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The Role of Certain Congenital Infections in Aplastic Anemia and Prognostic Value of Fetal Hemoglobin as a Follow-Up Marker

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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: TORCH infection has a role in aplastic anemia (AA). Fetal hemoglobin may be high in certain acquired hematological conditions such as aplastic anemia. We conducted this study to evaluate the correlation between certain congenital infections and severity of aplastic anemia and to study fetal Hb as a follow up marker during treatment of aplastic anemia. The aim of study was to correlation between certain congenital infection and severity of aplastic anemia and to study of hemoglobin F (HbF) as a follow up marker during treatment of aplastic anemia.
Methods: Our prospective study was conducted on 20 children aged up to 18 years diagnosed with aplastic anemia following either bone marrow aspiration or biopsy that proves bone marrow hypocellularity with absence infiltrative BM disease or inherited BM disease recruited from Pediatric Hematology-Oncology Unit of Tanta University Hospital. Patients were classified according to level of HbF in to high HbF group and normal HbF group.
Results: TORCH infections were detected in certain numbers of patients . HbF decreased in high HbF group after treatment. There was significant increase in CBC parameters in high HbF group

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than normal HbF group after treatment. There was insignificant decrease in mortality in high HbF group than normal HbF group. Mild to moderate cases were significantly higher with TORCH IgM +ve cases

Conclusions: Acquired AA is associated with TORCH infection. In treated cases of AA, improvement of hematological parameters is associated with high HbF and from these results, it can be used as a prognostic marker to monitor the successful response of these cases to the used line of treatment.

Keywords: Congenital infections; aplastic anemia; fetal hemoglobin; TORCH infection.

1. INTRODUCTION

Aplastic anemia (AA) is a rare disorder characterized by pancytopenia and a hypocellular bone marrow. Injury to or loss of pluripotent hematopoietic stem cells, in the absence of infiltrative disease of the bone marrow, is the major pathophysiologic characteristic of the disease [1]. In contrast, bone marrow failure is a more encompassing term that describes pancytopenia from a variety of different mechanisms, including bone marrow replacement by tumor or fibrosis, disordered cellular maturation (e.g., vitamin B 12 deficiency), and myelodysplasia. In either conditions, the associated neutropenia and thrombocytopenia can lead to potentially life-threatening infections and bleeding, respectively [2].

A few patients develop AA as part of inherited syndromes. Irradiation and chemotherapy for malignant disease may produce severe prolonged, focal, diffuse marrow aplasia. Certain drugs produce reversible dose-related marrow suppression or less often, idiosyncratic dose-unrelated severe AA. For other drugs or chemicals an association, with AA is supported only by statistical correlations or suggestively related clinical events. At least 50% of cases of marrow aplasia are of unknown etiology. Viruses are rarely mentioned as causes of AA [3].

Most of the viruses known to be associated with anemia in human tend to persistently infect their host and are non-cytopathic or poorly cytopathic for blood cell progenitors. Infection with Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, human herpes virus 6 (HHV-6), B19 parvovirus, human immunodeficiency virus, hepatitis A and C viruses and the putative viral agent associated with non-A-G post hepatitis AA has been reported in association with AA [4].

Clinical manifestations are proportional to peripheral blood cyotpenias and may include dyspnea on exertion, fatigue, easy bruising, petechiae, epistaxis, gingival bleeding, headache and fever. A complete blood count, leukocyte differential and bone marrow aspirate and biopsy can establish the diagnosis. AA is classified as non-severe (NSAA), severe (SAA) and very severe based on the degree of peripheral blood cyotpenias [5].

Treating immune mediated AA involves suppression of the immune system, or in more severe cases, a bone marrow transplant, can be the potential cure. In young patients with an HLA matched sibling donor bone marrow transplantation can be considered as first line treatment, patients lacking matched sibling donor typically pursue immunosuppression as a first line treatment and matched unrelated donor transplantation are considered as second line therapy [6].

It is known that increased production of alkali-resistant or fetal hemoglobin is usually associated with some genetically determined anemias such as thalassemia and sickle-cell anemia. Scattered reports have also indicated that production of fetal hemoglobin may be reactivated in some acquired disorders such as pernicious anemia, multiple myeloma, molar pregnancy and AA. The evaluation of alkali-resistant hemoglobin in this last condition, however, has yielded conflicting results. Although some investigators have found abnormal amounts of this hemoglobin [7].

Up till now the direct relation between viral infections either congenital or acquired and AA are not settled. There is no follow up marker except reticulocyte count in peripheral blood and/or bone marrow examination.

The aim of study was to correlation between certain congenital infection and severity of AA and to study of fetal Hb as a follow up marker during treatment of AA.

2. SUBJECTS AND METHODS

Our prospective interventional study was conducted on 20 children aged up to 18 years diagnosed with AA following either bone marrow aspiration or biopsy that proves bone marrow hypocellularity with absence infiltrative BM disease or inherited BM disease recruited from Pediatric Hematology-Oncology Unit of Tanta University Hospital after approved of Tanta University Institutional Review Board and written informed consent was obtained from each participant in the study.

Exclusion criteria were patients with pancytopenia associated with infiltrative diseases of the bone or marrow, myelodysplasia. Severe infections causing AA (Sepsis). Inherited BM disease (Fanconi anemia).

Patients were classified according to HbF into two groups: High HbF group that included 8 patients with high HbF before treatment. Those patients had good response to treatment (BMT) with less complications. After treatment, HbF became within the normal values. Mortality was in one case only. Normal HbF group that included 12 patients with normal level of HbF before treatment. Those cases had a poor response and more complications. Mortality was higher (5cases).

All patients were subjected to the following: full history, clinical examinations and laboratory investigations.

Diagnosis of AA by CBC, Reticulocytes count and Bone marrow aspiration and trephine biopsy.

Diagnosis of congenital infection: Toxoplasma IgG, IgM, EBV antibodies (Epstein-Barr virus), rubella virus antibodies, herpes virus antibodies, parvovirus B 19 antibodies, CMV antibodies and hepatitis viruses antibodies

TORCH infection by ELISA: Enzyme-linked immunosorbent assay (ELISA) is a method of target antigen (or antibody) capture in samples using a specific antibody (or antigen), and of target molecule detection/quantitation using an enzyme reaction with its substrate.

Estimation of fetal hemoglobin before and after treatment using Automatic Glycohemoglobin Analyzer and compared our values of hemoglobin F by normal values as standard values Mentioned by (Schroter and Nufz) [8].

Age	Number tested	Mean	2 SD	Range
1–7 days	10	74.7	5.4	61–79.6
2 weeks	13	74.9	5.7	66–88.5
1 month	11	60.2	6.3	45.7–67.3
2 months	10	45.6	10.1	29.4–60.8
3 months	10	26.6	14.5	14.8–55.9
4 months	10	17.7	6.1	9.4–28.5
5 months	10	10.4	6.7	2.3–22.4
6 months	15	6.5	3.0	2.7–13.0
8 months	11	5.1	3.6	2.3–11.9
10 months	10	2.1	0.7	1.5–3.5
12 months	10	2.6	1.5	1.3–5.0
1–14 years and adults	100	0.6	0.4	–

Chart 1. Percentage of HbF in the first year of life [8]

2.1 Treatment of Acquired AA

All cases received supportive treatment (e.g. packed RBC transfusion, platelet transfusion) All cases with severe acquired AA and cases with congenital AA were directed for Bone marrow transplantation (BMT). Matched sibling donor BMT was done for 5 cases, out of the 20 cases of acquired AA, 7 more cases were referred for Haploidentical BMT. Another case refused BMT. The remaining cases received immunosuppressive therapy.

Cases received immunosuppressive therapy in the form of Methylprednisolone (2 mg/kg/d IV on days 14. Divide into 0.5 mg/kg/dose IV every 6 h. Prednisone oral taper following the 4-day course of IV methylprednisolone. On days 5 through 14, start prednisone, 1.52 mg/kg/d PO to be divided into two equal daily doses. After day 14 institute a slow taper (e.g., on days 15 and 16, prednisone, 1 mg/kg/d PO to be divided into two equal daily doses). On days 17 and 18, prednisone, 0.5 mg/kg/d PO to be divided into two equal daily doses. On day 19, prednisone, 0.25 mg/kg/d PO to be given in one dose)

Sandimmune (10 mg/kg/d PO initially starting on day 1, divided into two equal daily doses. Serum drug levels should be monitored as needed with the first level at 72 h post initiation of therapy. CSA dose to be adjusted to keep serum trough levels between 200 and 400 ng/ml. CSA should be continued for one year until and after a trilineage response is achieved. Decrease the dose by 2.0 mg/kg every 2 weeks once the taper is begun, watching for signs of recurrence of AA). Growth factors as G-CSF and Eltrombopag.

2.2 Statistical Analysis

Statistical analysis was done by SPSS version 25 (IBM Inc., Chicago, IL, USA). Normality of data was checked with Shapiro-Wilks test. Numerical variables with normal distribution were presented as mean, standard deviation (SD) and range and were compared between the two groups utilizing Student's t- test. Numerical variables with abnormal distribution were presented as median and range and were compared between the two groups utilizing Mann-Whitney U test. Categorical variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed P value < 0.05 was considered significant.

3. RESULTS

There was a significant increase (improvement) of Hb, platelet, TLC, HbA1 and reticulocyte count and a significant decrease in HbA2 and HbF (Table 2).

Patients were classified according to HbF into two groups:

1) High HbF group that included 8 patients.
2) Normal HbF group that included 12 patients.

There was significant increase in high HbF group than normal HbF group as regard to hemoglobin, platelets, and TLC. Also, they was insignificant difference between both groups as regard to reticulocytes after treatment (Table 3).

There was insignificant difference between both groups as regard to HbA2 before treatment, but they were significant decrease in high HbF group than normal HbF group as regard to HbA1 and HbF after treatment. There was insignificant difference between both groups as regard to HbA1, HbA2 and HbF after treatment Table 4.

The mild to moderate cases were significantly higher with TORCH IgM +ve cases (Table 5).

Table 2. CBC and Hemoglobin electrophoresis of the studied patients before and after treatment

	Before	After	P value
Hemoglobin (g/dL)	6.13 ± 0.67	9.27 ± 1.08	<0.001*
Platelets (*10^3/mm^3)	17.65 ± 5.91	145.5 ± 59.5	<0.001*
TLC (*10^3/mm^3)	1.84 ± 0.6	3.87 ± 1.6	<0.001*
Reticulocyte count (%)	0.37 ± 0.13	1.5 ± 0.29	<0.001*
HbA1	93.3% ± 3.0%	96.5% ± 0.5%	<0.001*
HbA2	2.4% ± 0.6%	2.0% ± 0.6%	0.042*
HbF	3.7% ± 3.1%	1.5% ± 0.3%	<0.001*

**Significant as P value <0.05*

Table 3. CBC and Hemoglobin electrophoresis after treatment of the studied groups

	High HbF (n = 8)	Normal HbF (n = 12)	P value
Hemoglobin (g/dL)	9.54 ± 0.95	8.84 ± 1.00	0.025*
Platelets (*10^3/mm^3)	178.75 ± 39.44	123.3 ± 61.55	0.037*
TLC (*10^3/mm^3)	4.94 ± 0.69	3.16 ± 1.66	0.011*
Reticulocyte count (%)	1.53 ± 0.38	1.48 ± 0.23	0.764

**Significant as P value <0.05*

Table 4. Hemoglobin electrophoresis before and after treatment of the studied groups

Before Treatment	High HbF (n = 8)	Normal HbF (n = 12)	P value
HbA1	90.5% ± 1.4%	96.2% ± 0.6%	<0.001*
HbA2	2.4% ± 0.6%	2.4% ± 0.6%	0.914
HbF	7.2% ± 1.6%	1.4% ± 0.3%	<0.001*
After Treatment	**High HbF (n = 8)**	**Normal HbF (n = 12)**	**P value**
HbA1	96.5% ± 0.6%	69.5% ± 0.5%	0.987
HbA2	2.1% ± 0.6%	2% ± 0.6%	0.861
HbF	1.5% ± 0.4%	1.5% ± 0.3%	0.736

Table 5. Relation between TORCH infection and severity

		Severity		P value
		Mild to moderate	Severe	
TORCH	IgM +ve	7	1	**0.005***
	IgM -ve	2	10	

4. DISCUSSION

The etiology of acquired AA in our patients has been linked to many drugs, chemicals, toxins and viruses such as hepatitis virus, parvovirus, Epstein Barr virus and cytomegalovirus. In our study, 35.0% developed herpes IgG, 25.0% developed CMV IgG, 20.0% developed EBV IgG, 15.0% developed toxoplasma IgG, 5.0% developed rubella IgG, CMV IgM, hepatitis A and no patient (0%) developed toxoplasma IgM or rubella IgM or Parvo virus B 19 IgM or hepatitis B or C.

In study by Gupta et al., viral markers for hepatitis A, B, C, E and EBV were carried out in 120 patients. Parvovirus IgM was tested in 66 patients, of which one fourth patients were found to be positive. Two patients were positive for both EBV and parvovirus IgM. Both had severe AA. All patients were negative for HIV infection. Six patients had history of varicella infection within 6 months of developing features of AA [9].

According to Gonzalez-Casas et al., hepatitis associated AA (HAAA) is a variant of AA in which AA develops within 12 months of a documented episode of hepatitis [10].

In addition, 5-year study by Nair et al., Of the 185 patients, 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].

In Xiao et al., case, a high level of CMV DNA (9.69×108 copies/ml) was revealed, which indicated that CMV infection contributed to the occurrence of AA [12].

Another interesting observation by two studies was preceding history of varicella infection within 6 months of developing AA. There are occasional case reports of varicella leading to AA [13,14].

In Yetgin et al., series of 32 pediatric patients an unusually high association of varicella-zoster infection was found with AA. There is lack of

information regarding hepatitis and varicella associated AA from Yetgin et al., country [15].

This work was in line with the study done by Howard et al. They found there was no significant correlation between bone marrow cellularity reflected by reticulocyte count or the percentage of hemoglobin F at diagnosis [16].

Similarly, Olaniyi et al., found that, the mean levels of fetal hemoglobin (HbF) for males (4.71±3.49) compared to that of females (4.99) were statistically similar (p =0.773) but they also observed that the mean HbF level appears to be declining as age advances [17].

In a Kotila et al., study, males were found to have higher HbF levels (7.6±3.9%) than their female counterparts (6.7±3.6%), but the difference was not statistically significant [18].

Moreover, Parikh NS et al., reported a 16-year-old girl, who presented with a long-standing anemia and normal blood screening tests except an elevated HbF (16%); diagnosis of unstable hemoglobinopathy (Hb Hradec Kralove) was made after gene sequencing of the beta-globin chain. The interesting finding in the case report was reticulocytosis at the time of presentation, which is an indicator of erythropoietic stress in a case of hemolytic anemia which can be correlated with the present case and hence causing a rise in HbF levels [19].

However, Howard et al., found no significant correlation between bone marrow cellularity or the percentage of hemoglobin F at diagnosis, nor in the nadir of the absolute neutrophil count (ANC) and the subsequent clinical course [16].

Unlike our literature, Morris et al., were unable to demonstrate a higher HbF level in females in comparison to male patients. It would appear that the X-linked factor, which influences HbF production and was suspected to be due to the hormonal effects of puberty [20].

In addition, Olufemi et al., shows that females had higher HbF levels than the male counterparts [21].

This study was also in disagreement with Mason et al. study showing that, after the age of 10, HbF levels were consistently higher in females than in males, and this was statistically significant [22].

In a study estimating HbF levels in SCD, male sickle cell patients were found to have significantly lower levels of HbF than their female counterparts [23]. On the other hands, Alter et al., found that, HbF was higher in males than females; decreased with age at a similar rate in both genders; was higher in anemic patients and in those with elevated MCV [24].

To our knowledge, this was the first study that explored the protective effect of high HBF among pediatric diagnosed with AA and its relation to TORCH infection. We tried to explain our results by some reported data in previous studies.

Early study by Powars et al., also demonstrated a protective effect of HbF on the symptomatology and organ dysfunction associated with the disease. It was estimated that an Hb F level of 20% protects against end-organ damage, while patients with HbF of 6 30% are symptom free [25].

Moreover, according to Bloom and Diamond, total fetal hemoglobin values were determined in 30 children with acquired AA. Seventeen of 18 patients who died (95%) had less than 400 mg per 100 ml of total fetal hemoglobin whereas 11 of 12 who are alive (92%) and doing well had more than 400 mg per 100 ml of total fetal hemoglobin at the initial examination. The results suggest that the total fetal hemoglobin concentration may reflect the extent of injury to the bone marrow and may be of prognostic value in determining which patients with acquired AA are likely to respond to treatment [26].

According to Mandal and Kartthik, high HbF diseases include pernicious anemia, paroxysmal nocturnal hemoglobinuria (PNH), sideroblastic anemia, pure red cell aplasia, AA, pregnancy, recovery from bone marrow transplant [27].

In addition, Shimamura and Alter, reported that, Patients with inherited bone marrow failure syndromes (IBMFS) frequently have manifestations of what has been called “stress hematopoiesis” whose features include increased (HbF) [28].

Similarly, Amato et al., found any erythropoietic stress in vivo may be associated with high HbF. Thus, accelerated erythropoiesis can be sufficient to produce more HbF (6–10%), or no HbF at all, depending upon enhancing factors. One of this stress was AA [29].

Another study by reported that, in presence of chronic juvenile myeloid leukemia, variable HbF levels (20–80%) have been reported, increasing in time during the progression of the disease. Also, in other leukemic forms, particularly in the acute leukemia in the remission phase after drug treatment, remarkable increased HbF levels (up to 15%) have been reported HbF is also increased in congenital AA and in erythroid hypoplasias. In Fanconi anemia HbF seems to be always increased, even after remission after steroidal therapy [30].

We also compared our study by normal references as regards CBC from a study done by professor Shebl Said Shebl [31] in a group of patients from hematological unit, pediatric department, Tanta University.

We compared our study by normal references as regards HbF from a the values mentioned by Schröter and Nafz [8].

5. CONCLUSIONS

Acquired AA is associated with TORCH infection. In treated cases of AA, improvement of hematological parameters is associated with high HbF and from these results, it can be used as a prognostic marker to monitor the successful response of these cases to the used line of treatment.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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