sup> The incidence has been rising in the last two decades.<sup>3</sup> The number of Dengue cases in Delhi in the year 2015 amounted to more than 15,000

making it the worst outbreak of the vector-borne disease in Delhi including NCR areas.<sup>4,5</sup> Nearly 20 years ago, the deadly virus had claimed more than 420 lives, while the mortality count in 2015 was 45. 2-5. All four serotypes of Dengue virus (DENV) - DENV1, DENV2, DENV3, and DENV4 can cause clinical manifestations ranging from self-limiting asymptomatic subclinical infection to the more serious and often fatal Dengue Hemorrhagic Fever (DHF) & Dengue Shock Syndrome (DSS).<sup>1,2</sup> Clinically, a patient infected with DENV presents with acute onset fever, headache, retro-orbital pain, and severe back pain along with intense myalgia because of which it has received a colloquial term 'Break Bone Fever'.<sup>3,4</sup> Epistaxis, blanching erythematous macular rash and scattered petechiae sometimes are seen in uncomplicated dengue.<sup>3</sup>

Atypical presentations of dengue such as encephalitis, myocarditis, hepatitis, cholecystitis, acute kidney injury, and acute parotitis have also been reported.<sup>3,8</sup> Although dengue classically presents as asymptomatic or mild acute undifferentiated fever (AUF) but in recent times a paradigm shift in clinical presentation of the dengue illness have been reported.<sup>8</sup> Such paradigm shifts in clinical presentations tends to cloud the index of clinical suspicion posing ever new challenges, especially during outbreak periods, in particular, in cases that are seronegative.<sup>2-4,8</sup>

## **II. Objective**

The objective of the present study was to know the current trends in clinical presentations of acute dengue infection, including paradigm shifts if any, in serologically confirmed IgM positive cases.

## **Inclusion criteria**

Five hundred patients of either sex, less than 60 years age who presented to the Departments of Medicine, Paediatrics & Clinical Microbiology, Vardhman Mahavir

Medical College & Safdarjung Hospital with acute febrile illness, clinically suspected to be dengue fever, were profiled as a part of this study. After taking informed consent and detailed history, clinical examination was performed.

## **Exclusion criteria**

Patients aged more than 60 years and those having an alternative diagnosis like malaria, typhoid, urinary tract infection, and chikungunya were excluded from this study.

## **Controls**

Fifty age and gender matched patients with febrile illness due to any cause other than dengue were included as controls.

## **Data Collection**

The data was collected & recorded into a preformatted questionnaire (Data Collection Forms) (DCF). It was transferred to excel sheets for analyses by SPSS (IBM SPSS Statistics V21.0 for windows, United States) software.

## **Ethical Clearance**

The study was approved by the Institutional IEC.

## **III. Materials & Methods**

Sera from all the 500 cases were tested for Dengue IgM antibody by IgM Antibody Capture ELISA (MAC ELISA) kits supplied by National Institute of Virology (NIV), Pune. In addition, rapid malaria antigen test, peripheral smear for malaria parasite, blood culture, widal test, chikungunya serology and urine routine examination & microscopic examination (RE/ME) and bacteriology culture testing was also done on all blood samples to rule out alternative diagnosis, if any.

## **IV. Results**

All 500 patients with febrile illness, clinically suggestive of dengue, presented **within 10 days of the illness (duration of illness at the time of presentation)**. (Table I)

Table I: Clinical presentations in 169 IgM seropositive patients.

Clinical features	IgM antibody seropositive (169)	p-value
Fever	169 (100 %)	0.0325
Retro-orbital pain	43 (61.22%)	0.0035
Calf-tenderness	43 (55.71%)	0.0225
Rashes/ petechiae	36 (39.13%)	0.855
Bleeding manifestations	21(39.62%)	0.875
Serositis	16 (25%)	0.985
Organomegaly	18 (43.28%)	0.558

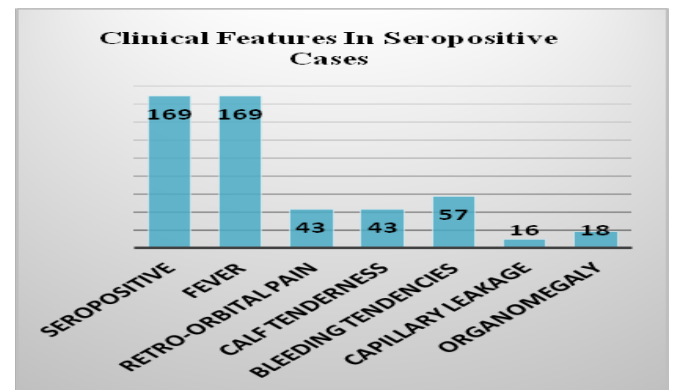
**Retro-orbital pain:** Retro orbital pain, typical of dengue fever, was seen in 98 (19.60%) cases. Forty three of these 98 (61.22%) were IgM seropositive (p-value 0.0035). **Calf tenderness** lasting for 2-6 days was present in 84/500 (16.80%) & 43/84 (55.71%) were IgM seropositive (p-value 0.0225).

**Rashes and petechiae:** These were primarily seen over upper and lower limb and rarely on abdomen and back. It was the primary complaint in 92 (18.40%) patients; amongst which 36 (39.13%) were, similarly, IgM seropositive (p-value 0.875).

‘Other bleeding manifestations’ viz. sub conjunctival hemorrhage, epistaxis, hematuria, hematemesis, hemoptysis, and malaena were altogether seen in 53/500 (10.60 %) patients. Of these 53 patients, **21 (39.62%) were seropositive for IgM antibody (p-value 0.875).** Amongst these 21 IgM seropositive, 10 (47.61%) patients had **epistaxis**, 5 (23.80%) suffered from **hemoptysis**, and 6 (28.57%) had **malaena**. However **no patient had subconjunctival hemorrhage, hematemesis, or scleral injection. Sixty three of 500 i.e. 12.6% patients presented with features of serositis**

**that included anasarca - 09 cases, ascites - 13 cases, and pleural effusion - 41 cases.** Of these 63 patients, 16 (25.39 %) were IgM seropositive. Among these 16 IgM positive, 05 (31.25%) patients had **ascitis**, 07 (43.75%) pleural effusion, and 04 (25%) **anasarca.** (p - value 0.985).

**Visceral organomegaly:** Ultrasonogram assessment based **visceral organomegaly** was recorded in 46 **Figure I showing percent distribution of clinical signs and symptoms in dengue IgM seropositive cases.**



(9.2%) patients at the time of evaluation. No patient had **splenomegaly** alone while **hepatomegaly only** was seen in 16 (34.78%) patients. **Hepatosplenomegaly** was seen in 30/46 (65.21%) patients. **Among these 46 patients, only 18 (43.28%) were IgM seropositive.** Further, for these 18, 02 (11.11%) with hepatomegaly and 16 (89.99%) with hepatosplenomegaly were IgM antibody positive (p-value 0.558). (Fig 1)

**Atypical dengue illness clinical presentations – Eleven patients (02.20%),** had atypical presenting features which have been infrequently reported in literature. **These included 03 patients with ultrasonogram evidence of acalculous cholecystitis; 07 (63.07%) with gall bladder wall edema, and only 01 (09.07%) had diarrhoea of nonspecific origin. (Table2)**

Table II: Atypical clinical presentations in 11 patients who were serologically confirmed IgM positive for dengue infection.

Atypical presentation	Number (%)
Acalculous cholecystitis.	03 (25%)
Gall bladder wall edema.	07 (63.07%)
Diarrhoea.	01 (09.07%)

## V. Discussion

All 500 patients had fever in the duration range 3-10 days suggestive of acute infection (p-value 0.0325). Among the 169 seropositive cases, 146 (86.39%) presented with fever of more than 5 days duration while rest 23 (13.60%) presented with fever of less than 5 days. It is well documented finding that dengue illness fever manifests as biphasic (saddle back) and lasts for 5-7 days (case) of onset of infection.

**IgM antibody response** comes to detectable level usually after 3<sup>rd</sup> day of infection and peaks about 5<sup>th</sup> day.<sup>2,7</sup> Following infection with DENV, the first class of antibody produced is the IgM antibody and it can be detected from day 3 onwards of illness; by day 10 almost 99% of individuals mount a detectable IgM response.<sup>2,6,7</sup> The IgM seropositivity rate of 33.8% in our study correlates with the acute phase of the disease.

**Retro-orbital pain** was seen in 98 (19.60%) patients. Of these 98 cases, 43 (61.22%) were seropositive for IgM antibody (p-value 0.0035) revealing that IgM seropositivity has a **significant correlation with retro-orbital pain**. A similar finding has been reported by Gogna et al who observed retro-orbital pain to the extent of 44.5% in IgM seropositive cases<sup>8,9</sup>. In another study by Sreejith and George P, retro-orbital pains has been reported up to 44% involving 200 cases.<sup>10</sup> A 3 year hospital based study by Samantha et al have reported retro-orbital pain in more than 60% of IgM confirmed cases<sup>11</sup>.

**Calf tenderness** was seen in 84 (16.80%) patients lasting for 2-6 days. Of these 84 cases, 43 (55.7%) were **IgM antibody sero-positive (p-value 0.0225)**. This finding assumes significance as calf tenderness, a constitutional symptom, has not been consistently reported in literature with a well-defined correlation with Dengue IgM serological status.

**About rashes and petechiae**, ninety two (18.40%) patients suffered from rashes and petechiae primarily over the upper and lower limbs but rarely on abdomen and back. Of these 92 (18.40%) patients that developed rashes and petechiae, 36 (39.13%) patients were IgM antibody seropositive. However, **statistically it is not significant (p-value 0.872) and it reflects that rash and other haemorrhagic cutaneous manifestations do not bear much significant correlation with the serological status of the individual**. It is important to mention that the cutaneous manifestations are reported nearly to the extent of 22.9% when individuals are infected by DENV-1, 6.8% with DENV-2, 14.6% with DENV-3, and 44.9% with DENV-4.<sup>12</sup>

**Sub-conjunctival hemorrhage, epistaxis, hemoptysis, hematemesis, hematuria, and melena were observed in 53 (10.60%) patients and 21 (39.62%) of these were sero-positive for IgM antibody in our study**. Among these 21 sero-positive cases - 10 had epistaxis, 5 hemoptysis, and 6 melena. **These findings are statistically not significant (p-value 0.875), suggesting that the cutaneous haemorrhagic manifestations are relatively less specific for diagnosis of dengue fever**. Study involving large number of patients is needed to establish the significance, if any, of the role of cutaneous haemorrhagic manifestations in the diagnosis of dengue, especially in serologically confirmed IgM positive cases. None of the patients had a history of sub-conjunctival hemorrhage or scleral injection or haematemesis in the

present study. It is critical to note that the number of patients with bleeding manifestation is just 10.60%. A well-documented study in Indian context has reported bleeding manifestation to the extent of 19/58 (32.2%) of patients in cases of DF in Delhi in 2011.<sup>9</sup> Among these more than half i.e. 52.6% were seropositive. Another study from Southern India by Mamidi N et al in the year 2013 reported bleeding manifestation to the extent of 25%.<sup>13</sup> These studies reflect wide variations in the hemorrhagic manifestations but little correlation with the IgM sero-status.

**A significant number - 64/500 (12.8%) presented with features of serositis like anasarca, ascites and pleural effusion. Of these 64 patients, 16 (25.00%) were IgM seropositive.** Among these 16, 05 (07.24%) patients with ascites, 07(51.69%) with pleural effusion, and 04 (25%) patients having anasarca were IgM antibody seropositive (p-value 0.985). In a study from Delhi in 2013, ascites and pleural effusion have been reported to the extent of 10.3% and 8.6%. respectively.<sup>9,10</sup> Samantha et al in a 3 year hospital based study at Nicaragua, observed 'plasma leakage associated clinical presentations' in the range from 11% to 40% in adults with ascitis 3%, pleural effusion 3%, haemo-concentration 13%, & plasma leakage 15%.<sup>12</sup> **In our study, the fluid collection or plasma leakage seen as 25% is suggestive of the well-known observation that principal complication of DF is increased vascular permeability which declines as the age advances as also is true that greater capillary fragility in younger age accounts for this age related association. Such findings have been reported earlier also.**<sup>2-4, 14</sup>

**Visceral organomegaly** on ultrasonogram was seen only in 46 (9.2%) patients. No patient had splenomegaly alone while hepatomegaly only was seen in 16 (34.78%) patients at the time of initial evaluation. The rest 30

(65.21%) patients had both i.e. hepatomegaly as well as splenomegaly together. **Among these 46 patients, 18 (43.28%) were seropositive.** Of these 18, 02 (02.89%) with hepatomegaly and 16 (76.59%) with hepatosplenomegaly were IgM antibody positive (p-value 0.558). The incidence of hepatomegaly varies from 4-11% in adults in various series of case reports documented by Daniel et al in 2001 in Kerala, and also by Sharma S et al from DHF in adults during 1996 outbreak in Delhi, and, Bhaskar ME et al from Chennai in 2010.<sup>15 - 17</sup> On the contrary, a much higher incidence of hepatomegaly as 62.5% & splenomegaly as 60% has been reported in children from North India, for which no definite explanations exist.<sup>18</sup> The lower incidence of visceral organomegaly observed in our study, could be attributed to our exclusion of patients with malaria and typhoid which was not the case with most other studies. In an extensive study by Eric S Halsey et al involving 1716 patients and their clinical correlation with DENV-1, 2, 3 and 4 serotypes has revealed hepatosplenomegaly only in 20 (1.2%) patients in total, and of these - 0.7%, 0%, 1.5% and 1.6% respectively were in association with DENV1, DENV-2, DEN-3 and DENV- 4 serotypes infections respectively.<sup>12</sup> In the similar series by the same authors, splenomegaly has been reported as 0.4% followed by 0.2%, 0%, 0.6%, 0.8%, respectively for DENV1, DENV-2, DEN-3 and DENV-4 serotypes infections respectively.<sup>12</sup> A higher percentage of hepatosplenomegaly i.e. 76.59 % in our IgM antibody confirmed cases is difficult to explain when compared with reports in literature. Although statistically not significant (p-value 0.558) but **such occurrences are in accordance with WHO criteria for DF/DHF.**<sup>9</sup> This observation also implies that systematically planned, statistically approved studies with appropriate sample



sizes need be done to ascertain the precise significance and plausible explanations for such organomegaly cases.

**Atypical clinical presentations, in the present study were seen in 11 (02.40%) cases.** This included 03 patients (25%) with ultrasound showing acalculous cholecystitis; 07(63.07%) with gall bladder wall edema and 01(09.07%) patient with diarrhoea of nonspecific origin. Atypical clinical presentation are well documented<sup>10</sup> including a study from Delhi in 2011.<sup>9</sup> All these 11 patients in our study recovered completely with standard recommended treatment protocols. These acute abdomen manifestations are mainly attributed to increased vascular permeability leading to gall bladder wall oedema and wall thickening which is usually self-limiting.

The World Health Organization (WHO) has coined the term **Expanded Dengue** to describe cases which do not fall into either dengue shock syndrome or dengue hemorrhagic fever. This has incorporated several atypical findings of dengue. Dengue illness is a great mimic of co-existing epidemics like Malaria, Chikungunya and Zika virus disease, which are also mosquito-borne diseases.<sup>21</sup> Such atypical clinical presentations pose a diagnostic challenge as all cases do not buildup a positive evidence for IgM seropositivity.

Our study with significant findings in particular about the clinical presentations suggests that there is evolving a gradual, yet very significant, change in the clinical presentation of dengue virus infection. Knowledge of expanded dengue helps to clinch the diagnosis of dengue early, especially during ongoing epidemics, avoiding further battery of investigations. The notable observation is that in the last decade there is a shift from DHF/DSS cases to atypical presentations with organ dysfunctions, especially in the Asian subcontinent.<sup>3,9,12</sup>

### **Limitations of the study**

Viral studies are not done in routine in our institution. Although it is known that all the four serotypes are in circulation in the community<sup>20</sup> but precisely which serotypes are likely to be responsible for the changes in the trends of the clinical presentations is difficult to comment. The study is a retrospective analysis and not a prospective one.

Co infections, although ruled out in the inclusion criteria, but if any, may have may have to a very limited extent over shadowed the results due to lack of precision and accuracies of the laboratory tests applied. Scrub typhus serology is not done in routine due to very poor index of clinical suspicion among physicians, therefore, such cases may not have been ruled out in the study. The detailed results of other investigations especially haematology, biochemistry & radiology in cases of atypical presentations have not been included due to very poor sharing of data across hospital divisions and other laboratories. Despite these limitations, it is felt that our study has met with very useful conclusions.

### **VI. Conclusion**

Our study reflects a gradual paradigm shift in clinical presentations of dengue virus infection. A high index of clinical suspicion aided by increased awareness about such changing trends in clinical presentations' would help in timely diagnosis and hence enable initiate right line of treatment. It is expected to lead to significant **reduction in morbidity and mortality** in present as well as future dengue outbreaks that are currently knocking not only at the doors of capital city of **Delhi & NCR but in the country as a whole.**

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