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ORIGINAL ARTICLE

Frequency of leukocytosis in culture proven enteric fever in children.

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ABSTRACT… Objective: To determine the frequency of leukocytosis in patients of culture proven enteric fever in children over one year period. **Study Design:** Retrospective Cross-sectional study. **Setting:** Department of Paediatrics, at Fatima Memorial Hospital, Shadman Lahore. **Period:** January 2020 to December 2020. **Material & Methods:** The case record of patients diagnosed with enteric fever on blood culture were reviewed. All patients in the age group of one year to 15 years with a discharge diagnosis of enteric fever for admitted inpatient or from Outpatient Department (OPD) were included in the study. **Results:** Median age was 61.3 (IQR 38) months and slight female preponderance 61 out of 110 patients (55.5%) was observed. Median duration of fever before presentation was eight days with IQR of 7.3 days and 95 patients has shown anorexia (86.4%), which was the most common symptom after fever. S. Typhi was found in 76.4% (84 patients out of 110) of positive blood cultures and 23.6% of positive culture (26 cases) found S. Paratyphi A,B,C. Only 8 cases (5 %) of enteric fever were multisensitive with 93% of isolates (102 cases) were either multidrug resistant (45 cases (41%) or 57 cases Extended drug resistant (52%).18 out of 110 patients (16%) has shown leukocytosis and leukocyte count was normal in 73% patients (80 out of 110). Among leukocytosis group strikingly, 89% of patients (16 out of 18) had shown extended drug resistant pattern (XDR). **Conclusion:** Leukocytosis in Typhoid fever is not uncommon and culture proven Typhoid Fever can be associated with leukocytosis in children. Once there is leukocytosis in culture proven Typhoid fever, there is a high incidence of XDR typhoid.

Key words: Enteric Fever, Leukocytosis in Typhoid, XDR Typhoid.

INTRODUCTION

Typhoid fever is a systemic infection that is caused by Salmonella Typhi, usually through ingestion of contaminated food or water. Children usually have high grade fever with variety of associated features like, myalgia, anorexia, vomiting, diarrhea, abdominal pain, cough and hepatosplenomegaly. A similar but often less severe disease, paratyphoid fever, is caused by Salmonella Paratyphi A and B or uncommonly Paratyphi C.[1] Enteric fever continues to be a major public health problem and it is endemic in Pakistan. According to the most recent estimates, between 11 and 21 million cases and 128 000 to 161 000 typhoid-related deaths occur annually worldwide.[2] In most developed countries incidence is <15/100,000 population while estimates in developing countries is 100-1,000/100,000 population.[2] Ochiai LR et al[3], in their review of disease burden due to enteric fever from five Asian countries reported a higher incidence of typhoid fever from India, Indonesia and Pakistan.

There is a wide spectrum of clinical presentation of enteric fever so clinical diagnosis is difficult.[4,5] Blood culture is considered as the gold standard for the diagnosis and gives information about antibiotic sensitivity of the isolate.[6] However, the cost of investigations, lack of laboratory facilities, administration of prior antibiotics and poor awareness amongst health care professionals are hurdles to the diagnosis. By the end of 1990s, salmonella typhoid developed resistance simultaneously to all first line drugs like chloramphenicol, cotrimoxazole and ampicillin.[5] Now in the current epidemic in Pakistan we have to face the extremely drug resistant cases

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of enteric fever where the pathogen is resistant to the second line drugs that is quinolones and ceftriaxone.[7]

Historically leucopenia is commonly associated with enteric fever[8,9], With the recent outbreak of multidrug (MDR) and Extended drug resistant(XDR) typhoid fever, in Pakistan[10,11] and Globally[12], we have found a clear trend of high Total leukocyte count (TLC) in Complete blood count (CBC) of few typhoid patients at our hospital and that was the main stimulus to explore, To determine the frequency of leukocytosis in patients of culture proven enteric fever in children, So that it can be helpful in choice of antibiotics at the time of presentation to treat the patients.

MATERIAL & METHODS

This was a retrospective cross-sectional study, conducted in the Department of Paediatrics, at Fatima memorial hospital, shadman Lahore, Pakistan over a one year period (January 2020 to December 2020). The record of patients diagnosed with enteric fever on blood culture were being reviewed. All patients in the age group of one year to 15 years with a discharge diagnosis of enteric fever for admitted inpatient or from Outpatient Department (OPD) were included in the study. All the malnourished, immunocompromised, patients taking steroids and with other chronic comorbid conditions affecting white blood cells counts like marked splenomegaly or Aplastic anemia were excluded.

All the patients fulfilling the inclusion criteria were enrolled in the study. The leukocyte count at the time of presentation in complete blood picture was noted. All study cases were divided in to three Categories (Normal WBC 4000-12000/micro L, Leukopenia <4000/micro L and Leukocytosis >12000/micro L) depending on the TLC value (total leukocytes Count).

All the information was recorded in a pre-designed proforma. Information on the socio-demographic profile, duration of symptoms and, presenting symptoms, duration of illness, Clinical examination like coated tongue, pallor, hepatosplenomegaly (Liver >2 cm below costal margin and spleen clinically palpable) were included in recorded data. All patients had complete blood counts (CBC), blood culture and sensitivity pattern, hepatic enzymes like ALT (normal<40 IU/L) and CRP (normal<5) done. Cases were diagnosed as a culture positive enteric fever if the blood culture was positive for S. Typhi or S. Paratyphi A,B,C.

Data was entered and analyzed in IBM SPSS version 23. Distribution of the continuous data was assessed by using Kolmogrov Smirnov test. For between group comparison of continuous variables like age, fever duration, and lab variables, Kruskal Wallis H test was applied. For the between group comparison of categorical variables chi square test was used.

Permission from the hospital ethical board was taken for using the data of the patients in the research (FMH-03-2020-IRB-748-M).

RESULTS

During the study period, a total of 110 children diagnosed with enteric fever on blood culture. leukopenia was found in 11% cases (12 out of 110), 18 out of 110 patients (16%) has shown leukocytosis and leukocyte count was normal in 73% patients (80 out of 110).

Majority of the patients were in the age range of two to nine years old with median age was 61.3 (IQR 38) months and slight female preponderance 61 out of 110 patients (55.5%)was observed. Median duration of fever before presentation was eight days (IQR 7.3 days) and anorexia (86.4%) was the most common symptom found in 95 cases after fever, followed by coated tongue 78 cases (70.9%) and vomiting with Abdominal pain 71 cases out of 110 (64.5%). 62 cases (56.4) has shown fever with chills, rigors and sweating pattern [Table-I]. Hepatomegaly and splenomegaly were seen in 37.3% (41 cases) and 32.7% (36 patients) respectively. Splenomegaly was observed in 72% (13 out of 18 cases) of patients with leukocytosis and P value was found to be significant (0.001).

Median Haemoglobin and Platelets were 8.3 (IQR 2), 156 (IQR156.3) respectively. Median C-reactive protein (normal CRP<5) found to be

7.1(IQR 34.6) and Liver transaminases (SGPT) was elevated with median of 60.5 (IQR44.3) (normal <40).

S. Typhi and S. Paratyphi A,B,C were found in 84 cases (76.4%), 26 (23.6%) respectively of 110 positive blood culture. The antibiotic susceptibility of Salmonella Typhi and Paratyphi for Ampicillin, Cotrimoxazole, Chloramphenicol (first line antibiotics) Fluoroquinolone, Ceftriaxone, Cefixime (2nd line antibiotics) Imipenem, meropenem, and Azithromycin, is presented in [Table-II]. Majority of Salmonella Typhi and Paratyphi A,B,C showed resistance to first line antibiotics (Ampicillin, Cotrimoxazole, Chloramphenicol). Only 8 (5%) cases of enteric fever were multisensitive with 93% (102 cases) of isolates were either multi drug resistant (45 cases (41%) or 57 cases Extended drug resistant (52%). Among leukocytosis Group strikingly, 88.9% of patients (16 out of 18) has shown Extended drug resistant pattern with P value of <0.001. three isolate of S. Paratyphi A were resistant to azithromycin as well and only sensitive to meropenem. In our study, we did not find any resistance to meropenem.

Isolate is multisensitive if sensitive to first line antibiotics (Ampicillin, Cotrimoxazole, Chloramphenicol), labeled as a multidrug resistant (MDR) if sensitive to 2nd line antibiotics (Fluoroquinolone, Ceftriaxone, Cefixime) but resistant to first line and called as a Extended Drug resistance (XDR) if sensitive only to Carbapanems and macrolides (Azithromycin).

Parameter	Leukopenia N (%)	Normal WBC N (%)	Leukocytosis N (%)	Total N (%)	P-Value
Age in months*	66(55)	55(30)	63(30)	61.3(38)	.45
Female Sex	8(66.7)	45(56.3)	8(44.4)	61(55.5)	.469
Fever duration*	8.5(6)	8(4)	8(12)	8(7.3)	.398
Loose motions	8(66.7)	45(56.3)	15(83.3)	68(61.8)	.095
Vomiting	6(50)	53(66.3)	12(66.7)	71(64.5)	.53
Abdominal pain	9(75)	51(63.8)	11(61.1)	71(64.5)	.43
Anorexia	9(75)	69(86.3)	17(94.4)	95(86.4)	.314
Cough	5(41.7)	28(35)	5(27.8)	38(34.5)	.72
Chills and rigors	7(58.3)	42(52.5)	13(72.2)	62(56.4)	.31
Sweating	7(58.3)	51(63)	9(50)	67(60.9)	.54
Pallor	1(8.3)	16(20)	8(44)	25(22.7)	.037
Coated tongue	8(66.7)	55(68.8)	15(83.3)	78(70.9)	.44
Hepatomegaly	5(41.7)	29(36.2)	7(38.9)	41(37.3)	.92
Splenomegaly	3(25)	20(25)	13(72.2)	36(32.7)	.001
Haemoglobin*	9(2)	8(2)	8(2)	8.3(2)	4.1
Platelets*	123(219)	123(135)	222(115)	156(156.3)	3.5
CRP*	6(3.75)	6(50)	9.35(50.25)	7.1(34.6)	1.6
ALT*	66(45)	66(34)	49.5(54)	60.5(44.3)	.98
Blood culture S.Typhi	9(75)	64(80)	11(61.1)	84(76.4)	.23
Blood culture S.Paratyphi A,B,C	3(25)	16(20)	7(38.9)	26(23.6)	.23

Table-I. Clinical and laboratory parameters of culture proven enteric fever (N=110)
***Median(IQR) (for comparsion Kruskal Wallis H test is used)**

Antibiotics Sensitivity	Leukopenia	Normal WBC	Leukocytosis	Total
Multi sensitive	0	4(5.0%)	1(5.6%)	5(4.5%)
Multi drug resistance	7(58.3%)	37(46.3%)	1(5.6%)	45(40.9%)
Extended Drug resistance **P value (<0.001)**	3(25.0%)	38(47.5%)	16(88.9%)	57(51.8%)
Meropenem only	2(16.7%)	1(1.3%)	0	3(2.7%)

Table-II. Antibiotics sensitivity of enteric fever in children

DISCUSSION

In this hospital based series of children (both inpatient and OPD) with blood culture proven enteric fever, we have observed that leukocytosis in enteric fever is not uncommon and enteric fever can be associated with leukocytosis in Children. These findings are not similar to those reported in the past with confirmed enteric fever cases, as leukopenia thought to be a characteristic finding in patients with enteric fever.[8,9] In this study leukopenia was observed in 12 (11%) of total cases, but 18 cases out of 110 patients (16%) has shown leukocytosis which was quite unusual and not previously documented in literature. We have observed recently this trend of finding high WBC counts in enteric fever especially in patients diagnosed with multidrug resistance (MDR) and extended drug resistance (XDR) isolates. Overall, 51.8% (57 cases) of isolates has shown extended drug resistance pattern, little higher than to others studies documented locally[7,10,11] and globally.[12] In our data we have found among leukocytosis Group strikingly, 89% of patients (16 out of 18) has shown Extended drug resistant pattern with P value of <0.001, which is quite significant finding, and may be explained with a recent widespread outbreak of extended drug resistance pattern in Pakistan only sensitive to carbapenems or Macrolides, predominantly with high CRP and high hospital admission rates for intravenous treatment.[10,11]

Majority of the patients were in the age range of two to nine years old with median age was 61.3 (IQR 38) months and slight female preponderance 61 out of 110 patients (55.5%) was observed.. median duration of fever before presentation was eight days (IQR 7.3 days) and anorexia (86.4%) was the most common symptom found in 95 cases after fever which was consistent with the previous data.[1,4,5] Splenomegaly was seen in 32.7% (41 patients) of cases overall but was observed in 72% (13 out of 18) of patients with leukocytosis and P value was found to be significant (0.001), contrary to previously reported in literature[1,4] and we explained this has relation with recent XDR enteric fever outbreak in Pakistan.

In our data, S. Typhi was found in 84 cases (76.4%) of positive blood cultures and 26 cases (23.6%) of positive culture found S. Paratyphi A,B,C, and this trend was consistent with the current literature.[1,4,5] Both S. Typhi and S. Paratyphi had similar susceptibility pattern to third generation cephalosporins, carbapanems and azithromycin. Very high resistance to first line drugs like amoxycillin, chloramphenicol and cotrimoxazole, was observed (only 5% isolates were sensitive to first line drugs drugs) which was also evident in similar studies in the region.[7,10,11,13,-16] In our study 45 (41%) of culture isolates were multi drug resistant which was slight high as compared to regional similar data[7,10,11,13-16] but in consistent with the trend recently and reflecting judiciuous use of these drugs by general practioners (GPs) and using these drugs in the past for typhoid fever, as a first line antibiotics, without doing blood culture in resource limited countries like Pakistan.

The main limitation of this study is nature of data was hospital-based, which may not reflect the actual situation in the community. The retrospective nature of data and small sample size were other potential pitfalls. There have been recently, overwhelming reports of MDR and XDR Salmonella Typhi, and paratyphi indicating a potential Global threat[7,10,11,13-15] High antimicrobrial resistance was observed in our study which was also observed in similar local studies recently.[10,11]

CONCLUSION

We conclude that Leukocytosis in culture proven enteric fever is not uncommon and once there is leukocytosis in culture proven Typhoid fever, there is a high incidence of XDR typhoid, which need to be validated by more regional well designed studies having said that emergence of XDR typhoid is no more regional concern, rather it's a global emergency in public health.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Abid Rafiq Chaudhry	Corresponding author, Collected data and written results.	
2	Muhammad Yaqub Kazi	Coined the idea with observation about high WBC count in enteric fever.	
3	Muhammad Usman	Written introduction.	
4	Rashid Ayub	Helped in writing discussion.