High incidence of aplastic anemia is linked with lower socioeconomic status of Indian population

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ABSTRACT

Background  The incidence of aplastic anemia (AA) is common in Asia than in western countries.

Methods  In a case–control study conducted at a tertiary care hematology center in northern India, 102 patients of AA and 201 controls of other blood disorders (OBD) were included. Sociodemographic data and exposure to drugs, toxins and radiation were collected from the study population using a standard questionnaire. Socioeconomic status (SES) was classified based on a calculated standard of living (SL) score. Univariate and multivariate analyses were carried out to delineate the factors associated with incidence of AA.

Results  Patients with AA were significantly younger than those in control groups (mean age 27.5 ± 12.3 years, P < 0.01). The mean SL score was significantly lower in AA group (26.76 ± 12.88, P < 0.01) than in the controls. The mean monthly family income was significantly lower in AA group than in the controls (83.3% with monthly income <8000 INR, P < 0.01). On univariate analysis, AA group with lower SL score had 3 times higher odds of having the disease (odds ratio 3.41, 95% confidence interval 1.72–6.79, P < 0.0001) compared with the controls. On multivariate analysis, young age and low SES were found to be significantly associated with AA.

Conclusions  Lower SES is associated with higher incidence of AA in Indian population.

Keywords  blood and immune disorders, chronic disease, environment

Introduction

Aplastic anemia (AA) is a bone marrow failure syndrome characterized by peripheral blood pancytopenia and hypocellular bone marrow, in the absence of abnormal infiltrate or increased marrow reticulin. The disorder can be congenital or acquired and generally affects the age group between 15 and 25 years, with a second smaller peak after 60 years. Constitutional factors are present only in a minority of patients with AA.1 Hence, most of the patients who have acquired AA are labeled as idiopathic. Various genetic, environmental, immunological factors have been proposed to be responsible for this condition.2 Its incidence varies from 1.4 to 14 cases per million population and is higher in the Asian countries than West.3-5 The reason for this discrepancy is unclear, although variation in the socioeconomic status (SES) of the population is implicated. Consistent with this hypothesis, most developing countries in Asia have common factors like lower SES and higher exposure to pesticides, chemicals, toxins and pathogens which have been implicated in the pathogenesis of AA.6 In India, systematic national studies describing the incidence of AA are lacking, although a prior study in the pediatric population predicted the incidence of AA to be around 6.8 per million in Lucknow region.6 With lower SES being common in India, it is plausible to think that the incidence of AA would be higher. However, there is

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paucity of data about AA and its association with SES and environmental factors in India. In the present study, we have aimed to delineate the impact of these factors and determine its association with AA.

Materials and methods

We performed a case–control study with AA patients attending hematology clinic at a tertiary care hospital in Northwest India between July 2006 and December 2007.

Patient selection

Cases

All patients with age >12 years, diagnosed with AA based on peripheral blood cytopenia and bone marrow (BM) hypocellularity as suggested by the following criteria—(i) BM cellularity <25% or 25–50% with <30% of residual hematopoietic cells and (ii) at least two of the following peripheral blood counts: absolute neutrophil count (ANC) <500/µl, Platelet count <20 000/µl or hemoglobin <10 g/dl.

Controls

Two groups of patients attending the same clinic were included as controls. (i) Patients with immune thrombocytopenic purpura (ITP); (ii) patients with other blood disorders (OBD).

Patient charts were reviewed for obtaining baseline demographic information, clinical history and examination findings, lab results like complete blood count and bone marrow examination. The study participants were interviewed with a structured questionnaire individually by a physician (G.V.). The questionnaire included demographic details pertaining to SES that included education, type of house, source of drinking water, toilet facilities, agricultural land, livestock, etc. The SES was based on NFHS (National Family health survey) classification. Scores were given to individual variables for calculating standard of living score (SL score) according to NFHS criteria. Minimum score was zero and the maximum score was 67. Patients with scores of 0–14, 15–24 and 25–67 were categorized into low, medium and high SES, respectively. Educational standard was classified as illiteracy (patients who cannot read and write in at least one language), Grade 1 through 5 as primary level, Grade 6 through 10 as middle level and upto Grade 12 as secondary level. Patients with higher education were further classified as graduates and post graduates. Informed consent was obtained from all study participants prior to their enrollment, and the study was conducted in compliance with declaration of Helsinki. The study was approved by the institutional review board.

Data on exposure

Using the questionnaire provided, we estimated the number of patients who had exposure to the following risk factors in the last 6 months.

1. Tobacco use—Data on the number of patients who were current tobacco users were collected. Data on patients who had used tobacco in the form of smoking (current smokers) versus chewing (current tobacco chewers) were obtained separately.

2. Alcohol—Data on number of patients who had regular consumption (more than two times per week) of alcohol were obtained.

3. Pesticides—Data on exposure to pesticides like organophosphates and organochlorides were obtained from patients. Exposure to pesticides was defined as any form of patient contact with the pesticide, regardless of the pattern of exposure (frequent or occasional) or the involvement of patient directly in applying the pesticide.

4. Drugs—Data on exposure to drugs known to be associated with AA such as chloramphenicol, sulfonamides, phenylbutazone, indomethacin, diclofenac, naproxen, phenytoin, carbamazepine and phenothiazines were obtained from the patients.

5. Radiation exposure—Data on exposure to radiation (accidental, occupational, radiographic and therapeutic) were obtained from the patients. Occupational/accidental exposure to radiation was defined as patient’s contact with radiation during their daily work or exposure to radiation accidentally. Patients were enquired about their occupation such as working in atomic plants or in industries handling materials with radiation hazard. If the patient had exposure to radiation, frequency of exposure was further enquired. If the patient had exposure to radiation not as a part of their occupation, it constituted accidental exposure to radiation and its frequency and duration were enquired.

Statistical analysis

The sample estimates for this study were calculated using descriptive statistics. Quantitative variables were described using their mean and 95% confidence interval. Qualitative variables were described as proportions. Baseline sociodemographic variables were compared among the study groups using χ² and Fisher’s exact tests. Odds ratios were calculated for these variables in univariate analysis. Quantitative variables among cases and two groups of controls were compared using one-way ANOVA with post hoc analysis (Tukey’s), wherever significant relationships were found. Kruskal–Wallis test was used to compare the three groups for variables that were not
normally distributed. Multivariate logistic regression analysis was carried out to identify factors that were associated with higher chances of AA diagnosis. All results were two-tailed, and \( P < 0.05 \) was taken as significant.

**Results**

A total of 303 patients were included in the study with 102 patients of AA (cases), 100 patients of ITP (first control group) and 101 patients with OBD (second control group). The OBD group included patients with chronic myeloid leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma and myelodysplastic syndrome. Baseline demographic characteristics of the cases and control are described in Table 1. Patients with AA were significantly younger compared with control groups (median age 24 versus 34 years, \( P < 0.01 \)). There were more males than females in AA (58.8%) and OBD groups (60.4%), whereas ITP group had more females (67%) (\( P = 0.04 \)). Significant number of AA patients were in low SES than in both control groups (\( P = 0.001 \)) (Table 1). Similarly, AA group had more number of patients with low monthly income (83.3% with monthly income < 8000 INR, \( P < 0.01 \)) and lower mean SL score (26.76 ± 12.88, \( P < 0.01 \)). Compared with the control group, AA group had more patients who were unmarried (51%, \( P < 0.01 \)).

Both cases and controls had smaller and statistically non-significant number of patients with antecedent history of exposure to pesticides, drugs, tobacco, alcohol and radiation. On further analysis of various factors, age, SL score and monthly family income were found to be significantly associated with AA as shown in Tables 2 and 3. When a pair wise analysis (post hoc analysis) was done in the three study groups, we found that the mean age of AA group was less than that of the control groups (Table 2). The mean SL score and monthly family income was also lower in patients with AA compared with the control group (Table 2).

The association of AA with educational status, smoking, tobacco chewing, alcohol, radiation exposure and insecticide exposure was not found to be significant. On univariate analysis, AA group with lower SES had higher odds of having the disease (odds ratio 3.41, 95% confidence interval (CI) 1.72–6.79, \( P < 0.0001 \)) compared with higher SES and middle SES (odds ratio 2.92, 95% CI 1.20–7.12, \( P = 0.01 \)) (Table 3). There was a trend towards increased risk of AA with decreasing monthly family income <8000 INR (odds ratio 4.35, 95% CI 1.76–10.7, \( P = 0.001 \)). On multivariate analysis, age (odds ratio 0.96, CI 0.94–0.98, \( P < 0.0001 \)) and low SES

<table>
<thead>
<tr>
<th>Variable</th>
<th>AA (n = 102) (%)</th>
<th>ITP (n = 100) (%)</th>
<th>OBD (n = 101) (%)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>24</td>
<td>28</td>
<td>40</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60 (58.8)</td>
<td>33 (33)</td>
<td>61 (60.4)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Female</td>
<td>42 (41.2)</td>
<td>67 (67)</td>
<td>40 (39.6)</td>
<td></td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (n = 41)</td>
<td>24 (23.5)</td>
<td>4 (4)</td>
<td>13 (12.8)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Medium (n = 43)</td>
<td>14 (13.7)</td>
<td>12 (12)</td>
<td>17 (16.8)</td>
<td></td>
</tr>
<tr>
<td>High (n = 219)</td>
<td>64 (62.8)</td>
<td>84 (84)</td>
<td>71 (70.4)</td>
<td></td>
</tr>
<tr>
<td>Monthly income (&lt;8000 INR)</td>
<td>85 (83.3)</td>
<td>60 (60)</td>
<td>67 (66.3)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Total standard of living score</td>
<td>26.76 ± 12.88</td>
<td>35.48 ± 10.27</td>
<td>29.54 ± 11.35</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried (n = 109)</td>
<td>52 (51)</td>
<td>36 (36)</td>
<td>21 (20.8)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Married (n = 194)</td>
<td>50 (49)</td>
<td>64 (64)</td>
<td>80 (79.2)</td>
<td></td>
</tr>
<tr>
<td>Radiation exposure (n = 2)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>—</td>
<td>0.22</td>
</tr>
<tr>
<td>Pesticide exposure (n = 6)</td>
<td>4 (3.9)</td>
<td>2 (2)</td>
<td>—</td>
<td>0.18</td>
</tr>
<tr>
<td>Drugs (n = 5)</td>
<td>4 (4)</td>
<td>1 (1)</td>
<td>—</td>
<td>0.06</td>
</tr>
<tr>
<td>Current smokers (n = 19)</td>
<td>8 (7.8)</td>
<td>3 (3)</td>
<td>8 (7.9%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Current tobacco chewers (n = 4)</td>
<td>3 (2.9)</td>
<td>1 (1)</td>
<td>—</td>
<td>0.07</td>
</tr>
<tr>
<td>Current alcohol use (n = 16)</td>
<td>8 (7.9)</td>
<td>6 (6)</td>
<td>2 (2)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

AA, aplastic anemia; ITP, idiopathic thrombocytopenic purpura; OBD, other blood disorders; INR, Indian national rupees ($1 = INR 62).

\* \( P < 0.05 \).
were found to be significantly associated with AA (Table 4). Odds of developing AA were over two times (odds ratio 2.32, 95% CI 1.10–4.87, \( P = 0.02 \)) among patients with low SES in reference to high SES group.

### Discussion

AA is characterized by bone marrow hypoplasia with resultant pancytopenia. Ever since the initial description by Paul Ehrlich in 19th century, the etiology of AA has been unclear. An immunological attack to the bone marrow precursor cells along with a complex interplay of genetic and environmental factors is postulated to be responsible for the disease.8–13

In the present study, we found that AA in India is more common in patients with younger age and lower SES as depicted by their low SL score and a low per capita income. The number of patients with exposure to factors implicated in AA pathogenesis like radiation, toxic medications and pesticides was relatively low to make definite conclusion about its etiological role in the present study.

Discrepancies in the incidence of AA between Asia and western parts of the world suggest that environmental factors play a major role in the pathogenesis of AA. In Europe and Israel, the incidence of AA is around 2 per million per year as suggested by the International Agranulocytosis and Aplastic Anemia Study (IAAAS).14 Studies from Thailand (3.9 per
millon in metropolitan Bangkok area and 5 per million cases in khonkaen area) and Malaysia (5 per million cases in Sabah area) have shown much higher incidence of AA compared with the west. Lower SES commonly seen in this population is an indirect indicator of increased exposure to environmental factors that have been implicated in the pathogenesis of AA.

Our study portrays the Indian perspective of the role of socioeconomic and environmental factors in association with AA. Of note, SES classification in India is highly complicated, involving many groups and subgroups. This was measured in our present study using the NFHS-II (National Family Health Survey) criteria which ensured uniformity and reliability of the data. Also, it is important to note that personal income is a sensitive subject in India, and people are often reluctant to reveal this information, which could have been responsible for the lack of its statistical significance on multivariate analysis. In our study, AA was more commonly seen in males, similar to the study from Thailand. However, the IAAAS study had more number of females with AA compared with males and the Barcelona study had nearly equal number of males and females with AA. Hence, there is a heterogeneity of gender preponderance of AA according to various studies, although one might expect that AA being an immunologically mediated disorder is more common in females. Patients with AA had a nearly uniform distribution of educational status in our study compared with ITP patients who had a higher level of education. We decided to have two control groups for the study to learn the influence of socioeconomic factors in various disease processes and compare them with AA. While AA and ITP are benign disorders, inclusion of malignant hematological conditions added strength to the control group by ensuring comparison against a broad spectrum of hematological conditions.

The limitations of the present study include representation of the data from a single tertiary care referral center and the recall bias among patients about their exposure to drugs and other environmental factors. This could have been responsible for the lack of association of these factors with AA in our study. However, this is one of the larger studies in recent times from India highlighting the importance of socioeconomic factors in relation to the disease incidence. Future national studies from India would be able to provide more information about the role of environmental factors and its association with AA.

| Table 4 Multivariate analysis of sociodemographic risk factors in relation to AA |
|-----------------|-----------------|-----------------|-----------------|
| **Risk factor** | **Odds ratio** | **95% CI** | **P-value** |
| Age | 0.96 | 0.94–0.98 | <0.0001* |
| Male gender | 0.55 | 0.92–2.60 | 0.09 |
| Monthly family income | 0.00 | 1.00–1.00 | 0.07 |
| Standard of living (Ref: High reference group) | | | |
| Low SES | 2.32 | 1.10–4.87 | 0.02* |
| Medium SES | 0.78 | 0.36–1.67 | 0.53 |

SES, socioeconomic status.

*P < 0.05.

References
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