TYPHOID FEVER — ITS PREDICTION WITHOUT BLOOD CULTURE

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SUMMARY

To diagnose typhoid fever on clinical ground without blood culture, a study was conducted in Medical A Unit Postgraduate Medical Institute, Lady Reading Hospital, Peshawar on 25 patients with typhoid fever. 24 (96%) blood cultures yielded the growth of salmonella typhi and 1 (4%) of S parathphi A. Fever for more than 7 days was noted in 20 (80%) patients. Toxic look and coated lips were present in 17 (68%) and cough with few basal crackles were recorded on 15 (60%) cases. Spleen was enlarged in 15 (60%) and pain abdomen with diarrhea were complained by 14 (56%) patients. The TO and AO titres, of the widal test, were raised to ≥ 1/320 in 16 (64%) cases. Clinical diagnosis of typhoid fever was suggested by the following 6 events: duration of fever for more than 7 days, toxic look and coated lips, dry cough with few crackles, soft splenomegally, pain abdomen with diarrhea and a positive widal test at screening dilution of ≥ 1/320.

INTRODUCTION

Diagnosis of enteric fever remains a challenge even in this modern age of technology. Tests, both sensitive and specific are available for most other diseases yet causative organisms of typhoid is difficult to culture. This article is an attempt to highlight a small number of clinical features that are usually associated with typhoid fever.

The most definitive method of diagnosing typhoid fever is the blood culture. Blood cultures are usually positive between days 7 and 10 of the acute illness. The best yield of the culture is from the bone marrow. It has the added advantage of providing cultures that are often positive for some days after the start of antibiotic therapy.[1] The positivity of cultures is very low in endemic areas for various reasons like;-

- Self prescribed antibiotics, delay in seeking medical advice.
- Use of suboptimal blood culture methods like inappropriate blood to broth ratio (1:10 ratio optimal)
- The laboratory technician do not inactivate antibacterial substances and often lack the necessary antisera for grouping and typing the organism. Financial cost of the test.

All these factors contribute to the low use of this test.[2]

The purpose of this article is to diagnose typhoid fever on basis of small number of clinical and laboratory features when blood culture is not possible. Rose and Ibraham suggested six out of total of 8 features with 80 percent specificity and 92 percent sensitivity in a setting where culture cannot be done.[3]

MATERIAL AND METHODS

All those patients from OPD or casualty who were running a temperature of 101° F

TABLE – 1

MAJOR SYMPTOMS AND PHYSICAL SIGNS IN 25 PATIENTS WITH ENTERIC FEVER.

		NO. OF PATIENT	PERCENTAGE
1.	Fever	25	(100%)
	Remittent	19	(76%)
	Intermittent	6	(24%)
2.	Toxic look and coated lips	17	(72%)
3.	Cough/Sore throat	15	(60%)
4.	Diarrhea/Constipation	14	(56%)
5.	Spleenomegaly	15	(60%)
6.	Hepatomegaly	10	(40%)
7.	Confusion/Neck stiffness	2	(08%)

or above admitted in Medical "A" Ward of PMGI, Peshawar from Jan. 1993 to Jan. 1995. A proforma was prepared which included symptoms, signs and various laboratory investigations like haemoglobin, total leucocyte count (TLC), differential leucocyte count (DLC), Urine analysis, MP, X-ray chest PA, LFTs, and widal test. Blood cultures were taken and only those positive for salmonella were included in the study.

RESULTS

A total of 25 patients were included in this study. The blood cultures of 24 patients yielded growth of S. typhi and only one showed S. paratyphi-A.

Fever was recorded in all. Five patients (20%) had fever for the past 7 days and in the rest the duration ranged from 2 weeks to more than 4 weeks. It was gradual in onset in 20 patients (80%) and remittent in 19 (76%). Chills were noted in 15 (60 %) and rigors in 1 (4%). The skin was dry and hot with a toxic look and coated angles of the mouth in 17 (68%). Cough with sore throat and scattered wheezes and crepitations with normal X-ray chest was noted in 15 (60%) patients. Pain abdomen/right illiac fossa with diarrhea were complained by 14 (56%). Hepatomegaly and splenomegaly were present in 10 (40 %) and in 15 (56%) patients. Two patients were admitted in a confused state with neck stiffness (Table-1).

Only 5 patients (20%) were anemic (Hb < 12gm %). Total leucocyte count was less than 7 x 10^3 in 13 patients (52%) and leucopenia (<4000 mm) was observed in only 4 (15%). The neutrophilic count of less than 4 x 10^3/lit was seen only in 7 (28%) patients and erythrocyte sedimentation rate (ESR) was high in 10 (40%) (Table-2).

Serum bilirubin and alanine aminotransferase levels were elevated in 4 (16%). Trace to moderate proteinurea and occasional red or white cells were seen in the urine of 4 (16%) patients (Table-2).

The results of the widal test were; raised T O titers to ≥ 1:320 in 15 (60%), ≥ 1:160 in 6 (24%) and < 1/80 in 3 (12%). The AO titres were elevated to ≥ 1:320 in 1 (4%) patient. T.H and A.H titres were elevated to ≥ 320 in all (Table-2). Seroconversion (four fold rise after one week) was observed in 2 (8%) patients only. MP (Malarial parasite) was detected in one (4%) patient. G6PD deficiency was detected in another patient. Blood culture yielded growth of Salmonella

TABLE – 2

LABORATORY RESULTS IN 25 PATIENTS OF TYPHOID FEVER.

		NO. OF PATIENTS	PERCENTAGE
HAEMATOLOGY			
Haemoglobin (< 12gm%)		05	(20%)
Total leucocyte count (< 7X10/Lit)		13	(52%)
Neutrophilic count (< 4X10/Lit)		07	(28%)
Malarial parasite detected		01	(04%)
SEROLOGY (WIDAL TEST)			
T O Titres	(> 1/320)	15	(60%)
	(> 1/160)	06	(24%)
	(> 1/80)	03	(12%)
A O Titres	(>1/320)	01	(04%)
T H	(>1/320)	24	(100%)
A H	(> 4320)	01	(100%)
BIOCHEMICAL			
Raised Bilirubin and SGPT		04	(16%)

Urine analysis-few patients showed trace to moderate proteinurea and occasional Red or White cells.

typhi in 24 (96%) patients and paratyphi A in one (4%).

DISCUSSION

Typhoid fever is a significant health problem in many areas of Asia, Africa and South America. The incidence of this disease is estimated at 450 cases per 100,000 people in developing countries where it is endemic because of contaminated water and poor sanitation.[4] In the west the increase in the out break is associated with mass production of food products, particularly poultry, which is frequently contaminated. In the United States the vast majority of infections are caused by serotypes not specifically adapted to human or animal hosts, whereas the most frequent isolate in the developing countries is highly adapted to human hosts.[5] It results in high mortality and morbidity in areas where medical facilities are limited and patients may present with advance disease in a moribond state.[6,7]

In the past much has been made of step-wise contour of temperature chart in cases observed during the first week of illness. Of much more value to the clinician is the knowledge that this fever rarely shows an abrupt onset, that rigors are uncommon, chills may occur in upto one third of the patients and that, when fully developed, the fever of typhoid reaches a high plateau of 39 to 40 C , which shows strikingly little diurnal variation compared to other fevers. By the end of the first week, the patient's skin is characteristically hot and dry and has a toxic look. Exception to this are seen in late or complicated typhoid and in patients treated with Aspin.[1,2] Other prominent features are respiratory symptoms (sore throat, cough, bronchitis), abdominal pain and diarrhea (which is more common than constipation), hepatomegaly (25.50%) and

TABLE – 3

COMPLICATIONS OF TYPHOID

ABDOMINAL	
Intestinal Perforation	Spontaneous splenic rupture
Intestinal Haemorrhage	Rupture and Haemorrhage from Mesenteric Nodes
Hepatitis	Pancreatitis
Cholecystitis	
GENITOURINARY	
Retention of Urine	Cystitis
Glomerulonephritis	Orchitis
Pyelonephritis	
CARDIOVASCULAR	
Myocadritis	Phlebitis and arteritis
Pericarditis	Deep Venous thrombosis
Endocarditis	Gangrene
Asymptomatic ECG changes	Shock
	Suden death.
RESPIRATORY	
Bronchitis	Pneumonia (S. Typhi, strep, Pneumonia)
Laryngeal Ulceration	
Glottal Oedema	
NEURO-PSYCHIATRIC	
Delirium	Transverse Myelitis
Psychotic States	Signs of upper motor-neuron lesions
Depression	Signs of extrapyramidal disorder
Deafness	Impairment of coordination
Meningitis	Optic neuritis
Encephalomylitis	Peripheral and cranial neuropathy
	Guillain barre syndrome
	Pseudomotor cerebri.
HAEMATOLOGICAL	
Disseminated Interavascular Coagulation (usually sub-clinical).	
Anaemia	
Haemolysis	
Haemolytic Uraemic Syndrome	
OTHER	
Focal Infections	Relapse
Hypercalcaemia	Myopathy
Abortion	

splenomegaly (40.60%). Rose spots and relative bradycardia occur in less than 10% of cases.[2,8]

It is common to hear adventitious sounds, mostly scattered wheezes, when examining the chest of typhoid patients. On

occasions the respiratory symptoms and signs may be so prominent as to suggest a diagnosis of pneumonia. These findings with a normal chest radiograph in patients with high fever should always alert the physician to the possibility of typhoid.[1] One of the most striking features of typhoid in patients progressing into the third week of illness is the facial appearance, termed as typhoid facies. Typically this face is thin, flushed, with bright eyes and a dull, heavy, staring, apathetic expression.[1]

Occasionally, a complication dominates the clinical picture and deflects the attention from the underlying diagnosis of typhoid. The more common and important complications of typhoid are given in the table No. 3.[1]

Common haematological findings include normochromic anemia and an increased erythrocyte sedimentation rate. The presence of leucocytosis usually indicates complication. The white cell count ranges from 1.5 to 10.00 x 10^3/lit with a mean of 6.3 x 10^3/lit. Leucopenia (white cell count < 4 x 10^3/lit) is observed in 10% of the patients. The thrombocytopenia observed is unrelated to the disease severity or complication.[8,9]

Many serological methods (passive haemagglutination, latex agglutination, counter-immune-electrophoresis,radio-immune assay, enzyme immunoassay, indirect fluorescent antibody test, monoclonal antibodies 1g M capture, DNA probes) for the detection of antibodies to O, H, and Vi as well as to an array of newly defined S. typhi antigens, and for the direct detection of these antigens and salmonella DNA in body fluids, have been described with prominent results. Many of these are more sensitive than conventional widal testing, but doubts remain about specificity and cost in field conditions.[10,11,12] Antibodies to commercially available O and H antigens can be demonstrated rapidly using a slide agglutination technique. Salmonella typhi antigens in the body fluids can be demonstrated by agglutinating Staph aureus coated with specific antisera or, more recently, using monoclonal antibodie.[1]

For various reasons, the widal serological method has become the single most frequently used and "popular" method of diagnosing typhoid fever in the developing countries. The "O" and "H" antibodies are measured in the widal agglutination reaction. In the non immune, following typhoid fever, antibodies are detected as early as 4-5 days in the majority of patients. However 80% of the patients have elevated antibody titres at two weeks while a few patients never develop rise in "O" or "H" antibody.[2]

The "O" antigen is a component of the bacterial cell wall whereas the "H" antigen is flageller. The anti "O" agglutinating is composed mainly of 1gM, whereas the "H" agglutinating is mainly 1gG. The 1gM is the first to rise and is useful in diagnosis of the acute illness. The "H" antibody may reach higher levels, remain longer in circulation, and is more variable than anti "O". "H" titres are subject to anamnestic reaction. It should, therefore, not be relied upon in diagnosing acute enteric fever.

This test has some shortcomings. False negative results can be obtained for patients with known typhoid fever because;

- Of early treatment with antimicrobial agents.
- Sera may not be collected at the optimal time, which should be 7-14 days after onset of clinical illness.
- Patient may not develop diagnostic titres of antibody, this is more likely to occur in the non-endemic countries.
- Of faulty technique and use of out-dated reagents.

Causes of false positive reactions include previous immunization, previous infections by salmonella sp sharing common antigens with S. typhi, for example,

paratyphi A and B, and S. enteritidis and occasionally other non-typhoid febrile illnesses or unrelated disorders like rheumatoid arthritis and other autoimmune disease.[2]

Although conventional teaching specifies evaluation of acute and convalescent serum samples, and demonstration of a 4 fold or greater change in titres for serologic diagnosis, this is not practical for patient management, except for retrospective diagnosis. Besides, this rise may not always be found in true disease. The single titre widal test has thus become popular in many countries where typhoid fever is endemic. Its use however, requires that the base line titre in the community or population be known, as well as correlation with proper clinical information on the patient being evaluated. The increased incidence of false positive widal reports is worrisome. The majority of these laboratories use commercial kits whose reliability is not proven, and certainly without prior screening of the base line population for diagnostic titres.[2]

The diagnosis of enteric fever is suspected on clinical grounds. Therefore, a physician must be familiar with its common signs and simple laboratory investigation.[6,7]

Bayes theorem is based on calculated 19 clinical and laboratory events to predict enteric fever. Ross and Ibraham (1986) described 8 discriminating events in order of importance as; the white cell count, the salmonella typhi H agglutination titre, body temperature, the salmonella typhi O agglutination titre, the S. paratyphi A-H agglutination titre, the S. paratyphi B H agglutination titre, age and the fever pattern. This study showed that the objective variables like the widal titres were useful in predicting enteric fever. Later these authors in another larger trail suggested the following events; a positive widal test at a screening dilution of 1:40; a peak temperature greater than 39 degree c:, previous treatment for the fever; a white cell count less than 9 x 10^3/lit; splenomegaly, a polymorphonuclear leucocyte count less than 3.5 x 10^3/lit, fever duration greater than 7 days and hepatomegaly. When the probability of enteric fever was determined prospectively in patients using only 6 (six) of these discriminating events, the probability of patients with a positive prediction having enteric fever (diagnostic specificity) was 95 percent. The probability of those with a negative prediction not having enteric fever the diagnostic sensitivity was over 95 percent.[3,13] It is obvious that a small number of clinical and laboratory features can objectively discriminate enteric fever from other causes of fever in the majority of patients.

In our day to day routine our physicians rely more on the commonly noticed symptoms and signs rather than laboratory results. These results are not accurate due to the various reasons described in the text. During the period mentioned e.g. two years, we must have admitted about two thousand patient in this unit but the blood cultures were positive in 25 patients only. This gives us the lowest percentage in the world and thus we can not wait for such low positive laboratory results. So it becomes essential to be familiar with the clinical symptoms and signs in our day to day routine. The following criteria stand the best in this part of the world in diagnosing enteric fever.

- Insidious onset of temperature, of more than 7 days, which is continuous and may rise up to 40°C or more.
- Patients having dry cough and a few crackles/rhonchi here and there with normal chest radiograph.
- Abdominal pain specially in right iliac fossa with diarrhea for a few days is the third common finding.
- Toxic look and coated lips (which clears up with application of towel).
- Mild to moderate soft splenomegaly.

And the last the positive widal agglutination test (TO titre ≥ 1/320) or total leucocyte count less than 7 x 10^3/litre.

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