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Haematological parameters in acyanotic congenital heart disease with secondary pulmonary hypertension

Sadeel Osama Taha Alshabkhoon
Health Department of Nineveh, Nineveh Health Directorate, Iraq

Abstract
A case series study includes 35 patients, age between (3-14) years old, with acyanotic heart disease and secondary pulmonary hypertension, patients presented with sign and symptoms of infection at time of study and patients receiving antiplatelet drugs had been excluded from this study, in addition to those, if patient have anaemia or thrombocytopenia, should be excluded from platelet function test. Tests had been done for all patients are complete blood count, prothrombin time, activated partial thromboplastin time and platelet function test by PFA 200. This study reveals that there is a differences between the mean of the results for ACCH-PHT patients and the results of the normal control. 54%(19/35) patients had abnormalities in haemoglobin and erythrocytes (RBC) parameters, leucocytes (WBC) count normal in 97% (34/35) and platelet normal in 94% (33/35), the mean of the results was different from those of the normal control, In opposite platelet indices were abnormal in 97% (34/35)-mean platelet volume(MPV) was low in 65.7% (23/35) cases, plateletcrit (PCT) was low in 74.3% (26/35) cases. Platelet function was abnormal in 85% (29/34) cases. Prothrombin time was within normal range while activated partial thromboplastin time was prolonged in 11.5% (4/35) cases.

Keywords: Congenital, heart, disease

Introduction

Congenital Heart Disease

It's a structural heart anomalies presented at birth, incidence varies between 4-5/1000 live births, either affects heart valves, heart walls, or large vessels which carry blood to the hearts, severity of the illness varies from very mild to life threatened depending on the site and size of the defect.

In general, congenital heart disease is classified into two major groups;

1. Cyanotic heart disease.
2. Acyanotic heart disease.

These two major groups are also subdivided depending on whether normal, decreased, or increased pulmonary vascular marking. The most common lesion of the acyanotic heart disease is ventricular septal defect, while tetralogy of fallot is the most common lesion of the cyanotic heart disease.

In acyanotic heart disease, the defect is characterized by left to right shunt so the oxygen concentration in blood will not affected in opposite to the cyanotic heart disease were the main pathophysiology, symptoms and complication is a consequence of hypoxia. In general acyanotic heart disease is considered milder than cyanotic, but may end with pulmonary hypertension and right sided heart hypertrophy, the symptoms is largely depending on the extended of the malformation.

Pulmonary arterial hypertension: In spite of advances in the early detection and surgical intervention of congenital heart disease, still there is high prevalence rate of secondary arterial hypertension mainly in case of uncorrected left to right shunt and usually associated with high morbidity and mortality rate [1, 2, 3, 4, 5, 6].

-In general cardiac diseases lead to decrease oxygen supply to the tissues, hypoxia will increase erythropoiesis activities via stimulation of erythropoietin leading to increase erythrocytes production, haemoglobin (secondary polycythaemia) and blood hyperviscosity. Increasing erythropoiesis may increase iron consumption and leads to iron deficiency. These events is reflected on the results of the complete blood count, as high or near upper normal haemoglobin, hematocrit. erythrocytes, while red blood cell indices including mean cell volume, mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration results reflect iron state, these changes as other symptoms is largely depended on the extent and type of the malformation. So in acyanotic heart disease and due to the absence of hypoxia the red blood cell and its incidence is matched with normal population at same ages.

-The effects on the coagulation include both platelet and coagulation factors, thrombopoiesis like erythropoiesis is highly affected by hypoxia, this results in platelet short life span and stimulation of thrombopoiesis in order to compensate thrombocytopenia. Coagulation factors also have been affected, hypoxia and blood hyper viscosity will interfere with normal circulation and oxygen supply to the liver results in decreasing coagulation factors production. Many studies concentrate on the platelet count, platelet indices, platelet function test, Prothrombin time, activated partial thromboplastin time, D-dimer and coagulation factors, there are significant changes in the all parameters, and in addition to the pathophysiological factors, other study suggested that there is a continuous compensated DIC (disseminated intravascular coagulopathy).

In complicated cases (those associated with pulmonary hypertension), the heamtological changes is mainly functional, the pathophysiology of the changes is complex and multifactorial primarily affect platelet, coagulation pathway and to a little instant leucocytes [7, 8, 9, 10, 11, 12, 13, 14].

Methods

This study included 35 patients with history of congenital heart disease and secondary pulmonary hypertension, age between (3-14) years, referred from pediatric department to the laboratory (Haematopathology unit)/ Al Salam hospital in Mosul as a part of general assessment, between Oct/2013-Jun/2014.

All tests performed within one hour of blood collection to avoid any error which could results from the delay. Patient who was complaining from fever or other signs and symptoms of infection were excluded from this study.

The tests which had been done for all patients are

1. Complete blood Count (CBC) by auto analyzer Ruby cell dine (5 diff), using EDTA (Ethylene di amine tetra-acetic acid) tubes for blood collections.

Including

- WBC (leucocytes count) and differential count
- Hb (haemoglobin), HCT(haematocrit), RBC(red blood cell count), and RBC indices- MCV(mean cell volume), MCH(mean cell haemoglobin), MCHC(mean cell haemoglobin concentration)- and RDW (red distribution width)
- Platelet count and indices – PCT (plateletcrit), MPV (mean platelet volume), PDW (platelet distribution width).

2. Tests to assess coagulation process using tubes containing sodium citrate 3.2% in ratio 1/9 blood.

Including

- P.T. (prothrombin time), and A.P.T.T. (activated partial thromboplastin time), both tests were performed according to standard manual methods [15].
- Platelet function tests by PAF 200(platelet function analyzer) using two kits- Coll/Epi, Coll/ADP-.

Not forget that platelet count and platelet indices also is a first line assessment of coagulation.

All patients included in this study, not received any type of anticoagulant, anti-platelet, or any drug which may interfere with platelet function.

Note: D-dimer was done for all patients to exclude presence of subclinical DIC.

Results

All results summarized in table -1-. The variation in the results illustrated in table-2-,

Table 1: Summaries results of all tests

	WBC	RBC	Hb	HCT	MCV	MCH	MCHC	RDW	Plat.	PCT	MPV	PDW	PT	APTT	C/E	C/A
1	6.03	5.74	17.5	49.5	86.2	30.4	35.3	12.2	195	.207	10.6	21.1	16	48	300	286
2	12.5	5.64	13.2	39.8	70.5	23.3	33.1	14.9	293	.157	5.36	18.3	16	32	200	137
3	14.5	5.34	11.5	38.2	65.9	21.6	32.8	14.4	432	.279	6.45	18.3	15.8	28	216	194
4	6.08	3.77	11.1	32.8	86.9	29.5	34	14.3	237	.189	6.93	19.8	14	40	190	140
5	6.60	4.53	12.4	38.2	79.9	27.4	34.3	12.4	348	.226	6.50	19.0	16	34	76	92
6	13.7	4.64	11.5	34.9	75.3	24.8	32.9	15.9	391	.234	5.98	18.2	16	50	247	271
7	11.0	4.59	13.4	39.7	86.6	29.3	33.8	12.3	228	.199	8.17	21.4	19	48	290	296
8	10.8	5.03	13.1	37.8	75.2	26	34.6	15.4	444	.228	5.14	18.2	15	35	285	271
9	11.8	4.19	10.6	34.2	81.6	25.4	31.1	20.1	195	.170	8.69	21.5	16	37	222	150
10	9.13	4.25	13.0	37.6	88.5	30.5	34.5	12.8	224	.232	10.3	21.5	15.5	50	300	147
11	7.70	4.51	10.9	31.8	70.5	24.2	34.3	12.7	259	.147	5.66	18.6	15.3	35	143	100
12	8.60	4.37	12.2	36.5	83.6	28	33.5	13.1	212	.152	7.17	19.5	15	36	300	143
13	13.0	5.09	14.0	41.5	81.6	27.5	33.7	12.9	248	.179	7.20	19.7	15	37	300	299
14	7.92	4.75	12.9	36.4	76.6	27.1	35.4	13.5	265	.163	6.17	19.1	12	32	260	224
15	9.74	4.52	12.6	36.6	81	27.8	34.3	11.5	328	.225	6.87	19.1	13.5	40	176	93
16	7.74	4.88	13.2	38.8	79.4	27	34	11.9	235	.158	6.73	18.3	16	36	300	290
17	20.2	5.05	13.8	40.7	80.7	27.4	34	14.1	317	.178	5.16	19.0	16	35	182	120
18	7.76	5.67	10.4	33.3	58.8	18	31.1	15.3	341	.226	6.62	18.2	15.2	34	248	280
19	7.73	4.77	14.7	43.1	90.3	30.8	34.1	11.5	202	.189	9.36	21.4	16	36	260	212
20	7.74	4.88	13.2	38.8	79.4	27	34	11.9	235	.158	6.73	18.3	16	36	295	280
21	7.85	3.19	11.9	34.3	87.5	30.3	34.6	12.7	372	.192	5.16	17.8	16	36	240	219
22	8.38	4.69	9.43	28.2	65.4	20.1	30.8	18.2	519	.259	4.99	18.2	13.3	30	260	133
23	7.39	4.85	14.5	45.5	93.7	29.8	31.8	15.2	199	.133	6.70	19.3	13	40	300	270
24	9.12	4.14	12.9	37.5	90.6	31.1	34.3	11.8	204	.181	8.87	21.1	13	36	286	186
25	6.82	4.40	11.7	33.6	76.4	26.6	34.8	11.7	235	.142	6.04	19.9	15	35	180	100
26	6.03	5.00	14.8	43.7	87.4	29.7	33.9	12.7	185	.143	7.74	21.3	15.8	37	300	265
27	9.51	5.42	14.4	42.4	78	26.5	33.9	11.8	339	.157	7.24	20.9	13	30	300	260
28	7.77	4.69	14.5	41.8	89	30.8	34.6	12.7	214	.16	5.60	17.8	15.2	33	283	179
29	16.4	6.1	16.4	49	80	26.8	33.4	14.4	214	.11	5.30	17.8	15	33	297	253
30	10.3	7	21.6	62	86	30.1	34.8	14.5	172	.187	10.9	21.9	15	32	300	285
31	8.4	4.1	13.2	38	92	31	34	11.2	191	.11	5.70	16.7	14	35	276	199
32	12.2	4.79	13.7	41	85.5	28.5	33.2	13	233	.197	8.84	16.0	15	30	300	200
33	11.3	7.7	17.4	55	73	22	30	17.6	243	.170	6.80	15.4	16	32	241	210
34	9.7	5.97	16.4	51.8	86.7	27.5	31.7	14.7	384	.266	7.66	17.4	13	32	185	151
35	6.87	3.95	9.53	29.8	75.3	24.2	32.2	14	99	.069	6.99	23.3	12	33		

Table 2: Illustration the variation in the results

	WBC	RBC	Hb	HCT	MCV	MCH	MCHC	RDW	Plat.	PCT	MPV	PDW	PT	APTT	C/Epi	C/ADP
1		↑	↑	↑						↓				↑	↑	↑
2		↑			↓	↓		↑		↓	↓				↑	↑
3		↑			↓	↓		↑			↓				↑	↑
4		↓						↑		↓	↓				↑	↑
5											↓					
6								↑			↓			↑	↑	↑
7										↓				↑	↑	↑
8								↑			↓				↑	↑
9			↓				↓	↑		↓					↑	↑
10														↑	↑	↑
11			↓	↓	↓					↓	↓					
12										↓	↓				↑	↑
13										↓					↑	↑
14										↓	↓				↑	↑
15											↓					
16										↓	↓				↑	↑
17	↑							↑		↓	↓					
18		↑	↓		↓	↓	↓	↑			↓				↑	↑
19										↓					↑	↑
20										↓	↓				↑	↑
21		↓								↓	↓				↑	↑
22			↓	↓	↓	↓	↓	↑	↑	↑	↓				↑	↑
23							↓	↑		↓	↓				↑	↑
24										↓					↑	↑
25										↓	↓					
26										↓					↑	↑
27		↑								↓					↑	↑
28										↓	↓				↑	↑
29		↑	↑	↑				↑		↓	↓				↑	↑
30		↑	↑	↑				↑		↓					↑	↑
31										↓	↓				↑	↑
32										↓					↑	↑
33		↑	↑	↑	↓	↓	↓	↑		↓	↓				↑	↑
34		↑	↑	↑			↓	↑		↑					↑	↑
35		↓	↓	↓		↓		↑	↓	↓	↓				x	X
Total Normal	34	23	25	27	29	29	29	20	33	7	12	35	35	31	5	5
Total High	1	9	5	5	0	0	0	15	1	2	0	0	0	4	29	29
Total Low	0	3	5	3	6	6	6		1	26	23	0	0	0		

1-CBC was compared with normal persons at same age.

WBC for patients ranges between 6.03-20.2 x10^9 /L, normal range for same age group (5-16x10^9) [15], only one result is higher than normal, WBC for normal control range between (6.94-10.7x10^9/L).

Hb in this study is between (9.53 – 17.5 g/dl), control group is between (10.5-15.3 g/dl), normal rang for this age group is (11 -15.5 g/dl) [15]. Mean value for the patients is 13.6 g/dl while for normal control is 12.4 g/dl. About 71.4% (25/35) of patient have Hb within normal range. About 14.25% (5/35) of patient have Hb more than normal range, and also about 14.25 % (5/35) have Hb below normal.

Platelet count in this study ranges between (99-530x10^9/L), while normal control (178-300x10^9/L), normal range for this age group (170-550x10^9/L) [15], only one patient has mild thrombocytosis and one patients has thrombocytopenia, and 94% (33/35) are normal. PDW are within normal range for all patients, MPV ranges between 5.14-10.9 fl, normal control ranges between 7.4-8.8, it is low in 65.7%(23/35) patients, while PCT is low in 74.3%(26/35), high in 5.7% (2/35) and normal in 20% (7/35).

Normal range for platelet indices: MPV; 7.2-11.7 fl, PDW; 8.3-56.6 10(GSD), PCT; 0.22-0.24 [21, 22]. The mean value for CBC parameters is illustrated in table -3-.

Table 3: mean value for the CBC parameters

	WBC x109/L	RBC X1012/l	Hb g/dL	HCT %	MCV fL	MCH pg	MCHC g/dl	RDW %	Plat. X109/L	PCT %	MPV fL	PDW 10(GSD)
Patient Mean	9.488	5.36	13.36	39.80	80.48	27.08	33.5	13.72	269	0.182	7.18	19.28
Control Mean	8.56	4.70	12.40	38.23	81.34	26.38	32.38	13.14	298	0.231	8.14	19.20

2-Coagulation tests: Prothrombin time for patients ranges between (12-16sec), normal control range is between (11-13sec), normal range is (11-16sec) [15]. Activated partial thromboplastin time is ranged between (30-50 sec) for patients, while normal control range is between (30-35 sec). Normal range is between (30-40 sec) [15]. The results of P.T. for all patients are within normal ranges. The results of A.P.T.T., 91.4 % (32) of patients are within normal range, 8.6% (3) of patients are higher than normal. The mean value of P.T. and A.P.T.T. for both patients and control illustrated in table -4-.

Table 4: mean value of P.T., A.P.T.T

	P.T. sec	A.P.T.T. sec
Patient mean	14.96	12.6
Control mean	36.09	34.2

Platelet Function Analyzer: One case had been excluded because the platelet was bellow $100x10^9$/L. for other patients we start with Col/Epi, normal closure time (<183 sec), normal value excludes presence of platelet dysfunction, if prolonged then Col/ADP is performed, prolonged both Col/Epi >183 seconds, Col/ADP>122 seconds indicate significant platelet dysfunction. 85% (29/34) of cases are associated with prolonged both Col/Epi, and Col/ADP which indicates platelet dysfunction.

Discussion

In this study we concentrate on cases of cyanotic heart disease with secondary pulmonary hypertension, many researchers studied thoroughly Haematological abnormalities in cyanotic heart disease and focus on hypoxia as a leader factor for these secondary haematological changes, so due to the absence of hypoxia in ACCHD, there are rare significant haematological changes [7, 16, 17]. But these finding may differ in ACCHD-PHT [19] which still a common complication in spite of advances in diagnosis and management of the illness. To start with the results of complete blood count, this study show that 94%(33/35) patients have one abnormality or more (table-1, 2), this differ from other study which showed that 75 % of patients have single abnormality or more, this results equal in both CCHD and ACCHD [18]. In this study, although the mean WBC count ($9.488x10^9$/L) is higher than control group within same age, it was within normal rage for this age group.

Concerning the RBC count (table-3-0), the mean count ($5.36x10^9$/L) is higher than the control group and higher than the upper normal limit ($5.2x10^{12}$/L). Other parameters Hb, and RBC incidence, also there are significant changes, near to 30% (10/35) of patients have abnormal haemoglobin level 14.25% (5/35) have haemoglobin less than normal (anaemia), 2/5 of anaemic patients have hypochromic microcytic anaemia, and same number 14.25% (5/35) have higher haemoglobin level 2/5 considered as polycythaemia. 3 Patients have parameters of hypochromic microcytic RBC without anaemia, most probably iron deficient haemopoiesis (low MCV, LOW MCH, High RDW), 1/3 case has polycythaemia accompanied by hypochromic microcytic. Theses significant variation indicate that cases of ACCHD are liable for haematological complication, most probably the pathogenesis is multifactorial, and considers as a significant biomarkers of the severity of the illness, other researchers also concentrate on the changes in RBC parameters in the cardiovascular diseases, as it is an independent biomarkers [17, 18, 19, 20].

This study also concentrated on the importance of variations which could be occur in platelet count, platelet indices and platelet function. The variation in platelet indices is widely studied in the last decades as a land markers in many diseases, the variation is considered as a marker for thrombopoiesis especially if associated with abnormal count, and also consider as a marker of platelet function, low MPV is usually associated decreased platelet activity, high MPV associated with increased platelet activity [21, 22, 23]. In this study, platelet count is normal in 94% (33/35). Only one case has thrombocytopenia, and one case has thrombocytosis, the mean value is lower than control, these results differ from those found in CCHD in which thrombocytopenia is considered a part of secondary haematological complications [7, 16, 17]. there is significant changes in platelet indices, 65.7% (23/35) patients have low MPV, 74.3%(26/35) of cases have low PCT (the value of PCT is dependent on MPV and platelet count), and two cases with high MPV, these finding is consistent with other study which done on platelet activation in PHT secondary to left to right shunt CHD [24]. Other researcher concentrate on the relation between the level of platelet indices and the severity of illness whether PHT is primary or secondary whom found that high MPV is associated with more severe illness [25, 26].

As part of coagulation screen in secondary pulmonary hypertension, In this study we concentrate on prothrombin time, all tests are within normal range (11-16 sec), but still the mean is higher than the mean of normal control, this finding is similar to other study which suggest that these finding is most probably due to delay in the hepatic function. APTT (activated partial thromboplastin time), also the mean is higher than normal control, in addition to this finding 11.5% (4/35) are higher than normal range (30-40sec). In general these changes is milder than that occurs in cyanotic congenital heart disease [17, 18, 27].

Assessment of platelet function in this study done by Platelet function analyzer 200 (PFA 200), which is the essential role of it, is to investigate platelet function disorders, and to follow patients receive antiplatelet medication. All patients included in this study did not receive any type of antiplatelet, 85% (29/34) of cases have higher level than normal for both Col/Epi, and Col/ADP (one case have been excluded because that the level of platelet is less than $100x10^9$/L and Hct less than 30%), this indicate that there is significant platelet dysfunction. Although few studies done on platelet function in secondary pulmonary hypertension, few studies preoperatively done in both CCHD and ACCHD in order to predict the possible postoperative bleeding [28, 29]. A study done on 21 patients with pulmonary hypertension reveals that 90% of PAH have prolonged closure time in one parameter or more (by PFA 100) platelet which indicate impairment in primary haemostasis and significant platelet dysfunction [30].

Conclusion

Although haematological parameters is mildly affected in acyanotic congenital heart disease, there is a significant variation in the haematological parameters in ACCHD-PHT in pediatric age group, and these changes can be considered as a criteria for the presence of secondary complications of the initial illness (acyanotic heart disease). Platelet indices and platelet function are more frequently affected followed by erythrocytes parameters.

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