A Review of Typhoid Fever Cases on the Medical Service at Patan Hospital

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Summary

Seventy two cases of typhoid fever treated on the medical service at Patan Hospital in 2043 were reviewed. Headache was present in 53% of cases, cough in 40%, diarrhea and/or constipation in 42%, splenomegaly in 42%, hepatomegaly in 47%, and delirium in 27%. The majority of patients had a normal white blood count. Complications included lower gastrointestinal bleeding in 8 cases, mild hepatitis in 2, persistent psychotic behavior in 2 and "typhoid nephritis" with renal failure in one. Two patients died. Chloramphenicol is still the drug of choice and fever resolved on the average of 4-5 days after treatment was initiated. Neuropsychiatric symptoms are more common in developing countries and may be the presenting symptom or sign. Typhoid fever is a common disease with varied presentations and severity and should be considered in the differential diagnosis of all patients with fever.

Introduction

Typhoid fever is an acute systemic illness caused by the organism *Salmonella typhi* and is commonly diagnosed in Kathmandu Valley. The clinical manifestations and duration of the illness vary markedly in different patients. Classically typhoid fever has an insidious onset with fever, anorexia, headache, malaise and myalgia. The fever is remittent and often gradually increasing each evening to a range of 40° c by the end

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of the first week. Hepatomegaly, splenomegaly and leukopenia are other commonly reported findings.³ The purpose of this study is to review the experience with typhoid fever on the medical service at Patan Hospital over one year with the emphasis on clinical characteristics, physical examination, laboratory results, response to treatment and complications.

Method

The medical service at Patan Hospital cares for patients with medical illnesses who are 13 years of age or older. Charts of patients discharged from the medical service with a diagnosis of typhoid fever or possible/probable typhoid were reviewed. In year 2043 (mid July 1986 to mid July 1987) 81 cases with a diagnosis of typhoid fever hospitalized on the medical service. Of these patients 27 were culture positive for *Salmonella typhi* (26 blood; 1 urine) and 26 charts were available for review. Of the other 54 cases, 4 charts were unavailable for review and 4 patients in retrospect had a low probability of having typhoid fever and were excluded from the review. The remaining 46 cases had either a negative blood culture (25), contaminated blood culture (8), lost blood result (4) or no blood culture (9). A total of 72 charts were reviewed.

Results

In the Nepali year 2043, 8.5% of the medical discharges at Patan Hospital had a diagnosis of definite or probable typhoid fever. (For the previous 2 years the incidence was 8.3% and 9.4% respectively). Cases were seen in every month, but the highest incidence was in Shrawan, Bhadra and Asoj (mid July to mid October). The age range was 13 to 74 years with 83% of the patients under the age of 40 years. There were 43 females and 29 males for a female to male ratio of 1.5:1. (In 2042 the ratio was 1:1. The increase in females admitted with typhoid cannot be explained).

The history recorded on the chart was not always complete, therefore the incidence of any given symptom is the minimum that one would expect. The chief or presenting complaint is also unable to be accurately determined from the record, but all patients of fever. The length of fever before admission varied from 2 days to one and half months. Ten patients had fever of less than five days at admission and some of these had pattern of acute onset typhoid. Fortysix percent of the patients had received some form of antibiotic therapy before admission. Headache was noted in 53% of cases, cough in 40%, diarrhea and/or constipation in 42%, history of delirium in 28% and abdominal pain in 17%. (See Table I for a breakdown between culture positive cases and those without a positive culture).

Forty-two percent of the patients were noted to have splenomegaly, and 47% had hepatomegaly. Twenty-six percent were described as delirious sometime during their hospitalization and an additional 15% of the patients had a history of delirium. (Many more patients were mentally dull or mildly confused). (See Table I).

Sixty-eight patients had a white blood count (WBC) done. The average WBC was 7600 cells per cu.mm. with a range from 2300 to 15,600 cells per cu.mm. Sixty-two per cent of patients had a WBC in the range of 5,000 to 10,000 cells per cu.mm. The neutrophil count ranged from 32% to 91% of the total WBC. (See Table II for the difference between cases with and without a positive culture).

Eleven patients had a urine check for albumin and 10 of these had proteinuria from trace to 2 plus by dipstick. Twenty-one patients had a urine microscopy done. Fifteen had significant pyuria and 8 had microscopic hematuria. One patient had a urine culture positive for *Salmonella typhi* and another patient had *E. coli* (not thought to be the cause of the systemic illness).

During the year of this study many patients were seen in the outpatient department with the diagnosis of typhoid fever. In general patients were admitted because they were more toxic, delirious, had complications or because the diagnosis was uncertain. Eight patients (11%) had lower gastrointestinal bleeding. (Three of these patients had a positive blood culture). In all but one the rectal bleeding was present on admission. Some required transfusion of up to 1000 ml. of whole blood. Two patients had persistent psychotic behavior after the resolution of fever and other physical signs of typhoid and were referred to a psychiatrist. One of the blood culture positive cases had clinical acute cholecystitis. (During 2043 on the surgical service there were two gallbladder cultures positive for *Salmonella typhi* and 8 patients were operated on for a typhoid perforation).

Two patients had mild hepatitis with clinical jaundice. It was uncertain whether this was "typhoid hepatitis" or coincidental viral hepatitis. In one patient the jaundice occurred with a relapse of culture positive typhoid fever. Five patients were given corticosteroid therapy because of severe toxicity. Three patients completed a 3 day course of either prednisone (60 mg, 40 mg, 20 mg) or dexamethasone (9 mg, 6 mg, 3 mg). (Two were blood culture positive). The other two patients only had one dose of dexamethasone before they died.

The two deaths were: 1) a 20 year old male had fever for 9 days with headache, constipation and delirium. The WBC was 7,800 cells per cu.mm. with 80% neutrophils. The platelet count was 85,000 per cu.mm. The blood culture result has been lost. The CSF culture was negative. He received 2½ days of chloramphenicol. Dexamethasone was added because of increasing toxicity but he died 12 hours later. 2) A 20 year old female had fever for 5-6 days (maximum 105°F) with loose stools and delirium. She had been started on Cotrimoxazole the day before admission for a possible UTI. She received 3½ days of chloramphenicol before her death with no response. (The blood culture was subsequently negative). Her course was complicated by acute renal failure (probably "typhoid nephritis") and a urinary tract infection (*E. coli* on culture).

All but one patient was treated with chloramphenicol (50 mg/Kg until afebrile, then 30 mg/Kg for a total of 14 days). The other patient was treated with cotrimoxazole. One patient developed a rash 5 days of chloramphenicol and was switched to cotrimoxa-

zole to complete two weeks of treatment. Almost half of the patients had antibiotic treatment before admission and two patients were initially given ampicillin on admission but this was changed to chloramphenicol after a clinical diagnosis of typhoid was made. The number of days after chloramphenicol was started that the patient became afebrile ranged from 2 to 8 days (average 4-5 days) for blood culture positive patients and 1 to 9 days (average 4-5 days) for the other patients.

Discussion

Typhoid fever is a common diagnosis on the medical ward at Patan Hospital and even more common in the Outpatient Department. The diagnosis is most often made on clinical presentation and physical findings. Khosla (1986) from North India has found that they no longer see the classical picture of typhoid but that a large majority of patients present with atypical forms, e. g. acute onset, resembling an upper respiratory infection, predominance of GI symptoms or clinic picture by complications.⁵ A variety of presentations and severity of illness would be expected and the majority of patients on the medical service at Patan Hospital fit the classical presentation or the more common atypical presentations as described in standard medical textbooks.^{1,3,7}

Typhoid can have an acute onset which is said to be more common in children but can also occur in adults and be confused with other types of bacterial sepsis. Most of our patients were admitted near the end of the first week of fever or later in the course but some could be considered acute onset typhoid. I think that the doctors at Patan Hospital are very suspicious of typhoid in any febrile patient, and we probably tend to overdiagnose the illness rather than underdiagnose it. The differential diagnosis should include brucellosis, leptospirosis, prodrome of infectious hepatitis, infectious mononucleosis, miliary tuberculosis, malaria, lymphoma, rheumatic fever and other bacterial septic illnesses (e. g. staph sepsis with normal WBC).⁸

The incidence of common symptoms and signs is similar to other reported studies of typhoid. (See Table I). The incidence of symptoms in our cases would have even been higher if the recorded histories had been more complete. It has been reported that neuropsychiatric symptoms often dominate the picture in typhoid fever patients in Africa and India¹, and the incidence is thought to be on the increase in both developed and underdeveloped countries.⁶ Khosla (1986, 1982) has reported a definite rise in neuropsychiatric complications at his hospital in North India.^{5,6} He studied 410 patients with proven typhoid or paratyphoid fever. One hundred and eighty-six cases (45%) had dominant neuropsychiatric manifestations. Of these about half (95 patients) presented as acute onset of either acute delirium/confusional states with or without convulsions, behavior disturbances or irrelevant talk. There was some degree of neck rigidity but the fever was not high and the degree of delirium had no relation to the level of the temperature. Another large group (54 patients) had an insidious course with fever followed by coma or semicoma, neck rigidity and Parkinsonian rigidity. Other less common neuropsychiatric manifestations included "acute brain syndrome", generalized

myoclonus, catatonic schizophrenia, and acute mania. Four patients had initially been admitted to the psychiatric unit. Khosla (1982) found that 104 patients (56%) had "slow delirium" and behavioral changes which persisted for one to three weeks after the subsidence of fever, and two patients still had features of schizophrenia two months later.⁶

Over one fourth of our patients had delirium (and another 15% gave a history of delirium) and others were mentally dull or confused. This percentage would be lower if the patients seen in outpatient clinic with typhoid were also included. Unlike what Khosla reports, the majority of patients with delirium had a typical presentation for typhoid and had high fever. Of the two patients with persistent psychotic behavior one had been admitted initially to the mental hospital. The increased incidence of neuropsychiatric symptoms in developing countries seems to be related to poor nutrition and social background. Khosla did not see any case in the higher socio-economic patients. He believes that certain biochemical changes take place in the neurons during the febrile illness which leaves behind some degree of transient psychosis.⁶

The records of our patients were not complete enough to decide if some of our patients fit into the various categories that Khosla describes. This would take a prospective study in order to determine if the incidence of neuropsychiatric complications is the same here in our patient population. The incidence of delirium seems greater than in cases reported in the west but not to the degree and complexity as reported by Khosla. His patient population may have been more susceptible because of poorer health or lower socioeconomic status (mortality rate was 15% for those with neuropsychiatric symptoms). However, we also may be missing the diagnosis of typhoid when neuropsychiatric symptoms are predominant.

Only 36% of our patients had a positive culture for *Salmonella typhi*. The organism can usually be isolated in the first 7-10 days of the illness (70-90%) and often in the second and third weeks (30-40%).^{1,8} The number of organisms in the blood may be quite small and it is recommended that the culture be kept 10-12 days.¹ (At Patan Hospital cultures are kept for 7 days). The low incidence of positive blood culture was due to a combination of factors including antibiotics before admission of the blood culture, contamination of the blood culture with another organism, blood culture drawn late in the illness or in some cases not drawn at all. We have found that the blood culture result in suspected typhoid cases, although it confirms the diagnosis if positive, is more useful in detecting other septic states that present like typhoid (e.g. staphylococcus sepsis with normal WBC and no obvious source of infection).

Leukopenia of 3000 to 4000 white blood cells is said to be characteristic of the febrile phase of typhoid⁹ but less than 20% of our patients had leukopenia (less than 5000 cells). In other studies the WBC ranged from 1200 to 20,000 cells per cu.mm. in apparently uncomplicated cases⁶ and in an outbreak in Dale County, 74% of the patients had a normal WBC.¹ The leukocytosis tends to be in the first 7-10 days⁷; however in our culture positive patients the average WBC was 5100 cells per cu.mm. in those with 10

days or less of fever and 7300 per cu.mm. in those with over 10 days of fever. We have found the WBC mainly useful in ruling out typhoid for if the WBC is greater than 20,000 per cu.mm. our attention is turned to other causes of sepsis.

The major complication noted in our series of patients was lower gastrointestinal bleeding (11%). In the pre-antibiotic era the incidence was reported to be 7-21% while in studies in the post-antibiotic era (with patients who were in good health before the onset of typhoid) the incidence was 1-3%.¹ I would expect our reported incidence to be higher because this is only a study of inpatients (or the sicker typhoid patients) and the total number of typhoid patients treated at Patan Hospital is not known. All the intestinal perforations during this period were admitted directly to the surgical service.

Transient mild elevations of liver enzymes are common during the acute illness but jaundice secondary to extensive mononuclear infiltration of the liver and hepatic cell necrosis or fulminant hepatic failure are rare complications of typhoid fever.^{3,6} Both of our patients with mild elevations of bilirubin and SGOT may have had "typhoid hepatitis".

Transient mild proteinuria is common during the first week of illness.⁶ "Typhoid nephritis" with renal pain and hematuria and acute renal failure have been reported.³ In Khosla's study 3 of 410 patients had "typhoid nephritis" and all died. We had one typhoid patient with "typhoid nephritis" and acute renal failure who died.

Chloramphenicol is still the drug of choice for the treatment of typhoid fever.^{4,6} Christie (1980) feels that ampicillin is very inferior to chloramphenicol and we agree.⁵ Cook (1985) recommends 30 mg/Kg/day as the ampicillin dose² but Harrison's textbook recommends 80/Kg/day.³ From our experience those patients who were treated with ampicillin (1.5 to 2 gm/day) before admission failed to show any response (maybe they would have responded to a higher dose). Khosla (1985) reports that at his hospital in North India typhoid is sometimes refractory to treatment with chloramphenicol and ampicillin or amoxycillin, or ampicillin plus cotrimoxazole is better.⁵ Christie (1980) reports a study in which the duration of fever was 1½ days shorter in patients treated with ampicillin and chloramphenicol when compared to treatment with chloramphenicol alone.¹ Patients usually respond in 3-5 days to chloramphenicol therapy but the response depends on the stage of the disease and complications. The length of treatment and the dose must be adequate or the disease course will just be interrupted and continue again when the drug is stopped.¹ We have found good response to adequate doses of chloramphenicol with patients becoming afebrile on the average of 4-5 days after treatment was started.

Corticosteroids have been shown to produce a more rapid fall in body temperature but this treatment is not recommended for routine use because of interference with the immune response.¹ However, corticosteroid therapy has been shown to be beneficial in the seriously ill patients to decrease morbidity and mortality.^{2,5} We reserve steroid use for the seriously ill toxic patients.

Conclusions

Typhoid fever is a common disease which if untreated or if the treatment is delayed can lead to significant morbidity and sometimes even death. This diagnosis should be considered in all patients presenting with fever, both those with an acute onset and those with insidious onset. Knowledge of the classical presentations of typhoid and the more common atypical presentations is helpful in making the diagnosis in most cases. Laboratory tests like white blood counts and blood cultures, although they may confirm the clinical diagnosis, are more useful in making the diagnosis of another septic process which may mimic typhoid. Neuropsychiatric symptoms are reported to be more common in developing countries and the incidence is believed to be increasing. The mental disturbance may even precede the onset of the fever.⁵ It is important for the doctor to be alert to the possibility of typhoid fever in its various presentations and severity, especially predominant neuropsychiatric presentations, in order to treat this disease quickly and effectively.

Table-I

	Group I 26 cases	Group II 46 cases	Group III 81 cases	Group IV 105 cases	Group V 507 cases
Symptoms					
Headache	38%	61%	37%	59%	78%
Cough	46%	37%	40%	28%	37%
Constipation and/or diarrhea	46%	39%	42%	C-10%	C-38%
Delirium	23%	30%	11%	D-57%	D-37%
Abdominal pain	27%	11%	—	39%	—
Signs					
Splenomegaly	54%	35%	36%	40%	39%
Hepatomegaly	46%	48%	28%	52%	15%
Delirium	31%	24%	14%	5%*	12%*

I *Salmonella typhi* Culture cases positive, Patan Hospital Medical Ward 2043.

II Cases of presumed typhoid not confirmed by positive culture Medical Ward 2043.

III Unpublished study of 81 culture positive *Salmonella typhi* and *Paratyphi A* cases Patan Hospital 2043. includes all ages, inpatient and the 26 cases in Group I.

IV 105 blood culture positive cases of *Salmonella Typhi* in Dale County 1973.⁴

V Typhoid fever outbreak in Abersden 1964, 507 patients.⁶

* Percent of "neurological manifestations".

Table-II

Laboratory Results

	<i>Salmonella typhi</i> culture positive cases (26)	Presumed typhoid on clinical grounds (46)	Culture positive cases of <i>S. typhi</i> and <i>paratyphi A</i> (81) 9 (includes the 26 cases in column 1)
Average total WBC (Per cu.mm.)	6400 (24/26)	7900 (44/46)	7700 (71/81)
WBC range (per cu.mm.)	2500 to 12,400	2300 to 15,600	2200 to 20,500
Average neutrophil count (per cu.mm.)	4500	5700	5400

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