

Predictive value of clinical and laboratory findings in the diagnosis of the enteric fever

Ceren Kuvandik¹, Ilkay Karaoglan², Mustafa Namiduru³, Ibrahim Baydar⁴

¹Department of Infectious Diseases, Government Hospital, Kırıkhan, Turkey;

²Gaziantep University, School of Medicine, Departments of Infectious Diseases, Gaziantep, Turkey;

³Gaziantep University, School of Medicine, Departments of Infectious Diseases, Gaziantep;

⁴Gaziantep University, School of Medicine, Departments of Infectious Diseases, Gaziantep, Turkey

SUMMARY

Although the definitive diagnosis of enteric fever requires the isolation of *Salmonella enterica serotype typhi* or *paratyphi*, the diagnosis is usually made according to clinical and laboratory findings. There is usually a diagnostic dilemma. The aim of this study was to determine the minimum required parameters that could be valuable in the diagnosis of enteric fever. A retrospective study was performed to compare the clinical and laboratory findings in 60 patients who proved to have enteric fever by cultures and 58 patients with non-enteric fever. Features independently predictive of enteric fever were assessed by multivariate logistic regression. Sensitivity, specificity and positive predictive and negative predictive values were estimated. Significant clinical features of enteric fever were hepatomegaly, splenomegaly, relative bradycardia, rose spots, leucopenia, trombocytopenia, eosinopenia and elevated AST level. Five of these features were found to be predictive for the diagnosis of enteric fever; splenomegaly, relative bradycardia, rose spots and trombocytopenia and elevated AST level.

In conclusion, clinical and laboratory findings can help the clinician to diagnose enteric fever in the absence of microbiological confirmation.

KEY WORDS: Enteric fever, Diagnosis, Clinical and laboratory findings

Received March 28, 2008

Accepted June 13, 2008

INTRODUCTION

Salmonella enterica serotype Typhi is the etiologic agent of typhoid fever and serotype *paratyphi* is the etiologic agent of paratyphoid fever. Enteric fever is the general name of typhoid and paratyphoid diseases (Pegues *et al.*, 2005, Wilke 2002). It still remains as an important morbidity and mortality cause in many countries of the developing

world (Pang *et al.*, 1995, Sinha *et al.*, 1999). Every year, an average of 33 million new cases occur in the world of which 13 million appear in Asia. India, South and Central America and Africa are the regions where the disease is seen endemically due to the rapid population increase, increasing urbanization, restricted water resources and insufficient infrastructure and health services (Pang *et al.*, 1995, Wilke *et al.*, 2002).

Enteric fever is an endemic disease also in Turkey and sometimes can cause epidemic outbreaks (Wilke 2002, Wilke *et al.*, 2002). Serious complications are encountered in the enteric diseases that are untreated. These are intestinal bleeding, intestinal perforation, and rarely spleen abscess (Peques *et al.*, 2005).

The definitive diagnosis of enteric fever is possible with the isolation of the causative agent.

Corresponding author

Ilkay Karaoglan
Gaziantep University School of Medicine,
Department of Infectious Diseases,
Sahinbey Medical Center,
Gaziantep, TR-27310 (Turkey)
E-mail: ilkaykaraoglan@yahoo.com
ikaraoglan10@hotmail.com

However, the availability of microbiological culturing facilities is often limited in regions in which enteric fever is endemic. In addition cultures can be negative when patients used antibiotic therapy prior to diagnosis (House *et al.*, 2001, Chart *et al.* 2000). Patients with enteric fever are diagnosed with Widal test or clinical signs. Clinical signs are diverse in enteric fever. These signs may be observed in enteric fever as well as in many other infectious diseases. This may lead to unnecessary use of antibiotics in some other disorders causing febrile conditions. The aim of this study was to find out the minimum required laboratory and clinical parameters that can be used in the early diagnosis of enteric fever.

MATERIALS AND METHODS

This study was performed retrospectively in the Gaziantep University School of Medicine between 2000 and 2005. Our study group with an initial diagnosis of enteric fever was selected from patients admitted to the clinic with the signs of fever $\geq 38.0^{\circ}\text{C}$ for about >4 days and at least one of the clinical signs nausea, vomiting, abdominal pain, headache, lack of the appetite, rash and cough. Blood cultures were collected from the all patients during the fever period. Patients with positive blood cultures for *Salmonella typhi* or *Salmonella paratyphi* were included in Group 1 as enteric fever patients.

Patients were researched for fever etiology when *Salmonella typhi* or *Salmonella paratyphi* were not detected from blood cultures or other body fluids were included in Group 2 as non-enteric fever patients.

The clinical (hepatomegaly, splenomegaly, relative bradycardia, roseol) and laboratory (leukocyte, trombocyte, eozinophil, hemoglobin, alanin amino transferase, aspartat aminotransferase, O agglutinin titer, H agglutinin titer) findings were recorded then compared between the two groups. Patients with a diagnosis of non-enteric fever which could not be confirmed by the microbiological methods and patients with different severity of clinical, laboratory findings like acute hepatitis were excluded from the study group. Group 1 had 60 patients with enteric fever whose diagnoses were confirmed by the isolaton of *S. typhi* or *S. paratyphi* in the blood. There were 32 males

and 28 females with a mean age of 28.8 ± 10.5 years. Group 2 had 58 patients with diagnoses of other infections. There were 30 males and 28 females with a mean age of 30.6 ± 12.2 years.

Blood cultures were performed using BACTEC (Becton, Dickinson USA) or BacT Alert 3D (France) automatized blood culture systems. The culture tubes in which some colonies were observed were centrifuged at 3000 rpm for three to five minutes. After the centrifugation, subculture was performed into blood and EMB agar. Positive colonies were biochemically identified by Vitex 32 Biomeriux automatized system (France).

STATISTICAL METHOD

Independent samples-t and χ^2 tests were used to compare the clinical and laboratory parameters of the groups. Logistic regression analysis was performed to evaluate correlation of the variables with enteric fever.

RESULTS

In the blood culture of 60 enteric fever patients, *S. typhi* was isolated in 28 patients, *S. paratyphi A* was isolated in 20 patients, and *S. paratyphi B* was isolated in 12 patients. The final diagnosis of non enteric fever patients were brucellosis 27 patients, staphylococcal infection 10 patients, meningitis due to *Mycobacterium tuberculosis* 5 patients, urinary tract infection due to *Escherichia coli* 8 patients, pneumonia due to *Streptococcus pneumonia* 8 patients.

There was no significant difference between the ages of the patients in the enteric fever patients and non enteric fever patients ($p=0.386$). When the clinical parameters of the groups were compared, there was a significant difference between the groups regarding hepatomegaly, splenomegaly, rose spots, relative bradycardia, leucopenia, trombocytopenia, eosinopenia and elevated AST level (Table 1). Sensitivity, specificity, and positive and negative predictive values are shown in Table 2. Accordingly, on clinical examination, when splenomegaly and rose spots coexisted in a patient with fever, the positive predictive value (PPV) of this condition was found to be 61.0% whereas the

negative predictive value (NPV) was 31.7%. The sensitivity and specificity of these findings in the diagnosis of enteric fever were 78.3% and 48.3%, respectively.

When splenomegaly, rose spots and relative bradycardia coexisted in a patient with enteric fever, PPV was 59.1%, NPV was 20.0%, sensitivity was 91.7% and specificity was 34.5%. When splenomegaly, rose spots, relative bradycardia, a titer of O antibody 1/200 coexisted in a patient with fever, PPV was 58%, NPV was 11.1%, sensitivity was 96.7% and specificity was 27.6%. When splenomegaly, rose spots, relative bradycardia, a titer of O antibody 1/200, normal leukocyte count ($<10800/\text{mm}^3$) coexisted in patient with fever, PPV was 53.6%, and the diagnosis was definitely enteric fever. The sensitivity and specificity of detection of these findings in the diagnosis of enteric fever were 100% and 10.3% respectively. When splenomegaly, rose spots, relative brady-

cardia, a titer of O antibody 1/200, and leucopenia ($<4300/\text{mm}^3$) coexisted in patient with fever, PPV was 55.8%, NPV was 14.3%, sensitivity was 96.7% and specificity was 20.7%.

Logistic regression analysis revealed that splenomegaly, relative bradycardia, rose spots, thrombocytopenia and elevated AST level were found as independent risk factors in the diagnosis of the enteric fever. Independent risk factors increase the probability of the patient having enteric fever (Table 3).

According to the data we obtained in patients with fever, the probability of enteric fever with splenomegaly was 8.16 fold more than that of enteric fever without splenomegaly. The probability of enteric fever in the patients with relative bradycardia was 17.26 fold more than those without relative bradycardia. The probability of enteric fever in the patients with rose spots was 4.94 more than those without rose spots. The

TABLE 1 - Clinical and laboratory findings among patients with culture proven enteric fever and patients with non-enteric fever.

Parameters	EFP n: 60(%)	NEFP, n: 58(%)	P	OR (95% CI)
Gender (M/F)	32/28	30/28	0.386	1.07 (0.49-2.34)
Hepatomegaly	43 (70)	30 (51.7)	0.042	2.36 (1.03-5.44)
Splenomegaly	36 (60)	20 (34.5)	0.005	2.85 (1.26-6.47)
Relative bradycardia	46 (76.7)	14 (24.1)	0.000	10.33 (4.10-26.63)
Rose spots	26 (43.3)	14 (24.1)	0.02	2.40 (1.02-5.72)
Typhoid tongue	38 (63.3)	30 (51.7)	0.202	1.61 (0.72-3.60)
Anemia ($<13\text{g/dl}$)	28 (46)	24 (41)	0.56	1.24 (0.56-2.74)
Leucopenia ($<4300/\text{mm}^3$)	32 (53.3)	16 (27.6)	0.004	3.00 (1.30-6.97)
Trombocytopenia ($<130.000/\text{mm}^3$)	44 (73.3)	20 (34.5)	0.000	5.22 (2.22-12.47)
Eosinopenia (0-1%)	48 (80)	30 (51.7)	0.000	4.00 (1.66-9.78)
AST ($>45\text{U/L}$)	42 (70)	26 (44.7)	0.005	2.87 (1.26-6.59)
ALT ($>45\text{U/L}$)	28 (46.6)	28 (50)	0.86	0.94 (0.43-2.06)
LDH ($>500\text{U/L}$)	32 (53.3)	30 (51.7)	0.861	1,07 (0.49-2.34)
CRP (>20)	37 (61.6)	28 (48.2)	0.143	1.72 (0.78-3.83)

EFP: enteric fever patients; NEFP: non-enteric fever patients; CI: confidence interval.

TABLE 2 - Sensitivity, specificity and predictive values (%) of combined clinical and laboratory findings in patients with enteric fever.

	Sensitivity	Specificity	(+) Predictive value	(-) Predictive value
SM + RS	%78.3	%48.3	%61.0	%31.7
SM + RS + RB	%91.7	%34.5	%59.1	%20.0
SM + RS + O (1/100)	%96.7	%24.1	%56.9	%12.5
SM + RS + O (1/200)	%83.3	%37.9	%58.1	%31.3
SM + RS + RB + O (1/200)	%96.7	%27.6	%58.0	%11.1
SM + RS + RB + O (1/200) + L (<10800)	%100.0	%10.3	%53.6	%0.0
SM + RS + RB+ O (1/200)+ L (<4300)	%96.7	%20.7	%55.8	%14.3

SM: splenomegaly, RS: rose spots, RB: relative bradycardia, O (1/100): O antibody titer = 1/100, O(1/200): O antibody titer = 1/200, L(<10.800): Leucocyte count <10800/mm³, L(<4.300): Leucocyte count <4300/mm³.

TABLE 3 - Logistic regression analysis, predictor variables for enteric fever cases.

Predictor variables	P	OR (95% CI)
Splenomegaly	0.004	8.16 (1.68-16.28)
Relative bradycardia	0.000	17.26 (3.20-25.59)
Trombositopenia	0.005	7.92 (1.63-15.36)
Rose spots	0.026	4.94 (1.16-11.15)
Elavated AST level	0.003	5.4 (1.7-14.1)

CI: confidence interval.

TABLE 4 - Distribution of O antibody titers in patients with enteric fever.

'O' agglutinin titres (TO, AO, BO)	EFP, n: 60 (%)	NEFP, n: 58 (%)
(-)	16 (26.7)	24 (41.4)
1/50	8 (13.3)	12 (20.7)
1/100	14 (23.3)	14 (24.1)
1/200	8 (13.3)	6 (10.3)
1/400	14 (23.3)	2 (3.4)

EFP: enteric fever patients, NEFP: non-enteric fever patients, p=0.002, X² = 9.36

probability of enteric fever in the patients with thrombocytopenia was 7.92 fold more than those without thrombocytopenia.

It was detected that if 'O' antibody titration increases, the probability of enteric fever will increase (Table 4).

DISCUSSION

Enteric fever is the major cause of community-acquired septicemia in Southeastern Turkey and in many other areas in the developing world. The definitive diagnosis is achieved by isolating *S. typhi* or *Paratyphi* from blood, urine, feces and/or

bone marrow (Pegues *et al.*, 2005, Sinha *et al.*, 1999). However microbiological documentation may not be done routinely and a certain time interval is required for identification. Furthermore, due to prior antibiotic therapy and low level of bacteria in the blood (<15 microorganisms/ml), bacterial isolation rate is almost 40-70%.

Other infections such as viral etiologies may initially be confused with enteric fever (Pegues *et al.*, 2005, Wilke *et al.*, 2002)). This may lead to unnecessary exposure to antibiotic agent and spread of increasingly common multidrug resistant strains (Vollaard *et al.*, 2005). On the other hand, isolation of the bacterium is not awaited

to initiate the treatment for enteric fever because of the long duration, the frequency of complications, accompanying death rates and prolonged hospital stay. However, no laboratory and clinical finding with higher sensitivity and specificity has been defined apart from bacterial isolation (Vollaard *et al.*, 2005, Chan Ping Su *et al.*, 2004). In addition, serological tests such as Widal test have no diagnostic value (Vollaard *et al.*, 2005, Bhutta *et al.*, 1999, Saha *et al.*, 1996, House *et al.*, 2001). In enteric fever, hepatomegaly is seen in 60.5% to 85.3%, splenomegaly in 17.5% to 50%, rose spots in 49%, bradycardia in 82% to 94.7%, and typhoid tongue in 94% (Vollaard *et al.*, 2005, Caumes *et al.*, 2001, Yew *et al.*, 1991, Malik *et al.*, 2001, Wain *et al.*, 2001, Kadhiraivan *et al.*, 2005, Haq *et al.*, 1997).

For a positive Widal test, a titration of $\geq 1/40$ to $\geq 1/480$ is necessary in different countries (Wilke *et al.*, 2002, Shukla *et al.*, 1997). Widal test has been used extensively as a diagnostic tool in many developing countries. This test requires both acute and convalescent sera and results are often found to be unreliable in endemic areas (Khan *et al.*, 1998).

According to a previous study, hepatomegaly, preadmission duration of fever ≥ 7 days, leucopenia due to absolute neutropenia with relative lymphocytosis, leucocyte count of $< 10,000/\text{mm}^3$ were found to be associated with typhoid fever (Khan *et al.*, 1998).

Another study from Turkey showed that age, abdominal distention, confusion, relative bradycardia, typhoid tongue, Widal test positivity and leucopenia are the predictive factors for enteric fever (Hosoglu S *et al.*, 2006). In our study, splenomegaly, rose spots, relative bradycardia and thrombocytopenia and elevated AST level were found to have a predictive value for enteric fever. Therefore, the diagnosis of enteric fever can be made prior to microbiological test results when these findings are present in the first 24 hours of hospitalization. In addition, splenomegaly, rose spots, relative bradycardia, a titer of O antibody 1/200, normal leukocyte count ($< 10,800/\text{mm}^3$) or leucopenia ($< 4,300/\text{mm}^3$) in patient with fever have a high sensitivity in the diagnosis of enteric fever.

In conclusion, clinical and laboratory findings can help the clinician to diagnose enteric fever in the absence of microbiological confirmation.

REFERENCES

- BHUTTA Z.A., MANSURALI N. (1999). Rapid serologic diagnosis of pediatric typhoid fever in an endemic area: a prospective comparative evaluation of two dot-enzyme immunoassays and the Widal tests. *Am. J. Trop. Med. Hyg.* **61** (4), 654-657.
- CHAN PING S.U., YEE CHUN CHEN, SHAN-CHWEN. (2004). Changing characteristics of typhoid fever in Taiwan. *J. Microbiol. Immunol. Infect.* **37** (2), 109-114.
- CHART H., CHEESBROUGH J.S., WOGHORN D.J. (2000). The serodiagnosis of infection with *Salmonella typhi*. *J. Clin. Pathol.* **53** (11), 851-853.
- CAUMES E., EHYA N., NGUYEN J., BRICAIRE F. (2001). Typhoid and paratyphoid fever: a 10-year retrospective study of 41 cases in Parisian Hospital. *J. Travel. Med.* **8** (6), 293-297.
- HAQ S.A., ALAM M.N., HOSSAIN S.M., AHMED T., TAHIR M. (1997). Value of clinical features in the diagnosis of enteric fever. *Bangladesh Med. Res. Counc. Bull.* **23** (2), 42-46.
- HOSOGLU S., GEYIK M.F., AKALIN S., AYAZ C., KOKOGLU O.M., LOEB M. (2006). A simple validated prediction rule to diagnose typhoid fever in Turkey. *Trans. R. Soc. Trop. Med. Hyg.* **100** (11), 1068-1074.
- HOUSE D., WAIN J., VO A H.O., DIEP T.S., CHINH N.T., BAY P.V., VINH H., ET AL. (2001). Serology of typhoid fever in an area of endemicity and relevance to diagnosis. *Journal of Clin. Microbiology.* **39** (3)1002-1007.
- KADHIRAVAN T., WIG N., KAPIL A., KABRA S., RENUKA K., MISRA A. (2005). Clinical outcomes in typhoid fever: adverse impact of infection with nalidixic acid-resistant *Salmonella typhi*. *BMC Infect. Dis.* **5** (1), 37-47.
- KHAN M., COOVADIA Y.M., CONNOLLY C., STURM A.W. (1998). The early diagnosis of typhoid fever prior to the widal test and bacteriological culture results. *Acta Tropica.* **69** (2), 165-173.
- MALIK A.S., MALIK R.H. (2001). Typhoid fever in Malaysian children. *Med. J. Malaysia.* **56** (4), 478-490.
- PANG T., BHUTTAZA, FINLAY B.B., ALTWEGG M. PANG T. (1995). Typhoid fever and other salmonellosis: a continuing challenge. *Trends Microbiol.* **3** (7), 253-255.
- PEGUES D.A., OHL M.E., MILLER S.I. (2005). *Salmonella species*, Including *Salmonella typhi*. In: Mandel G.L., Bennett J.E., Dolin R., eds. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases* (6th ed). New York, Elsevier Churchill Livingstone, 2636-2654.
- SAHA S.K., RHULAMIN M., HANIF M., ISLAM M., KHAN W.A. (1996). Interpretation of the Widal test in the diagnosis of typhoid fever in Bangladeshi children. *Ann. Trop. Paediatr.* **16** (1), 75-78.
- SHUKLA S., PATEL B., CHITNIS D.S. (1997). 100 years of

- Widal test and its reappraisal in an endemic area. *Indian. Med. Res.* **105**, 53-57.
- SINHA A., SAZAWAL S., KUMAR R., SOOD S., REDDAIAH V.P., SINGH B., ET AL. (1999). Typhoid fever in children aged less than 5 years. *Lancet.* **354** (9180), 754-758.
- VOLLAARD A.M., ALI S., WIDJAJA S., VAN ASTEN HENRI A.G.H. VISSER LEO G., SURJADI C., VAN DISSEL J.T. (2005). Identification of typhoid fever and paratyphoid fever cases at the presentation in outpatient clinics in Jakarta, Indonesia. *T. Roy. Soc. Trop. Med. Hyg.* **99** (6), 440-450.
- WAIN J., BAY V. PHAN, VINH H.A., DUONG N.M., DIEP T.S., WASH L.A., ET AL. (2001). Quantitation of bacteria in bone marrow from patients with typhoid fever: relationship between counts and clinical features. *J. Clin. Microbiology.* **39** (4), 1571-1576.
- WILKE A., SOZEN T.H., GULTAN K., BALIK I. (1988) Tifo: 100 hastanın klinik, laboratuvar ve tedavi yönünden de erlendirilmesi. *Ankara Tıp. Bülteni.* **10** (1), 53-62.
- WILKE A. (2002). Tifo ve tifo dışı salmonellozlar. In: Wilke A, Söyletir G, Do anay M, eds. *nfeksiyon Hastalıkları ve Mikrobiyolojisi* (2nd ed). Ankara, Nobel Tıp Kitapevleri, 642-658.
- WILKE A., ERGONUL O., BAYAR B. (2002). Widal test in Diagnosis of typhoid fever in Turkey. *Clinical and Diagnostic Laboratory Immunology.* **9** (4), 938-941.
- YEW F.S., CHEW S.K., GOH K.T, MONTERIO E.H., LIM Y.S. (1991). Typhoid fever in Singapore: a review of 370 cases. *J. Trop. Med. Hyg.* **94** (5), 352-357.