

Study of association of pancreatitis with enteric fever of age group 1 to 15 years

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Introduction: Enteric fever is endemic in India. 1% of children up to 17 years of age suffer from Enteric fever. Enteric fever is a systemic disease characterized by fever and abdominal pain caused by the dissemination of *Salmonella typhi* or *S. paratyphi*. The term enteric fever includes both typhoid fever and paratyphoid fever. Many case reports of severe acute pancreatitis during salmonellosis have been reported, suggesting that serious pancreatic disease may represent a complication of Salmonella infection. **Aim and objective:** To find out the frequency of acute pancreatitis considering clinical features, biochemical changes (serum amylase and lipase), and ultra-sonographic evidence of pancreatic involvement in the pediatric population by estimating serum amylase and lipase level in the pediatric population who were admitted with the diagnosis of Enteric fever. **Material and Method:** The present prospective study was conducted in the S V P PG Institute of pediatrics and SCB Medical College, Cuttack, Odisha, India which is a premier referral institute of eastern India. **Result:** Overall the proportion of patients with raised levels of serum amylase and lipase in the Enteric fever group was 44.68% (n=21). Comparing these values with the control group shows that the rise in serum amylase and serum lipase levels were statistically more significant (‘p’ value <0.05). **Conclusion:** Hence, salmonella may be considered as a causative agent of subclinical pancreatitis with biochemical and radiological changes.

Keywords: Pancreatitis, Enteric fever, Serum Amylases, Lipase

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Introduction

Enteric fever is a systemic disease characterized by fever and abdominal pain caused by the dissemination of *Salmonella typhi* or *S. paratyphi*. The term enteric fever includes both typhoid fever and paratyphoid fever [1]. Man is the only known reservoir of infection, both cases, and carriers. A case (or carrier) is infectious as long as bacilli appear in the stool or urine [2]. Carriers may be temporary (incubatory; convalescent) or chronic. Carriers excrete the bacilli for 6 to 8 weeks, after which their number diminishes rapidly. By the end of one year, the average carrier rate is around 3%. The clinical presentation varies from mild illness with low-grade fever to a severe clinical picture with abdominal discomfort and multiple complications [3]. The famous case of Mary Mallon (Typhoid Mary) who gave rise to more than 1300 carriers in her lifetime is a good example of a chronic carrier. Mallon was the first apparently perfectly healthy person known to be responsible for an epidemic. Fecal carriers are more common than urinary carriers as suggested by Park et al [2].

Pancreatitis is defined as inflammation of the pancreas resulting in an acinar cell injury caused by the destructive effects of pancreatic enzymes. It is a relatively infrequent illness in pediatrics, affecting males and females equally and involving all ages. The etiology of pancreatitis in pediatrics is diverse in nature, with a grossly unpredictable clinical course and prognosis. The diagnosis requires a high index of suspicion and should be considered in all children admitted with abdominal pain and elevated pancreatic enzymes. The disease is classified into acute and chronic forms or single and recurring episodes, respectively [4].

A wide variety of infectious agents have been associated with acute pancreatitis. Pathologic and radiological evidence of pancreatitis in the course of well-documented infection has been associated with viruses, bacteria, fungi, and parasites [5]. In particular, a high incidence of acute pancreatitis in adult patients with *Salmonella* infection has been reported by Renner et al [6]. In this study, although pancreatic enlargement was demonstrated by abdominal sonography in about half of patients, the course of pancreatitis was mild or moderate with complete recovery. However, many case reports of severe acute pancreatitis during salmonellosis have been reported, suggesting that serious pancreatic disease may represent a complication of *Salmonella*

infection [7-9]. Viral infections may be associated with acute pancreatitis. The virus most commonly identified includes mumps, rubella, coxsackie B, Epstein-Barr, and measles virus [10]. Pancreatitis complicating infection with influenza A [11] and varicella [12] also has been observed. Up till now, only a few prospective studies have been reported on pancreatic abnormalities during typhoid fever in the pediatric population. The present study was performed in S V P PG Institute of pediatrics and S C B Medical College, Cuttack, Odisha, India, which is a referral tertiary pediatric institution, to evaluate the frequency of acute pancreatitis considering clinical features, biochemical changes (serum amylase and lipase) and ultrasonographic evidence of pancreatic involvement in the pediatric population who were admitted with the diagnosis of Enteric fever.

Aims And Objectives

The present study was conducted at S V P PG Institute of pediatrics and S C B Medical College, Cuttack, Odisha, India to find out the frequency of acute pancreatitis considering clinical features, biochemical changes (serum amylase and lipase) and ultra-sonographic evidence of pancreatic involvement in pediatric population by estimating serum amylase and lipase level in the pediatric population who were admitted with the diagnosis of Enteric fever. Children with fever for at least 3 days and /or jaundice of age group 1-15 years and of both sexes were selected randomly and allocated to study and control groups. Serum amylase and lipase level were done in all patients.

The aims and objectives of the study were:

Aims: To find out the association of acute pancreatitis in patients with Enteric fever of age group 1 to 15 years.

Objective: To determine the frequency of pancreatitis in patients with Enteric fever of age group 1 to 15 years and to compare the results with control.

Materials and Methods

The present prospective study was conducted in the S V P PG Institute of pediatrics and S C B Medical College, Cuttack, Odisha, India which is a premier referral institute. After obtaining clearance from institutional ethical committee, children in the age group 1-15 years and from both sexes coming from

Urban and semi-urban areas of Cuttack, neighboring districts and states like West Bengal, Jharkhand, Chhattisgarh attending the Outpatient department and getting admitted were selected at randomly. The study period of study was from January 2017 to December 2019 and studied accordingly. No ethnic, socioeconomic, cultural discriminations were considered during the selection of the children for this study.

Children under study were divided into two groups:

01. **Study group (Enteric fever)**- Those who had clinical features strongly suggestive of enteric fever and subsequently confirmed by blood culture and / or Widal test.
02. **Control group**-Those who admitted with fever and /or jaundice and subsequently diagnosed to have disease other than Enteric fever.

Inclusion criteria: Children with the following conditions were included in the study group:

Study group (Enteric Fever) – added as per Clinical criteria studied by Neopane et.al [13]. Three Major Criteria and three or more Minor Criteria Major Criteria given as below.

Major criteria: i. Fever, ii. Headache, iii. Relative bradycardia

Minor criteria: i. Pain abdomen, ii. Splenomegaly, iii. Diarrhea, iv. Chills, v. Vomiting

01. Control group-Those who admitted with fever and subsequently diagnosed to have disease other than Enteric fever.

Exclusion criteria

A. Study group (Enteric Fever)-

01. Past history of Enteric fever.
02. Past history of pancreatic, renal, liver, or salivary gland disease.
03. H/o any febrile illness prior to the present illness in the last 1 month.
04. H/o immunization with typhoid vaccine.v.Children who did not have a fever during inpatient observation
05. Children once enrolled for the study were not enrolled for the second time in the study.

B. Control group-

01. Past history of enteric fever.
02. Past history of pancreatic, renal, liver, or salivary gland disease.

03. H/o immunization with typhoid vaccine.

04. Children once enrolled for the study were not enrolled for the second time in the study.

The following clinical and laboratory data were recorded in all patients:

Detailed history including drug history, past history of suffering from a similar illness, immunization history, and family history of the concerned disease. A thorough clinical examination was done in each and every case.

The following laboratory investigations were done in all patients

01. HB, TLC, DC, ESR, Platelet, MP
02. RBS, S.Urea, S.Creatinine, Sodium, Potassium, Calcium
03. Liver Function Test including Total Bilirubin (conjugated and unconjugated), SGOT, SGPT, and Alkaline Phosphatase,
04. CRP,
05. Serum Amylase and Lipase: 1st time recorded on the 1st day of admission and 2ndtime recorded 10 days after,
06. CXR (PA view)
07. Stright X-ray Abdomen,
08. Mantoux test
09. Urine for RE/ME and C/S
10. Stools for RE/ME
11. USG of the abdomen (especially pancreas)

Special Test: For Typhoid fever –

12. Blood culture esp. for *S. Typhi* on the 1st day of admission
13. Widal test- on the 8th day of fever and above.
14. Typhidot M test.

Serum amylase estimation: EPS-G7 method, Serum lipase estimation: Turbidimetric method

Interpretation of results: Serum amylase and lipase activity of each patient were recorded and methodically plotted.

These values then statistically analyzed using the 'z' test. 'P' value of less than 0.05 was considered statistically significant. Mean, ranges, standard deviation, and frequency were used as descriptive statistics.

Results

In the present study, there were 44 children who had a diagnosis other than enteric fever. Among 44 children 24 cases (54.54%) were males and 20 cases (45.46%) were females. The male-female ratio was 1.2:1. The mean age of children in this group was 9.52 years.

Table 1:Age group and sex-wise distribution of Control group (n=44).

Age Group	Sex		Row Marginal	%
	Male	Female		
1 year-5 year	1	2	3	6.8
6 year-10 year	9	7	16	36.4
11 year-15 year	14	11	25	56.8
Column Marginal	24	20	n=44	100
%	54.54	45.46	-	-
Ratio	1.2	1	-	-

The above table shows that the maximum of cases under the control group falls in the age group of 11 to 15 years and the minimum number in the age group of 1 to 5 years.

Disease distribution in control group: Of 44 control patients, the main final diagnostic groups were Acute respiratory tract infection (ARI) (17 or 38.6%), Acute Gastro-enteritis (AGE)(12 or 27.2%), Dysentery (9 or 20.6%), Tuberculosis (TB) (3 or 6.8%), Malaria (3 or 6.8%).

A total of 83 cases were included in the study group. Diagnosis of Enteric fever was made in 47 children (Study group), of whom 18 were blood culture positive and 29 were blood culture negative. Among 47 children diagnosed to have Enteric fever, 25 cases (53.2%) were male and 22 cases (46.8%) were female. The male-female ratio was 1.14:1. The mean age group of children in the Enteric fever group was 9.16 years.

Table 2: The age and sex-wise distribution of the patients with Enteric fever (Study group) (n=47).

Age Group	Sex		Row Marginal	%
	Male	Female		
1 year-5 year	4	5	9	19.15
6 year-10 year	8	6	14	29.79
11 year-15 year	13	11	24	51.06
Column Marginal	25	22	n=47	100
%	53.2	42.6	-	-
Ratio	1.14	1	-	-

The above table shows that the maximum number of cases under the enteric fever group falls in the age group of 11 to 15 years and the minimum number in the age group of 1 to 5 years, males are more affected than the female in Enteric fever group.

Table-3: Analysis of Blood culture (n=47).

Sex	Blood culture		Total
	Positive	Negative	
Male	11	14	25
Female	7	15	22
Total	18	29	47

Table 3 shows out of 47 enteric cases 18 were culture positive of which 11 were male (61.11%) and 7 were female (38.89%). Among 25 male patients, 11 cases (44%) shows a positive result and among 22 female patients, 7 cases (38.82%) show a positive result.

A total of 44 patients were included in the control group. Of the 44 cases, only 5 patients had raised serum amylase levels at the time of the initial assessment. They were divided into groups based on the magnitude of elevation of serum amylase depicted as follows:

01. The normal value of serum amylase (39 cases: 88.64%) (A1)
02. Serum amylase rose to less than 3 times normal (5 cases: 11.36%) (A2)

Table 4:Analysis of serum amylase in the control group (n=44).

Group	Serum Amylase	No of patient	%
A1	Normal	39	88.64
A2	Raised but less than 3 times the normal	5	11.36

The magnitude of the rise in serum amylase levels in patients belonging to the group A2 varied from 103-153 U/L with a mean value of 128±20.66 U/L.

On repeat evaluation of the serum amylase value after 10 days, 4 patients (80%) had normalized the raised values while in 1 (20%), the value remained raised to less than twice the normal.

A total of 47 patients were included in the study group -1 who were diagnosed as Enteric fever based on blood culture and/or serology. Of the 47 enteric patients, 21 patients had raised serum amylase levels at the time of initial assessment. The

Cases were divided into groups based on the magnitude of elevation of serum amylase depicted as follows:

01. The normal value of serum amylase (26 cases: 55.32%) (B1)
02. Serum amylase rose to less than 3 times the normal (16 cases: 34.04%) (B2)
03. Serum amylase rose to more than 3 times the normal (5 cases: 10.64%) (B3)

Table-5: Analysis of serum amylase in patients with Enteric fever(n=47).

Group	Serum Amylase	No of patient	%
B1	Normal	26	55.32
B2	Raised but less than 3 times the normal	16	34.04
B3	Raised more than 3 times the normal	5	10.64

The magnitude of the rise in serum amylase levels in patients belonging to group B2 varied from 146-291 U/L with a mean value of 192±43.88 U/L and to group B3, it varied from 307-452 U/L with a mean value of 376±47.50 U/L.

Thus, it was observed that in the Enteric group 21 patients had raised serum amylase values while in the control group (vide Table 6) only 5 had raised serum amylase levels. Using 'z' test a 'p' value of less than 0.05 was obtained which was statistically significant i.e. hyperamylasemia was associated with a significant number of patients in Enteric fever compared to the controls.

Serum amylase levels were repeated in these 21 patients after 10 days. The results in the case group are as follows:

01. Of the 16 patients included in the B2 group, 13 had normal serum amylase value; 3 patients showed values which were above the normal range but remained below twice the normal.
02. Of the 5 patients in the B3 group, 4 patients had values in the normal range while 1 had serum amylase value which was above the normal range but was below twice the normal range.

Table-6: Analysis of repeat serum amylase in the Control group and the Enteric fever group.

Group	Serum Amylase		No of patient
	Normal	Raised but less than 3 times the normal	
Control	4	1	5
Enteric fever	17	4	21

A raised serum amylase level on initial assessment but on repeat assessment had done 10 days after, only 1 control patient, 4 Typhoid fever patients.

Analysis of serum lipase in the control group: None of the patients under the control group showed any elevation of serum lipase.

Of the 47 Enteric patients, 8 patients had raised serum lipase levels at the time of initial assessment. The cases were divided into groups based on the magnitude of elevation of serum lipase depicted as follows:

01. The normal value of serum amylase (39 cases: 82.98%) (C1)
02. Serum amylase rose to less than 3 times the normal (8 cases: 17.02%) (C2).

Table 7: Analysis of serum lipase in patients with Enteric fever (n=47).

Group	Serum lipase	No of patient	%
C1	Normal	39	82.98
C2	Raised but less than 3 times than normal	8	17.02

The magnitude of the rise in serum lipase levels in patients belonging to the group C2 varied from 33-79 U/l with a mean value of 53±17.04 U/L. Serum lipase levels were repeated in these 8 patients after 10 days. All values came down to the normal range.

Table 8: Analysis of repeat serum Lipase in patients with Enteric fever.

Group	Serum lipase		No of patient
	Normal	Raised but less than 3 times the normal	
Enteric fever	8	0	8

8 Enteric fever patient shows raised serum amylase level on initial assessment, on repeat assessment done after 10 days, no patients show elevation of serum amylase.

Table-9: Analysis of serum Amylase and Lipase in the Control group and Enteric fever patient.

Group	Serum Amylase			Serum Lipase		
	Normal	(↑)	(↑↑)	Normal	(↑)	(↑↑)
Control	39	5	-	-	-	-
Enteric fever	26	16	5	39	8	-

[(↑↑) = more than 3 times the normal; (↑) = less than 3 times normal; (-) = no rise]

88.64% (n=39) patients under the Control group are of normal serum amylase level and 11.36% (n=5) shows the mild elevation of serum amylase.

In Enteric fever group, 55.32% (n=26) patients show normal serum amylase, 10.64% (n=5) patients shows a significant rise of serum amylase

(More than 3 times the normal) and mild rise of serum amylase (raised but less than 3 times normal) found in 34.04% (n=16) patients.

In the same group mild rise of serum lipase found in 17.02% (n=8) patients and serum lipase level was normal in 82.98% (n=39) patients.

Table-10: Analysis of serum Amylase and Lipase in Enteric fever patient when considered together.

Group	Serum amylase	Serum lipase	No of patient	%
D1	N	N	26	55.31
D2	↑↑	↑	4	8.51
D3	↑↑	N	1	2.13
D4	↑	↑	4	8.51
D5	↑	N	12	25.53

[(↑↑) = more than 3 times the normal; (↑) = less than 3 times normal; (N) = normal]

Enteric fever patients were divided into groups based on the magnitude of elevation of both serum amylase and lipase when considered together depicted as follows:

01. Both the serum amylase and lipase values were within the normal range (n=26: 55.31%) (D1)
02. Serum amylase was significantly raised (more than 3 times the normal) with or without the rise of serum lipase (n=5: 10.64%) (D2 and 3)
03. Serum amylase was significantly or mildly raised with the mild rise of serum lipase (n=8: 17.02%) (D2 and 4)
04. Both Serum amylase and lipase was raised mildly (less than 3 times normal) (n=4: 8.5%) (D4)
05. Serum amylase was mildly raised (less than 3 times the normal) without the rise of serum lipase (n=12: 25.53%) (D5):

Table-11: Analysis of ultrasonography of abdomen in the control group, enteric fever patient.

Group	No of the patient showing abnormal pancreas	No of total patient	%
Control	0	44	00.00
Enteric fever	2	47	4.26

Among 47 patient of Enteric fever, only 2 cases (4.26%) shows bulky pancreas.

Discussion

Among 47 children diagnosed to have Enteric fever, 25 cases (53.2%) were male and 22 cases (46.8%) were female. The mean age group of children in the Enteric fever group was 9.14 years. In the present study out of 47 Enteric fever patients, 38 cases (80.85%) were above 5 years of age of which the maximum number of Enteric fever patients (51.06%; n=24) fall in the age group of 11 to 15 years and minimum number (19.15 %; n=9) in the age group of 1 to 5 years. This finding is corroborated with those obtained by Sekarwana et al [14] in their study that 64% of Enteric fever patients were above 5 years of age and 51.2% were males. Out of 47 Enteric patients, only 18 cases (38.3%) were blood culture positive and 29 cases (61.7%) were blood culture-negative which corroborated with the observation of Abdul Haque et al [15] that the sensitivity of blood culture in Enteric fever was 34.1% whereas Tanyigna et al [16] found 28.6% positive and Mogasale et al [17] found 61% positive for blood culture. The present study is similar to the study done by Abdul Haque et al [15].

In the present study, the incidence of hyperamylasemia and hyperlipasemia was noted in 44.68% and 17.02% respectively in the Enteric fever group. The mean serum amylase in patients with Enteric fever with pancreatic involvement was 246.8±82.83 U/L and means serum lipase was 53±17.04 U/L. This figure stands in contrast to the study done by Tossiti et al [8] in which they noted an incidence of 10.2%. None of the patients in the present series developed acute pancreatitis as defined previously. In the observation made by Tossiti et al, although hyperamylasemia over four times the normal values were found in three cases in a total of 507 patients, the clinical features of acute pancreatitis were recorded in only one case (0.1%). In another study done by Pezzilli et al [18], where they prospectively evaluated the frequency of acute pancreatitis, pancreatic enzyme elevation, and morphological pancreatic abnormalities in patients with salmonella infection, the incidence of hyperamylasemia in the case group was calculated to be 6.7%. None of the patients developed acute pancreatitis. The incidence of hyperamylasemia in the control group in this study was also noted to be 6.7% while the same in the present study conducted by us was 11.36%. It was found that elevated serum lipase levels above the normal range were 17.02% in the Enteric fever group and in the control group, no patient had elevated serum

Lipase levels. This pattern matches with those, found by Pezzili et al [18] in which they noted elevated serum lipase levels above the normal range in 16.7% in the study group while 3.3% of the patients in the control group had elevated serum lipase values.

Another observation made by Hermans et al [11] in 14 adult Enteric fever patients, clinical pancreatitis was noted in 28.57% (n=4) of cases and biological signs of pancreatitis were noted in 50% (n=7) of cases. In this study, the mean amylase levels noted were 81 IU (range: 30-201IU) whereas the mean lipase value was 949 IU (range: 468-2000 IU).

Renner et al [9] in their study of adult patients demonstrated that 62% of them infected with salmonella had raised amylase and lipase levels. In this study, although pancreatic enlargement was demonstrated by abdominal ultrasonography in about half of patients, the course of pancreatitis was mild or moderate with complete recovery.

In the present study, 4 patients (8.51%) with Enteric fever showed serum amylase above three times the normal and serum lipase elevation less than three times. In this group, 2 (4.26%) had a morphological alteration in the pancreas demonstrated by ultrasonography.

In the Enteric fever group, there were 21 patients (44.68%) who had raised serum amylase levels initially. Repeat serum amylase after 10 days revealed that only 4 of them (8.51%) had persistently raised levels of the parameter but none had raised values above three times the normal. Similarly, the raised serum lipase values initially were present in 8 patients (17.02%) but repeat examination failed to reveal raised values in any of them.

The discrepancy of findings between the previous studies and the present study may be explained by the fact that only pediatric population was included in the present study as well as there may be other nonspecific infections of the gastrointestinal tract which may have infected the pancreas causing hyperamylasemia and hyperlipasemia in patients with Enteric fever.

In the control group, 5 patients (11.36%) had raised amylase levels initially but on repeat examination after 10 days, only one (2.27%) had raised values which were less than thrice the normal values. The serum lipase values were not raised in any of the patients belonging to the control group.

The above-noted findings may be explained by the fact that there may be prevalence in the environment of other unknown organisms that may have infected the pancreas but could not be detected. These organisms may be responsible for chronic low-grade inflammation of the pancreas which may be present in the asymptomatic form.

The elevation of serum pancreatic enzymes during the course of Enteric fever due to *Salmonella* infection could be explained in several ways. Intestinal inflammation could lead to increased permeability which allows the reabsorption of macromolecules such as amylase as suggested by Gnadinger et al [19].

These authors demonstrated an increased intestinal permeability for oral. Cr-EDTA in two patients with elevated serum amylase levels in the course of entero-invasive salmonellosis. Hyperamylasemia and hyperlipasemia could also be the result of a reduced excretion due to either impaired renal or liver function [20,21].

Hyperamylasemia and hyperlipasemia could represent the effect of direct pancreatic localization of bacteria through a hematogenous route as suggested by Schmid et al [22].

This hypothesis was not confirmed; in fact, Tosittiet al [8] found that, in those patients in whom *Salmonella typhi*. was isolated from blood cultures, hyperamylasemia was not detected. Finally, there is also some evidence that Salmonella are present in bile fluid and gallstone cultures [23,24], in this way, bacteria may directly infect the pancreas via the biliary duct system [25]. This may explain, at least in part, the presence of hyperamylasemia and hyperlipasemia in our patients infected by *Salmonella typhi*.

Conclusion

Of the total number of patients in the Enteric fever group who showed a significant rise in serum amylase values, only two had evidence of bulky pancreas on ultrasound.

Therefore it may be concluded that the hyperamylasemia and hyperlipasemia were associated with Enteric fever patients but did not show clinical parameter consistent with acute pancreatitis and the significant rise of pancreatic enzymes were seen in enteric fever group with radiological evidence of bulky pancreas.

What does this study add to the existing knowledge?

Salmonella may be considered as a causative agent of subclinical pancreatitis with biochemical and radiological changes. More studies are needed in the future for this association.

Author's contribution

Dr. Dillip Kumar Das: Concept, study design

Dr. Suprabha Shukla: Manuscript preparation

Dr. Mangal Charan Murmu: Data analysis and manuscript preparation

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