Assessment of Raised Alanine Aminotransferase (ALT) and its Relation with Antibiotic Resistance in Enteric Fever Among Children

Irshad Hussain, Sughra Wahid, Maliha Akhtar Qureshi, Fasih Ul Hashmi*

Khan Research Laboratories Hospital, Islamabad Pakistan, *Allama Iqbal Open University, Islamabad Pakistan

ABSTRACT

Objective: To study the abnormality of alanine aminotransferase (ALT) in enteric fever among children and test the association between raised alanine aminotransferase and antibiotic resistance.

Study Design: Prospective longitudinal study.

Place and Duration of Study: Paediatric Department, KRL Hospital, Islamabad, from Oct 2018 to Mar 2020.

Methodology: A total of 100 patients were enrolled as per inclusion criteria. Detailed clinical history was taken, and a physical examination was done. In addition, laboratory tests, i.e., complete blood count, liver function tests and blood culture, were performed to validate the inclusion and exclusion criteria and to collect the data of required variables mentioned in a structured proforma.

Results: Out of 100 culture-proven typhoid fever patients, 57% were male and 43% female. The average age was 7.79 ± 3.3 years. Raised alanine aminotransferase (>45 U/l) was observed in 60%. The alanine aminotransferase was raised in at least 51% of the population having typhoid fever with a *p*-value of 0.035. The results also showed that the proportion of extensive drug-resistant (XDR) typhoid was more significant in patients with raised alanine aminotransferase than in patients with normal alanine aminotransferase with a *p*-value of 0.003.

***Conclusion*:** Based on our study, we concluded that high alanine aminotransferase is related to enteric fever. We also observed that those having raised alanine aminotransferase have more chances of extensively drug-resistant typhoid.

Keywords: Alanine aminotransferase (ALT), Antibiotic resistance, Children, Enteric fever, Extensive drug-resistant typhoid fever (XDR), Typhoid fever.

How to Cite This Article: *Hussain I, Wahid S, Qureshi MA, Hashmi FU. Assessment of Raised Alanine Aminotransferase (ALT) and its Relation with Antibiotic Resistance in Enteric Fever among Children. Pak Armed Forces Med J 2022; 72(3): 811-815. DOI: https://doi.org/ 10.51253/pafmj.v72i3.6067*

INTRODUCTION

Typhoid and paratyphoid fevers, together known as enteric fever, are caused by systemic infection with Salmonella enterica subspecies serovars Typhi and Paratyphi A, B, and C.[1] In 2019, it was estimated that up to 27 million people worldwide suffer from enteric fever every year, of which up to 0.12-0.22 million patients die.[2] A total of 3.6 cases per 100000 person-years are estimated in South Asia, including Pakistan. Among the prevalent countries for enteric fever in Asia, residents of the Sindh and Punjab provinces of Pakistan were at the highest risk of contracting enteric fever.[3]

Several studies show that the incidence of enteric fever is common in children younger than 15 years. For example, in the study of Qamar *et al,* 79% while in that of Stanaway *et al*. 55.9% of the patients were children younger than 15 years 2, 4. In 2017, 63% of the total typhoid cases and 70% of deaths due to typhoid in Pakistan were among children ≤15 years of age.[5]

With the emergence and spread of XDR typhoid fever in Pakistan, its management has become a challenge, raising fears of antibiotics failure globally**.** According to the Pakistan health authorities, the outbreak of XDR typhoid fever in Sindh province from 2016-to 2018 showed 5274 cases (64.4%) of XDR typhoid fever out of the total 8188 typhoid cases.[6]

Enteric fever is a highly contagious infection contracted by taking contaminated food or drink.[7] It is common in places with a lack of clean drinking water, poor sanitary measures, and unhygienic food handlers.[6] It presents as an acute, febrile illness with high-grade fever, abdominal pain, anorexia, nausea or vomiting, loose stools, headache, fatigue, malaise, and cough and with fatal complications like hepatitis, intestinal perforation, pneumonia, encephalopathy or encephalitis.[7]

Although multiple organs are known to be affected by the disease, hepatic involvement is consi-

Correspondence: Dr Irshad Hussain, Department of Peadiatric, KRL Hospital, Islamabad-Pakistan

Received: 07 Jan 2021; revision received: 10 Mar 2021; accepted: 16 Mar 2021

dered the foremost important one, as studies have shown its association with a higher relapse rate.[8]

Enteric fever can cause a wide range of hepatic complications, from hepatomegaly and mild to moderate increase in ALT to severe hepatic involvement simulating acute viral hepatitis.[8] Many studies have reported raised ALT in patients with enteric fever. Pommelet *et al,* conducted a study on 50 children with enteric fever and reported raised ALT in 87% of their patients, while the study of Jain *et al,* showed raised ALT in 46% of the cases.[9,10]

While searching the relation between raised ALT with XDR typhoid fever, we could not find any national or international published study. However, during routine dealing with such patients in our setup, we learned that most of our patients with enteric fever having raised ALT showed extensive drug resistance on blood culture & sensitivity. Therefore, it may be a pioneer study in this regard, both nationally and internationally. Therefore, our study aimed to study the abnormality of ALT in enteric fever among children and test the association between raised ALT with antibiotic resistance.

METHODOLOGY

This hospital-based prospective longitudinal study was carried out from October 2018 to March 2020 at the Pediatric department of KRL Hospital, Islamabad, a tertiary care hospital, recognized by the College of Physicians and Surgeons Pakistan for post-graduate training in many fields, including Paediatrics. The sample size was calculated from the study conducted by Jain *et al,* in Indor (MP), which showed that the raised SGPT (ALT) was observed in 25 out of 54 (46.3%) enteric fever children.[10] We used the WHO sample size calculator for sample size calculation, which was used for sample size calculation for a single proportion.

Keeping the proportion of raised ALT at 0.463 with a level of significance of 5% and absolute precision of 10%, the minimum sample size of our study was 96. So, we took 100 diagnosed cases of enteric fever through consecutive sampling. Data was collected after the approval by the Ethical Review Committee of the hospital with approval certificate No. ERC-18/09/02 and informed consent were taken from the parents/guardians.

Inclusion Criteria: Patients with a history of high-grade fever ≥3 days, diagnosed enteric fever patients from blood culture, and having age less than 14 years were included in this study.

Exclusion Criteria: Patients with a history of liver disease, jaundice, or intake of hepatotoxic drugs were excluded.

Typhoid fever was divided into Multidrug-resistant (MDR) and XDR types based on the blood culture sensitivity. After blood culture reports, cases with simple enteric fever cases were also excluded from the study. MDR strain was labelled if *S. Typhi* was resistant to three first-line drugs (Ampicillin, Chloramphenicol and Trimethoprim-Sulfamethoxazole). XDR was labelled if *S. Typhi* was resistant to all the recommended antibiotics for typhoid fever (First line drugs, Fluoroquinolones and third-generation Cephalosporin).[7]

After detailed clinical history and thorough physical examination, the patients fulfilling the inclu-sion and exclusion criteria were admitted to the hospital. Laboratory investigations, including Full blood count, liver function test, and blood culture and sensitivity of the enrolled patients, were noted in a structured proforma.

All the patients were given IV antibiotics during the hospital stay. They were started on injection Ceftriaxone empirically at admission, except those who were toxic or had ALT ≥2 times were started on injection Meropenem. Once the patients got afebrile for 48 hours, they were discharged on oral antibiotics based on their blood culture sensitivity. All the patients remained uneventful, and all were discharged in good condition.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Descriptive analysis of qualitative and quantitative variables of the study was presented in the form of frequency and percentage and meant and standard deviation, respectively. One sample t-test was used to estimate the proportion of raised ALT in the population. Chi-square and likelihood ratio tests were used to test the proportion of sensitive patients between laboratory parameters and with different signs and symptoms. The *p*-value of ≤0.05 was considered significant.

RESULTS

One hundred patients with culture-proven typhoid fever were enrolled in the study. Out of which 57% were male, and 43% were female. The average age of the patients was 7.79 ± 3.3years ranging from 2 to 14 years. MDR strain was found in 52%, while XDR in

48% of the cases. The signs and symptoms of enteric fever patients were mentioned with respect to the type of sensitivity in the Table-I.

Table-I: Clinical features of pediatric patients with enteric fever.

Signs and Symptoms	Category	Type of Sensitivity n (%)		*p*-value
		Multi Drug Resistance Typhoid	Extensive Drug Resistance Typhoid	
Anorexia	Yes	47 (53.4)	41 (46.6)	0.445
	No	5 (41.7)	7 (58.3)	
Coated Tongue	Yes	42 (51.2)	40 (48.8)	0.739
	No	10 (55.6)	8 (44.4)	
Hepatomegaly	Yes	33 (45.8)	39 (54.2)	0.048*
	No	19 (67.9)	9 (32.1)	
Abdominal Pain	Yes	22 (42.3)	30 (57.7)	0.043*
	No	30 (62.5)	18 (37.5)	
Nausea or Vomiting	Yes	24 (46.2)	28 (53.8)	0.223
	No	28 (58.3)	20 (41.7)	
Splenomegaly	Yes	16 (45.7)	19 (54.3)	0.356
	No	36 (55.4)	29 (44.6)	
Hepatosplenomegaly	Yes	14 (45.2)	17 (54.8)	0.359
	No	38 (55.1)	31 (44.9)	
Pallor	Yes	15 (50)	15 (50)	0.793
	No	37 (52.9)	33 (47.1)	
Loose stools (Diarrhea)	Yes	13 (54.2)	11 (45.8)	0.807
	No	39 (51.3)	37 (48.7)	
Headache	Yes	9 (50)	9 (50)	0.851
	No	43 (52.4)	39 (47.6)	
Abdominal Tenderness	Yes	4 (25)	12 (75)	0.018*
	No	48 (57.1)	36 (42.9)	
Abdominal Distension	Yes	5 (41.7)	7 (58.3)	0.445
	No	47 (53.4)	41 (46.6)	
Constipation	Yes	4 (57.1)	3 (42.9)	0.778
	No	48 (51.6)	45 (48.4)	
Cough	Yes	4 (57.1)	3 (42.9)	0.778
	No	48 (51.6)	45 (48.4)	
Jaundice	Yes	4 (57.1)	3 (42.9)	0.778
	No	48 (51.6)	45 (48.4)	
Congested Throat	Yes	2 (50)	2 (50)	0.935
	No	50 (52.1)	46 (47.9)	
Altered mental Status	Yes	2 (66.6)	1 (33.4)	0.606
	No	50 (51.5)	47 (48.5)	
Meningism	Yes	2 (100)	0 (0)	0.103
	No	50 (51)	48 (49)	

The proportion of Hepatomegaly, Abdominal Pain, and Abdominal tenderness was significantly different between MDR and XDR at a 5% significance level. On the other hand, the proportion of abdominal pain, tenderness and hepatomegaly were high in XDR. Hence, we can differentiate the patients with MDR and XDR through these signs and symptoms.

Among the laboratory parameters, raised ALT was significantly different with respect to the drugs' sensitivity. Raised ALT from the reference range (>45 U/L) was found in 60% of cases, out of which 68.3% had ALT between 46-90 U/L, 18.3% had ALT levels between 90-135 U/L, 6.7% had ALT level between 136-450 U/L and in 6.7% it was > 450 U/L.The one-sample t-test was used to estimate the percentage of enteric fever pediatric patients having raised ALT. Our sample result concluded that in the confirmed cases of enteric fever, at least 51% of patients had raised ALT with a p-value of 0.035. Out of 100 patients, 48% had XDR typhoid fever, of which 36 (75%) had raised ALT, and just 12 (25%) had normal ALT. The proportion of XDR was higher in patients with raised ALT than the others with normal ALT, with a p-value of 0.003 (Table-II).

Thrombocytopenia was found in 39% of patients in our sample. Based on sample results, we concluded that at least 30% of patients with enteric fever were also affected by thrombocytopenia, with a p-value of 0.034. The thrombocytopenia was observed in 15 out of 52 (28.8%) in MDR. In contrast, in XDR, this percentage

was 24 out of 48 (50%), significantly higher at a 5% level of significance with a p-value of 0.03. (Table-II).

After one time discharged from the hospital, only two patients (2%) were readmitted as relapse cases after three weeks of the initial recovery.

Table-II: Association between blood culture sensitivity and laboratory variables.

Laboratory Variables	Categories	Type of Sensitivity		*p*-value
		Multi Drug Resistance Typhoid	Extensive Drug Resistance Typhoid	
Raised ALT	Yes	24 (40)	36 (60)	0.003*
	No	28 (70)	12 (30)	
Hyperbilirubinemia	Yes	9 (47.4)	10 (52.6)	0.653
	No	43 (53.1)	38 (46.9)	
Anemia	Yes	29 (45.3)	35 (54.7)	0.074
	No	23 (63.9)	13 (36.1)	
Thrombocytopenia	Yes	15 (38.5)	24 (61.5)	0.03*
	No	37 (60.7)	24 (39.3)	
Leukopenia	Yes	3 (42.9)	4 (57.1)	0.615**
	No	49 (52.7)	44 (47.3)	
Leukocytosis	Yes	12 (60)	8 (40)	0.423
	No	40 (50)	40 (50)	

**Significant at 5% level of significance, ** Likelihood ratio test applied due to expected frequency less than 5*

DISCUSSION

Fever is considered a consistent feature of enteric fever in children, almost in 97-100% of cases.[11] In our study, fever was present in 100% of the patients at admission, as this is the inclusion criteria in our study. A similar methodology was adopted in the study conducted by Jain *et al.* and Ahmed which included only confirmed cases of enteric fever in their research; hence, the fever was in 100% of their sample 10, 12. In most studies where researchers studied enteric fever, patients, have a very high percentage of High-Grade Fever (HGF). In the studies conducted by Qamar *et al,* and Shafqat *et al,* HGF was found in 97% and 100% of the patients, respectively.[4,13]

A study on enteric fever conducted by Pommelet *et al,* showed clinical features of the patients in which abdominal pain (50%), nausea (18%), vomiting (48%), constipation 6%, jaundice (12%), abdominal tenderness (48%), hepatomegaly (26%) and splenomegaly (6%) were recorded.[9] Similarly, in another study, Jain *et al,* showed the signs and symptoms in children with enteric fever were cough (48.14%), vomiting (51.85%), diarrhoea (14.81%), abdominal pain (66.66%), abdominal distension (25.92%) and jaundice (3%).[10]

The results of the above two reference studies are similar to ours except for the proportion of hepatomegaly and splenomegaly, which was observed higher at 72% and 35%, respectively. At the same time, abdominal tenderness was 16%, abdominal distension 12%, and cough was reported in just 7% of cases.

Pommelet *et al,* showed that anaemia was observed in 66%, leucopenia in 4%, thrombocytopenia in 18%, and ALT 60%.[9] Similarly, raised ALT was observed in 46.3% of cases in the study of Jain *et al,* and 56.6% in Ahmed.[10,12] In a few other studies, raised ALT was observed in 68.3% and 42%, while high bilirubin was found in 12.4% and 10%.[13,14]

The laboratory features in our study were also the same as those mentioned in the reference studies, except for thrombocytopenia at 39%, which was slightly higher with respect to the reference studies' results.[9,13,14] In addition, many other researchers recently studied enteric fever and observed signs, symptoms, and laboratory features in the adult population.[13-15]

In our study, we also examined the blood culture sensitivity. XDR typhoid fever was spotted at 48% in our sample. Therefore, we further investigated the patients with respect to blood culture sensitivity. In XDR patients, the percentage of raised ALT and thrombocytopenia was significantly high compared to MDR patients.

Extensive drug-resistant typhoid fever is a global health concern and needs to be addressed through simple but effective health measures. It can be achieved by providing safe drinking water, improving sanitation, awareness of hygiene and hand washing, and most importantly, through typhoid vaccination programs.[16-18] Vaccination has a significant role in decreasing the burden of the disease and stalling the emergence of resistant strains.[19,20] The Ty21a (an oral vaccine) and injectable Vi polysaccharide vaccines are not recommended in children younger than two years.[16] However, the conjugated Typbar-TCV is safe to use in infants older than six months and was approved by WHO in January 2018.[18,21,22]

Based on the results of our study, we recommend multi-centre studies to see the similar association of raised ALT with XDR typhoid fever and molecular level study to find the mechanism of this association.

CONCLUSION

There is liver involvement in pediatric enteric fever patients with high ALT and hepatomegaly. Therefore, we may conclude that the patients having raised ALT have more chances of XDR typhoid fever. So, children with a clinical diagnosis of enteric fever with significant raised ALT can be given the drugs recommended for XDR typhoid fever (carbapenems and azithromycin) as the first line before the availability of blood culture sensitivity. However, multicenter studies must make proper guidelines for starting these drugs earlier based on raised ALT. It can result in hindering complications of the disease and significantly reduce the number of hospital admission days.

Conflict of Interest: None.

Authors' Contribution

IH: Writing of the manuscript, corresponding author, SW: Study conception, design, supervision, MAQ: Data collection, critical revision of the article, FUH: Data analysis, interpretation.

REFERENCES

1. Harris JB, Brooks WA. Typhoid and paratyphoid (enteric) fever. In: Magill AJ, Ryan ET, Hill DR, Solomon T, editors. Hunter's tropical medicine and emerging infectious diseases. 9th ed. Philadelphia: Elsevier 2013. 568-576. [Internet] Available at: https://jhu.pure.elsevier.com/en/publications/typhoid-and-paratyphoid-enteric-fever-4
2. Stanaway JD, Reiner RC, Blacker BF, Goldberg EM, Khalil IA, Troeger CE, et al. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Infect Dis 2019; 19(4): 369-381.
3. Antillón M, Warren JL, Crawford FW. The burden of typhoid fever in low- and middle-income countries: A meta-regression approach. PLoS Negl Trop Dis 2017; 11(2): e0005376.
4. Qamar FN, Yousafzai MT, Sultana S, Baig A. A retrospective study of laboratory-based enteric fever surveillance, Pakistan, 2012-2014. J Infect Dis 2018; 2018(Suppl-4): S201-S205.
5. World Health Organization Eastern Mediterranean Regional Office (WHO EMRO). Pakistan first country to introduce new typhoid vaccine into routine immunization programme. Available from: http://www.emro.who.int/pak/pakistannews/pakistan-first-country-to-introduce-new-typhoid-vaccine-into-routine-imm-programme.html. [Accessed on December 3, 2020].
6. World Health Organization. Typhoid fever-Islamic Republic of Pakistan. Available from: https://www.who.int/csr/don/27-december-2018-typhoid-pakistan/en/. [Accessed Dec 3, 2020].
7. Medical Microbiology & Infectious Disease Society (MMIDS). Typhoid Management Guidelines. Available from: https://www.mmidsp.com/typhoid-management-guidelines-2019/. [Accessed on April 6, 2020].
8. Khosla SN, Singh R, Singh GP. The spectrum of hepatic injury in enteric fever. Am J Gastroenterol 1988; 83(4): 413-416.
9. Pommelet V, Mariani P, Basmaci R, Tourdjman M, Morin L, Gaschignard J, et al. Enteric fever among children: 50 cases in a French tertiary care centre. J Travel Med 2018; 25(1). [Internet] Available at: https://pubmed.ncbi.nlm.nih.gov/30060197/
10. Jain H, Arya S, Ikram S, Mandloi R, Xess V. An assessment of liver function test in typhoid fever in children. Int J Pediatr Res 2016; 3(7): 493-497.
11. Azmatullah A, Qamar FN, Thaver D, Zaidi AK, Bhutta ZA. Systemic review of the global epidemiology, clinical and laboratory profile of enteric fever. J Glob Health 2015; 5(2): 020407.
12. Ahmad S. Assessment of liver function tests in children with typhoid fever: A hospital bases study. J Nepalgunj Med Coll 2019; 17(2): 21-22.
13. Shafqat F, Iqbal Z, Khan AA, Iqbal F, Alam A, Butt AK, et al. Hepatic Involvement with typhoid fever. Proceeding Shaikh Zayed Post-Grad Med Inst 1994; 8(1-2): 38-42.
14. Srikanth N, Kumar S. Liver function tests abnormalities in enteric fever- A recent update. Int Org Sci Res J Dent Med Sci 2015; 14(3): 17-24.
15. Abro AH, Abdou AM, Gangwani JL, Ustadi AM, Younis NJ, Hussaini HS. Hematological and Biochemical changes in typhoid fever. Pak J Med Sci 2009; 25(2): 166-171.
16. Azhar A, Khalid A. The Implications of Extensive Drug-resistant Typhoid Fever: A Case Report. Cureus 2019; 11(6): e5032.
17. Klemm EJ, Shakoor S, Page AJ, Qamar FN, Judge K, Saeed DK, et al. Emergence of an extensively drug-resistant Salmonella enterica serovar Typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins. mBio 2018; 9(1): e00105–00108.
18. Syed K, Saluja T, Cho H, Hsiao A, Shaikh H, Wartel T, et al. Review on the Recent Advances on Typhoid Vaccine Development and Challenges Ahead. Clin Infect Dis 2020; 71(Suppl 2): S141-S150.
19. Parry CM, Ribeiro I, Wailia K, Rupali P, Baker S, Basnyat B. Multidrug resistant enteric fever in South Asia: unmet medical needs and opportunities. BMJ 2019; 364(1): k5322.
20. Qamar FN, Azmatullah A, Kazi AM, Khan E, Zaidi AK. A three-year review of antimicrobial resistance of Salmonella enterica serovars Typhi and Paratyphi A in Pakistan. J Infect Dev Ctries 2014; 8(8): 981-986.
21. World Health Organization. WHO. Typbar TCV from Bharat Biotech, world's first typhoid conjugate vaccine prequalified by WHO. Available from: https://www.who.int/medicines/news/2017/Bharat-Biotech-TypbarTCV-WHO-PQ-Press-Release-Global-Final.pdf?ua=1. [Accessed on May 25, 2020].
22. Rasheed MK, Hasan SS, Babar ZD. Extensively drug-resistant typhoid fever in Pakistan. Lancet Infect Dis 2019; 19(3): 242-243.