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Original Research Paper

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DENGUE AND ENTERIC FEVER CO-INFECTION : A CLINICIAN'S DILEMMA

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ABSTRACT

Introduction: The coinfection of Dengue and Enteric fever presents diagnostic as well as therapeutic dilemma for a clinician due to similarity in symptoms and requirements of additional laboratory tests and possible use of antibiotics in case of proven coinfection. This study was designed to find out the co- infection rates of dengue and enteric fever by using standard laboratory based tests.

Material and Methods: This is longitudinal descriptive study. A total 191 consecutive cases of Dengue fever admitted during Jan 2018 to Dec 2019 at our centre were studied. All the patients were tested by IgM card test for S. Typhi. Blood cultures were done only for those with a positive card test.

Results: 23 out of 191 admitted dengue fever patients had positive IgM typhi card test. However, only 7 of these 23 patients had blood culture positive for Salmonella Typhi and needed appropriate antibiotics. The overall true Dengue Enteric fever coinfection rate was 3.66%. Average duration of febrile phase in isolated dengue fever patients was 4.89 days. While the same for dengue-enteric coinfection was 7.91 days. All the patients recovered well without any fatality.

Conclusion: While treating the dengue fever with prolonged febrile phase, coinfection with enteric fever needs to be investigated and treated accordingly.

KEYWORDS : Dengue Fever, Enteric Fever, Co-infection

INTRODUCTION

Acute febrile illness is one of the common causes of hospital admissions in India burdening an already stretched healthcare system.[1] The common causes of acute febrile illness in India are infectious diseases like Dengue, malaria, typhoid fever, scrub typhus etc.[1,2,3]

Dengue fever is caused by one of the four serotypes (DEN1–4) of the genus Flavivirus.[4] It is one of the most widespread arthropod-borne viral diseases and is transmitted in humans by Aedes mosquitoes. In dengue endemic areas, clinical picture of dengue may mimic other diseases causing acute febrile illness.[5,6]

National Vector Borne Disease Control Programme (NVBDCP) describes the common clinical features of dengue fever as "An acute febrile illness of 2-7 days duration with two or more of the following manifestations: (i) Headache, (ii) retro-orbital pain, (iii) myalgia, (iv) arthralgia, (v) rash, (vi) haemorrhagic manifestations".[7]

Many other causes of acute febrile illness like Typhoid, other viral illnesses, malaria etc have some/all of the above clinical features. This becomes important while dealing with cases with prolonged febrile course. There have been reports in various studies about coinfection of dengue and enteric fever [1,8,9]

The co-infection of Dengue as well as Typhoid fever presents diagnostic as well as therapeutic dilemma. The similarity in symptoms and differential diagnoses of these two diseases often makes accurate clinical diagnosis and treatment difficult without laboratory confirmation.[6]

Their management is also different. While isolated Dengue fever needs only the supportive management, presence of typhoid fever needs management with full course of appropriate antibiotics like ceftriaxone and Azythromycin. The coinfection of these two illnesses hence becomes a therapeutic challenge.

Dengue and typhoid fever, if not managed timely, may lead to life threatening consequences.[5,10,11,12] Dengue co- infection with malaria and other Acute Febrile Illnesses, their epidemiology, course of infection and complications have been studied worldwide.[2,3] Although studies exist that show co-infection of various vector borne diseases but the data regarding dengue and typhoid co- infection is scant. 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 standard laboratory based tests.

MATERIAL AND METHODS

This was a longitudinal descriptive study carried out at a zonal multi-speciality hospital in western India from Jan 2018 to Dec 2019. During the study period of over 24 months, a total of 224 dengue like febrile illnesses were admitted to our hospital out of which 191 were diagnosed as dengue fever as per the WHO clinical and laboratory criteria and were included in our study.

The diagnosis of Dengue fever was based on the typical clinical presentation described in NVBDCP guidelines for dengue fever as well as in WHO guidelines for Dengue fever available on the WHO website www.who.int.[7,13] The Laboratory tests used were in the form of NS1Ag and/or IgM for Dengue fever.

A detailed clinical and epidemiological history was elicited for every admitted case of dengue fever. The positive clinical examination findings of all patients were recorded in a separate proforma.

Dengue specific IgM and IgG antibodies and Dengue NS1 antigen were detected in human serum/plasma by Rapid solid phase immuno-chromatographic test for the qualitative detection of Dengue NS1 antigen and differential detection of IgM and IgG antibodies to dengue virus by Rapid Card test kit (J MITRA & CO. PVT LTD). Tests were carried out

strictly in accordance with the manufacturer's instructions.

All these patients of dengue fever were also tested for S. typhi by Typhoid IgG/IgM Rapid Card test kit (CTK Biotech, Inc USA) for salmonella typhi. It is a rapid, qualitative, chromatographic immunoassay which utilizes the principle of immunochromatography to detect IgM antibodies to S. typhi in the given sample.

A blood culture was done for all dengue fever patients who tested positive for S. Typhi by IgM antibody testing. For the purpose of this study, only patients who were S. Typhi IgM positive and IgG negative were considered in the results.

BACTEC 9120 adult aerobic culture bottles were used to receive the blood culture samples. All samples were processed as per the recommendations of the manufacturer. Gram stain was performed directly from bottles which were positive on culture. Gram stain revealed gram negative bacilli. Subsequently, subculture was carried out on MacConkey agar and 5% sheep blood agar plates. Drug sensitivity testing was carried out on the culture which grew S.Typhi.

All the dengue fever patients were also tested for their total leucocyte count, platelet counts and liver transaminases (AST, ALT).

RESULTS

During the study period of over 24 months, a total of 224 dengue like febrile illnesses were admitted to our hospital out of which 191 were diagnosed as dengue fever as per the WHO clinical and laboratory criteria. The mean age was 22.84 ± 11.6 years (range: 17-63)

Of these, 161 (84.29%) were NS1 Antigen as well as IgM positive, 30 (14.65%) were only IgM positive for Dengue fever, The cases of dengue like illnesses which were neither NS1 Ag nor IgM Dengue positive were excluded from the study.

All the 191 diagnosed cases of Dengue fever were tested for S. typhi by Typhoid IgG/IgM Rapid Card test kit, (CTK Biotech, Inc USA) for salmonella typhi.

Our study showed that 23 out of 191 diagnosed cases of dengue fever also tested positive for S. Typhi by IgM Rapid Card test kit.

Blood culture for S. Typhi was carried out for all these 23 patients. Salmonella Typhi was grown on blood cultures of only 7 of these 23 patients. 5 of these 7 cultures were sensitive to ceftriaxone as well as Azythromycin whereas 2 samples was resistant to ceftriaxone. All the culture samples were resistant to ciprofloxacin.

The average hospital stay for all these Dengue fever patients excluding typhoid coinfections was 6.84 days (SD 2.88, range 4 to 10 days). Whereas the same for the 7 culture positive typhoid Dengue coinfections was 13.2 day (range 9 to 17 days).

The commonest clinical feature in isolated dengue fever cases as well as in dengue typhoid coinfections was fever. Other specific clinical features observed in all dengue typhoid coinfections were headache and relative bradycardia.

Mean (Standard Deviation) of haemoglobin, packed cell volume, total leucocyte count, platelet count and liver function tests i.e Aspartate Transaminase and Alanine Transaminase on day 5 of the illness is tabulated in Table 1. The transaminases, AST and ALT were found to be raised in almost all of the cases, The USG abdomen in these cases revealed features of acalculus cholecystitis in 78% of the cases. However, all these cases had recovered well with transaminases settled to normal values. Percentage of cases with Dengue and Typhoid co-infection; and percentage of typhoid cases which showed a positive result on blood culture is tabulated in Table 2.

Table 1: Mean (standard Deviation) Of Haemoglobin, Packed Cell Volume, Total Leucocyte Count, Platelet Count, Aspartate Transaminase And Alanine Transaminase On Day 5 Of The Illnesses

Mean (SD) Haemoglobin (Gm%)	Mean (SD) Packed cellvolume(%)	Mean (SD) Total Leucocyte count (Per cubicmillimetre)	Mean (SD) Platelet count(Permm^3)	Mean Aspartate Transaminase (IU/litre)	Mean Alanine Transaminase (IU/litre)
15.3(1.04)	45.58(3.04)	3848(1629.44)	83260(49746.26)	167.7	130.7

Table 2: Percentage Of Dengue-typhoid Coinfection

Confirmed Dengue (Clinical & Labcriteria) Ns1Ag&/IgM+ve	IgMforS.Typhi +ve	CultureforS.Typhi +ve	Dengue-TyphoidCo-infection
191	23	7	7outof191Dengue
	12.04%	3.66%	3.66%

All patients of dengue fever were treated with paracetamol and oral/parenteral fluids. Only 17 patients required platelet transfusions for profound thrombocytopenia and/or bleeding. Antibiotics were administered only for the culture positive enteric fever cases. No antibiotics were administered for the IgM positive but culture negative S. typhi patients.

All the patients recovered well and there was no death.

DISCUSSION

It has been widely documented that in tropical countries most of the acute febrile diseases have similar signs and symptoms which can often mimic dengue, making it difficult to diagnose without laboratory confirmation, thus increasing the disease burden.[3]

Although the National Vector Borne Diseases Control Programme (NVBDCP) guidelines for dengue fever recommends the ELISA, PCR or viral culture as the recommended tests for laboratory confirmation of Dengue fever, all these tests are costly and are not available at most of the smaller centres. On the contrary, IgM & Ig G card tests are cheaper, widely available and are helpful in initial screening/ diagnosis of dengue fever.

The sensitivity as well as specificity of these rapid diagnostic NS1Ag, IgM & IgG dengue card tests is high and has been estimated to be 92 % and 98% respectively for NS1 Ag and 90% and 100 % respectively for IgM & IgG dengue card tests.[14]

During the acute phase, the combined uses of these tests provide reliable results for all dengue fever cases. The patients of laboratory confirmed dengue fever with a prolonged febrile phase need evaluation for any alternate/associated cause for fever. Evaluation for other common causes of febrile illnesses like malaria and typhoid

fever becomes essential especially in tropical countries.

In our study, there were 23 cases of laboratory confirmed dengue fever who also tested positive for anti-S. Typhi IgM antibodies. However, only 7 of them were culture positive for S. typhi and needed a course of antibiotics to treat them. Other patients of dengue fever who tested positive for anti-S. Typhi IgM antibodies but were culture negative for S. typhi might have been having cross-reactivity as a cause for their positive test for anti-S. Typhi IgM antibodies results.

Worldwide several authors have reported Enteric fever and dengue fever to be a major cause of morbidity and mortality.[15,16,17,18] A single case of Dengue and typhoid fever was reported in Indonesia in 1998 by Sudjana P and Jusuf H.[19] More recently Bansal R, Bansal P and Tomar LR reported two cases of Dengue fever and typhoid co-infection in 2015.[20] A high coinfection rate of 7.8% was reported by Sharma Y, Arya V, Jain S, Kumar M, Deka L, Mathur A wherein they reported eleven cases of typhoid co-infection out of 141 cases of dengue, in North Delhi.[3] In the paediatric age group, a case of Dengue and Enteric fever co-infection was reported by Srinivasaraghavan R, Narayanan P, Kanimozhi T.[21] PMP Singh and Sukhmeet Minhas reported five cases of culture positive Salmonella Typhi out of seventeen cases of Dengue fever.[8] Our study has reported 23 cases of IgM antibody positive for S. Typhi out of which, 7 cases were culture positive for S. typhi thereby giving a co-infection rate of 3.66 %. The feature of this study is to rely on the antibiotics in treatment of only culture positive enteric fever infections. Other 16 cases of dengue fever where IgM typhi card test was positive but typhi culture was negative were managed successfully without need of antibiotics further reiterating that there IgM typhi positivity might be due to cross reaction.

Recommendations

While managing dengue fever cases, co-infection with enteric fever should be invariably kept in mind by every clinician, while dealing with cases of dengue especially with a prolonged febrile phase. The diagnosis of coinfection with enteric fever should not be based on rapid card test alone which may give false positive reports due to cross reactivity. Blood cultures for salmonella typhi is recommended for all such cases to confirm the coinfection with enteric fever. Only the culture confirmed enteric fever cases need treatment with a course of culture sensitive antibiotics. Strict emphasis should be given on improvement of sanitation and personal hygiene, besides advocating vaccination against typhoid. As regards Dengue fever, all strictest possible preventive measures to control the breeding of Aedes mosquito must be implemented. Such measures are easily implementable as the Aedes mosquito breeds in artificial containers of water.

CONCLUSION:

The authors conclude that Dengue and Enteric fever co-infection is common especially in endemic areas, as the same is being reported frequently by several authors.[8,19,20,21,22] The authors would like to emphasise that high index of suspicion for such coinfections must be kept especially while treating the dengue fever cases with atypical presentations and prolonged febrile phase.

Conflicts of Interest

None identified

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