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Original Article

Clinical and Microbiological Profile of Suspected Enteric Fever Cases Admitted In Pediatrics Department of Northern Railway Central Hospital, New Delhi

Kathakali Das[1], Tanushree Joshi[2], Dave Himanshu Satya Narayan[3], Zeeshan Rafi[1]

[1]Associate Professor, Department of Pediatrics, Indian Railway Postgraduate Institute of Medical Sciences and Research, New Delhi, India, [2]Professor, Department of Pediatrics, Indian Railway Postgraduate Institute of Medical Sciences and Research, New Delhi, India, [3]DNB Student, Department of Pediatrics, Indian Railway Postgraduate Institute of Medical Sciences and Research, New Delhi, India.

Abstract

Introduction: Enteric fever is a potentially fatal multisystemic disease due to the causative organism salmonella enterica serovar typhi (Typhi). A relatively milder disease is caused by *Salmonella Paratyphoid* A, B, and C. The term enteric fever comprises both typhoid and paratyphoid fever. It continues to be a global health problem, especially in the tropics and subtropics in many developing countries, due to poor standards of hygiene and sanitation. Without delay in treatment with appropriate drugs, typhoid fever is usually a short-term illness, but if left untreated may be a life-threatening disease due to the increasing prevalence of antibacterial resistance and incomplete treatment.

Aim: To study the clinical and microbiological profile of suspected enteric fever cases admitted in the Pediatric department of Indian Railway Postgraduate Institute of Medical Sciences and Research, New Delhi.

Results: This study found that typhidot M is a rapid, accurate, and reliable tool for the diagnosis of typhoid fever as compared to Widal. A combination of blood culture and typhidot M test will significantly improve the diagnostic yield.

Conclusion: The above study concludes that typhidot M is useful for early detection of typhoid fever and better then Widal test is patients with 3 days or more of fever without any obvious focus of infection.

Key words: *Salmonella Typhi,* Typhidot M, Typhoid fever, Widal

INTRODUCTION

Enteric fever is a potentially fatal multisystemic disease due to the causative organism Salmonella enterica serovar typhi (S. typhi). A related but milder disease is caused by *Salmonella Paratyphi* A and less frequently by *S. Paratyphi* B and *S. Paratyphi* C. The term enteric fever comprises both typhoid and paratyphoid fever.[1]

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It continues to be a global health problem, especially in the tropics and subtropics.[1-3] Fever for at least three out of seven consecutive days in an endemic area or following travel from an endemic area, or fever for at least three out of seven consecutive days within 28 days of being in household contact with a confirmed case of typhoid or paratyphoid fever. Laboratory confirmation by detection of S. typhi in blood culture from a normally sterile site.[4,5]

The clinical spectrum ranges from a mild febrile illness with low-grade fever, malaise, and dry cough to a lethal disease due to multiple complications.

Serological Test

1) Antibody detection-Widal test: This test detects agglutinating antibodies to O and H antigens of

Corresponding Author: Dr. Kathakali Das, Flat 704, Tower 4, Uniworld Garden–I, Sector 47, Gurugram, Haryana, India.

S. typhi and H antigens of *S. Paratyphi* A and B. This test becomes positive toward the end of the 1st week and reaches the highest point during the 3rd week of illness.

2) Typhidot M assay: This is a dot-blot enzyme-linked immunosorbent assay which can detect specific immunoglobulin (Ig)M and IgG antibodies to a 50 kDa Outer Membrane Protein of *S. Typhi* 7 and becomes positive as early as the 1st week of fever (usually after 3 days).[4-7]

The primary objective of our study was to establish the efficacy of the Typhi dot M assay as an early diagnostic marker for typhoid fever by calculating the sensitivity and specificity, taking blood culture growth as a gold standard. Clinical profile of the suspected enteric fever cases is studied and compared with those of blood culture-positive cases.

Aims and Objectives

Research question

Will Typhidot M diagnose the disease typhoid fever early?

Aim

To study the clinical and microbiological profile of suspected enteric fever cases admitted in Pediatrics department of Northern Railway Central Hospital, New Delhi.

Primary objective

To establish the efficacy of the Typhidot M assay as a tool for early detection of typhoid fever by calculating the sensitivity and specificity, taking blood culture growth as a gold standard.

Secondary objective

To study and compare the clinical profile of enteric fever in suspected and blood culture-positive cases.

MATERIALS AND METHODS

Study Method

Study area

The study was carried out in the Department of Pediatrics, Northern Railway Central Hospital, New Delhi.

Study duration

Eight months (Dec 2019–July 2020)

Study design

This study was a hospital-based, prospective observational study. Patients with suspected enteric fever, that is, fever for more than 3 days without any other focus of infection, were evaluated by a panel of tests for typhoid fever and for other possible causes. Clinical profile of suspected and proven typhoid fever (positive blood culture) was studied in detail.

Inclusion criterion

All cases of fever for ≥3 days without an obvious focus of infection are admitted in Pediatrics ward of Northern Railway Central Hospital.

Exclusion criterion

Children with documented enteric fever within the past 8 weeks. Previously treated with antibiotics. Any known focus of infection (ex: Tonsillitis, Pharyngitis, Abscess, LRTI).

Sample size

All the patients during the study duration admitted in the pediatric ward of NRCH with a fever of ≥3 days duration without any obvious focus of infection were enrolled in the study. In this study, a total of 90 patients were included, as they fulfilled the inclusion criteria.

Working Definitions

Suspected case of enteric fever for case finding

Fever for at least three out of seven consecutive days in an endemic area or following travel from an endemic area or fever for at least three out of seven consecutive days within 28 days of being in household contact with a confirmed case of typhoid or paratyphoid fever.[2,3,8]

Confirmed case of enteric fever

Laboratory confirmation by blood culture showing growth of *S. typhi*/paratyphi.[2,3]

Procedure

After obtaining consent from parents/guardians; all children enrolled were subjected to detailed history and clinical examination. The following tests were done on the day of admission: * CBC/PSMP * Peripheral smear * Urine R/M and culture, sensitivity * Stool R/M and culture * Liver function test * Kidney function test * Serum electrolytes * Ultrasound abdomen * Serum Widal test * Typhidot M assay * Blood culture (Culture bottles with BacT/ALERT Microbial Detection System) * Any other test if required *

Empirical treatment with Ceftriaxone/Cefotaxime was started if any of the serological tests were positive. In cases showing no clinical improvement or in culture-positive cases, antibiotics were changed according to the culture and sensitivity report.

OBSERVATIONS AND RESULTS

Patients with fever without any obvious focus of infection and fulfilling the WHO definition of "Suspected" Enteric

fever cases admitted in the Pediatrics department of NRCH during the study duration were enrolled in the study. A total of 90 patients of age group 1–14 years of both genders were studied, who were admitted with ≥3 days of fever as per the inclusion criteria. Previously antibiotic-treated patients, patients with localized infection and those with a history of enteric fever in the past 8 weeks were excluded from the study. This study was carried out for a period of 8 months. Detailed history and examination findings were filled in a pro forma. Investigations were done and the three main tests, namely, blood culture, Typhi dot-M, and Serum Widal, were analyzed. Efficacy of Typhi dot-M as a rapid diagnostic test was evaluated keeping blood culture as gold standard. Clinical profile of these patients was studied in detail and a comparison was made between blood culture-positive and negative cases. Demographic, clinical data, and laboratory parameter details were noted on an Excel sheet and analyzed statistically by using appropriate tests wherever required. Epi Info CDC software was used for statistical calculations. $P < 0.05$ was considered to be statistically significant using 95% confidence interval.

In our study, patients in the age group 6–10 years were maximally affected by typhoid fever, followed by 1–5 years age group. The least number of cases were found in 11–14 years age group. In all the age groups, males were affected more than females.

In our study, out of 26 blood culture-positive patients, 18 were male, and 8 were female. Among the remaining 64 culture-negative patients, 35 were male, and 29 were female. Thus, we can say that in both blood culture-positive and negative groups, males were affected more than females.

In our study, 38 out of 90 enrolled cases (42.22%) were found to be Typhi dot-M positive.

In our study, 42.22% cases were positive for the Typhi dot-M test, followed by 33.33% positive for the S. Widal test. Only 28.88% cases were positive for Blood culture [Figures 1-3 and Tables 1-3].

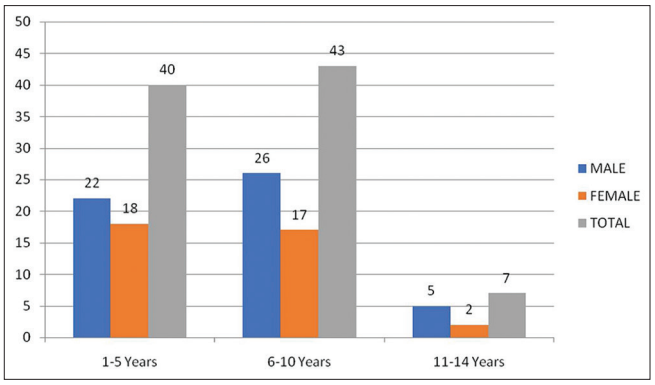

Figure 1: Age-wise gender distribution of patients (*n* = 90)

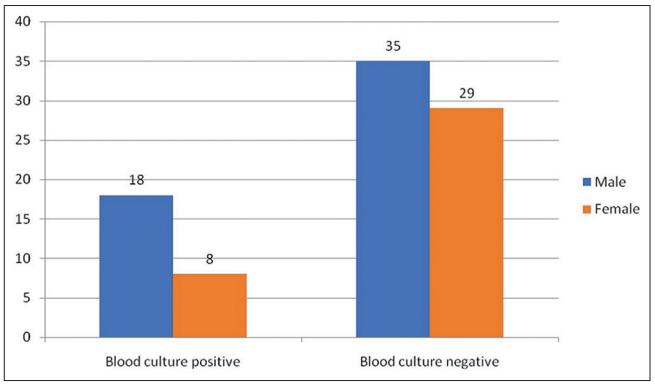

Figure 2: Blood culture * gender (2 * 2 contingency table)

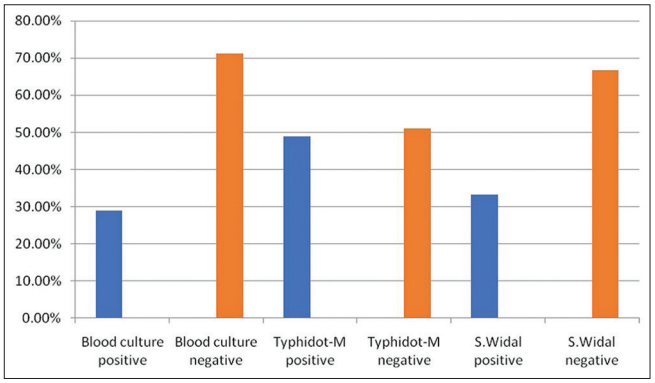

Figure 3: Results in (%) of three tests, positive cases, and negative cases

DISCUSSION

We calculated the sensitivity, specificity, positive predictive value, and negative predictive value of Typhi dot-M and Serum Widal test by keeping blood culture positive cases as the gold standard and found that the Typhi dot M test was better in diagnosing typhoid fever at an early stage with more reliability as compared to the Widal test. The sensitivity and specificity of the Typhi dot-M test was 92.3% and 78.12%, respectively. Positive and Negative predictive values were 63.15%and 95.15%, respectively. *P* value for this test was <0.001, that is, statistically significant. Furthermore, the kappa value (measure of agreement) for the Typhi dot M test was 0.619 (61.9%) in our study, which is much higher than Widal test. This reflects that there is more reliability between Typhi dot M and blood culture as compared to the Widal test and blood culture. The sensitivity and specificity of the Widal test was 53.84% and 75%, respectively. Positive and negative predictive values were 46.66% and 80.0%, respectively. *P*-value for this test came out to be <0.05, which was statistically significant. The kappa value (measure of agreement) for Widal was 0.276 (27.6%), which is not

Table 1: Frequency of Typhi dot-M Test (*n*=90)

Positive	38	42.22%
Negative	52	57.78%
Total	90	100%

Table 2: Typhi dot-M test

Sensitivity	92.30%
Specificity	78.12%
Positive predictive value	63.15%
Negative predictive value	96.15%

Table 3: Comparison of our results with various studies done for evaluation of Typhidot-M test

Author	Year of test	Test	Sn	Sp	PPV	NPV
Olsen *et al*.[6]	2002	Typhidot M	79	89	96	59
Jesudason *et al*.[4]	2003	Typhidot M	92.3	98.8	88.7	99.4
Zohra *et al*.[9]	2006	Typhidot M	98.85	90	76.47	97.29
Dutta *et al*.[10]	2006	Typhidot M	47	43	85	42
Naheed *et al*.[11]	2008	Typhidot M	67	54	85	81
Beig *et al*.[12]	2010	Typhidot M	90	100	100	92.1
Khoharo *et al*.[10]	2010	Typhidot M	96	89.5	95	
Narayanapa *et al*.[13]	2010	Typhidot M	92.6	37.5	48.7	88.8
Krishna *et al*.[14]	2011	Typhidot M	100	95.5	89.2	100
Muthaiyan *et al*.[15]	2016	Typhidot M	88.46	81.56	46.94	97.46
Ghosh *et al*.[16]	2016	Typhidot M	100	74.35	94.87	100
Our results	2020	Typhidot M	92.30	78.12	63.15	96.15

very much significant, that is, there is less "Reliability "between the Widal test and blood culture. Typhi dot-M test, evaluated by other researchers in the past, also found that this test is superior to the Widal test in sensitivity and specificity.

Summary

- Enteric fever is endemic in our country and its early diagnosis is essential to keep check on the mortality, morbidity, inadvertent use of antibiotics, and cost of prolonged hospital stay. Keeping this in Typhi dot-M diagnose the disease typhoid fever early?" Our aims and objectives were to establish the efficacy of Typhi dot M assay as a tool for early detection of typhoid fever by calculating the sensitivity and specificity, taking blood culture growth as a gold standard and also to study and compare the clinical profile of enteric fever in suspected and blood culture positive cases.
- This observational study was conducted in the Pediatrics department of Northern Railway Central Hospital, New Delhi. Our aims and objectives were to establish the efficacy of Typhi dot M assay as a tool for early detection of typhoid fever and also to study and compare clinical profile of enteric fever in suspected and blood culture positive cases. Efficacy of Typhi dot-M in diagnosing typhoid fever at an early stage was evaluated by calculating its sensitivity, specificity, NPV, and PPV, keeping blood culture-positive cases of typhoid fever as the gold standard.
- Study of 90 patients to evaluate Typhi dot-M test shows the sensitivity, specificity, positive predictive value and negative predictive value of the Typhi dot-M test to be 92.35, 78.12%, 63.15%, and 96.15%, respectively; which is higher as compared to Serum Widal test which shows sensitivity, specificity, positive predictive value and negative predictive value of 53.84%, 75.0%, 46.66% and 80.0%, respectively, in our study; keeping blood culture for Salmonella typhi growth as gold standard.
- Sensitivity, specificity, positive predictive value, and negative predictive value of the Typhi dot-M test were better than Serum Widal test in our study.
- Typhi dot-M test positivity is significantly associated with blood culture positivity, showing $P < 0.001$. This association is highly significant statistically. Furthermore, the measure of agreement "kappa" value is 0.619, which shows that the Typhi dot M test has 61.9% reliability, which is much higher than that of the Widal test (27.6%) in our study.
- Association of Widal test positivity is also significantly associated with blood culture-positivity ($P < 0.05$), but its sensitivity, specificity, and reliability are low as compared to the Typhi dot M test.
- Typhidot-M test results are available within an hour as compared to the Widal test, which takes longer duration for its interpretation.
- When we analyzed the clinical profile of blood culture positive patients, we analyzed that more males were affected with typhoid fever and the most common age group affected was 6–10 years. However, the association of both the gender and age was found to be statistically insignificant ($P > 0.05$).
- Blood culture positivity is seen in 28.88% of cases, which could be because of less amount of sample being available in children and inadvertent use of antibiotics.
- In the blood culture positive enteric fever patients of our study, the most common symptoms were fever (100%), anorexia (88.46%), abdominal pain (88.46%), chills (61.53%), diarrhea (57.69%), and vomiting (53.84%). The common signs were toxic look (76.92%), hepatomegaly (69.23%), and coated tongue (69.23%). Less frequent symptoms in our study were myalgia, headache, joint pain, cough, constipation and epistaxis which were present in 46.15%, 38.46%, 30.76%, 23.07%, 19.23% and3.84% of the culture-positive patients, respectively. The less common physical signs in our study were splenomegaly (46.15%), pallor (34.61%), lymphadenopathy (7.69%),

and relative bradycardia (3.84%).

- When the presence of clinical features was compared between blood culture positive (n = 26) and blood culture negative (n = 64) groups; symptoms, such as abdominal pain, chills/rigors, diarrhea, myalgia, and headache, were found to be statistically significant ($P < 0.05$) in culture positive cases. Signs, such as toxic look, hepatomegaly, coated tongue, and splenomegaly, were statistically significant ($P < 0.05$) in blood culture positive patients.
- The most common abnormal laboratory findings seen in culture-positive enteric fever patients in our study were raised serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and erythrocyte sedimentation rate (ESR), seen in 96.15%, 88.46% and80.76% of patients, respectively. Parameters, such as raised SGOT, raised SGPT, increased ESR, and eosinopenia, were found to be statistically significant ($P < 0.05$) in culture-positive cases.

CONCLUSION

To conclude, we can say that:

- Typhi dot-M is the rapid, accurate, and reliable tool for the diagnosis of typhoid fever at the earliest; as compared to the Widal test.
- A combination of blood culture and Typhi dot- M test will significantly improve the diagnostic yield of these investigations.
- Typhi dot-M is easy to perform and does not require trained staff. Results are available rapidly, so it can be used as an early diagnostic marker of typhoid fever in settings where blood culture tests are not readily available.
- The Widal test alone is not a very useful or reliable test for the diagnosis of enteric fever.
- Despite the high cost of Typhi dot-M as compared to the Widal test, the early detection by Typhi dot-M would help in decreasing unnecessary use of antibiotics and hospital stay and thus ultimately reducing the cost of treatment in today's era of antibiotic resistance.
- Fever, anorexia, abdominal pain, toxic look, hepatomegaly, and coated tongue, along with deranged laboratory parameters, such as raised SGOT, SGPT, and ESR, are the most common findings seen in blood culture positive enteric fever patients.
- Symptoms, such as abdominal pain, chills/rigors, diarrhea, myalgia, headache; signs, such as toxic look, hepatomegaly, coated tongue, splenomegaly, and laboratory parameters, such as raised SGOT, raised SGPT, increased ESR, and eosinopenia, are found to have statistically significant association with culture-positive cases.

Limitations of Study

The sample size is smaller in this study. If more children were enrolled in the study, a more detailed picture of clinical features and laboratory features could be obtained. Large scale prospective evaluation of the typhi dot assay in endemic populations should be done to find the exact usefulness of the typhi dot assay.

RECOMMENDATIONS

The present study concludes that the Typhi dot M test is useful for early detection of Typhoid fever (as early as within the first 3 days of fever) and is better than the Widal test. Hence, were commend the use of Typhi dot M as an early diagnostic test in suspected enteric fever cases, that is, in patients with more than or equal to 3 days of fever without any obvious focus of infection.

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