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An association between typhoid fever and Age, Sex and Blood Phenotypes ABO and Rh among Children – a Study in a Tertiary Care Hospital, Dhaka, Bangladesh

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***Abstract**: A case-control type of study was conducted over a period of 6 (Six) months following approval in the Department of Paediatric of Dhaka Shishu Hospital, Dhakato assess the association the association betweenTyphoid fever and age, sex and blood phenotypes ABO and Rh among children. The sample size for this study was 240 (120 cases and 120 controls). Out of 120 participants in each group 79.2% cases and 68.3% controls respondents were mother of the children. In both groups most of the study participants were from younger age group ≤ 5 years; 63.3% of cases and 80.8% of control. Mean ± SD of age were (5.1042 ± 3.11575) for cases and (3.5951 ± 2.50218) for controls Age distribution of the children was statisticallysignificant where p -value was 0.0001 for t-test and 0.01151045 for chi-square (p<0.05).Most of the children were urban dwellers 89.2% cases and 96.7% controls. The difference was statistically significant (χ^2 = 4.134, p = 0.04202989) and 35.0% of cases drunk supply water in comparison with only 13.3% of controls. There was positive association of drinking supply water with typhoid fever (RR=2.6316 and OR=3.5101 and χ^2 =12.85; p-value = 0.000337). Crowdie habitat was reported by 38.3% of Cases and 10.8% of Controls. There may be strong association of crowdie condition of habitat with typhoid fever (RR = 3.5463; OR = 5.1269 and χ^2 = 20.41; p =0.0001). There was no positive association of different blood group but when each group was individually considered, blood group 'B' indicated there may be some positive association (RR = 1.4505, OR = 1.8713 and χ^2 = 4.66, p = 0.030873). Only 3.3% children in case group and 4.2% in control group had Rh negative blood group. Widal test result was positive in 83.3% of cases; the remaining 16.7% were found to be Widal negative. The difference was statistically significant (χ^2 = 18.22, p =0.0001. Blood culture was done in only 50 (41.7%) participant from the case group; out of them negative culture was obtained in 4 individuals, the difference was statistically significant (χ^2 = 52.585, p = 0. (P< 0.05). Typhoid fever has a strong relation with socio-economic conditions and blood phenotypes.*

***Key words:** Typhoid fever, blood phenotype ABO, Rh*

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I. Introduction

Typhoid fever is a systematic clinical syndrome by certain salmonella organism. It encompasses produced by certain *Salmonella typhi*, and Para typhoid fever is caused by *Salmonella paratyphi*.[1] Typhoid fever is rare in industrial countries but continues to be a significant public-health issue in developing countries.[2] A detail study of the disease was presented by Bretonneau (1826) who identified the intestinal lesions. The name of enteric was given by Louis (1829) to distinguish it from typhus fever. Budd (1856) pointed out that the disease was transmitted through the excreta of patients. Elberth (1880) described the typhoid bacillus, and Gaffky (1884) isolated it in pure culture. Its causative role was confirmed by Metchnikoff and Bessedka (1900) by infecting experimentally.[2] The incidence, mode of transmission and consequences of typhoid fever differs significantly in developed and developing countries. The incidence has decreased markedly in developed countries. In the United States about 400 cases of enteric fever are reported each year giving an annual incidence of less than 0.2% per 1,00,000 population which is similar to that in western, Europe and Japan.[3]

Typhoid fever is transmitted via the faecal oral route or urine. This may take place directly through soiled hands, contaminated with faeces or urine of cases or carrier or indirectly by ingestion of contaminated water, milk, food or through flies.[4] Typhoid fever is an important cause of morbidity and mortality in many developing countries. In 2000, it was estimated that over 2.16 million episodes of typhoid occurred worldwide, resulting in 216 000 deaths, and that more than 90% of this morbidity and mortality occurred in Asia.[5] Typhoid fever is endemic in all parts of Bangladesh and still constitutes a significant health hazard. The resistance of *Salmonella enterica* subspecies *enterica* serovar typhi (*S*. Typhi) to chloramphenicol was first reported in India from Kerala, where a substantial outbreak took place in 1972. Since then multidrug-resistant strains of *S. typhi* have escalated into a worldwide problem. The steadily increasing multidrug resistance in *S. typhi* strains is a cause of grave concern in Bangladesh, where such strains are endemic in many parts.[6] Typhoid fever may occur at any age, but it is considered to be a disease mainly of children and young adults. In endemic areas, the highest rate occurs in children aged 8-13 years. In a recent study from slums of Delhi, it was found that contrary to popular belief, the disease affects even children aged one to five years. About 20-30% of typhoid fever cases are children below ten years.[3] According to Indonesia Demographic and Health Survey (2002 – 03) report prevalence of typhoid fever in children under five years of age was 26%.[8]

Human ABO blood group have been associated with susceptibility to certain infection.[9,10] It has been observed that some historical pandemics have influenced the current distribution of the ABO gene frequencies in different part of the world.[11] Various adaptations of people with different phenotypes of ABO blood group are considered to be the result of screening mutagens. Immunologists explain this by the presence of some pathogens of antigens similar to antigens of human blood.[12]

During long-term observations it is found that the holders of blood groups O, A, B, and AB have different predisposition to diseases. Statistical studies confirm that holders of blood group A get sick of viral hepatitis more often, and O-type people are less resistant to influenza virus.[12] According on the blood group, children under 7 years old usually get sick with diseases such as paratyphoid fever, rubella, scarlet fever, colibacillosis, and among children with blood group A it fails to develop immunity against smallpox even at re-vaccination.[12]

Purification of supply water, improvement of basic sanitation and promotion of food hygiene are essential measures to interrupt transmission of typhoid fever.[13]

So, there is a great need for the people to be aware of all the consequences of typhoid fever and it is the most important area where the health personnel should take serious measures to create an understanding and awareness among the public regarding typhoid fever and its risk factors. Typhoid fever continues to be a major health problem in Bangladesh. In the topical areas however, it is endemic in many places, due to the low standard of living, unprotected water supply and unhygienic methods in the preparation and handling of food. Many children with Typhoid fever are admitted in the hospital with various complications.

Few studies have been performed worldwide about these particular topics of Typhoid fever. But in Bangladesh such studies is practically absent. If these can be done then probably we will be able to increase the awareness about Typhoid fever so they may enjoy a good quality of life

II. Objectives

General objective:

1. To assess an association between typhoid fever and age, sex and blood phenotypes ABO and Rh among children.

Specific objectives:

1. To find out the socio-economic status of children with typhoid fever.
2. To find out the socio-demographic pattern of children of typhoid fever especially with food habit, sanitation, drinking water, personal hygiene and nutritional status.
3. To assess the incidence of Typhoid fever among children of different age groups.

III. Materials and Methods

We conducted a case-control study among the child admitted with fever in Dhaka Shishu (children) hospital. After getting written permission from the concerned authority of the selected Institute the patients were approached. The study included children of paediatric age group both male and female. For each baby detailed history of age, sex, socio-economic information, and blood group were recorded. Subjects were grouped on the basis of age, sex, blood phenotypes, ABO and Rh into the case (Typhoid positive) and controls (Typhoid negative). Then assessed association between fever and socio-economic, demographic and environmental conditions. 240 samples were purposively selected for the study which was divided into 120 cases and 120 controls. 1 to 18 years old children and toddlers were included in the study who were suffering from typhoid as case and suffering from any febrile illness, other than typhoid fever as control group. Participants suffered from meningitis, febrile convulsion, immune-compromised children, unwillingness to participate were excluded from the study. Prior to data collection, a questionnaire was designed for this study by reviewing all the available questionnaire of previous studies. The questionnaire was finalized following pretesting. Prior to answering the semi-structured questionnaire, every respondent had to undersign an informed written consent. All the data were collected and recorded systematically in a questionnaire and was analyzed using computer software SPSS - 17 (Statistical Package for Social Sciences).

IV. Results

This study was undertaken with the objective to assess the association between Typhoid fever and age, sex and blood phenotypes ABO and Rh group among children. A total of 240 children, out of whom 120 were suffering from typhoid fever (cases) and 120 were non-typhoid (controls), were included in this study.

Table: 1 Demographic characteristics of the respondents (n=240)

Respondents	Case (%)	Control (%)	χ2	P-value
Gender			3.069	0.07979854
Male	20.8	31.7		
Female	79.2	68.3		
Age groups of the children			4.009(t-test)	0.0001
≤ 5	63.3	80.8		
5-10	26.7	16.7		
10>	10.0	2.5		
Religion			1.709	0.42549589
Muslim	95.0	90.9		
Hindu	5.0	8.3		
Others	0	0		
Educational status of the respondents			48.024	0. 0001
Illiterate	4.2	0.8		
Primary	30.8	7.5		
Secondary	21.7	28.3		
Higher secondary	15.0	51.7		
Graduate	20.0	11.7		
University	8.3	0.0		
Occupation of the respondents			10.676	0.00480547
Job	57.5	65.8		
Business	28.3	32.5		
Others	14.2	1.7		

The most of the caregiver of the children were female, 79.2% in cases and 68.3% in controls. χ2 = 3.069, df = 1, p-value = 0.07979854; which means there are no any association between different gender groups. By age distributions of both groups were in the '≤ 5 years' age group; 63.3% of Cases group and 80.8% of Controls group were in the age group. Mean ± SD of age was calculated to be, (5.1042 ± 3.11575) for Cases group and for Controls group (3.5951 ± 2.50218). The p-value was 0.0001 for t-test and 0.01151045 for chi-square, which means there was an association in age distribution between the groups. ($p<0.05$). It is illustrated that more than half of the participants in both Cases group [83 (69.2%)] and Controls group [66 (55.0%)] were Males. Male and Female ratio was about 2.25:1 in cases and 1.2:1 in controls. There might be a positive association between male gender and typhoid fever. Accordingly, the difference in male-female distribution between the groups was statistically significant (χ2 = 4.284, df = 1; p-value = 0.03847271) ($p<0.05$).

Table-2: Socio-economic and environmental condition of the respondents (n=240)

Respondents	Case (%), n=120	Control(%), n=120	Statistical Analysis	χ2	P-value
≤ 10,000	27.5	16.7		0.160	0.87
10,000-20,000	51.7	61.6			
> 20,000	20.8	21.7			
Mean ± SD	5.1042 ± 3.11575	3.5951 ± 2.50218			
Area of Residence					
Urban	89.20	96.70		4.134	0.04
Rural	10.80	3.30			
Water consumption					
Boiled water	61.7	76.7	RR=0.8044; 95% CI: 0.6663-0.9713	5.28	0.02
			OR=0.4894; 95% CI: 0.2647-0.9047		
Tube well	3.3	10.0	RR=0.33; 95% CI: 0.0981-1.11	3.62	0.05
			OR=0.3071; 95% CI: 0.0857-1.1013		
Supply water	35.0	13.3	RR=2.6316; 95% CI: 1.4923-4.6405	12.85	0.0003
			OR=3.5101; 95% CI: 1.7283-7.1291		
Habitat					
Neat	61.7	89.2	RR=3.5463; 95% CI: 1.9158-6.5645	20.41	0.0001
Crowdie	38.3	10.8	OR=5.1269; 95% CI: 2.4237-10.8452		
Sanitation					
Sanitary	95.9	98		4.186	0.04
Hanging	3.3	1			
Open	0.8	1			
Food Habits					
Raw food	18.1	5.8		7.37	0.006
No raw food	89.9	94.2			

Above table shows that low incoming family was more in cases [33 (17.5%)] than controls [20 (16.7%)]. Mean ± SD of monthly income was (17,350.00 ± 8,799.016) in cases and (17,175.00 ± 6,847.268) in controls. There was no association between the groups (t-test = 0.16, p-value = 0.873 and χ2 = 3.523, df = 2, p-value = 0.17178699). Most of the children were urban dwellers (89.2% cases and 96.7% controls); the difference was statistically significant (χ2 = 4.134, p = 0.04202989). 35.0% of cases drink supply water in comparison with only 13.3% of controls. There was positive association of drinking supply water with typhoid fever (RR=2.6316 and OR=3.5101 and χ2 =12.85; p-value = 0.000337). Crowdie habitat was reported by 38.3% of Cases and 10.8% of Controls. There may be strong association of crowdie condition of habitat with typhoid fever (RR = 3.5463; OR = 5.1269 and χ2 = 20.41; p < 0.0001). Out of total 240 participants 5 cases used non-sanitary latrine (χ2 = 4.186, p = 0.04075916). 18.3% of cases and 5.8% of controls were found to have the practice of 'Eating raw or under cooked food'

Table-3: Laboratory findings of all study participants (n=240)

Blood Group	Cases (n=120) Percent	Controls (n=120) Percent	Statistical calculations
O	16.7	27.5	RR=0.6073; 95% CI: 0.3535-1.0433 OR=0.5285; 95% CI: 0.2665-1.0482 $\chi^2 = 3.39$; p-value = 0.065593
A	25.0	25.0	RR=1.0; 95% CI: 0.5272-1.6162 OR=1.0; 95% CI: 0.6187-1.8967 $\chi^2 = 0.0$; p-value = 1.0
B	48.3	33.3	RR=1.4505; 95% CI: 1.0287-2.0452 OR=1.8713; 95% CI: 1.0565-3.3144 $\chi^2 = 4.66$; p-value = 0.030873
AB	10.0	14.2	RR=0.7042; 95% CI: 0.3293-1.5061 OR=0.6714; 95% CI: 0.2837-1.5889 $\chi^2 = 0.83$; p-value = 0.362273

It is illustrates that in a gross calculation, there was no statistically difference in distribution of ABO blood group of the children between cases and controls ($\chi2 = 6.125$ df = 3; p-value = 0.10568457). However, when each group was individually considered, blood group 'B' indicated there may be some positive association with typhoid fever [RR = 1.4505 (95% CI: 1.0287-2.0452) and OR = 1.8713 (95% CI: 1.0565-3.3144)]. The difference was statistically significant $\chi2 = 4.66$, df = 1; p-value = 0.030873. ($p < 0.05$)

Table-4: Laboratory findings of all study participants (n=240)

Blood group	Cases (n=120) Percent	Controls (n=120) Percent	Statistical calculations
Rh typing of Blood			
Positive	96.7	95.8	RR=0.7857; 95% CI: 0.1909-3.2341
Negative	3.3	4.2	OR=0.7784; 95% CI: 0.1791-3.3828
			χ^2=0.112 df=1; p-value = 0.73787855
Widal Test			
Positive	83.3	0	$\chi^2 = 18.22$ df = 1; p-value =0.0001
Negative	16.7	100	
Blood Culture			
Not done	58.3	100	$\chi2 = 52.585$; df = 2; p-value = 0
Positive	38.3	0	
Negative	3.3	0	

Above Table shows that only 3.3% children in case group and 4.2% in control group had Rh negative blood group. There was no positive association [RR = 0.7857 (95% CI: 0.1909-3.2341) and OR = 0.7784 (95% CI: 0.1791-3.3828. Widal test result was positive in 83.3% of cases; the remaining 16.7% negative in case group and all (100.0%) of the controls were found to be Widal negative in control group. The difference of Widal test result between the groups was statistically significant $\chi2 = 18.22$, df = 1; p-value <.0001. ($p < 0.05$). Participants were included on the basis of their blood culture and/or Widal test findings; patients who had already done either one or both of the tests were considered for this study. Thus, blood culture was done in 50 (41.7%) participants from the case group; out of them negative culture was obtained in 4 (3.3%) individual and the remaining 46 (38.3%) were culture positive. The difference was statistically significant $\chi2 = 52.585$, df = 2; p-value = 0. ($p < 0.05$)

V. Discussion

This study was aimed to assess the association of Typhoid fever with age, sex and blood phenotypes ABO and Rh among children. A total of 120 cases (typhoid fever) and 120 controls (non-typhoid) were included in this study. In both groups most of the study participants were in the '≤ 5 years' age group , Mean ± SD of age was, (5.1042 ± 3.11575) for cases and for controls (3.5951 ± 2.50218), p-value was 0.0001 for t-test and 0.01151045 for chi-square, which means there was statistically deference in age distribution between the groups ($p<0.05$). A study in Dhaka Metropolitan Area found, the age-specific incidence rate was highest for the 0–4 years age group (277 cases). More than half of the participants in both groups (69.2% cases and 55.0% controls) were Males. Male: Female ratio was about 2.25:1 in cases and 1.2:1 in controls. There was positive association with male gender and typhoid fever (RR=1.2582 and OR=1.8383). Accordingly, the difference in male-female distribution between the groups was statistically significant ($\chi2 = 4.284$, df = 1; p-value = 0.03847271) ($p<0.05$). Valenzuela CY and Herrera P found a mild susceptibility to males. The male-female ratio of typhoid cases was found to be 1.36 by Dewan AM, Comer R, Hashizume M and Ongee ET, suggesting that in this population males are either more susceptible to typhoid, or more likely to present for hospital treatment, than females. Statistical differences of educational status of the respondent is significant $\chi2 = 48.024$, df = 5, p-value = 0.0001. There was a statistically significant difference between the groups ($\chi2 = 4.134$, df = 2, p-value = 0.04202989) of occupational differences. In a study conducted in Dhaka Metropolitan Area (DMA) of Bangladesh, the Student's t test revealed that there is no significant difference on the occurrence of typhoid between urban and rural environments ($p>0.05$) but there was a positive association of drinking supply water with typhoid fever [RR=2.6316 (95% CI: 1.4923-4.6405); OR=3.5101 (95% CI: 1.7283-7.1291) and $\chi2$ =12.85; p-value = 0.000337]. There statistically significant difference between the groups in the source of drinking water ($\chi2$ = 14.75 df = 2; p-value = 0.00062673). In Kamalapur, Dhaka, Bangladesh, cases were 7·6 times more likely than controls to report drinking any unboiled water at home during the 14-day exposure period (mOR 7·6, 95% CI 2·2–26·5, P=0·002). There may be strong association of crowdie condition of habitat with typhoid fever [RR = 3.5463 (95% CI: 1.9158-6.5645) and OR = 5.1269 (95% CI: 2.4237-10.8452)]. $\chi2$ = 20.41; p-value < 0.0001. The difference was statistically significant between the two groups ($\chi2$ = 4.186 and p-value = 0.04075916). Ram PK, et.al. found that, cases were less likely than controls to use a latrine for defecation (mOR 0·3, 95% CI 0·1–1·0, P=0·053). Out of 120 participants in each groups 18.3% of cases and 5.8% of controls were found to have the practice of 'Eating raw or under cooked food'statistically strong positive association of eating raw or under cooked food and typhoid fever [RR = 3.1552 (95% CI: 1.2933-7.6977) and OR = 3.6379 (95% CI: 1.3656-9.6914)]$\chi2$ = 7.37 df = 1; p-value = 0.006632). In Kamalapur, cases were 3·6 times (95% CI 1·1–11·2, P=0·03) more likely to report eating food from a restaurant or street stall during the 14-day exposure period than their matched controls. On gross calculation, there was no statistically difference in distribution of ABO blood group of the children between cases and controls ($\chi2$ = 6.125 df = 3; p-value = 0.10568457). However, when each group was individually considered, blood group 'B' indicated there may be some positive association with typhoid fever [RR = 1.4505 (95% CI: 1.0287-2.0452) and OR = 1.8713 (95% CI: 1.0565-3.3144)]. The difference was statistically significant $\chi2 = 4.66$, df = 1; p-value = 0.030873. Valenzuela CY and Herrera P found that, the B allele conferred protection to females. Herrera P et.ai. Tested a hypothesis that blood phenotype B is associated to typhoid fever either directly or interacting with other phenotypes of the Rh or MNSs blood systems.38 Only 3.3% children in case group and 4.2% in control group had Rh negative blood group. There was no positive association [RR = 0.7857 (95% CI: 0.1909-3.2341) and OR = 0.7784 (95% CI: 0.1791-3.3828)]; nor any statistically difference in distribution of the blood group of the children between cases and controls ($\chi2$=0.112 df=1; p-value = 0.73787855). Valenzuela CY and Herrera P reported the CDe haplotype (or the RH3 phenotype, mostly CDe/CDe) was associated with protection against Salmonella in both sexes, while cDE (or RH7, mostly cDE/cDE, and RH8, mostly cDE/cde) was associated with susceptibility to typhoid fever. Widal test result was positive in 83.3% of cases; the remaining 16.7% of cases and all (100.0%) of the controls were found to be Widal negative. The difference of Widal test result between the groups was statistically significant $\chi2 = 18.22$, df = 1; p-value <.0001. Blood culture was done in 50 (41.7%) participant from the case group; out of them negative culture was obtained in 4 (3.3%) individual and the remaining 46 (38.3%) were culture positive. The difference was statistically significant $\chi2 = 52.585$, df = 2; p-value = 0.

Limitations of the study

This study was conducted in a tertiary care hospital in Dhaka. So the study findings may not reflect the exact scenario of all around the country regarding typhoid fever. The current study was conducted among 240 febrile children, not a large study to draw a definite conclusion about typhoid fever. Very limited study so far found regarding fever associated with environmental conditions, not only in Bangladesh but also in the whole world. So, difficulty was faced to compare the findings to other research findings

VI. Conclusion and Recommendations

Risk of typhoid fever is higher in children aged ≤ 5 years. Male are more susceptible to develop Typhoid fever has positive association with the risk factors, such as, drinking supply water, eating raw or under cooked food, crowdie habitat and, use non-sanitary latrine. So, our recommendations are to Improvements of water-supply infrastructure or promotions of household disinfection of water represent important measures to reducing the burden of typhoid fever in endemic areas. This was a small-scale study done at a single centre over a brief period of time. A large scale, multi-centre study over long duration will give a complete picture on association of typhoid fever with various factors

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