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Aplastic Anaemia: Experience with Management in a Resource Limited Setting

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Authors' contributions

This work was carried out in collaboration among all authors. Author GIO designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors EGK and C managed the analyses of the study. Author GIO managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Aplastic anaemia is syndrome of bone marrow failure characterized by peripheral pancytopenia and loss of haemopoietic stem cells in the bone marrow. It is a relatively rare disease with high risk of death if untreated.
Objective: To evaluate the incidence, management and outcome of aplastic anaemia in children, over a four-year period, at the University of Port Harcourt Teaching Hospital(UPTH), Nigeria.
Subjects and Methods: This was a retrospective study of case notes of all children with anaemia and bone marrow aspiration reports suggestive of aplastic anaemia in the Haematology and Oncology Units of the Department of Paediatrics, UPTH, from 1st January 2015 to 31stDecember 2018.Data retrieved included bio data, clinical and laboratory profile, and outcome. Data entry and analysis were done using the Statistical Package for Social Sciences (SPSS) version 22. Data analysis were done using descriptive statistics (proportions and frequencies) and presented in prose and frequency tables. Mean and standard deviations of quantitative data were obtained.
Results: A total of six children were treated for a plastic anaemia during the period under review, giving an annual incidence of 0.0049 cases per year. Their ages ranged from 3 to 11 years (mean 8.2±3.7), with a male to female ratio of 2:1.At presentation, they had a mean (±SD) packed cell volume of 15± 3.2%, white cell count of 2.72± 0.76x 10^9/L, Absolute neutrophil count (ANC) of 0.25± 0.17 x 10^9/L, and platelets count of 17.33± 21.36 x 10^9/L. They all (100%) had severe aplastic

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anaemia at diagnosis. Among others, they received transfusion support with unbanked fresh whole blood, platelet concentrates, antibiotics, antifungal and antiviral, oral cyclosporine and intravenous methyl-prednisolone. They were all blood transfusion dependent. The mean survival from diagnosis was 7.3± 3.08 months.
None of the patients benefited from bone marrow transplantation and anti-thymocyte immunoglobulin. Mortality rate was 83.3% and major cause of death was sepsis with thrombocytopaenic bleeding.
Conclusion: Aplastic anaemia is rare with short survival rate. There is need for the Federal Government to ensure that bone marrow/stem cell transplantation centres are available and accessible across the country, and to make drugs such as cyclosporine and anti-thymocyte immunoglobulin affordable to ameliorate the condition.

Keywords: Aplastic anaemia; children; Port Harcourt; Nigeria.

1. INTRODUCTION

Aplastic anemia (AA) is a serious form of bone marrow failure which, if not treated, is associated with very high mortality. It is characterized by pancytopenia and hypocellular bone marrowwith resultant serious clinical manifestations such as chronic anemia, hemorrhage, and infection [1]. It has also been linked to environmental or occupational toxins such as benzene, viral infection, contaminated water sources, and exposure to animal fertilizers and agricultural pesticides [2,3].

The incidence of AA in the Western countries is approximately 2 per million per year, but it occurs more commonly in the Far East, with a 2 to 3-fold higher [4]. The incidence varies according to geographical location. With the advent of immunosuppressive therapy (IST) with antithymocyte globulin (ATG) and allogeneic stem cell transplantation (SCT) in the 1980–90s, improved outcome has been reported in several series, with a 5-year overall survival approximating 70–80% [5].

Several variables, including age, disease severity and choice of the initial treatment have been found to influence the outcome of patients with severe AA [6]. However, treatment by allogeneic stem-cell trans-plantation or immune suppression has improved the prognosis in recent years, and greater than 75% of patients arenow expected to have long-term survival with either therapy.Unfortunately, this is not the case in Nigeriawhere facilities for bone marrow/stem cell transplantation are not available and immunosuppressive drug therapy with antithymocyte globulin and cyclosporine are also not readily accessible to patients with AA. We therefore decided to evaluate the incidence, management and outcome of aplastic anaemia in children, over a four-year period, in our Hospital in Port Harcourt, Nigeria.

2. SUBJECTS AND METHODS

The study was conducted at the University of Port Harcourt Teaching Hospital (UPTH) which is located in Rivers State, southern region of Nigeria. It is a tertiary care hospital which serves as a major referral centre for patients in Port Harcourt and its environs.

This was a retrospective study of all children with anaemia and bone marrow aspiration reports suggestive of aplastic anaemia in the Haematology and Oncology Units of the Department of Paediatrics. TheCase notes of all patients with established diagnosis of aplastic anaemia from 1st January 2015 to 31st December 2018 were reviewed.

Exclusion criteria for the study included: patients who were receiving chemotherapy for cancer/ radiotherapy, patients with lymphomas with bone marrow involvement, and patients with hypersplenism.Variables studied included age, gender, date of diagnosis, haematologic parameters at presentation (White blood cell count, Haematocrit, Platelet count) and outcome.

The widely accepted criteria described by Camitta et al. was used for defining the severity of AA [7]. Thus, severe disease was defined as the presence in two of three blood counts of an ANC<0.5×10^9/L, platelet count <20×10^9/L, and reticulocytes <1%; whereas extreme neutropenia (ANC<0.2×10^9/L) defined very severe AA.All other cases were defined as moderate.The duration of survival was taken as the interval between date of diagnosis and death, or date when the patient was last seen on follow up.

Data entry and analysis was done using the Statistical Package for Social Sciences (SPSS) version 22. Data analysis were done using descriptive statistics (proportions and frequencies) and presented in prose and

frequency tables. Mean and standard deviations of quantitative data were obtained.

3. RESULTS

A total of six children were treated for a plastic anaemia over the period under review, giving an annual incidence of 0.0049 cases per year. Their ages ranged from 3 to 11 years (mean 8.2±3.7), with a male to female ratio of 2:1(Table 1).

Table 1. Age and gender distribution of children with aplastic anaemia

Age(years)	Male	Female	Total
0-<5	0	1	1
5-<10	0	1	1
10-<15	1	3	4
Total	1	5	6

All the patients presented with fever, paleness of the body and bleeding from the mouth and nose, while the duration of the illness ranged from 2-6 weeks prior to presentation.

The haematological profile of the subjects are as shown in Table 2. The mean (±SD) packed cell volume at presentation was15± 3.2%, white cell count 2.72± 0.76x 10^9/L, ANC0.25± 0.17 x 10^9/L, and platelets 17.33± 21.36 x 10^9/L.Blood film reports of all the 6 cases reviewed uniformly showed normocytic, normochromic anaemia with leucopenia, neutropenia with predominant lymphocytes. Platelets were reduced but with normal morphology.There were no appreciable dysplasia.

Bone marrow aspirate of the 6 patients were markedly hypocellular. Erythrocytes and neutrophils were markedly reduced.Lymphocytes were the majority of the cells seen. Plasma cells were reduced and megakaryopoiesis were severely decreased.

The diagnosis of severe AA was made for all 6 patients. They were managed with transfusion support with unbanked fresh whole blood, platelet concentrate, antibiotics, antifungal, antiviral and oral cyclosporine and intravenous methyl-prednisolone. All patients were blood transfusion dependent. The mean survival from diagnosis was 7.3± 3.08 months, while the longest duration of follow up of patient was 1year. Late presentation was an important issue in the majority of cases.

None of the patients benefited frombone marrow transplantation and anti-thymocyte immunoglobulin. Mortality rate was 5(83.3%) while sepsis with thrombocytopaenic bleeding were the major causes of death.

4. DISCUSSION

The incidence of aplastic anaemia in this study was0.0049 cases per year. Depending on time and geographical location, earlier epidemiological studies have shown a wide variation in incidence of AA [8]. In the 1960–70s, very high incidences (6 to 10 cases of AA per million per year) were reported in series from Europe and USA [8]. In addition, an association with toxic agricultural substances was found in some studies [8-10], which was later confirmed in a study from Spain published in 2008, with an overall incidence of 2.34 per million per year [11]. In some studies, the incidence has been reported to be slightly higher among females [5,8], whereas data from Turkey and Bangkok have instead shown a male predominance [5,8], which agrees with our study.However, Krista et al in Sweden reported no gender difference in incidence of AA [8].

The age range of affected patients in this study shows that the school age population is largely affected. Comparing to other recent studies, the mean survival of patients with AA in this series is low. This is most likely due to bleeding and sepsis as a result of markedly low platelet and absolute neutrophil counts at presentation. Furthermore, laboratory parameters at presentation showed severe AA at diagnosis. This could also be a contributory factor to the short duration of survival.

Managing thrombocytopaenic bleeding presents a distinct challenge when adequate platelet support services are lacking, and red cell transfusion are not helpful and may indeed aggravate the situation and provoke further bleeding [11]. This is because red cell diapedesis is heightened in thrombocytopaenic states and microvascular capillary bleeding is thus worsened.With platelet concentratesnot readily available, the management of AA in this study was suboptimal.

The mean survival from diagnosis was 7.3± 3.08 months.When optimal management facilities and therapeutic options are available, survival rates are significantly higher with reports of five- year survival rate of 70-90% and 51% at fifteen years [2].

Table 2. Haematological parameters of children with aplastic anaemia at presentation

Patients	PCV	WBC (x10 ^{9}/l)	Neutrophil (%)	Lymphocyte (%)	ANC (x10 ^{3}/l)	Platelet (x10 ^{9}/l)	Ret (%)
1	14	3.76	17.5	78.3	0.02	3	1.93
2	18	3.20	22	72.9	0.47	16	1.02
3	12	3.1	6.2	88.9	0.16	11	0.11
4	17	2.12	5	94	0.15	7	0.14
5	19	2.6	9	88	0.38	60	0.08
6	10	1.7	16	84	0.32	7	0.17
Mean	15±3.27	2.72± 0.76	12.6± 6.86	84.35± 7.14	0.25± 0.17	17.33± 19.50	0.58± 0.75

The non-availability of bone marrow/stem cell transplantation facilities, which is a major contributory factor to the very short survival recorded in this study, has been previously reported by Arewa et al in a 1992 Nigerian review [12]. Bone marrow transplantation is now considered as the definitive management modality for a number of haematologic disorders including AA [13]. It is thus unfortunate that centres offering this treatment modality is scarce in a country with a population of over 150 million inhabitants.

Table 3. Duration of survival of the patients with aplastic anaemia

Patients	Duration of survival (in months)
1	4
2	10
3	6
4	5
5	7
6	12
Mean	7.3± 3.08

Immunosuppressive therapy is an important alternative to bone marrow/stem cell transplantation in the management of AA. Effective immunosuppressive drugs such as antithymocyte globulin was scarce and not affordable. Nonetheless,steroids such as prednisolone, known to be ineffective in achieving the expectedeffect, was used as adjunct in the management of these patients and in the absence of the potent immunosuppressive ones such methyl prednisolone. Also, there wasscarce transfusion support service for the supply of the muchneeded blood component (red cell and platelet concentrates) required for transfusing the patients as necessary. Platelet concentrates were not readily available, necessitating the use of fresh whole blood in the management of severe thrombocytopenia.

5. CONCLUSION

Aplastic anaemia is rare with short survival rate. There is need for Federal Government to ensure that bone marrow/stem cell transplantation centres are available and accessible across the country, and to make drugs such as cyclosporine and anti-thymocyte immunoglobulin affordable to ameliorate the condition.

CONSENT

As per international standard, parental written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

Ethical clearance was obtained from the Ethical Committee of the UPTH.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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