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THE ROLE OF LONG TERM ANTIMICROBIAL THERAPY IN THE DEVELOPMENT OF ACQUIRED APLASTIC ANEMIA

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Abstract:

Background: *Aplastic anemia (AA) is a rare hematological disorder and it carries very poor prognosis associated with high mortality rate. It has been remains an important public health concern for Asian population as it affects 2-3 fold more as compare to other part of world. Exposures of specific drugs, chemicals and others have been connected with an AA etiology. We aimed to examine the association of antimicrobial drugs exposures with AA.* ***Methods:*** *We done a case-control study in Karachi, Pakistan. Cases were patients showed at least two blood lineages depressed on bone marrow biopsy. Controls were without hematological disorder selected from outpatient department. For each case four age-sex matched control were enrolled. Information associated to socio-demographics and exposure to antibiotics was collected through a questionnaire by in personal interview. We computed odds ratios (OR) and 95% confidence intervals (CI).* ***Results:*** *We identified 191 cases (median age 26, range 1-66 years) and 696 controls. Predominate were male 67% (n=131), most affected age group 16-30 years. When the cases were compared with the controls, positive associations with antimicrobial drugs with AA were observed (49.7% exposure rate in cases, 29.3% in control: OR 2.3, 95% CI 1.7-3.3: P value 0.00). No statistically significant association were found when each drug i.e. Trimethoprim/Sulfamethoxazole, chloramphenicol, tetracycline, beta-lactam and macrolides used in univariate analysis.* ***Conclusion:*** *No association identified with use of antibiotics. However OR 2.3 with use of antibiotics showed connection with AA.*

Key Words: *Aplastic Anemia, antimicrobials, chronic use, exposure.*

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INTRODUCTION:

Idiosyncratic drug-induced aplastic anemia is an undesirable reaction against few drugs due to presence of abnormal susceptibility in certain individuals [1]. It depends on multiple internal and external factors like amount of drug exposure, physical and chemical properties of drug, genetic variation of recipient for drug metabolism [2]. Drug-induced aplastic anemia has variable and insidious onset, symptoms appear from days to months after exposure of the drug, with the average time period of about 6.5 weeks [3]. Drug-induced aplastic anemia was initially reported in the 1930s, associated with arsenicals and aminopyrines [4]. Epidemiologic studies documented that certain anti-infective, non-steroidal anti-inflammatory drug, anti-thyroid, diuretics, anticonvulsants, antihistamine and other miscellaneous drug have been implicated in the incidence of aplastic anemia [5]. Among the anti-infective drugs, chloramphenicol is the most notorious drug which often has been reported as a risk factor of aplastic anemia globally. The risk of chloramphenicol associated aplastic anemia is approximately 1 in 20,000 among patients treated with chloramphenicol [7]. Chloramphenicol was reported to be attributed for 22% cases of aplastic anemia while 44% of the drug-induced cases of aplastic anemia due to its frequent use probably [8]. The time between exposure and onset of symptoms of aplastic anemia was few months. Thiazide group of diuretics and Mebendazole from the anti-helminths were also reported to cause aplastic anemia [9]. This current research was carried out to determine association between repeated exposure to antimicrobial drugs and risk of developing aplastic anemia.

METHODOLOGY:

A case-control study was carried out in Karachi (capital of province Sindh), Pakistan. It has over 15 million population residing in 18 different towns. The participants included patients accessing healthcare in different hospitals from January 2014 to December 2017.

Sample size 885 (177 cases, 708 controls) were calculated by using StatCal of Epiinfo by using 7% exposure among control. With adding of 10% non-responders the final sample size was 974 (195 cases, 779 controls).

The eligible cases had at least two of the three criteria with hypocellular bone marrow (1) hemoglobin <100mg/dl (2) platelets count 50x 10^9 /L (3) neutrophil count 50x 10^9 /L. For each case four age-sex matched control were selected from different outpatient department of hospitals (e.g. patient with trauma, eye or ENT infection etc.)

We collected information on the drug exposures based on recall using a questionnaire. The drugs included were based on thorough literature review, which were previously identified as risk factors for developing aplastic anemia. An opinion from experts was also taken for including drug families in the questionnaire. An exposed subject was defined as one who had history of drug prescription 29-180 days before initial diagnoses. Exposure history less than one month was excluded because temporality could not be determined. Information on timing, frequency and duration (including use extending back beyond 6-month period) of use was recorded. Dosage information could not be determined due to poor recall of participants. Furthermore, it was found during pilot testing that drug names could not be recalled and hence information for drug families was taken.

Statistical Package for the Social Sciences (SPSS) version 22 were used for data analysis. Frequency distribution for cases and controls according to their exposure status was calculated. Univariate logistic regression model were used to find out the association of AA with exposure to antimicrobial drugs. Odds ratios were considered statistically significant with 95 percent confidence interval (CI) and p value < 0.05.

RESULTS:

The participation rate for AA cases was 98% (n=191) and for the healthy controls 89% (n=696). Among cases median age was 26 (range 1-66 years), predominate were male 67% (n=131) and most affected age group 16-30 years. High number was living in rural area 57% (n=107)

Among cases 95 (49.7%) were found to be exposed to antimicrobial drugs chronically while 96 (50.3%) were found to be non-exposed. In controls 204 (29.3%) gave history of chronic use of antibiotics while no such overuse was reported by 492 (70.7%) subjects. These findings shows positive associations of antimicrobial drugs with AA (OR 2.3, 95% CI 1.7-3.3: P value 0.00).Table 1

Use of each drug or group were analyzed during the exposure period are given in Table 2. Among these all were high but not statistically significant trimethoprim/sulfamethoxazole (OR 1.5, 95% CI 0.97-2.62: P value 0.06) chloramphenicol (tropical) (OR 1.8, 95% CI 0.94-3.73: P value 0.06), for ß-lactams (OR 1.9, 95% CI 0.93-3.69: P value 0.07), and tetracycline (OR 1.8, 95% CI 0.97-3.66: P value 0.05). For trimethoprim/sulfamethoxazole, the etiologic fraction of 5% for tropical use of

chloramphenicol, the corresponding estimates were 1.5%.

Table 1. **Use of antimicrobial drugs and risk of aplastic anemia in Karachi (N=887)**

Use of Antimicrobial	Cases (n=191)	Control (N=696)	OR	95% CI Lower – Upper	P value
Yes	95	204	2.3	1.7-3.3	0.00
No	96	492			

Table 2. **Antimicrobial Drug Use in Days 29 Through 180 Before Admission, Karachi (N=887)**

	Cases (n=191)	Control (N=696)	OR	95% CI Lower – Upper	P value
Trimethoprim/Sulfamethoxazole					
Yes	25	60	1.5	0.97-2.62	0.06
No	161	636			
Chloramphenicol (Tropical Use)					
Yes	13	26	1.8	0.94-3.73	0.06
No	181	670			
Tetracycline					
Yes	14	28	1.8	0.97-3.66	0.05
No	177	668			
Beta Lactam					
Yes	13	25	1.9	0.93-3.69	0.07
No	178	671			
Macrolides					
Yes	12	25	1.7	0.88-3.65	0.09
No	179	671			
Others					
Yes	18	40	1.7	0.95-3.02	0.06
No	175	656			

DISCUSSION:

Several studies illustrated a possible association between use of chloramphenicol and aplastic anemia [10]. In the current study we didn't found any link with the chloramphenicol, which may be associated with the limited (only tropical) use. We currently found significant association between the antimicrobial agents use with aplastic anemia that was inconsistent to a study results from Thailand with no significant association [11]. There are studies that have individually tested many other drugs with positive association. The results data from Kaufman et al showed the associated risk for aplastic anemia with trimethoprim [12]. However in current research we didn't observe relationship of trimethoprim with illness. This may be due to difference in study setting, sample size and information bias. Aplastic anemia is a potential rare fatal side effect of tetracycline group of antibiotics reported in patients with preexisting renal dysfunctions due to marrow toxicity possibly. Aplastic anemia reported with other antimicrobial groups like sulfonamides was already globally accepted [13]. Although the need of antimicrobial therapy is the utmost solution for infections but what it can done for the miss use or over use prevention in the community is to promote the culture and sensitivity tradition in the healthcare system all around the provinces of the country. This study deserves further investigation to investigate its role of antibiotics with association of AA.

CONCLUSION:

We could not find any association between the antimicrobial therapy and the development of aplastic anemia.

RECOMMENDATIONS:

It is recommended that physician based prospective studies should be arranged to further rule out the possibility of drug associated aplastic anemia. The drug regulatory authority should strictly develop guidelines for the use of antimicrobial drugs.

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