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Predictive value of complete hemogram in comparison to serum ferritin in the diagnosis of iron deficiency anaemia among paediatric population with congenital heart defect: A cross- sectional study

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ABSTRACT

Objective: Iron deficiency anaemia (IDA) is often associated with congenital heart defect (CHD) in children, especially in developing world. Often it remains undiagnosed due to the unaffordability to do costly tests like serum ferritin. We have done this study to know whether simple test like complete hemogram is sufficient to diagnose IDA in a child with CHD.

Materials and Methods: This hospital based observational study was done for a period of one and half year in paediatric ward of a district medical college of eastern India in children up to the age of 12 years with echocardiography confirmed CHD. Blood sample were tested for serum ferritin, mean corpuscular volume (MCV), mean corpuscular hemoglobin and hemoglobin concentration (MCH,MCHC) and red cell distribution width (RDW) to diagnose IDA.

Results: We found IDA in 46 children out of total 100 CHD cases based on serum ferritin level. Out of 46 IDA children, 40 children (87%) had low MCV, 39 children(84.8%) had low MCH, 33 children (71.7%) had low MCHC, 41 children (89.1%) had high RDW and 37children(80.4%) having microcytic hypochromic picture. In logistic regression analysis we found RDW as the independent predictor of IDA.

Conclusion: IDA is fairly common among children with CHD. Simple blood tests of complete hemogram including MCV, MCH, MCHC and RDW can diagnose it effectively where RDW shows the most predictive value in our study. So in resource limited developing countries we may not depend on costly gold standard tests like serum ferritin to diagnose IDA.

1. Introduction

Congenital heart disease(CHD) is a major determinant of mortality and morbidity in children all over the world including India.[1,2] In developing countries iron deficiency anemia (IDA) is often associated in children with CHD, though it remains underdiagnosed in many cases.. In CHD, the low arterial oxygen saturation and tissue hypoxia stimulates the bone marrow to increase the erythropoiesis, causing a compensatory rise in hemoglobin and hematocrit levels.[3] This excess production of red blood cells exhausted the storage iron in body and thus causing iron deficiency with microcytic hypochromic anemia even with normal or high hemoglobin levels.[4] So we cannot exclude anemia by looking only at hemoglobin or hematocrit level in cases of CHD. Total iron binding capacity (TIBC), transferrin saturation, ferritin and iron level in blood are the commonly used test to diagnose iron deficiency anemia ,but these tests are costly and every patient cannot afford these tests in developing countries. Even in the government hospitals

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these tests in every CHD patients cost a lot of funds. So we are in search of some baseline tests that can diagnose iron deficiency anemia in CHD specially in context of the resource limited developing countries. Some previous studies have shown that simple parameters like mean corpuscular volume (MCV), mean corpuscular hemoglobin and hemoglobin concentration(MCH and MCHC) and red cell distribution width(RDW) can indicate iron deficiency in Children with CHD, but there is scarcity of data available from developing countries like India regarding association of iron deficiency anaemia in CHD and convenient and economic test to diagnose it.[5] With this background we conducted a study in our hospital to determine the association of iron deficiency in a child presenting with CHD. We also have correlated simple blood tests like MCV, MCH, MCHC, RDW, peripheral smear with Gold standard tests like serum ferritin to find out whether they are both equivalent in diagnosis of IDA in these children with congenital heart disease.

2. Material and Methods

This cross-sectional observational study was conducted in the pediatric ward of a district medical college from Eastern India after approval by the institutional ethics committee for a period of one and half year from May 2018 to October 2019 among total 100 children with echocardiography confirmed cases of congenital heart disease. Children aged between 1months to 12yrs attending pediatric outpatient department or admitted in indoor ward with known or suspected heart disease were selected with exclusion criteria of 1.post-operative CHD child, 2.children already on iron therapy and 3.children with acute or chronic infection. First proper history taking and clinical examination was done in relevance to congenital heart disease. History of breathlessness, fatigue, frequent respiratory infections, cyanotic spells, feeding problems, history suggestive of heart failure were recorded. Presence of conjunctival suffusion, cyanosis, pallor, clubbing, respiratory distress, heart rate, blood pressure and oxygen saturation (spo2) were noted. Chest X ray, Electrocardiography and Echocardiography were done to establish the nature of heart disease. Then those children with confirmed CHD ware shortlisted for the study after taking proper consent or assent as applicable for the cases. Venous blood was drawn from each study participant and blood samples were sent for both definitive tests (serum ferritin) and simple tests (complete hemogram, and peripheral smear) to diagnose anemia. Complete hemogram was done by fully automated bidirectional analyser (sysmex xn 1000). Serum ferritin was done by fully automated bi-directionally interfaced chemiluminescence immunoassay. Peripheral smear was examined by hematologist. Data from the blood tests were collated and analyzed statistically to determine the prevalence of IDA and to detect which tests best predict the presence of iron deficiency. We used Serum ferritin value less than 12 ngm/ml (below 5years) and 15 ngm/ml (above 5yr of age) as reference value to diagnose iron deficiency. For other laboratory tests like MCV, MCH, MCHC and RDW to determine the iron deficiency anemia in CHD reference value for normal children were used.

2.1. Statistical analysis

All continuous variables were evaluated for their normality by Shapiro Wilk test. Comparison of categorical variables were completed using chi - square test or Fisher's exact test, as applicable. Independent sample t test was used to compare continuous variables. Further more measurements of agreement were done with kappa value where value of 0.21-0.40 is taken as fair, 0.41-0.60 moderate, 0.61-0.80 substantial and 0.81-1.00 as nearly full strength of agreement. A univariate analysis and a multivariate logistic regression was done to detect independent correlation of simple test with serum ferritin. Analysis was carried out by SSPS version 23.0. In all cases p values < 0.05 was taken as statistically significant.

3. Results

Out of one hundred child with CHD enrolled, we got 56 male and 44 female. Various heart diseases detected by echocardiography are Ventricular Septal Defect(31), Pulmonary Stenosis(12), Patent Ductus Arteriosus (12), Tetralogy of Fallot (10), Atrial Septal Defect (9), Aortic stenosis (7), Coarctation of aorta (5), Artioventricular canal defect (4), Transposition of Great Arteries (4), Truncus arteriosus (2), Double Outlet Right Ventricle (2), Total Anomalous Pulmonary Venous Connection (1) and Ebstein anomaly (1). Out of 100 children, we found 46 iron deficient and 54 iron sufficient children based on serum ferritin level. In the following tables we have shown the comparison of iron status based on serum ferritin and common baseline investigations in complete hemogram like MCV, MCH, MCHC, RDW and peripheral smear.

Table 1: MCV Vs serum ferritin

Ferritin based iron status			
	Iron deficient	**Iron sufficient**	**Total**
Low MCV	40(87.0%)	3(5.6%)	43(43.0%)
Normal MCV	6(13.0%)	51(94.4%)	57(57.0%)
Total	46(100.0%)	54(100.0%)	100(100.0%)

P-value: 0.000
Kappa value: 0.818

Table 1 shows that, Out of 46 iron deficient children based on ferritin level 40 children (87.0%) had low MCV and out of 54 iron sufficient children 51 (94.4%) children had normal MCV with statistically significant p-value.

Strength of agreement was almost perfect with kappa value of 0.818.

Table 2: MCH Vs Serum ferritin

Ferritin based iron status	Iron deficient	Iron sufficient	Total
Low MCH	39(84.8%)	4(7.4%)	43(43.0%)
Normal MCH	7(15.2%)	50(92.6%)	57(57.0%)
Total	46(100.0%)	54(100.0%)	100(100.0%)

P-value: 0.000
Kappa value: 0.778

Table 2 shows that, Out of 46 iron deficient children 39 children (84.8%) had low MCH level and out of 54 iron sufficient children 50 (92.6%) children had normal MCH level. So there is statistically significant correlation between ferritin based and MCH based iron status. Strength of agreement was substantial with kappa value of 0.778.

Table 3: MCHC Vs Serum ferritin.

Ferritin based iron status	Iron deficient	Iron sufficient	Total
Low MCHC	33(71.7%)	14(25.9%)	47(47.0%)
Normal MCHC	13 (28.3%)	40(74.1%)	53(53.0%)
Total	46(100.0%)	54(100.0%)	100(100.0%)

P-value: 0.000
Kappa value: 0.457

Table 3 shows that, Out of 46 iron deficient children 33 children (71.7%) had low MCHC level and out of 54 iron sufficient children 40 (74.1%) children had normal MCHC level, with statistically significant p-value. But strength of agreement was moderate with kappa value of 0.457.

Table 4: RDWVs Serum ferritin

Ferritin based iron status	Iron deficient	Iron sufficient	Total
High RDW	41(89.1%)	6(11.1%)	47(47.0%)
Normal RDW	5(10.9%)	48(88.9%)	53(53.0%)
Total	46(100.0%)	54(100.0%)	100(100.0%)

P-value: 0.000
Kappa value: 0.779

Table 4 shows that, Out of 46 iron deficient children 41 children (89.1%) had high RDW level and out of 54 iron sufficient children 48(88.9%) children had normal RDW level, which was statistically significant. Strength of agreement was substantial with kappa value of 0.779.

Table 5 shows that, Out of 46 iron deficient children 37children (80.4%) were having microcytic hypochromic picture and out of 54 iron sufficient children 50(92.6%) children had normocytic normochromic picture, with statistically significant p-value. Strength of agreement was substantial with kappa value of 0.736.

Table 5: Peripheral smear Vs Serum ferritin

Ferritin based iron status	Iron deficient	Iron sufficient	Total
Microcytic hypochromic	37(80.4%)	4(7.4%)	41(41.0%)
Normocytic normochromic	9(19.6%)	50(92.6%)	59(59.0%)
Total	46(100.0%)	54(100.0%)	100(100.0%)

P-value: 0.000
Kappa value: 0.736

Table 6: Logistic regression analysis with baseline investigations

Variable	B(unstandardized beta coefficient)	Standard error	p-value
MCV	1.987	1.494	0.183
MCH	-1.154	1.595	0.470
MCHC	1.457	1.043	0.162
RDW	2.018	1.017	0.047
Peripheral smear	1.542	1.286	0.230

To identify the independent predictor of iron deficiency, a logistic regression analysis was done with baseline investigation. In our study, RDW was found to be the independent predictor of iron deficiency, which was statistically significant (p-value 0.047).(shown in Table 6)

4. Discussion

Anemia is among one of the major cause of death and disability in children with cyanotic and acyanotic CHD.[6–8] It not only makes the child irritable, fatigued or causes poor physical and mental development but also may causes some life-threatening events like cardiac failure or thrombotic complications in the context of CHD. Increased compensatory erythropoesis due to tissue hypoxia in CHD can lead to hyper-viscosity which can further lead to cerebrovascular accidents and death.[9] Hence early diagnosis and treatment of anemia in children with CHD is extremely important along with the management of heart disease itself. As we know, even normal or incresed hemoglobin or hematocrit levels in such children may constitute anemia due to iron deficient RBCs, so diagnosis of anemia depending on hemoglobin and hematocrit is difficult in the children with CHD compared to normal children. Definitive test like serum ferritin, serum iron, TIBC, Transferrin saturation are often used to diagnose iron deficiency anemia in children with CHD. Though incidence of iron deficiency anemia is more in a child with CHD in developing countries, there is not enough research data available from India regarding prevalence of IDA in CHD

child and parameters for determining IDA in a child with CHD is still debatable.[10] Ferritin was the most common used investigation to diagnose iron deficiency in many of the studies we reviewed in our literature search.[6,10] Hence, we used serum ferritin as the gold standard test to diagnose iron deficiency and depending on serum ferritin prevalence of IDA in CHD was 46.0% in present study. IDA prevalence in CHD child from various studies ranges from 16.9% to 75.9% worldwide.[10–12] Study by Yu X et al found 39% of child with CHD were suffering from iron deficiency[13] and study by Lang'o MO et al found prevalence of IDA as 16.9% in Cyanotic CHD(CCHD) where they recommended routine screening for IDA in CCHD both by examining peripheral blood smear and serum ferritin.[11] In 2009 Maloku-Ceku et al. in his study found all children with CHD on admission had low serum iron.[14] Though levels of ferritin was by far the commonest method of diagnosing the presence of iron deficiency anemia, other simple parameters like MCV, MCH, MCHC and RDW were included in various studies also. Drossos C et al. showed MCHC as an easy and reliable marker for iron status among patients of CHD.[15]

A study from Asian country by Onur CB et al in 2003 found prevalence of iron deficiency anemia 63.6% where they observed that red cell distribution width was one of the most important parameter for diagnosing iron deficiency anemia.[10]

Children with acyanotic and cyanotic CHD may suffer from low iron levels, but children with cyanotic heart diseases do not show the corresponding fall in hemoglobin levels, termed by many authors as "relative anaemia".[16,17]OnurAmoozgardiagnose IDA. Measurement of MCV, MCH and to diagnose ID Apatients with CHD.[6,10]there is no standard reference level for

Iron status based on baseline investigation were compared with iron status based on serum ferritin by univariate analysis. Iron status based on MCV, MCH, MCHC, RDW, peripheral smear were statistically significant with serum ferritin (p-value<0.05). Following univariate analysis, strength of agreement was measured by using kappa value. In our study, iron status based on CV values with serum ferritin, the strength of agreement was almost perfect (kappa value >0.80). The strength of agreement for MCH, RDW, peripheral smear was substantially significant with kappa measurement 0.61 to 0.80. The power of agreement for MCHC was moderate significance (kappa value 0.41- 0.60). So our study shows that simple tests like MCV, MCH, MCHC, RDW or peripheral smear examinations can diagnose iron deficiency as effectively as serum ferritin in children with CHD.

In the research conducted by Olcay L et al, they found combination of hemoglobin, hematocrit, MCV and RBC indices were easy and inexpensive method and sufficient to diagnose iron deficiency in children with CHD.[18] To identify the independent predictor of IDA, a logistic regression analysis was done with baseline investigations. A total of five variables in baseline investigations were found to be significant in the univariate analysis with statistical significance of p -value <.05. Out of 5 variables, only red cell distribution width (p- value 0.047) was found to be the independent predictor of iron deficiency. RDW actually shows the variation of RBC size and an elevated RDW (anisocytosis) is the hallmark of iron deficiency anemia from our study.

Keeping ferritin as gold standard, we noted that other simple parameters of total hemogram correlated well in univariate analysis, whereas RDW was the only one which correlated significantly in multivariate analysis, thereby making it the most useful predictor of presence of IDA in a child with congenital heart disease.

5. Conclusion

Iron deficiency anemia is a frequent association in a child with CHD and its prevalence is 46.0% in our study. So every children with CHD should be screened for the presence of iron deficiency anemia as it may complicate the course of the heart disease itself. It is often remain unnoticed as hemoglobin and hematocrit alone cannot detect iron deficiency in children with CHD due to the polycythemia and relative anemia. Though ferritin is the gold standard tests to detect iron deficiency but it is costly and simple tests like MCV, MCH, MCHC or RDW can be as effective as ferritin for the diagnosis, as we have found in our study. In fact, we found RDW, which is a part of complete hemogram as the hallmark of iron deficiency anemia in children with congenital heart disease. So in resource limited countries like India we can detect iron deficiency by screening every children with CHD by simple test like complete hemogram instead of expensive gold standard test like serum ferritin.

6. Source of Funding

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7. Conflict of Interest

None.

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