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Aplastic Anaemia in Uyo, South-South Nigeria: A Review of Cases in a Tertiary Hospital

Idongesit Samuel Akpan[1*], Sony-Shakins Jimmy Umotong[1], Eniefiok Hezekiah Jumbo[1] and Ajayi Oyedele Oyewumi[2]

[1]Department of Haematology, University of Uyo Teaching Hospital, Uyo, Akwa Ibom State, Nigeria.
[2]Department of Histopathology, University of Uyo Teaching Hospital, Uyo, Akwa Ibom State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Aplastic anaemia (AA) is an uncommon condition characterized by pancytopaenia and loss of haemopoietic stem and progenitor cells in the bone marrow. Without treatment, it is inexorably fatal. However with the availability of current definitive treatment options, patients' clinical outcome is improving globally.
Objective: To determine the prevalence and outcome of aplastic anaemia in children and adults, over a five-year period, at University of Uyo Teaching Hospital (UUTH), Uyo, Nigeria.
Methods: This was a prospective study. We reviewed the cases of acquired aplastic anaemia managed in our hospital over a period of five years. Data analysis was done using the Statistical Package for Social Sciences (SPSS) version 23.
Results: A total of twelve cases were treated for aplastic anaemia during the period under review, giving an annual incidence of 2.4 cases per year. The ages of the patients ranged from 12 to 56 years (mean 27.8 $\pm$ 12.3 years) with a male to female ratio of 2.1. At presentation, they had a haemotocrit of 14.58$\pm$3.11, white cell count of 2.38$\pm$0.44, absolute neutrophil count of 0.30$\pm$0.17, platelet count of 18.42$\pm$6.35, reticulocyte count of 0.93$\pm$0.67. Nine (75%) patients had severe AA

**Corresponding author: E-mail: idongakpan200326@yahoo.com;*

while three (25%) patients had very severe AA at diagnosis. Management consisted of transfusion support with unbanked packed red cells and platelet concentrate, antibiotics, antifungal and antiviral agents, cyclosporin and methylprednisolone. The patients were all blood transfusion dependent. None of the patients benefited from bone marrow transplantation and anti-thymocyte globulin. The mean survival was 10.58±2.19 months with a mortality rate of 0.24%.

Conclusion: There is compelling need for the Federal Government to ensure that bone marrow/stem cell transplantation centres are available and accessible nationwide, and to make drugs such as cyclosporin and anti-thymocyte globulin affordable or free to reduce the high mortality associated with the condition.

Keywords: Aplastic anaemia; pancytopaenia; cyclosporine; anti-thymocyte globulin; bone marrow transplantation.

1. INTRODUCTION

Aplastic anaemia (AA) is a form of bone marrow failure characterized by pancytopaenia and a hypocellular marrow, with resultant distressing clinical manifestations such as chronic anaemia, infection, and thrombocytopaenic bleeding. AA may arise from several etiopathogenetic mechanisms. It could be inherited, idiopathic or primary acquired or due to the accumulated effects of noxious exposure to drugs, viruses and toxins, however the most common type is idiopathic or primary aplastic anaemia [1].

The incidence of aplastic anaemia shows considerable variation worldwide. It has been reported to be low in Europe, North America and Brazil, and relatively high in the Asian population [2]. This variability in incidence rates may mirror differences in exposure to environmental triggers like viruses, drugs and chemicals, genetic and ethnic background, diagnostic criteria and study designs. In Africa, there are limited population based studies on aplastic anemia. Patients with aplastic anaemia generally have varying clinical courses. A small proportion of the patients may have mild symptoms with an uneventful clinical outcome, while the vast majority present with severe complications that pose a formidable treatment challenge especially in resource-constrained settings found in most parts of Africa [3].

Several factors, including age at diagnosis, disease severity and choice of the initial treatment have been documented to influence the outcome of patients with severe AA [4]. The case fatality rate of severe AA is high although treatment by allogeneic stem cell transplantation or immunosuppression has improved the prognosis substantially in the last couple of years, and more than 75% of patients are now expected to have long-term survival with either therapy [2]. Regrettably, the reverse is the case in Nigeria where facilities for bone marrow/stem cell transplantation are unavailable and immunosuppressive therapy with anti-thymocyte globulin and cyclosporin is not affordable or readily available to patients with AA.

Despite the growing global public health significance of AA, data on the burden of this disease in Nigeria are few and far between. This study, the first in our environment, was therefore carried out to document the prevalence and outcome of treatment of patients with AA in our hospital, a tertiary level of care in Uyo, Akwa Ibom State, South-South Nigeria.

2. METHODOLOGY

2.1 Study Site

The study was conducted at the University of Uyo Teaching Hospital (UUTH), Uyo, South-South region of Nigeria. The hospital provides specialized healthcare services to patients in Akwa Ibom State and those of neighbouring states.

2.2 Study Design

This was a five-year (January, 2016 – December, 2020) prospective study of children and adults with anaemia, bone marrow aspiration and trephine biopsy reports suggestive of aplastic anaemia in the Haematology and Oncology units of the Departments of Paediatrics and Haematology.

2.3 Data Collection

Information obtained included age, gender, date of diagnosis, haematologic parameters at presentation (haematocrit, white blood cell count,

platelet count, reticulocyte count), date of death or date lost to follow up.

2.4 Inclusion and Exclusion Criteria

Only patients with established diagnosis of aplastic anaemia were included in the study. Patients on cancer chemotherapy, radiotherapy and those with hypersplenism or lymphomas with bone marrow involvement were excluded. The time-honoured criteria described by Camitta et al. [5] was used for defining the severity of AA. Severe disease was defined as the presence of two out of three of the following: an absolute neutrophil count (ANC) <0.5 x $10^{9/}$l, platelet count <20 x $10^{9/}$l, and reticulocytes <1%; while severe neutropenia (ANC <0.2 x $10^{9/}$l) defined very severe aplastic anaemia. All other cases were defined as moderately severe. Duration of survival was taken as the interval between the date of diagnosis and death or date patient was last seen on follow up.

2.5 Statistical Analysis

The data obtained were analyzed using the Statistical Package for Social Sciences (SPSS) version 23 and presented in prose and frequency tables.

3. RESULTS

A total of twelve patients were treated for aplastic anaemia over the period under review, giving an annual incidence of 2.4 cases per year. The age range of the patients was from 12 to 56 years (mean 27.8 + 12.3 years) with a male to female ratio of 2.1 (Table 1).

The patients presented with fever, weakness, easy fatigability, bleeding from one or more orifices; the duration of illness prior to presentation ranged from 2 – 8 weeks.

The haematological parameters of the subjects at presentation are as shown in Table 2. The mean (+SD)packed cell volume (PCV) was 14.58 + 3.11%, white cell count (WBC) 2.38 + 0.44 x $10^{9/}$l absolute neutrophil count (ANC) 0.30 + 0.17 x $10^{9/}$l, platelet count 18.42+6.35x$10^{9/}$l, reticulocyte count 0.93+ 0.67%. Peripheral blood film reports of the twelve patients uniformly showed normocytic, normochronic anaemia, occasional microcytic cells, leucopenia, neutropenia, lymphocytosis and thrombocytopaenia. There were no abnormal cells or dysplastic changes.

Bone marrow of the patients were spicular and showed marked hypocellularity. The lacunar spaces and haemopoietic cells were extensively replaced by fat cells. Erythropoiesis, myelopoiesis and megakaryopoiesis were markedly depressed; the residual cellularity were mostly lymphoid cells, mast cells and macrophages. Plasma cells were not increased. There were no foreign cells.

Nine (75)% and three (25%) of the patients presented with severe AA and very severe AA respectively at diagnosis. They were managed with unbanked packed red cells, platelet concentrates, antibiotics, antifungal and antiviral agents, cyclosporin and methylprednisolone. All the patients were transfusion dependent. Transfusion was often truncated due to inadequacy of blood donors and lack of blood components owing to poor financial status of the patients and their caregivers. The mean survival from diagnosis was 10.58±2.11 months and the longest surviving patient was followed up for 13 months. Late presentation was a crucial issue in the majority of cases. There was a positive correlation between survival and WBC (R=0.40) as well as ANC (r = 0.26) at diagnosis. Significant statistical difference was seen in relation to age (p=0.001).

None of the patients had access to bone marrow transplantation or anti-thymocyte immunoglobulin. Table 3 shows the causes of death.

Table 1. Age and gender distribution of the study subjects

Age (years)	Male	Female	Total
11 – 20	1	2	3
21 – 30	3	2	5
31 – 40	2	0	2
41 – 50	1	0	1
51 – 60	1	0	1

Table 2. Haematological profile of the subjects at presentation

Patients	PCV	WBC (x10$^{9/}$l)	Neutrophil (%)	Lymphocyte (%)	ANC (x10$^{9/}$l)	Platelet count (x10$^{9/}$l)	Reticulocyte count (%)	Duration of survival (in months)
1	10	1.7	16	84	0.27	21	1.8	12
2	12	2.3	6	88.2	0.14	16	0.3	12
3	18	2.7	9	88	0.24	13	0.2	11
4	9	2.6	8	79	0.21	15	0.1	12
5	17	1.9	17.5	78.2	0.33	25	1.5	6
6	14	2.1	5	94	0.11	26	1.7	9
7	16	3.0	22	72.5	0.66	28	1.6	13
8	15	2.8	6.2	86.8	0.17	16	0.1	12
9	13	2.5	10	87	0.25	9	1.0	7
10	19	1.8	18	80.6	0.32	18	0.4	11
11	17	2.9	20	75	0.58	24	1.3	12
12	15	2.2	12	81	0.26	10	1.1	10
Mean	14.58±3.11	2.38±0.44	12.48±5.96	82.86±6.23	0.30±0.17	18.42±6.35	0.93±0.67	10.58±2.19

Table 3. Causes of death in patients treated for aplastic anaemia in UUTH between January, 2016 and December, 2020

Causes of death	No. of patients	Percentage
Thrombocytopaenic bleeding	6	50
Overwhelming sepsis	3	25
Concomitant bleeding with sepsis	2	16.7
Undetermined	1	8.3

4. DISCUSSION

Aplastic anaemia is an uncommon and potentially fatal hematological disorder with reduced bone marrow ability to produce blood cells. It is characterized by the replacement of haemopoietic stem and progenitor cells in the bone marrow by fat cells and pancytopaenia in the peripheral blood. The treatment of this condition essentially requires supportive therapy with blood products and eventually the definitive treatment, where there are two established modalities: immunosuppressive therapy (IST) and allogeneic bone marrow transplantation [6,7]. The impact of each are comparable. However, some categories of patients fare better with one or the other. Allogeneic bone marrow transplantation is the treatment of choice for patients younger than 40 years. It results in the complete reconstitution of haemopoiesis, high cure rate, low risk for disease recurrence or the development of clonal disorders [8]. On the contrary, it has been well recognized that long-term high-risk for disease recurrence and secondary disorders such as Myelodysplastic Syndrome (MDS), Paroxysmal Nocturnal Haemoglobinuria (PNH) and Acute Myeloid Leukaemia (AML) are more common after immunosuppressive therapy [9]. However, some researchers have reported that survival rates after marrow transplantation in patients aged 20-40 years are similar to those observed for immunosuppressive therapy [6,10]. The standard regimen for immunosuppressive therapy is a combination of anti-thymocyte globulin and cyclosporin. This is usually indicated for moderately severe AA patients who do not have human leucocyte antigen (HLA) – matched sibling donors; or those older than 40 years of age [9]. Although IST is effective in correcting pancytopaenia in a number of patients, it is not, useful in all cases [6].

The age range of affected patients in this study showed that those between the ages of 21-30years were largely affected. This agrees with findings reported in some other studies [11-14]. However, some of the reported studies were multicentre studies and community based and essentially showed a bimodal peak age incidence; the first peak in the young adult age bracket and a second peak in the fifth to sixth decade. Montane et al in Spain [11], documented a bimodal peak age incidence at 15-24 years and 65 years and older patients. Similar finding has been reported in studies conducted in France and Thailand [14,15]. In addition to the reported studies being multicentre studies in contrast to the single-centre setting of the current study, the second peak may be as a result of a higher life expectancy in the European and Asian populations as against Nigeria where the average life expectancy is 53 years [16].

In our study, there were more affected male patients than females, with a male to female ratio of 2:1. This finding is consistent with that reported by Issaragrisil et al in Asia (15), though in dissonance with reports by other workers who found no difference in the incidence of aplastic anaemia by sex [10,17]. However, in US [18] female cases were reported to be almost twice as frequent as male cases. In comparison to earlier studies particularly those carried out in other climes, the mean survival of patients with AA in this series is short at 10 months. This is most likely due to bleeding and sepsis from low platelet and absolute neutrophil counts at presentation. Bleeding complication was the most common cause of death in this study. This is similar to findings from previous studies [12,13,17]. Many of the patients presented late in the course of the disease. Laboratory parameters at presentation showed severe and very severe AA at diagnosis. This could equally account for the short duration of survival.

Management of thrombocytopaenic bleeding presents an unnerving challenge when platelet support services are in short supply as red cell transfusion is not useful and may indeed exacerbate the situation and provoke further bleeding [19]. This is because red cell diapedesis is heightened in thrombocytopenic states and microvascular capillary bleeding is thus aggravated. With platelet concentrates not being

readily available, the management of AA in this study was suboptimal. Survival rates where optimal management facilities and desired therapeutic agents are available are considerably higher with reports of 70-90% five year survival [20] and 51% at fifteen years [11]. The unavailability of bone marrow/stem cell transportation is the principal factor that contributes to the short survival recorded in this series. Other workers have also identified non-availability of bone marrow transplant facility in Nigeria as an important factor responsible for the poor survival of AA patients in the country [12,13,17]. Given that bone marrow transplantation is now considered as the definitive treatment modality for a number of haematologic disorders including AA, it is disheartening that centres offering this treatment are scarce and where available are ill equipped in a country with a population of over 150 million.

Though immunosuppressive therapy is a pertinent alternative to bone marrow/stem cell transplantation in the management of AA, potent immunosuppressive drugs such as cyclosporin and anti-thymocyte globulin are not affordable and readily available in the country. Due to the high cost of cyclosporin which was out of reach of some of the patients, steroids such as methyl prednisolone known to be ineffective in achieving the expected therapeutic effect was used as an adjunct in the management of these patients. This resulted in unsatisfactory outcome. Furthermore, owing to the absence of adequate transfusion support service for the supply of the required blood components (red cell and platelet concentrates), near absence of a robust voluntary blood donor base as well as the clapped-out nature of the only available refrigerated centrifuge at our disposal and lack of aphaeresis machine for component preparation in our centre the availability of blood components was erratic and inadequate. All the aforementioned factors contributed to the dismal outcome in this series.

5. CONCLUSION

The present study shows that aplastic anaemia is a devastating haematological condition. Though there is somewhat improved survival of aplastic anaemia patients worldwide, the experience from our centre is appalling. There is a dire need for the Federal Government to ensure that bone marrow/stem cell transplantation centres are available and accessible in the country, and to make drugs such as cyclosporin and anti-thymocyte immunoglobulin affordable or free to reduce the eerie mortality figures. In furtherance of this, an effective and efficient health insurance scheme should be put in place to ensure that the healthcare needs of citizens are met.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethical approval was obtained from the Health Research ethical committee of the University of Uyo Teaching Hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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