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Original research article

HAEMATOLOGICAL PROFILE IN ENTERIC FEVER IN PAEDIATRIC AGE GROUP: A HOSPITAL BASED CROSS-SECTIONAL STUDY

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ABSTRACT

Background: In the western region of the state of West Bengal, it is difficult to diagnose enteric fever using blood cultures or even the Widal test. The best method to make a diagnosis and start treatment is with a high index of suspicion. In this setting, research into potential haematological alterations associated with enteric fever may offer the physician a critical clue for the early initiation of treatment and prevent further complications.

Aims: The goal of this study was to examine the haematological profile of children with Widal-positive enteric fever.

Method: A hospital-based cross-sectional study was carried out at Bankura Sammilani Medical College and Hospital (BSMCH) from March 1, 2020, to August 31, 2021. The study population consisted of 120 children, aged 1 to 12 years, who were admitted to the children's ward with Widal positive enteric fever. A pre-designed questionnaire was used to collect the relevant information. The data was entered into a Microsoft Excel spreadsheet and analyzed with Epi Info (version 3.5.1) Software.

Results: Anaemia (80%) was the most prominent haematological result in the current study. Raised ESR (65%), thrombocytopenia (28.33%), eosinopenia (23.33%), leucopenia (22.50%), erythropenia (20%), relative lymphocytosis (21.67%), neutropenia (17.5%), eosinophilia (5.83%), and leucocytosis (5.83%) were found in decreasing order. Leucocyte, platelet, haemoglobin, and ESR changes were all statistically significant (P-value = 0.000*).

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Changes in PCV, MCV, and MCH, with the exception of MCHC, were found to be statistically significant (P-value = 0.000*).

Conclusion: In the case of a 7-day fever with clinical features like anorexia, vomiting, diarrhoea, constipation, abdominal pain, a coated tongue, hepatomegaly, and headache, in addition to the aforementioned haematological changes, it may help the physician to initiate management of enteric fever without performing a serological test and testing for organism isolation via blood culture, which is not possible in remote areas.

Keywords: *children, enteric fever, haematological profile, Widal test*

INTRODUCTION

Enteric fever (more commonly known as typhoid fever) remains an endemic disease in many developing countries and is also observed in developed nations among travelers [I]. It affects an individual's multisystem and includes typhoid and paratyphoid fevers. Typhoid fever is caused by Salmonella enteric serotypeTyphi (*S. Typhi*) and Paratyphoid fever is caused by Salmonella enterica serotype *Paratyphi A, B or C.*

It is more common in developing nations like India, where the disease burden is considerable (214.2/100000 people/year) [2]. In developing countries, it is a substantial cause of illness and mortality [3]. The causes of endemicity in developing nations include low living standards, bad hygiene habits, poor sanitation, tainted food and water supplies, and a lack of universal vaccination. Children between the ages of five and 19 are the most commonly infected, while in some endemic regions of Asia, infants as young as two are also frequently affected [4]. Children between the ages of 2 and 4 have the highest incidence [5]. There are few statistics on enteric fever-related deaths in India. Enteric fever is thought to have a 1% overall case fatality rate [6].

The fundamental cause of typhoid fever is the invasion of *S. typhi* and its development within the mononuclear phagocytic cells in the liver, spleen, lymph nodes, and payer's patches of ileum [7]. A delay in diagnosis and treatment could cause severe complications since clinical signs are non-specific and can arise after an incubation period of between 10 to 14 days [8].The complaints that are being presented range from minor constitutional symptoms to serious problems affecting numerous organs. The basis of diagnosis is clinical suspicion. Fever, vomiting, diarrhoea, abdominal pain, coughing, headaches, and lethargy are typical manifestations. Along with physical ailments, typhoid fever's pathophysiological process causes changes in the infected person's haematological profile. The most frequent hematopoietic abnormalities identified are anaemia, leucopenia, eosinopenia, thrombocytopenia, and an elevated ESR [9]. Leucopenia is thought to be an important factor of enteric fever; however investigations have revealed that it only occurs in 20–25 percent of cases [10]. Leucopenia is a rather common occurrence of leucocytosis, or the existence of a leukocyte count within the normal range, according to the evidence [11, 12]. In actuality, children are more frequently than adults to experience leucocytosis, and younger children are more likely than older children to have a high leukocyte count (>4 times more likely) [13].

Blood cultures are the gold standard for diagnosis, although they come back negative in 70% of patients because antibiotics were used indiscriminately before admission [14]. The Widal

test has been preferred and is still extensively used, despite the difficulty in accessing information and the lengthier time needed to isolate the organism [15, 16]. However, by looking at the haematological profile, typhoid fever can be suspected early. However, not enough research has been done in this area. In order to diagnose Widal positive enteric fever earlier and, to some extent, close the information gap, this study seeks to identify haematological abnormalities in the disease.

AIMS

The goal of this study was to examine the haematological profile of children with Widal-positive enteric fever.

METHODS

Study design and area: It is a cross-sectional study conducted in the department of paediatrics at the BSMCH in Bankura, West Bengal, India. **Study period**: 18 months (March 2020–August 2021). **Ethics clearance:** The institutional ethics committee provided ethical clearance prior to the start of this study, per Memo No. BSMC/Aca-298, dated January 27, 2020. **Study population**: Inclusion criteria are: 1. Children of both sexes more than one year of age and less than 12 years of age admitted to the department of paediatrics; 2. Fever (temperature > 38 °F) for at least 7 days and Widal positive; and 3. Parents or caregivers of children who gave consent to participate in this study. Exclusion criteria include: 1. Children under the age of one year and those over the age of twelve; 2. Parents or caregivers of those children who have not given consent; 3. Proven localised infection; 4. Other tropical infectious diseases such as malaria, scrub typhus, and dengue fever; and 5. Children with a fever associated with a haematological disorder. **Sample size**: 120. It was calculated using the formula: n=(Z)2 P (1-P) / d2.Here Z_{α} = 1.96, the standard deviation at a 95% confidence interval, P = the prevalence of the event of interest, neutropenia in typhoid fever is 11.6% as per previous study [17], and d is the absolute precision, which is assumed to be 6. When we added all of these numbers together, we got n = 3.84 * 11.6 * 88.4 / 36 = 109. The revised sample size was n = 120, based on a 10% non-response rate. **Study instruments**: A predesigned, pretested, semi-structured questionnaire was used to collect data about the participant's demography, detailed history, clinical examination, and all relevant reports. To determine the haematological changes in typhoid fever, a complete haemogram was performed. A Widal test was advocated for confirmation of the diagnosis of typhoid fever. To rule out malaria, dengue, urinary tract infection, and nCovid-19 infection, malarial parasite dual antigen (MPDA), dengue serology, urinalysis, and RT-PCR have also been done. A liver function test and a renal function test were done to find out if there were any organ dysfunctions. A chest X-ray and Mantoux test were done to rule out tuberculosis. Imagine that studies such as ultrasonography (USG) and computed tomography were done when indicated. Following standard care as per unit protocol, all study participants were discharged home. **Statistical analysis:** The data was put into a Microsoft Excel sheet and analyzed by Epi Info (version 3.5.1) software. Continuous variables were expressed as mean and standard deviation, whereas categorical variables were expressed as percentages and ratio. ANOVA and t-test have done to compare the categorical variable and P-value of <0.05 was set as

statistically significant. **Case definition:** Enteric fever is defined by the presence of signs and symptoms suggestive of enteric fever and a positive blood culture for *Salmonella* or a positive rapid diagnostic test (TyphidotIgM, sensitivity 84% and specificity 79%), or a Widal positive (TO titre >1:160 or TH titre >1:160). [18]

RESULTS

Demographic characteristics

In this study, 120 children of both sexes aged 1 to 12 years who had a fever for 7 days and were later found to be HIV positive were enrolled. There were 57.5% (n = 69) males and 42.5% (n = 51) females among the 120 children. The male-to-female ratio was 1.35:1. The mean age of presentation was 5.40 ± 2.92 years. Under-5 children (40%, n = 48) were less affected than above-5 children (72%, n = 60). Table 1 depicts the age and gender distribution of the study population.

Clinical presentations

Among the study population, the most common presenting symptom was fever (100%, n = 100), followed by anorexia (77.50%, n = 93), and the least common was cough (9.17%, n = 11). Other symptoms were headache (42.5%, n = 51), vomiting (40.83%, n = 49), constipation (36.67%, n = 44), diarrhoea (31.66%, n = 38), and abdominal pain (29.17%, n = 35). Notable signs were pallor (80%, n = 96), coated tongue (74.17%, n = 89), hepatomegaly (65.83%, n = 79), skin rash (14.17%, n = 17), crepitation (6.67%, n = 8), and jaundice (2.5%, n = 3). Table 2 shows the clinical signs and symptoms of enteric fever.

Haematological characteristics

A complete blood count in a child with enteric fever shows several changes. In the current study, 80% (n = 96) of the children had anaemia, with 52.5% (n = 63) having mild anaemia. Anaemia was found to be moderate or severe in 20.5% (n = 25) and 6.67% (n = 8) of the children, respectively. The mean haemoglobin level was 9.49 ± 1.62. Normal leucocytes, leucocytosis, and leucopoenia were found in 71.67% (n = 86), 5.83% (n = 7), and 22.5% (n = 27) of children, respectively.

The mean leucocytes count was 7423.75 ± 2616.49.Thrombocytopenia was found in 28.33% (n = 34) of the children in this study. The mean platelet count was 2.04±0.71 ($\times 10^5/mm^3$). The erythrocyte sedimentation rate (ESR), an acute phase reactant, in the 1st hour was 65% (n = 78). The changes in haemoglobin, leukocytes, platelets and ESR, was statistically significant and P-value in each case was P=0.000*. Table 3 displays the homological profiles.

In the present study, neutropenia, eosinopenia, eosinophilia and lymphocytosis (relative) were revealed in 17.50% (n=21), 23.33% (n=28), 5.83% (n=7) and 21.67% (n=26) respectively. Table 4 displays absolute count of different leucocytes.

In the present study, there was significant changes in red cell indices were observed. Except changes in mean corpuscular haemoglobin concentration (MCHC), changes of red blood corpuscles (RBC), packed cell volume (PCV), mean corpuscular volume (MCV) and mean haemoglobin concentration (MCH) were statistically significant and p-value in each case was p=0.000*. Table 5 shows changes in different red cell indices.

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DISCUSSION

In low-resource nations, enteric fever, which includes typhoid and paratyphoid fever, is a significant public health issue [19]. Typhoid continues to be a public health concern due to the increased vulnerability of infants, young children, and teenagers as well as poor sanitation and food handling practises [20]. A number of things, including poor nutrition, endotoxemia, and a weakened immune system, can lead to complications [21].

Endotoxin may effect on the subject's reticuloendothelium system, including the liver, spleen, and other organs, even when it is not adequately discharged into circulation to cause distinct alterations in the haematological profile [9]. The numerous haematological presentations of typhoid fever have included anaemia, leucopoenia, and thrombocytopenia, but they are self-limited [22].We carried out this study to recognize and treat enteric fever early by interpreting the haematological profile, thereby avoiding various complications, including death, in an area where blood cultures, the gold standard diagnostic method, are not available and only the Widal test, which has low sensitivity and specificity, is available.

Male children constituted 57.50% (n = 69) of the study's population, while female children made up 42.50% (n = 51). The ratio of male to female children was 1.35 to 1. This result was consistent with a research by Malla T et al. that revealed a male preponderance [23]. Ganesh R et al. demonstrated a male-to-female ratio of 1:2 in contradiction to this study. [24]. In their investigation, Akbayram et al. revealed that the male to female ratio is 1:1. [25].

This gender inequality may be caused by parental child-rearing habits, gender differences in the study's study area, and, last but not least, the fact that male children participate in more outdoor activities than female children. 60% of the children (n = 72) in the present study were older than 6 years old. In their investigation, Chandrasekharet al. [26] found that 60% of typhoid patients were older than 5 years, which is congruent with the findings of the present study.Ganesh R et al. from Chennai, South India, conducted another study that reported 169 (53.48%) out of 316 cases of typhoid fever were older than 5 years old [24]. In contrast, in IIe-Ife, southwest Nigeria, Zailani et al. found no correlation between age, gender, or social class and the distribution patterns of Salmonella enteric serovar Typhi and Salmonella enteric serovar Paratyphi [27].

Fever was the most prevalent symptom in the current study, reported in 100% of the study population, echoing the results from Devaranadevangi RA et al. [28] and nearly approaching those from Behera J et al. from Odisha, India, who found 98.21% [29]. Other signs and symptoms were vomiting (40.83%; n=49), diarrhoea (31.66%; n=38), anorexia (77.5%; n=93), pain abdomen (29.17%; n=35), headache (42.50%; n=51), constipation (36.67%; n=44), cough (9.17%; n=11), coated tongue (74.17%; n=89), pallor (77.50%; n=93), hepatomegaly (65.83%; n=79), splenomegaly (20.83%; n=25), Jaundice (2.50%; n=3), skin rash (rose spot) (6.67%; n=8) and crepitation (6.67%; n=8). The common gastrointestinal

symptoms identified in studies conducted by various researchers were vomiting, abdominal pain, constipation, and diarrhoea [24, 30].

Enteric fever is associated with a number of haematological abnormalities, including anaemia, leucopenia, leucocytosis, thrombocytopenia, and eosinopenia, however these are self-limited, according to Dheer et al. [31]. These alterations in the haematology are brought on by the bone marrow's increased histiocyte phagocytic activity, a cessation of myeloid development, and a reduction in the quantity of megakaryocytic and erythroblasts [10].

In the present study, 80 % (n = 96) of the cases had anaemia. In 62.2% of individuals, anaemia was found by South Indian researchers Malini et al. [32]. The contrasting nutritional state of the two research populations may be the cause of the variations between the current study and the one conducted by Malini et al. Anaemia was most likely attributed to hemolysis, toxaemia, or less frequently, intestinal haemorrhage. In typhoid fever, anaemia doesn't need to be aggressively treated. Due to the fact that it is connected to endotoxemia and gets better during recovery [10]. Other significant haematological alterations identified in this study include neutropenia (17.50%), leucocytosis (5.83%), eosinopenia (23.33%), thrombocytopenia (28.33%), and increased erythrocyte sedimentation rate in 1st hour (65%).

Leukocyte count was normal in 71.67% (n = 86) of the study population, which is in conformity with the guidelines of the Indian Academy of Paediatrics for the diagnosis of enteric fever [33] and studies by Behera J et al. and Malini A et al., which reported that 70% and 63.8% of children, respectively, had normal leucocytes counts [29, 32]. The normal leucocytes count has also been reported by other researches [4, 34]. Typhoid fever complications manifest as leucocytosis. Leucocytosis was present in 5.83% (n = 7) of the study participants in the current study, all of whom had bronchitis. Leucocytosis of 8% was discovered in Azim AM et al. study's [35], which is comparable to the present study. It is claimed to frequently have leucopenia as a haematological sign. Leucopoenia affects 22.50% (n = 27) of the children in the present research. In a research by Azim *et al*. [35], leucopenia was found in 22% of children, which is congruent with the results of the current study. In a study conducted in Indonesia, Ringoring HP et al. found leucopenia in 17.24% of the children [36]. Qamar reported leucopenia in 48 patients (32% of the total) [37]. In the present study populations, neutropenia was observed in 17.50% (n =21) of the cases. In a study from North Bihar, India, Jyoti D et al. revealed that neutropenia affected 41.5% of the studied population [38]. The wider array may be caused by the length of the illness prior to presentation or by toxic bone marrow suppression, indicating the need for further research. Eosinopenia was found in 23.33% (n = 28) of cases, which is substantially less than earlier studies that revealed 58.93% [29] but comparable to a study done by Anabire NG et al. which showed that eosinopenia was present in 20% of study population with typhoid fever and is a significant marker of the illness [39]. Even though eosinophilia is uncommon in enteric fever, it was found in 5.83% (n = 7) of children, which is comparable to a research from North Bihar, India, by Jyoti D et al. that found 7.5% [38]. This hematopoietic alteration was also noticed by Ringoringo HP et al. [36]. Their investigation only revealed 3.64%, which is less than the results of the current study.

Typhoid fever complications and severity are both indicated by thrombocytopenia [4]. In the current study, thrombocytopenia was present in 28.33% of cases, which is equivalent to Malik AS's work, which revealed 26% thrombocytopenia in typhoid fever [40]. In contrast, Iftikaret al. in Pakistan reported thrombocytopenia in 65% of patients with enteric fever [41]. The fact that patients present to the specialised hospital later than usual may be the cause of the increased frequency in Pakistani children.

The current investigation has found some alterations in red cell indices. Their respective mean RBC, PCV, MCV, MCH, and MCHC values were 4.1 ± 0.65 (abnormal value 21.67%), 30.04 ± 4.60 (abnormal value 68.33%), 73.98 ± 7.86 (abnormal value 59.17%), 23.17 ± 2.66 (abnormal value 37.5%), and 31.32 ± 1.45 (abnormal value 13.33%). To our knowledge, no studies have been done to look at the changes in red cell indices in children with enteric fever.

Strengths of the present study

The haematological profile of children with Widal-positive enteric fever has undergone statistically significant alteration (P-value <0.05). There have been notable changes in other haematopoietic cell lineages as well as red cell indices.

Limitations of the study

The study was conducted at a tertiary health centre, and the children who were admitted had previously taken antibiotics, which could have an impact on both clinical symptoms and hematopoietic changes. 2. Selection bias still exists 3. Because so few children were enrolled in the study, the results cannot be applied to the general population. 4. Due to a lack of data, the percentage and index of reticulocytes as well as the red cell distribution width were not noted here. Therefore, we were unaware of the potential changes in these red cell indices associated with enteric fever.

Conclusion

Anemia (80%) was the most prominent haematological result in the current study. Raised ESR (65%), thrombocytopenia (28.33%), eosinopenia (23.33%), leucopenia (22.50%), erythropenia (20%), relative lymphocytosis (21.67%), neutropenia (17.5%), eosinophilia (5.83%), and leucocytosis (5.83%) each were the conditions that came next in decreasing order. Leucocyte, platelet, haemoglobin, and ESR changes were all statistically significant (P-value = 0.000*). PCV, MCV, MCH, and MCHC were among the red cell indices with low values, measuring 67.5%, 59.17%, 39.17%, and 21.67%, respectively. Changes in PCV, MCV, and MCH, with the exception of MCHC, were statistically significant (P-value = 0.000*). In the case of a 7-day fever with additional clinical features like anorexia, vomiting, diarrhoea, constipation, abdominal pain, a coated tongue, hepatomegaly, and headache, in addition to the aforementioned haematological changes, it may help the primary care physician initiate management of enteric fever without performing a serological test and testing for organism isolation via blood culture, which is not possible in our country's remote areas.

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Conflicts of interest: There are no conflicts of interest among authors

Ethical approval: The study has been approved by the respective Institutional Ethics Committee.

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TABLES:

Table 1: Depicts the age and gender distribution of the study population.

Age*/ Gender	Male	Female	Total (%)
1 – 5 Years	26	22	48 (40.00)
6 – 12 Years	43	29	72 (60.00)
Total (%)	69 (57.5)	51 (42.5)	120 (100)

*Mean age (year) – 5.40 ± 2.92

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Table 2: Shows the clinical signs and symptoms.

Variables	Number	Percentages
Symptoms		
Fever	120	100.00
Vomiting	49	40.83
Diarrhoea	38	31.66
Anorexia	93	77.50
Pain abdomen	35	29.17
Headache	51	42.50
Constipation	44	36.67
Cough	11	9.17
Signs		
Coated tongue	89	74.17
Pallor	96	80.00
Hepatomegaly	79	65.83
Splenomegaly	25	20.83
Jaundice	3	2.50
Skin rash	17	14.17
Crepitation	8	6.67

Table 3: Shows changes in haematological profile.

Variable	Number	Percentages	Mean ± SD	P-value
Haemoglobin (gram/dl)			9.49 ± 1.62	p = 0.000*
>11	24	20%		
9-11	63	52.5%		
7-9	25	20.5%		
<7	8	6.67%		
WBC ($\times 10^3$/ mm^3)			7423.75 ±	P=0.000*
>11	7	5.83%	2616.49	
4-11	86	71.67%		
<4	27	22.50%		
Platelets ($\times 10^5$/mm^3)			2.04	P=0.000*
1.5 – 4	86	71.67%	±	
<1.5	34	28.33%	0.71	
ESR (mm/1st hour)				P=0.000*
≤20	40	35.00%	29.86 ±	
>20	80	65.00%	12.75	

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Table 4: Shows absolute count of different leucocytes.

Variables	**Mean ± SD**	**< Normal (%)**	**Normal (%)**	**>Normal (%)**
Neutrophil	3301.34 ± 1505.33	21 (17.50%)	99(82.50%)	0
Eosinophil	164.11 ± 148.11	28 (23.33%)	85 (70.83%)	7 (5.83%)
Lymphocyte	3753.44 ± 1231.04	0	94 (78.33%)	26 (21.67%)
Monocyte	77.34± 66.29	0	120 (100%)	0

Table 5: Shows changes in different red cell indices.

Variables	**Mean ± SD**	**< Normal (%)**	**Normal (%)**	**>Normal (%)**	**P-value**
RBC	4.1 ± 0.65	24 (20%)	94 (78.33%)	2 (1.67%)	P=0.000*
PCV	30.04 ± 4.60	81 (67.5%)	39(32.5%)	0	P=0.000*
MCV	73.98 ± 7.86	71 (59.17%)	49 (40.83%)	0	P=0.000*
MCH	23.17 ± 2.66	47 (39.17%)	73 (60.83%)	0	P=0.000*
MCHC	31.32 ± 1.45	26 (21.67%)	94 (78.33%)	0	P=0.578