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RESEARCH ARTICLE

DENGUE –TYPHOID CO-INFECTION: A STUDY ON COEXISTENCE OF VIRAL AND BACTERIAL INFECTION IN ENDEMIC AREAS

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ABSTRACT

Background: Acute Febrile illness (AFI) is a common cause of patients seeking healthcare in India, especially between June and September. Co-infections with two or more infectious agents are also becoming a major health problem and the similarity of symptoms further makes accurate clinical diagnosis and treatment difficult without laboratory confirmation.

Material and methods: Total 3250 samples were tested for Dengue NS1 and IgM retrospectively from the patients with history of febrile illness between September to November 2015. Out of these, 251 positive Dengue NS1 and/or IgM samples requested for blood culture and/or Rapid Salmonella IgM test were studied for co-infection of Dengue and typhoid fever. Dengue NS1 and IgM antibodies were detected by Dengue NS1 and Dengue IgM antibody capture ELISA test. Diagnosis of *Salmonella* infection was done by blood culture and Rapid Salmonella IgM immunochromatography test in the laboratory.

Result: In total of 251 positive Dengue samples, 9 samples were found co-infected with typhoid fever. 4 patients were blood culture positive and 5 were Rapid Salmonella IgM test positive. Maximum number of dengue positive cases was found in age group 20- 40 y.

Conclusion: Acute febrile illnesses are highly prevalent during rainy season in endemic area like India and possibility of Dengue typhoid fever co infection cannot be ruled out. Meticulous history taking, careful clinical examination and right choice of laboratory tests for the diagnosis of these co-infections not only help in timely detection of the disease but also prevent from the fatal outcomes.

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INTRODUCTION

Epidemics of acute febrile illness have been causing major concerns in India (Anthony *et al*, 2007; Uneke, 2008). In areas, endemic for two or more infectious agents, co-infections are emerging as a major health problem which can lead to an illness with overlapping symptoms and develops a diagnostic challenge for the clinicians. Acute Febrile illness (AFI) is a common cause of patients seeking healthcare in India, especially between June and September (Joshi and Kalantri, 2015). Most AFI s are caused by malaria, dengue, leptospirosis, rickettsial infections especially scrub typhus, typhoid fever, Japanese encephalitis and influenza (R.Joshi and SP Kalantri, 2015; Rajnish Joshi *et al*, 2008; Yukti Sharma *et al*, 2014). Enteric fever is a prime cause of morbidity in the developing world and a predominant public health problem globally.

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In absence of effective treatment, it leads to case-fatality rate of 10–30% (Geoffrey C Buckle *et al*., 2012; Crump *et al*., 2004). Dengue is another disease caused by four serotypes (DEN1–4) of the genus Flavivirus (Whitehorn J, Simmons CP, 2011). Transmitted by Aedes mosquitoes; it is one of the most widespread of the arthropod-borne viral diseases. In dengue endemic areas, clinical picture of dengue may mimic other diseases causing acute febrile illness (Kariuki Samuel, 2008; Capeding *et al*., 2013). The similarity in symptoms and differential diagnoses of these diseases often makes accurate clinical diagnosis and treatment difficult without laboratory confirmation (Capeding *et al*., 2013). Management of acute febrile illnesses differs and is mainly based on the causative infectious agents. Dengue and typhoid fever, if not managed timely, may lead to life threatening consequences (Kariuki Samuel, 2008; Chrispal *et al*., 2010; Shrishu *et al*., 2006; Morgenstern R and Hayes, 1991). Dengue co- infection with malaria and other AFI, their epidemiology, course of infection and complications have been studied worldwide (Yukti sharma *et al*., 2014). Although studies are there that show co-infection

of various vector born diseases but the data regarding dengue and typhoid co- infection is published less in number. As both these infections are endemic in India, Dengue co-infection with Typhoid fever should be kept in mind. This study was designed to find out the co- infection rates of dengue and typhoid fever by using laboratory based tests.

MATERIALS AND METHODS

A retrospective study was done between September to November 2015. Total 3250 samples received from various centers to Oncquest lab ltd in Delhi, were tested for Dengue NS1 and/or IgM antibodies. Two hundred and fifty one (251) positive Dengue NS1 and/or IgM samples requested for blood culture and/or Rapid Salmonella IgM test (Enterochek-WB,Zephyr biomedicals, Goa) were included in this study. Rest positive Dengue NS1 and IgM samples with or without request of widal test were excluded from the study. Dengue specific IgM antibodies were detected by Dengue IgM antibody capture ELISA test and Dengue NS1 by Dengue NS1 ELISA test kit (J.mitra and Co. Pvt.Ltd). Tests were done as per the manufacturer's instructions. For diagnosis of typhoid fever, in our study, we have included all samples requested for blood culture and/or Typhidot IgM. Blood culture samples were received in BACTEC 9120 adult aerobic culture bottles. Samples were processed according to the recommendations of the BD diagnostics. When the bottles were flagged positive by the system, a gram stain was performed from the bottle directly which showed gram negative bacilli. Subculture was done on MacConkey agar and 5% sheep agar plates. Salmonella culture positive samples were confirmed by slide agglutination with specific Antisera for Salmonella typhi and paratyphi A. Enterochek-WB is a rapid, qualitative, sandwich immunoassay utilizes the principle of immunochromatography for the detection of IgM antibodies to S. typhi in human serum/plasma or whole blood sample. There is in built procedural control band that validates the result. Samples were tested using Enterochek-WB according to the manufacturer's instructions.

RESULTS

Total 251 samples received in Oncquest laboratories limited with the request for dengue NS1and/or Dengue IgM and Blood culture and/or Rapid Salmonella IgM test were tested retrospectively. Samples from 139 patients were positive only for Dengue NS1 and 40 samples for Dengue IgM. Out of 72 samples requested for both Dengue NS1 and IgM, 34 (47.2%) samples were positive for both and rest either NS1 or IgM positive. One hundred and three (103) samples were requested for Enterocheck IgM, 91 samples were requested for blood culture only, 57 samples requested for both. Samples from all age groups, positive for Dengue NS1 and IgM were taken as depicted in Table 1.

Table 1. Age-wise distribution of Dengue positive cases

Age group	Total positive	Dengue positive Male	Dengue positive Female
<20	101	62	39
20-40	102	57	45
>40	48	25	23

There were 107 females and 144 males. In all dengue positive cases, nine were found co- infected with typhoid fever (9/251= 3.5%). Four patients were blood culture positive and five were Rapid Salmonella IgM test positive as shown in Table 2

Table 2. Test-wise distribution of Dengue- Typhoid co-infection cases

Dengue and Salmonella co-infection	Rapid Salmonella IgM positive	Blood culture positive	Dengue Positive with	
			NS 1	IgM
<20 years	3	-	2	1
20-40	1	4	3	2
>40 years	1	-	1	-

Maximum number of dengue positive cases was found in age group 20- 40 y as illustrated in Table 3

Table 3. Age and Sex-wise distribution of Dengue- Typhoid co-infection

Dengue and Typhoid co-infection	Male	Female
<20 years	1	2
20-40	4	1
>40 years	-	1

Table 4. Comparative evaluation of Dengue and Typhoid fever in different studies

References	Method used for Salmonella testing	Total no. of samples tested positive for dengue	Co-infection Dengue + typhoid	Coinfection positivity	Other co infection found
Shrishu R. Kamath *et al*. (2006)	Not specified	858	6	0.6%	Leptospira, malaria, meningitis
Capeding *et al*. (2013)	S. Typhi (Salmonella Typhi IgM ELISA	71	17	5.9%	Chikungunya Influenza A Rickettsia
Vaddadi suresh *et al*. (2013)	Blood culture and widal test	1	1		Malaria
K.Mary Sushi *et al*. (2014)	Widal rapid & tube agglutination test	8	1	12.5	Leptospira
Yukti *et al*. (2014)	Widal test	141	11	7.8%	PID, URTI
Rangan Srinivasaraghavan *et al* (2015)	Blood culture and widal test	1	1	-	-
Present study	Blood culture and/or Rapid Salmonella IgM	251	10	3.5%	-

DISCUSSION

Acute febrile illnesses are very common during humid season especially from August to November in many areas of India including Delhi (Yukti Sharma *et al*, 2014) and etiological diagnosis becomes necessary in the clinical management (Peters, 2008). Among those, Dengue virus causes epidemic and sporadic cases year-round (Yukti Sharma *et al*, 2014; Dar *et al*, 1999). According to the NCVBDCP (National vector borne disease control programme) data, maximum number of Dengue cases were reported in Delhi in 2015 is 15836 in comparison to last four years that were 995 (2014), 5574 (2013), 2093 (2012) and 1131(2011) cases (NCVBDCP, 2015). Typhoid fever is also endemic in India with incidence around one percent of the population yearly in some of the areas (Bhan *et al*, 2005; Rangan Srinivasaraghavan *et al*, 2015). There are various tests available for the diagnosis of typhoid fever but Gold standard is blood culture (Parry *et al*, 2002). Widal test is widely used serological test in poor resource settings in Endemic areas like India for the diagnosis of Enteric fever. Reliability of widal test depends upon the demonstration of a rising titer of antibodies in paired samples 10 to 14 days apart but it lacks sensitivity and specificity (Parry *et al*, 2002; Prasad *et al*, 2015; Shyamala, 2012) that's why widal test results were not included in our study. Newer serological test are also available like Rapid salmonella IgM and/IgG that directly detects these antibodies against S.Typhi antigens as early as 4-5 days of fever (KJ Prasad *et al*, 2015). In our study we have included cases positive with blood culture or Rapid Salmonella IgM test. In our study Nine Dengue –typhoid co- infection positive cases were reported and there are studies with the similar findings as depicted in (Table 4).

In Nine Dengue positive cases, four samples were found positive with blood culture and five by rapid Salmonella IgM test. Various studies show 50-70% positivity of blood culture (Prasad *et al*, 2015; Farooqui *et al*, 1991). False negative results are common due to the irrational use and wide spread use of antibiotics (Prasad *et al*, 2015), but presence of Salmonella in blood culture itself is indicative of simultaneous infection with Dengue fever and can be considered true positive laboratory based co-infection cases. In other 5 cases, Rapid salmonella IgM test was positive. Sensitivity (73%-95%) and specificity (68%-95%) of these tests are variable in various studies but higher than Widal test (Prasad *et al*, 2015). In 4 among five patients, blood culture samples were not requested but positive Rapid Salmonella IgM sample can be a useful diagnostic test for the physicians to correlate with the clinical condition of the patient and helps in early diagnosis and management. It would always be better to combine Rapid Salmonella IgM and culture test to increase the possibility of detection of Salmonella infection in patient with high clinical suspicion of enteric fever co-infected with Dengue or any other fever in endemic areas. Although in all positive cases, requisition of widal test was received in only two cases and in both the samples Titer of TO and TH was >1:320. No major male and female preponderance of co-infection was found in our study as 5 male patient and 4 female patients were found with co-infection. Dengue fever and Enteric fever are different entities. Dengue is a mosquito borne disease and Enteric fever is transmitted through feco-oral route, but they can have similar clinical picture (Uneke, 2008). Signs and symptoms of Dengue infection and typhoid fever may overlap, especially during the first few days of illness and are indistinguishable from many other acute febrile illnesses (Basuki, 2003). Dengue fever can be presented from subclinical infection or mild febrile illness to severe and fatal dengue hemorrhagic fever. Patient may experience high grade fever that can last for 5 to 7d, a severe frontal and retro orbital headache, myalgias, leg pains, malaise, arthralgia and anorexia (Basuki, 2003; Nivedita Gupta *et al,* 2012).

In half of the dengue patients, transient macular or maculopapular rash may typically appear between two and five days after the onset of fever (Vijayalakshmi and Jayavardhana, 2013). In typhoid fever on other side, patient may have nonspecific sign or symptoms or present with gradual onset of sustained fever, chills, hepatosplenomegaly and abdominal pain. In some cases, patients experience rash, nausea, anorexia, diarrhea or constipation, headache, relative bradycardia and reduced level of consciousness, mild arthralgia involving multiple joints and vague, poorly localized back pain (Gomez HF *et al*, 1998). In dengue fever, constipation is occasionally reported; diarrhea and respiratory symptoms are frequently reported and may be due to concurrent infections (Gubler, 1998). Thus during Dengue outbreaks, co-infections with other common endemic pathogens can be a diagnostic challenge (Rangan Srinivasaraghavan *et al*, 2015). But with the help of various diagnostic tests available and their correlation with clinical condition of the patient may not only help in the early management of the patient but also prevent the patient from unusual severe complications. Although the reason of Dengue and enteric fever co infection is not much studied but sometimes prolonged fever (> 5 days) can be an independent risk factor for co-infection (Lee, *et al*, 2005). It is studied that dengue virus can be responsible for a diminished T cell proliferation in response to mitogens *in vitro* (Mathew *et al*, 1999). However, *in vivo* effects of these observations and its correlation with Enteric fever need to be studied further as these are two different modalities with different mode of transmission. There are a few limitations to this study. The study was undertaken in a Diagnostic Laboratory rather than a hospital. In a hospital setup, complete clinical picture of patients could have provided more information and better correlation. As Blood culture was not done in all the patients included in the present study to confirm the diagnosis of typhoid and paratyphoid fevers, there is possibility that more cases could have been detected.

Conclusion

Acute febrile illnesses are highly prevalent during rainy season in endemic area and possibility of co infection cannot be ruled out. The laboratory diagnosis can play an important role in determining the early diagnosis and management of these illnesses. Therefore clinicians must always alert on the possibility of Dengue fever and Enteric fever co-infection in patient with acute febrile illness. Meticulous history taking, careful clinical examination and right choice of laboratory tests may help in detecting the infections and prevention from the fatal outcomes.

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