Clinical and Demographic Profile of Pediatric Patients with Aplastic Anemia Seen in the Philippine National Tertiary Hospital from 2006 to 2013

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Abstract

Aim: Aplastic anemia is a rare syndrome of bone marrow failure. There is a dearth of data on the clinical and demographic profile of pediatric patients with aplastic anemia in the Philippines. This study provides data on pediatric patients with aplastic anemia seen in the Philippine national tertiary hospital in an 8-year period.

Methods: Records of patients below 19 years of age diagnosed with aplastic anemia at the Philippine General Hospital from 2006 to 2013 were retrieved. Only patients with bone marrow examination results confirming the diagnosis of aplastic anemia were included. The patients' clinical data and diagnostic results were presented using descriptive statistics.

Results: A total of 39 pediatric patients were diagnosed with aplastic anemia in the Philippine national tertiary hospital from 2006 to 2013. There were 25 males and 14 females. The median age was 13 years, and majority (66.7%) resided in urban dwellings. Thirteen patients had non-severe disease, 15 had severe, and 11 had very severe aplastic anemia. Majority (87.2%) were classified as idiopathic. Sixteen patients received cyclosporine (41.1%) and four received corticosteroids (10.2%). The rest received supportive therapy only. Seven patients died due to sepsis (18%), while the rest were lost to follow-up.

Conclusion: Management and long-term follow up of children with aplastic anemia in the Philippines need to be improved. Provision of financial and social support and the creation of a registry of aplastic anemia may improve the outcome of patients.

Brief Points

What is already known on this topic:

- Aplastic anemia is a syndrome of bone marrow failure that is more commonly seen in Asian countries.

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- Allogeneic bone marrow transplant from a human leucocyte antigen-identical sibling is the treatment of choice for patients less than 40 years old with severe or very severe aplastic anemia.
- The survival rate among patients treated with bone marrow transplantation is significantly better compared to those given alternative treatment modalities, with a five-year survival rate of greater than 90%.

What this paper adds:
- There were 39 pediatric patients were diagnosed with aplastic anemia in the Philippine national tertiary hospital from 2006 to 2013.
- None of the patients received bone marrow transplants or antithymocyte globulin. Sixteen patients received cyclosporine, 4 patients received corticosteroids, the remaining 19 patients received only supportive treatment. Outcome of this study was poor, with seven patients succumbing to sepsis and the rest lost to follow-up.
- There is still a huge potential for improvement in the management of patients with aplastic anemia, particularly in low-to-middle income countries such as the Philippines. Improved accessibility to recommended treatment modalities, provision of financial support, and international collaborations will help optimize the care and outcome of patients with aplastic anemia.

Introduction

Aplastic anemia is a syndrome of bone marrow failure characterized by peripheral pancytopenia and marrow hypoplasia [1]. It is an uncommon hematopoietic disorder caused by 3 principal mechanisms: defect of stem cells, defect in the microenvironment of the hematopoietic cells, and antibody-mediated mechanisms [2].

Patients with aplastic anemia are classified into non-severe, severe and very severe forms. Severe aplastic anemia is characterized by compromise of at least two cell components, including absolute neutrophil counts (ANC) less than 500 per cubic millimeter, platelet counts less than 20,000 per cubic millimeter, or a corrected reticulocyte count less than 1%. This compromise must occur in patients whose bone marrow biopsy material shows a cellularity of less than 25% or in patients with bone marrow cellularity of 25 to 50% with less than 30% residual hematopoietic cells [3]. In very severe aplastic anemia, the criteria for severe aplastic anemia is fulfilled but the ANC is less than 200 per cubic millimeter. Patients with peripheral pancytopenia that do not fulfill the criteria for severe or very severe forms are classified as non-severe [4].

Aplastic anemia is more common in Asian countries. The annual incidence of aplastic anemia in Europe is 2 per million population. In Thailand, the incidence is 4 per million population in urban areas, and 6 per million population in rural areas. The incidence in Japan is 31 to 48 per million population, while the incidence in China is 19 to 21 cases per million population [5]. The increased incidence in Asian countries is attributed to environmental risk factors rather than genetic factors, since increased incidence is not observed among Asians living in Western countries. There is no gender predilection in aplastic anemia. The disease affects all age groups, with biphasic peaks among patients 10 to 25 years old and patients older than age 60 years [6].

Etiology of aplastic anemia can be classified as congenital or acquired. Congenital causes account for 20% of cases. These causes include Fanconi anemia, dyskeratosis congenita, cartilage-hair hypoplasia, Pearson syndrome, amegakaryocytic thrombocytopenia, Shwachman-Diamond syndrome, Dubowitz syndrome, Diamond-Blackfan syndrome and familial aplastic anemia. Acquired causes account for 80% of cases. These include infections such as hepatitis virus, Epstein-Barr virus, human immunodeficiency virus, parvovirus, and mycobacteria; toxic exposure to radiation and chemicals; transfusion-associated graft-versus-host disease; and eosinophilic fasciitis. Majority of cases are considered idiopathic and classified as acquired

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aplastic anemia [7].

The most common clinical manifestations of patients with aplastic anemia are consequences of anemia and thrombocytopenia. Anemia manifests as pallor, headache, palpitations, dyspnea, and fatigue. Thrombocytopenia manifests as petechial rashes and mucosal or gingival bleeding. Patients may also present with visual disturbances due to retinal hemorrhage. Infection is a less common presentation. Diagnosis is confirmed using bone marrow aspiration with biopsy [7].

Allogeneic bone marrow transplant from a human leucocyte antigen (HLA)-identical sibling is the treatment of choice for patients less than 40 years old with severe or very severe aplastic anemia. Immunosuppressive therapy using antithymocyte globulin (ATG) and cyclosporine is recommended for patients more than 40 years of age with severe or very severe disease, and for patients with severe or very severe disease less than 40 years old but with no HLA-identical sibling donor. Matched unrelated donor bone marrow transplant may be considered in patients with severe aplastic anemia less than 50 years old who have no matched sibling donors, and have failed at least 1 course of ATG and cyclosporine [7]. The estimated five-year survival rate is 75% for patients receiving immunosuppression and greater than 90% for patients who underwent bone marrow transplantation. The mortality rate for patients given only supportive treatment such as blood transfusions and antibiotics is 70% [8].

Before the introduction of ATG and cyclosporine in the 1980's, aplastic anemia was treated with androgens and corticosteroids. These treatment modalities are no longer recommended. Androgens may increase erythropoiesis and produce a trilineage response in rare cases, but these are associated with adverse effects such as hepatotoxicity and virilisation [9]. Corticosteroids are ineffective and cause significant adverse effects such as infections and gastrointestinal bleeding [7].

Several international studies reported the clinical profiles of aplastic anemia in children. In a study by Goswami et al. conducted in West Bengal, India, the incidence of aplastic anemia was 1.96 per million population of children per year. Severe aplastic anemia was noted in 33.3% of the cases. The most common etiology was exposure to insecticides, fungicides and fertilizers. The most common symptoms that were found in all patients were weakness and pallor [10]. A 5-year study by Gupta et al. in India reported that 185 patients were diagnosed with aplastic anemia in a single institution. The median age of diagnosis was 8 years old with a male to female ratio of 2.4:1. Pallor (100%), bleeding (83.8%) and fever (73.5%) were the most common presenting symptoms. Of the 185 patients, 70% were classified as severe, 21% as very severe, and 9% as non-severe aplastic anemia. The most common etiology was viral infection, with parvovirus identified in 25.8%, Epstein-Barr virus in 20%, and hepatitis virus in 6.7% of the patients [11].

A study conducted in Serbia that included pediatric and adult patients with aplastic anemia reported that the average age of diagnosis was 40.2 years. The survival rate among patients treated with bone marrow transplantation was significantly better compared to those who received ATG and cyclosporine. Gender and age had no influence on the duration of survival [6].

A Philippine study conducted in 2000 reviewed the profile, survival and outcome of Filipino children with aplastic anemia over a five-year period. Of the 107 patients included in the study, 65% had mild to moderate disease, 30% had severe disease, and 5% had very severe disease. Majority of the patients (77%) were classified as having idiopathic disease. The patients were treated with prednisone and androgens. The median survival time was ten months. The mortality rate after one year was 66.2% for patients with mild to moderate disease and 85.7% for patients with severe to very severe disease [12].

This study will provide data on pediatric patients with aplastic anemia seen in the national tertiary hospital of the Philippines from 2006 to 2013. Through this data, it is hoped that improved

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awareness about aplastic anemia will increase funding and support for patients with this disease.

Methodology

The patient records of all children diagnosed with aplastic anemia seen at the Philippine General Hospital from January 1, 2006 to December 31, 2013 were retrieved. Only patients with bone marrow examination that confirmed the diagnosis of aplastic anemia were included in the study. The patients' age, gender, residence, clinical manifestation, laboratory work-up, treatment, and outcome were extracted and analyzed using appropriate statistical methods. This study employed descriptive statistics, using frequency distribution to analyze discrete variables and measures of central tendency to analyze continuous variables.

Results

There were 39 pediatric patients with bone marrow confirmed aplastic anemia seen at the Philippine General Hospital from 2006 to 2013. The number of pediatric patients diagnosed with aplastic anemia per year is shown in **Fig-1**.

There were 25 males (64.1%) and 14 females (35.9%). The median age of the patients was 13 years.
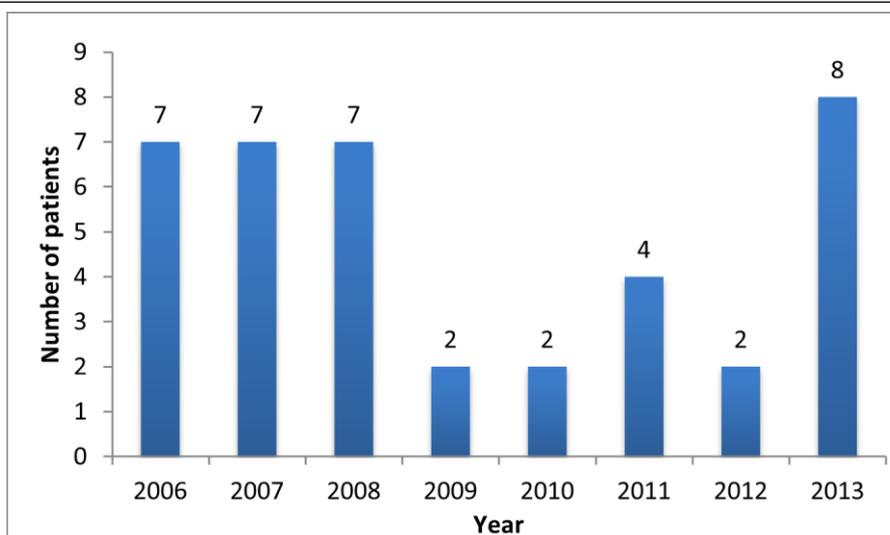
Of the 39 patients, 26 (66.7%) lived in urban areas

Fig-1:

Number of pediatric patients newly diagnosed with aplastic anemia from 2006 to 2013

and 12 (30.7%) lived in rural areas. One patient could not be classified as residing in either an urban or rural setting due to insufficient data on the patient's address. The classification into urban or rural areas was based on the Philippine Statistics Authority-National Statistical Coordination Board data [13].

Thirteen patients (33.3%) were classified as non-severe, 15 (38.5%) as severe, and 11 (28.2%) as very severe. Relevant histories of exposure were noted in five patients—hepatitis B infection in one case, tuberculosis infection in two cases, and exposure to chemicals, particularly pesticides, in two cases. The rest of the patients, comprising 87.2% of the study population, were classified as idiopathic.

The most common presenting symptoms were pallor (74.4%), mucosal bleeding (46.1%), and easy bruisability (35.9%), and fever (30.7%). Less common symptoms include fatigue, dizziness, petechial rashes, menorrhagia, dyspnea, syncope, headache and cough.

Only 16 patients (41.1%) received cyclosporine. Four patients (10.2%) were given corticosteroids. The remaining 19 patients (48.7%), received only supportive treatment in the form of blood transfusions. None of the patients received bone marrow transplants or ATG.

Of the 39 study patients, seven patients (18%) died due to sepsis. The remaining 32 patients (81%) were

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lost to follow-up. **Table-1** shows the outcome of patients according to disease severity.

Discussion

Although aplastic anemia is an uncommon hematologic disorder, a substantial number of patients are seen and treated in the national tertiary hospital in the Philippines. Nationwide incidence studies are needed to determine the full extent of the burden of this disease in the Filipino population.

Table-1: Outcome of pediatric patients with aplastic anemia per disease severity				
Outcome	Non-severe aplastic anemia	Severe aplastic anemia	Very severe aplastic anemia	Total
Mortality	2	1	4	7
Lost to follow-up	11	14	7	32
Total	13	15	11	39

Compared to the previous local study by Melicor et al. which identified 107 cases of aplastic anemia in a five-year period, the number of cases in this study is much lower. Various factors could have contributed to the decrease in number of aplastic anemia patients, such as better control and prevention of communicable diseases and stricter regulations in the use of pesticides and other harmful chemicals.

Global literature report that aplastic anemia does not have gender predilection. In this study however, a larger proportion of the patients were male, with a male to female ratio of 1.8:1. Although this study is limited to the Philippine national tertiary hospital only, it is important to note that the trend for male predilection was also observed in the study conducted by Gupta et al. in India [11]. One possible explanation for male predilection of aplastic anemia would be greater exposure of males to chemicals due to differences between typical male and female activities based on cultural norms.

Most of the patients in the study were in the adolescent group, particularly the middle adolescent group (14 to 16 years old). This finding is consistent with other studies stating that aplastic anemia commonly peaks in the 10 to 25 year old age group [6].

Majority of the patients lived in urban settings. This finding can be attributed to the greater exposure to various chemicals and infections in the urban setting due to higher population density.

Consistent with data from international and local studies, majority of the study patients were classified as idiopathic. Only five patients in our study were noted to have relevant exposure to infections and chemicals.

Although most of the patients in the study were candidates for bone marrow transplant, none of them underwent this procedure. Although it was not documented in the medical charts whether this treatment option was discussed with the family, it can be surmised that the lack of facilities and finances served as major hindrances in accessing this form of treatment. It is also worthwhile to note that even though cyclosporine and ATG were introduced since the 1980's as recommended immunosuppressive therapies, only 16 patients were given cyclosporine. Corticosteroids were still prescribed to some patients, despite studies recommending otherwise [7]. The rest of the patients received blood transfusion therapy and other supportive treatment modalities only. Outcome of this study was poor, with seven patients succumbing to sepsis and the rest were lost to follow-up.

This study demonstrates that there is still a huge potential for improvement in the management of patients with aplastic anemia, particularly in low-to-middle income countries such as the Philippines. Improved accessibility to recommended treatment modalities, provision of financial support, and international collaborations will help optimize the care and outcome of patients with aplastic anemia. The

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creation of a national registry for aplastic anemia can lead to more accurate data collection, improved patient follow-up, and provide a more efficient and centralized method for financial solicitation.

Conclusion

Aplastic anemia has a profound impact on the lives of Filipino patients and their families. Improved access to ideal treatment options will lead to improved outcome for these patients. Further research to document incidence and burden of the disease on a national scale is warranted. Creation of a national registry will help optimize long-term survival and quality of life of children with aplastic anemia.

Acknowledgment

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