Egyptian Journal of Medical Research (EJMR)

Study for registry and clinical spectrum of bone marrow failure in pediatrics; single centre experience

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Abstract:

Background: Bone marrow failure is a group of disorders characterized by the inability of bone marrow to produce sufficient blood cells. They can be divided into inherited disorders, acquired disorders and diseases infiltrating bone marrow. Acute leukemia is a serious cause of bone marrow failure which needs early diagnosis and management . **Purpose**: To study for registry, and clinical spectrum of bone marrow failure in Beni-Suef university hospital to detect the magnitude of the problem . **Patients and methods:** It is cross sectional study over a period of six months from January 2019 to June 2019, in which patients with bone marrow failure (monocytopenia, bicytopenia or pancytopenia) from pediatric age group (0-13 years) who were admitted in the pediatric department in Beni-Suef university hospital were included and followed up. They were subjected to a detailed history, full examination and laboratory investigation; complete blood count, reticulocyte cont, bone marrow aspirate & biopsy, virology study and accordingly other investigations were done such as flow cytometry for cd55 & cd59, glucocerebrosidase enzyme assay, chromosomal breakage analysis and imaging. **Results:** Out of 22000 outpatients and 1700 inpatients,55 patients had diagnosed as bone marrow failure during six months duration with percentage of o.23%. The most frequent diagnosis of bone marrow failure was acute Leukemia (30.9 %), followed by Idiopathic aplastic anemia (27.3%) then Fanconi anaemia (21.8%).

Conclusion: Bone marrow failure is not rare ,acute Leukemia should be considered strongly in the diagnosis of any case of bone marrow failure**.**

Keywords: Bone marrow failure, acute Leukemia, Beni-Suef.

1. Introduction:

Bone marrow failure is defined as a group of disorders characterized by the inability of bone marrow to produce sufficient blood cells. These disorders of hematopoietic stem cells can involve either one cell line or all of the three hematopoietic lineages; erythroid for red blood cells, myeloid for white blood cells, and megakaryocytic for platelets. (1). They can be divided into inherited and acquired disorders. The most common inherited disorders are Fanconi anemia, Schwachman-Diamond syndrome (SDA), Dyskeratosis congentia, Diamond Blackfan anemia, Congential Amegakaryocytic thrombocytopenia, Severe Congenital Neutropenia, Reticular dysgensis, Thrombocytopenia with Absent Radii (TAR), and Congential Dyserythropoietic anaemia (2). Acquired disorders mainly include Aplastic anaemia, Paroxysmal Nocturnal Hemoglobinuria and diseases infiltrating bone marrow such as Gaucher disease, Myelofibrosis, and Leukemia (3). Clinical picture of bone marrow failure are associated with the inability of bone marrow to produce sufficient blood cells causing anemia, thrombocytopenia and leucopenia and resulting in pallor, bleeding tendency,fever, and bacterial infections. Many patients have also extra medullary symptoms (4). Bone marrow failure syndromes are characterized by bad prognosis and elevation of cancer predisposition and deaths rate. The only cure of bone marrow failure syndromes stays hematopoietic stem cell transplantation. However, the choice of optimal time is very important for management especially before development of complications (5). Patients with severe bone marrow failure or those who have developed acute Leukemia or Myelodysplastic syndrome (MDS) are recommended to do Allogeneic hematopoietic stem cell transplant (6). Registry of the diseased cases with bone marrow failure and detection of the incidence in each country help in identifying the magnitude of the problem and consequently, understanding the genetic background of them, making an early accurate diagnosis and helping in exploration of appropriate management (1). We aimed to study the registry and clinical spectrum of bone marrow failure in Beni-Suef university hospital to detect the magnitude of the problem

and co-operate for exploring new ways of early diagnosis and management.

2. Patients and Methods:

It is a cross sectional study in which patients with bone marrow failure were registered from all pediatric age group (0-13 years) of the pediatric department in Beni-Suef university hospital in a duration of six months from January to June 2019 . Patients were subjected to; 1) history: age of onset, complain, consanguinity, family history, pallor, fever, recurrent infection, bleeding tendency, dark urine, body swellings organomegaly, arthralgia and history of blood transfusion 2) Clinical examination included: a- General examination for detection of pallor, bleeding spots, lymphadenopathy, congenital anomalies and anthropometric measurements for detection of growth retardation. b- Systemic examination for detection of congenital anomalies and hepatosplenomegaly. 3) Laboratory investigations were done to diagnose bone marrow failure and its etiology including:

a- Complete blood picture, reticulocytic count, and erythrocyte sedimentation rate: peripheral venous blood sample was obtained and divided into 2 parts, the first was saved in EDTA tube for hematological parameters and reticulocytes analysis, the second was for erythrocyte sedimentation rate and the third was for serum ferritin measurement.

b- Virology studies: CMV and Parvovirus B19 antibodies were tested by ELISA and confirmed by PCR test.

c- Bone marrow aspirate and biopsy: a small needle was inserted into bone to obtain a small amount of liquid bone marrow. Bone marrow biopsy was often done at the same time and a small amount of bone marrow tissue was removed.

d- Flow cytometric analysis of CD59 and CD55 expression on blood cells was performed for diagnosis of paroxysmal nocturnal hemoglobinuria. g- Glucoserebrosidase enzyme assay was performed for diagnosis of gaucher disease.

e- Chromosomal breakage analysis was performed for diagnosis of fanconi anemia: 5-10 ml blood in a sodium heparin vacutainer tube was taken and cells were cultured in the presence of clastogens mitomycin C and diepoxybutane. Metaphase chromosomes were prepared from each culture and stained with wright stain. Fifty metaphases were scored from each culture for the presence of breaks and radial formation.

f- Imaging was done including x-ray on the hand and forearm searching for congenital anomalies in inherited bone marrow failure syndromes. Echocardiogram was done in cases of Fanconi anemia and abdominal U/S was performed for detection of hepatosplenomegaly and lymphadenopathy in suspected cases of leukemia and detection of renal anomalies in Fanconi anemia.

Statistical analysis

Statistical analysis was done using statistical package for the social sciences version 22.0

(IBMcorp., Armonk, NY, USA). Data were described in the form of mean ± standard deviation for quantitative data and frequency and proportions for qualitative data. P <0.05 was considered statistically significant. Differences were analyzed between the groups by student t-test as regards normally distributed data; otherwise, Mann-Whitney U- test was used.

Ethical consideration

The study was approved by the research ethical committee of the faculty of medicine, Beni-Suef University. Approval No FWA00015574 FMBSUREC/04032019. Written consents were

obtained from the parents of the children.

3. Results:

In our study, out of 22000 outpatients and 1700 inpatients, 55 of patients had diagnosed as bone marrow failure during six months duration with percentage of o.23%. Pediatric department in Beni-Suef university hospital in a duration of six months from January 2019 to June 2019. We reported 55 bone marrow failure cases diagnosed as follow, 30.9% had acute leukemia, 27.3% had idiopathic aplastic anemia, 21.8% had Fanconi anemia, 7.3% had Gaucher disease, 5.5% had Diamond-Blackfan anemia, 3.6% had paroxysmal nocturnal hemoglobinuria,

1.8% had secondary aplastic anemia due to cytomegalovirus infection and 1.8% had Myelofibrosis.

The mean age of the studied group was 6.3 years old, positive consanguinity was found in 38%.

While 20 % of patients had positive family history. Also, 60% were males and 40% were females. Regarding clinical data of the studied group, pallor with recurrent infections and fever were the most common symptoms as shown in Table I

Table (I):Clinical data of the studied group.

		Frequency	Percent %
Fever		39	70.9
Pallor		55	100
Recurrent infection		47	85.5
Bleeding tendency		38	69.1
Generalizedlymphadenopathy		26	47.3
Artharlgia		25	45.5
Stunted growth		32	58.2
Organomegaly	None	27	49.1
	HM	7	12.7
	HSM	21	38.2

Laboratory data of the studied groups including complete blood count, reticulocytic count, erythrocyte sedimentation rate, flow cytometry (CD55& CD59), chromosomal breakage, cytomegalovirus PCR, parvovirus B19 PCR and glucocerebrosidase enzyme assay are demonstrated in table II.

Table (II): Laboratory data of the studied groups.

	Mini mum	Maximum	Mean	Std. Deviation
HB /g/dl	1.50	8.70	4.9745	1.78452

MCV	65.0 0	135.00	88.9296	11.83748
PLT 10^3 /cmm	3.00	553.00	75.9309	114.82246
TLC 10^3 /cmm	.60	117.00	6.1436	15.74644
Retics	.00	1.60	.5382	.35197
ESR	30	140.00	27.7818	41.99060
Flow cytometry CD59 & CD55	+ve	2 (3.6%)		
	-ve	53 (96.4%)		
Chromosomal breakage analysis	+ve	12 (21.8%)		
	-ve	43 (78.2%)		
Cytomegalovirus PCR	+ve	1 (1.8%)		
	-ve	54 (98.2%)		
Parvovirus B19 PCR	+ve	0		
	-ve	55		
Glucocerebrosidase deficiency	Yes	4 (7.3%)		
	No	51 (92.7%)		

Bone marrow biopsy findings in the studied group are demonstrated in Table III. Blast cell infiltration was detected in 23 cases not only in the 17Leukemia cases but also in 4 cases in Fanconi anemia,in one case of Idiopathic aplastic anemia and in one case of Diamond Blackfan anemia .

Table (III): Bone marrow biopsy findings in the studied group.

		Frequency	Percent
Hypocellular BM		55	100.0
Erythroid hypoplasia		55	100.0
Megakaryocytes	Normal	4	7.3
	Depressed	51	92.7
Myeloid cell	Normal	7	12.7
	Depressed	48	87.3
Gaucher cell infiltration		4	7.3
Blast cell infiltration		23	41.8
Myelofibrosis		1	1.8

The age and ESR were significantly higher in Acute Leukemia patients compared to the Fanconi anemia and Idiopathic Aplastic anemia patients as shown in Figure I and table IV.

Figure (I): Comparison between Fanconi anaemia, Idiopathic aplastic anemia and acute Leukemia as regarding age and laboratory data.

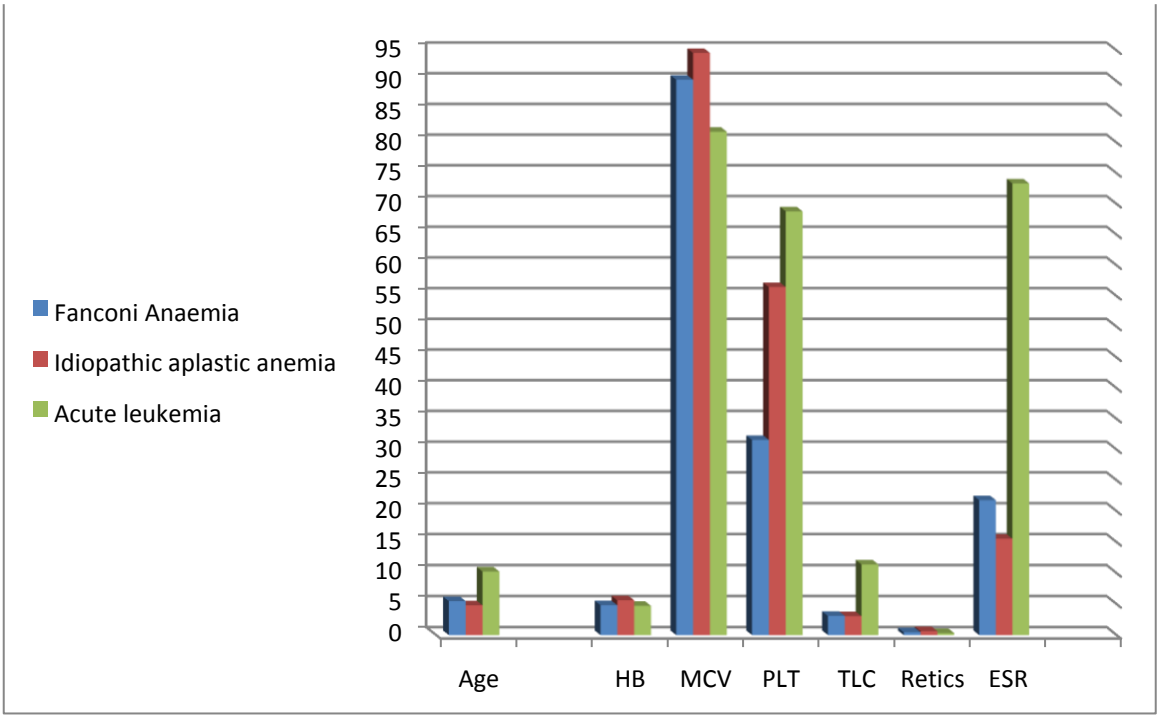

Table 1V: comparison between Fanconi anaemia , Idiopathic aplastic anemia and acute leukemia as regarding age and laboratory data.

	Fanconi Anaemia	Idiopathic aplastic anemia	Acute leukemia	p
Age/ Year	5.47 ± 2.48	4.80 ± 3.21	10.25± 2.34	.01
HB /g/dl	4.81±1.32	5.61 ± 1.97	4.70 ± 2.08	.35
MCV	90.23± 6.35	94.59 ± 15.13	81.76 ± 10.73	.01
PLT10^3 /cmm	31.56± 33.45	56.46± 40.76	68.79 ± 111.61	.43
TLC10^3	3.09± 1.00	3.04 ±.99	11.38± 27.82	.31

/cmm				
Retics	.45± .16	.62± .36	.31 ± .22	.009
ESR	21.76 ± 48.76	15.53± 27.79	73.33 ± 30.99	.001

4. Discussion:

In our study, 55 of patients had diagnosed as bone marrow failure . Of these patients, 30.9% had acute Leukemia, 27.3% had Idiopathic Aplastic anemia, 21.8% had Fanconi anemia, 7.3% had Gaucher disease, 5.5% had Diamond-Blackfan anemia, 3.6% had Paroxysmal Nocturnal Hemoglobinuria, 1.8% had secondary Aplastic anemia due to cytomegalovirus infection and 1.8% had Myelofibrosis.

While (Dokal, 2010) in his study on inherited bone marrow failure syndromes reported that, 52% had Fanconi anemia, 17% severe Congenital Neutropenia, 14% Diamond-Blackfan anemia, 6% Congenital Amegakaryocytic thrombocytopenia, 5% Dyskeratosis Congenita, 2% Shwachman Diamond syndrome, and 2% Thrombocytopenia with absent radii

This difference between our study and Dokal study due to short duration of our registery and Dokal registery was on inherited BMF only but our registery on all causes of BMF(inherited , acquired and BM infiltration).

In our study the median age of Leukemia was 10.5 years, the median age of Idiopathic aplastic anemia was 4.8 years and the median age of Fanconi anemia was about 5.5 years

In the study of (Shimamura & Alter, 2010), it was about 6.5 years. This difference may be due to this study included children and adults. In Fatih,2010 study the mean age of Fanconi was 6 ± 2.5, which is similar to us .

Male to Female ratio was 1.5: 1. Also,(Shimamura & Alter 2010) reported that male to female ratio was 1.2: 1. The cause of significant rising of bone marrow failure occurrence in males is unknown. In Fatih,2010,Male to female ratio was 1.47:1,which is similar to us.

In our study, 20 % of patients had positive family history and 38% had history of consanguineous parents' marriage. Also,(Dokal ,2010),which had done in Israel,reported high consanguinity (40%) due to Israel is closed population. This finding indicates the possible role of consanguinity in bone marrow failure

Regarding the patients with Fanconi anaemia,The most observed anomaly was stunted growth (58.3%) followed by microcephaly (50%) while absent thumb was in (16.6%) and renal anomalies was in (8.3%)

In shimamura,2010 study, The most observed anomaly was stunted growth(40%) then microcephaly(25%), this is may be due to small sample of our study.

In Faith,2011 study decided that the most observed anomaly was Microcephaly(73.8) then stunted growth (57.1%). this retropective study on 42 patients in 29 years.

In our registery ,The mean age of leukemia was 10.25 years.but in Pahloosye A,2011 study , the mean age of Leukemia was 9years .

In our study,Anemia in Leukemic patients was 100%, but in Pahloosye study was 85% (Pahloosye A,2011 study was on 100 patients of acute lymphoblastic leukemia in Shahid Sadoughi hospital in Iran for 4years)

In our study,male : female ratio was 35.3% : 64.7% ,HSM was 100%,fever was70.6% and leucocytosis was 11.7%.

But in Pahloosye A,2011 ,male : female ratio was 62%: 38%, HM was 34%,SM was 36% ,fever was 59% and Leucocytosis was 38%. This difference between 2 studies may be due to study duration and sample size difference (duration in Pahloosye study was 4 years and sample size was 100 patients).

Blast cells were found in 4 cases of patients with Fanconi anemia, 1case of patients with idiopathic aplastic anemia, and 1case of patient with Diamond Blackfan anaemia. This may be due to the associated transformation into acute Leukemia as a complication of these disorders. In addition, Shimamura& Alter (2010) stated that there were 300 patients of 2002 case with Fanconi anemia had malignant transformation.

Age and ESR were significantly higher in acute leukemia group compared to the Fanconi anemia and idiopathic aplastic anemia groups, while MCV and Retics were significantly lower in leukemia group.

5. Conclusion:

Bone marrow failure is not rare. Consanguinity has a high role in bone marrow failure and acute leukemia is suspected in any case of bone marrow failure due to the associated transformation into acute Leukemia as a complication of these disorders.

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