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The early diagnosis of typhoid fever prior to the Widal test and bacteriological culture results

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Abstract

In an attempt to evaluate various clinical and laboratory features available within 24 h of admission, prior to the Widal test and bacteriological culture results as potential diagnostic aids in typhoid fever, we undertook a retrospective unit-based case control study in 90 febrile adult and paediatric patients admitted to King Edward VIII Hospital, Durban, South Africa with an initial diagnosis of typhoid fever. A total of 30 blood culture-proven typhoid fever patients (cases) were matched to 60 patients confirmed as not having typhoid fever (controls) by age, sex, race and severity of illness on admission. Features significantly associated with a final diagnosis of typhoid fever were: a pre-admission duration of fever ≥ 7 days (odds ratio (OR) 6.9); hepatomegaly (OR 3.2); a normal leucocyte count (OR 10.8); a leucocyte count of $< 10.0 \times 10^3/\text{mm}^3$ (OR 30.2); and leucopenia due to absolute neutropenia with a relative lymphocytosis (OR 11.8). Although the sensitivity, specificity and predictive values of any of these features cannot be used reliably to distinguish typhoid fever from other non-typhoidal febrile illness, it is concluded that leucopenia due to absolute neutropenia with relative lymphocytosis, when present, is highly suggestive of typhoid fever. A leucocyte count of $> 10.0 \times 10^3/\text{mm}^3$ (OR 0.03) provides strong presumptive evidence against such a diagnosis.

Keywords: Typhoid fever; Diagnosis; Leucocyte count; South Africa

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1. Introduction

Typhoid fever, which is endemic in many parts of South Africa, including KwaZulu Natal, Northern Transvaal and Eastern Cape (Coovadia et al., 1992), does not always present with a distinct clinical picture (Coovadia et al., 1986); and other bacterial and even viral infections may mimic its presentation (Levine et al., 1978). This often leads to considerable diagnostic confusion (Chalmers, 1971; Wicks et al., 1971). Although bacteriological confirmation of clinically suspected typhoid fever remains the definitive diagnostic procedure, it is associated with a diagnostic delay of 48–72 h (Coovadia et al., 1986). Furthermore, many cultures are falsely negative due to prior antibiotic therapy (Pandya et al., 1995). In many developing countries, facilities for culture and isolation of *Salmonella typhi* are not routinely available (Kulkarni and Rego, 1994). Hence, the Widal test continues to be used extensively as a diagnostic tool in many such areas (Buck et al., 1987). This test requires both acute and convalescent sera and results are often found to be unreliable in endemic areas (Levine et al., 1978). Pary, as quoted by Ross and Abraham (1987), stated, ''diagnosis of typhoid fever is essentially clinical confirmed whenever possible by bacteriological culture''.

We, therefore, undertook a retrospective case control study to evaluate various clinical and laboratory features for the diagnosis of typhoid fever in an endemic area. To our knowledge, such a case control study has not previously been reported in the literature.

2. Materials and methods

Cases were selected by reviewing retrospectively, the medical records of all patients admitted to the medical or paediatric wards of King Edward VIII Hospital (KEH), Durban over a 12 month period (January 1, 1995–December 31, 1995) with an initial diagnosis of typhoid fever. The medical records of patients with blood culture-proven typhoid fever were reviewed further for age, sex, race, duration of illness before admission, severity of illness on admission, results of initial physical examination and laboratory investigations and final diagnosis (i.e. discharge diagnosis). Control patients were selected by reviewing the medical records of all patients admitted to these wards during the same period of time, with an initial diagnosis of typhoid fever, but later confirmed not to have typhoid fever. Control patients were matched to the study patients by age, sex, race and severity of illness on admission. The severity of illness was assessed by the clinicians caring for the patients and was not determined retrospectively by the authors. Wherever possible, typhoid fever patients were matched with more than one control. For the purpose of this study, the period of observation was defined as the first 24 h following admission before microbiological or serological results were available to the clinicians. An initial diagnosis of typhoid fever was acceptable only if the clinicians did not completely retract from this diagnosis during this period of observation. In some cases, a clear-cut initial diagnosis could not be obtained from the records and these cases were also excluded from further analysis.

Sensitivity, specificity, positive and negative predictive values were calculated by taking blood culture positivity for *S. typhi* as 'gold standard'. Sensitivity is the proportion of patients with culture-proven typhoid fever, who are also positive for a given feature, whilst specificity is the proportion of patients without typhoid fever who are negative for a given feature. The positive predictive value refers to the probability that a patient with a positive feature is correctly diagnosed as having typhoid fever and the negative predictive value as the probability that a patient without the feature is correctly diagnosed as not having typhoid fever.

Clinical and laboratory features in the cases and controls were compared by unpaired Student's t-test, χ^2 and Fisher's exact (two-tailed) test as appropriate with odd ratio as a measure of the strength of association between the feature and disease. All statistical tests were done, using statistical software (SAS Institute, 1990, Carey, NC). Statistical significance was defined as $P < 0.05$.

3. Results

Over the 12-month study period, 600 patients were admitted to the medical and pediatric services of KEH with the initial diagnosis of typhoid fever (as accepted for the purpose of this study). Complete medical records containing information on all the variables tested were available in 250 (41.6%) of these patients, 30 (12.0%) of whom had at least one blood culture positive for *S. typhi*.

The 30 blood culture-proven cases of typhoid fever were matched to 60 control patients who had non-typhoidal febrile illnesses. These included septicaemias (28), pulmonary tuberculosis (confirmed by sputa positive for AFB, eight), type B viral hepatitis (confirmed by serology, eight), malaria (confirmed by positive identification of malarial parasites in peripheral blood films, six), measles (five) and chicken pox (five). Septicaemias were due to *Escherichia coli* in ten; *Haemophilus influenzae* b in five; *Streptococcus pneumoniae* in 11 and *Staphylococcus aureus* in two patients. Of the 28 septicaemic patients, urinary tract was the source in ten; respiratory tract in seven; middle ear in five and skin in two patients. Sources of septicaemias were unknown in four patients. Typhoid fever was excluded in all control patients by repeated blood, stool and urine cultures. Furthermore, no patient with malaria or viral infection was treated with antibiotic. All eight patients with tuberculosis were treated only with isoniazid, ethambutol and pyrazinamide without rifampicin, presumably because of the presence of thrombocytopenia (platelet count range, $85.0–95.0 \times 10^3/\text{mm}^3$). All patients with malaria, viral infection and tuberculosis presented with acute or subacute illness and became afebrile within 2–4 days following admission.

The baseline characteristics of the cases and their controls are summarized in Table 1. They were similar with respect to age, sex, race and severity of illness on admission. In both cases and controls, men slightly outnumbered women by a ratio of 1.3 to 1.0 and 1.2 to 1.0, respectively.

The features significantly associated with the final diagnosis of typhoid fever were (Table 2): a pre-admission duration of fever ≥ 7 days (OR 6.9; $P = 0.001$; 95% CI

2.7–37.0); hepatomegaly (OR 3.2; $P = 0.03$; 95% CI 1.2–8.0); a normal leucocyte count (OR 10.8; $P < 0.001$; 95% CI 3.5–35.2); a leucocyte count of $< 10.0 \times 10^3/mm^3$ (OR 30.2; $P < 0.001$; 95% CI 6.3–276.2); and leucopenia due to absolute neutropenia and a relative lymphocytosis (OR 11.8; $P < 0.01$; 95% CI 1.2–5.0). A leucocyte count of $> 10.0 \times 10^3/mm^3$ was a strong indicator against a final diagnosis of typhoid fever (OR 0.03; $P < 0.001$; 95% CI 0.0–0.23).

Table 3 shows the sensitivity, specificity and predictive values for all clinical and laboratory features significantly associated (i.e. OR > 2.0 with $P < 0.05$) with a final diagnosis of typhoid fever. Individually, a leucocyte count of $< 10.0 \times 10^3/mm^3$ had the highest sensitivity (93.3%; 95% CI 84.4–100.0) and negative predictive value (95.3%; 95% CI 89.1–100.0) while, leucopenia due to absolute neutropenia and a relative lymphocytosis had the highest specificity (98.3%; 95% CI 95.1–100.0) and positive predictive value (83.3%; 95% CI 53.3–100.0). We neither found any significant differences between the adult and paediatric patients (age ≤ 15 years) in terms of frequency of all features evaluated in this study nor did we find any difference between these patient populations with regards to the diagnostic value of any particular feature when data were analysed separately.

4. Discussion

The prime purpose of this study was to evaluate various clinical and laboratory features, available within 24 h of admission as potential diagnostic aids in typhoid fever. In a prospective study in Malaysia, Ross and Abraham (1987) identified eight clinical and laboratory features to be significantly associated with a diagnosis of typhoid fever. A limiting factor in their study was that not only were cases and controls unmatched, but in 42.7% of cases, diagnosis of typhoid fever was not based on positive bacteriological proof. We identified five features available as

Table 1
Baseline characteristics of typhoid fever patients and their matched controls[a]

Characteristics	Typhoid fever patients ($n = 30$)	Controls ($n = 60$)	P
Age, years mean ± S.D.	17.6 ± 12.9	17.5 ± 11.6	0.99
Sex			
Male	17 (56.7)	33 (55.0)	0.88
Female	13 (43.3)	27 (45.0)	0.88
Race	All Africans	All Africans	nd
Severity of illness on admission			
Mild	10 (33.3)	15 (25.0)	0.56
Moderate	12 (40.0)	25 (41.7)	0.94
Severe	8 (26.7)	20 (33.3)	0.69
Pre-admission antibiotic therapy	0 (0)	0 (0)	nd

[a] Data are numbers (%) of patients except as noted; nd, not determined.

Table 2
Clinical and laboratory features of typhoid fever patients and their controls[a]

Features	Typhoid fever patients ($n = 30$)	Controls ($n = 60$)	P	OR	95% CI
Pre-admission duration of fever ≥ 7 days	19 (63.3)	12 (20.0)	0.001	6.9	2.7–37.0
Abdominal distention	8 (26.7)	7 (11.7)	0.13	2.8	0.9–8.3
Hepatomegaly	14 (46.7)	13 (21.7)	0.03	3.2	1.2–8.0
RLQ[b] tenderness in abdomen	3 (10.0)	5 (8.3)	0.90	1.2	0.2–6.8
Confusion	8 (26.7)	14 (23.3)	0.93	1.2	0.4–3.6
Deafness	0 (0.0)	0 (0.0)	nd	nd	nd
Cerebellar ataxia	0 (0.0)	0 (0.0)	nd	nd	nd
Rose spots	0 (0.0)	0 (0.0)	nd	nd	nd
Normal total leucocyte count (leucocyte, $4.0–11.0 \times 10^3/mm^3$)	23 (76.7)	14 (23.3)	<0.001	10.8	3.5–35.2
Leucopenia (leucocyte, $<4.0 \times 10^3/mm^3$)	6 (20.0)	15 (25.0)	0.79	0.75	0.3–2.2
Leucocyte count, $<10.0 \times 10^3/mm^3$	28 (93.3)	19 (31.7)	<0.001	30.2	6.3–276.2
Leucocyte count, $>10.0 \times 10^3/mm^3$	2 (6.7)	41 (68.3)	<0.001	0.03	0.0–0.2
Leucopenia due to absolute neutropenia and a relative Lymphocytosis (leucocyte, <4.0 with neutrophil $<2.0 \times 10^3/mm^3$ and lymphocyte, $>40.0\%$)	5 (16.7)	1 (1.7)	<0.01	11.8	1.2–5.0
Thrombocytopenia (platelet, $<150.0 \times 10^3/mm^3$)	5 (16.7)	11 (18.3)	0.92	0.89	0.22–3.2

[a] Data are numbers (%) of patients; nd, not determined.
[b] Right lower quadrant.

Table 3
Sensitivity, specificity and predictive values significantly associated with typhoid fever[a]

Features	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Pre-admission duration of fever ≥ 7 days	63.3 (46.1–80.6)	80.0 (69.9–90.1)	61.3 (44.1–78.4)	81.4 (71.4–91.3)
Hepatomegaly	46.7 (28.8–64.5)	78.3 (67.9–88.8)	51.9 (34.0–69.7)	74.6 (63.7–85.4)
Normal leucocyte count[b]	76.7 (61.5–91.8)	76.7 (66.0–87.4)	62.2 (46.5–77.8)	86.8 (77.7–95.9)
Leucocyte, $<10.0\times10^3/mm^3$	93.3 (84.4–100.0)	68.3 (56.6–80.1)	59.6 (45.5–73.6)	95.3 (89.1–100.0)
Leucopenia due to absolute neutropenia and a relative lymphocytosis[c]	16.7 (3.3–30.0)	98.3 (95.1–100.0)	83.3 (53.3–100.0)	70.2 (60.5–80.0)

[a] Expressed as percentage of different clinical and laboratory features.
[b] Leucocyte, $4.0–11.0\times10^3/mm^3$.
[c] Leucocyte, $<4.0\times10^3/mm^3$ with neutrophil, $<2.0\times10^3/mm^3$ and lymphocyte.

above to be significantly associated with a final diagnosis of typhoid fever: a pre-admission duration of fever ≥ 7 days; hepatomegaly; a normal leucocyte count; a leucocyte count of $< 10.0 \times 10^3/mm^3$ and leucopenia due to absolute neutropenia with relative lymphocytosis.

The association between a prolonged febrile period (≥ 7 days) before admission and final diagnosis of typhoid fever is not surprising. Typhoid fever is a well-recognized cause of pyrexia of unknown origin (PUO) in tropical countries (Walters, 1971), though none of our patients exactly fits the classical definition of PUO (Petersdorf and Beeson, 1961). Although typhoid fever characteristically has a slow insidious onset (Stuart and Pullen, 1946), over a third of the cases (and two thirds of control patients) presented to the hospital with only 3–4 days history of fever. This probably explains the reasonably high specificity and negative predictive value of prolonged fever before admission, despite its modest sensitivity (Table 3).

Isolated hepatomegaly, with or without splenomegaly, has been reported in 13–65% of cases of typhoid fever (Stuart and Pullen, 1946; Butler et al., 1978; Khosla et al., 1988). Although an outbreak of typhoid fever with only few signs and symptoms has been reported from a non-endemic area (Klotz et al., 1984), the low sensitivity and specificity of hepatomegaly alone in a febrile patient is of limited value in a typhoid endemic area such as KwaZulu Natal. The most likely reason for the low sensitivity of hepatomegaly is the variation in observer's skill in detecting it by palpation (Dunn, 1988) and its infrequenct occurrence during the first week of illness in typhoid fever (Stuart and Pullen, 1946). Also, one needs to bear in mind that typhoid fever may not necessarily be the commonest infection causing hepatomegaly in our environment (Maharaj et al., 1986).

Despite the common belief that leucopenia is a characteristic feature of the febrile phase of typhoid fever (Guerrant, 1987), in the majority of cases leucocyte count is normal (Gulati et al., 1968; Chalmers, 1971; Klotz et al., 1984). In our patients, the sensitivity and specificity, positive and negative predictive value of a normal leucocyte count was 76.7% (95% CI: 61.5–91.8); 76.7% (95% CI: 66.0–87.4); 62.2% (95% CI: 46.5–77.8) and 86.8% (95% CI: 77.1–95.4), respectively. These results indicate that while the presence of this feature may not be diagnostic of typhoid fever, its absence militates strongly against such diagnosis. Likewise, the presence of leucopenia was found to be of little value as leucopenia is also common in other conditions prevalent in our environment (Wicks et al., 1971). In fact, six control patients with malaria and eight with tuberculosis all had leucopenia. Although leucopenia due to absolute neutropenia with relative lymphocytosis is believed to be a common finding in typhoid fever (Huckstep, 1962), it occurred infrequently (16.7%) in our cases. Despite low sensitivity, a high predictive value, 83.3% (95% CI: 53.3–100.0) of a positive test indicates that, when present in a febrile patient, it is highly suggestive of typhoid fever. On the otherhand, its absence will not exclude such diagnosis in a substantial number of patients because of low predictive value (70.2%; 95% CI: 60.5–80.0) of a negative test. Our results also confirm the previously held view (Adams, 1987) that in typhoid fever a leucocyte count of $> 10.0 \times 10^3/mm^3$ is extremely unlikely (OR 0.03; 95% CI: 0.0–0.23). This is further supported by the fact that a leucocyte count of $< 10.0 \times 10^3$ was found to

be strongly associated (OR 30.2; 95% CI: 6.3–276.2) with a final diagnosis of typhoid fever in our patients.

Relative bradycardia was noted more frequently in cases as compared to control patients (43.3% vs. 21.7%; OR 2.8; $P = 0.06$; 95% CI 1.1–7.1). It has a sensitivity, specificity, positive and negative predictive value of 43.3% (95% CI: 25.6–61.1), 78.3% (95% CI: 67.9–88.8), 50.0% (95% CI: 30.8–69.2), and 73.4% (95% CI: 62.6–84.3), respectively. These data suggest that relative bradycardia as a feature of specific disease is more likely to be seen in typhoid fever, but it may not be useful for obtaining such a diagnosis in an individual patient.

In this study typhoid fever, not surprisingly, was often confused with other non-typhoidal septicaemic conditions, presumably because of frequent manifestations of diarrhoea (39.3%) and abdominal pain (25.0%) in the latter. Of note, 75.0% of the septicaemic patients in the control group were ≤ 15 years of age and a third of them presented with diarrhoea. Fever and diarrhoea, as presenting manifestations of septicaemia caused by organisms other than *Salmonella* or *Shigella* in children, have been well documented by others (Lepage et al., 1987).

Control patients with viral infections or malaria received no antibiotic following admission and tuberculosis patients were treated as noted. None had sustained pyrexial illness contrary to what is considered to be the hallmark in untreated typhoid fever (Guerrant, 1987).

Our results should be interpreted in the light of several limitations. The study was conducted at a tertiary care hospital, findings of which may not be applicable to other settings. As the data were analysed retrospectively, certain signs and symptoms might have been missed which would otherwise have been revealed by direct inquiry in a prospective study. Although, we meticulously matched cases and controls, bias may still have occurred by our failure to control all variables, which may have diagnostic significance in terms of differentiating cases from controls.

Despite these limitations, our results highlight the difficulties in diagnosing typhoid fever, using clinical criteria and simple laboratory values alone. Although none of the clinical and laboratory features were found to be completely reliable in distinguishing typhoid fever from other non-typhoidal febrile conditions, a leucocyte count of $> 10.0 \times 10^3/\text{mm}^3$ in a febrile patient provides strong presumptive evidence against the diagnosis of typhoid fever. When present, leucopenia due to absolute neutropenia and a relative lymphocytosis is highly suggestive of typhoid fever.

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