



Research article

Iron-deficiency anaemia in children with congenital heart diseases at a teaching hospital in Ghana

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ABSTRACT

Background: Uncorrected congenital heart lesions in children keep them in a state of constant hypoxia with compromised quality of life and reduced life expectancy. This requires early diagnosis and interventions including prevention and treatment of the resultant anaemia. Unfortunately, congenital heart disease (CHD) often goes unrecognized and thus untreated.**Objectives:** We determined the occurrence of CHD in children below 15 years at the Komfo Anokye Teaching Hospital (KATH), assessed the prevalence of relative iron deficiency anaemia in that cohort and the use of iron supplementation in these patients.**Methods:** We conducted a cross-sectional study, using a structured data collection tool, by retrospectively reviewing patient records from December 2015 to January 2010. Data was also obtained prospectively from January 2016 to March 2016.**Results:** Eighty cases (44 females and 36 males) of CHD were encountered. Tetralogy of Fallot was the most common (48.8%) CHD. Cases of cyanotic congenital heart disease were reported at autopsy. Of the 80 cases, 48 (72.7%) had signs of relative iron deficiency. Thirty (62.5%) of the 48 patients did not receive iron supplementation. In 14 cases, full blood count was not determined and yet 10 patients received iron at sub-optimal doses (<3 mg/kg/day) and one was given iron at 6 mg/kg/day.**Conclusion:** CHD is a common phenomenon among newborns at KATH. Use of iron supplementation was sub-optimal. Compliance with guidelines on the use of iron as well as structures for early detection of CHD for definitive interventions are advocated.

1. Introduction

Congenital heart disease (CHD) comprises a spectrum of structural heart diseases and great vessels present at birth. CHD accounts for nearly one-third of all congenital anomalies [1, 2]. Globally, an estimate of 8 defects per 1000 live births is reported [3]. CHD is classified according to its complexity as: (i) simple defects like ventricular septal defects, atrial septal defects, pulmonary stenosis, and persistence of ductus arteriosus; (ii) defects with moderate complexity like Tetralogy of Fallot, aortic stenosis, pulmonary stenosis, and ostium primum atrial septal defect, total anomalous pulmonary venous return (TAPVR),

partial anomalous pulmonary venous return (PAPVR) and common atrium; (iii) complex congenital heart disease group which includes dextro-Transposition of the great arteries (DTGA), double-outlet right ventricle (DORV), tricuspid atresia, pulmonary atresia, congenitally corrected transposition of great arteries, atrioventricular septal defect (AVSD) and truncus arteriosus [4].

CHD patients frequently have low oxygen saturation in their blood because of inappropriate intra-cardiac communication. The need for an increased circulating haemoglobin mass in cyanotic infants puts a severe stress on their endogenous and dietary iron supplies resulting in relative iron deficiency anaemia. Such patients are at a high risk of

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increased tissue hypoxia and blood viscosity culminating in metabolic acidosis, hyper-cyanotic attacks and thrombo-embolic events especially in children under 4 years of age [5]. Historically, most of the patients with congenital heart defects had little chance of survival. Majority of the conditions were diagnosed at post-mortem examinations [6, 7]. However, early detection and appropriate interventional advances, in particular, surgery and improved medicines have now transformed the treatment of congenital heart disease (CHD) in children. Consequently, CHD patients can now survive into adulthood creating a new and steadily growing patient population described as “patients with grown-up congenital heart disease” [8, 9, 10]. Despite these advances, children with CHD receive little or no intervention in our setting as there is a dearth of research on the subject. This study seeks to find out the prevalence of iron deficiency anaemia in children under 14 years with cyanotic congenital heart disease at Komfo Anokye Teaching Hospital (KATH), its management, outcome and assess the use of iron supplements and other pharmaceutical care issues.

2. Methods

2.1. Study site

Paediatric cardiology unit of the Komfo Anokye Teaching Hospital (KATH). KATH is the second largest tertiary health facility in Ghana and a major referral centre for the northern sector of the country and the northern parts of neighboring West African countries like La Cote d'Ivoire, and the southern parts of Burkina Faso and Mali. KATH has an average annual attendance of 1,560 for children.

2.2. Study population

All children under the age of 14 diagnosed with CHD between January 2010 and March 2016.

2.3. Study design and data collection

The study was cross-sectional. The data collection tool was structured to obtain information on patient demographics, diagnosis of CHD, erythrocyte indices and treatment with iron preparations. Erythrocyte indices recorded included Packed Cell Volume (PCV), Haemoglobin (Hb), Haematocrit (Hct), Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH) and Red Cell Distribution Width (RDW).

Data was retrieved retrospectively from case notes of patients diagnosed with CHD, between January 2010 and December 2015. The records were retrieved from the main archives of the KATH medical records unit. In addition, data was collected prospectively from case notes of newborns and children admitted to the paediatric cardiology ward as well as the OPD clinics from January 2016 to March 2016.

Quality of anaemia management in the patients was evaluated using the standard from the Ghana National Standard Treatment Guidelines, 2017 (STG). A variety of proprietary iron preparations are prescribed depending on the preference of the prescriber. The most commonly prescribed formulations were Zincofer, 200ml syrup (Apex Laboratories pvt Ltd.); Ferup syrup (Zyodus Candila Healthcare Ltd.); Haematovite syrup (Kinapharma Ltd, Ghana) and Maxiron (Iron III hydroxide polymaltose complex) [Mission Vivacare Ltd.], all of these taken orally.

2.4. Ethical clearance

The study was approved and registered by the Research and Development Committee of KATH. In addition, ethical clearance was obtained from the Committee on Human Research, Publications and Ethics (CHRPE) of the School of Medical Sciences of the Kwame Nkrumah University of Science & Technology (KNUST), Kumasi.

2.5. Data analysis

The data obtained was coded, stored and then analyzed using IBM SPSS Statistics for (Windows, Version 21.0. Armonk, NY: IBM Corp.) for frequency distribution and descriptive statistics.

3. Results

Demography of patients: Eighty (females:44, males:36) cases of CHD were recorded between January 2010 and March 2016. The annual case distribution over the period is indicated in Table 1. Fifty percent of the cases occurred in children from birth to less than a year, 38.8% occurred in those aged 1–5 years and 11.3% of the cases were in children over 5 years (Table 1). Over the period (2010–2016) a gradual increase in the annual occurrence of the defects was recorded with majority of the cases detected in 2014 (27.5%) and 2015 (35%). Autopsy reports on children, from the pathology department revealed some missed cases of CHD attributable to cyanotic congenital heart disease (Figures 1A, 1B, 1C).

3.1. Types of CHD encountered

Tetralogy of Fallot was the most frequently encountered CHD (48.8%), followed by persistent truncus arteriosus (10%), transposition of great arteries (8.8%), and complete channel defect being 7.5% of the cases (Figure 2). Pulmonary atresia (1.3%), tricuspid atresia (2.5%) and double outlet right ventricle (2.5%) were least common. Of the 80 CHD patients, 6 (7.5%) were cyanotic (Figure 1).

3.2. Erythrocyte indices

Of the 80 children with CHD, 66 had full blood count (FBC) carried out. Erythrocyte indices recorded were haemoglobin (Hb), red blood cell (RBC), mean corpuscular volume (MCV), red blood cell distribution width (RDW), packed cell volume (PCV) and mean corpuscular haemoglobin concentration (MCHC) (Figure 3 and Table 2). Thirty children had Hb levels above the maximum considered normal (14.0 g/dL) and 11 had Hb values below the lower limit of 11.0 g/dL. Though the median Hb value (13.6 g/dL), was normal, there was a wide inter-patient variability with haemoglobin content of RBCs ranging from a minimum of 8.0 to a maximum of 24.3 g/dL (interquartile range, 11.0–18.7).

The reference value for RBC count is $3.8\text{--}5.4 \times 10^6/\mu\text{l}$. RBC counts in five children were low and 46 had high RBC counts. This is represented in Figure 2 (min: 2.7, max: $9.9 \times 10^6/\mu\text{l}$; interquartile range: 4.5–8.1; median 5.8).

The upper limit of RBC count was $9.9 \times 10^6/\mu\text{l}$ corresponding with the extreme Hb value of 24.3 g/dL. The median MCV value (74.6 fL) and MCH value (25.1 pg) are well below the lower reference ranges of 85.0 fl and 31.0 pg respectively. The median RDW-SD (53.5 fl) is also higher than those in the reference range (39.0–46.0).

3.3. Use of iron supplements

Out of the 66 patients with FBC determined, 48 (72.7%) had relative iron-deficiency anaemia. Of the 48 children with relative iron-deficiency anaemia, 30 (62.5%) did not receive iron supplementation, 7 (14.6%) received iron in doses higher than 3 mg/kg/day and 11 (22.9%) received iron at dose levels lower than 3 mg/kg/day. In 18 children without anaemia, 2 (11.1%) received iron at doses higher than 3 mg/kg/day and 3 (16.7%) had iron at doses lower than 3 mg/kg/day.

In 14 cases in which FBC was not determined, 11 received iron supplementation presumptively. Ten (10) of these patients received iron at doses less than 3 mg/kg/day and one (1) was given iron at 6 mg/kg/day. Iron supplements administered include Zincofer, 200ml syrup (Apex Laboratories pvt Ltd.); Ferup syrup (Zyodus Candila Healthcare Ltd.); Haematovite syrup (Kinapharma Ltd, Ghana) or Maxiron (Iron III hydroxide polymaltose complex) [Mission Vivacare Ltd.].

Table 1. Occurrence of CHD in children at KATH between January 2010 and March 2016.

Year	Occurrence of CHD in different age groups (years)			Total (%)
	<1 yr	1–4 yr	5–14 yr	
2010	1	1	0	2 (2.5)
2011	1	2	0	3 (3.8)
2012	3	1	1	5 (6.3)
2013	4	8	2	14 (17.5)
2014	10	9	3	22 (27.5)
2015	17	9	2	28 (35.0)
2016*	4	1	1	6 (7.5)
Total n(%)	40 (50)	31 (38.8)	9 (11.3)	80 (100)

* Cases for 2016 covered only 3 months (January–March).

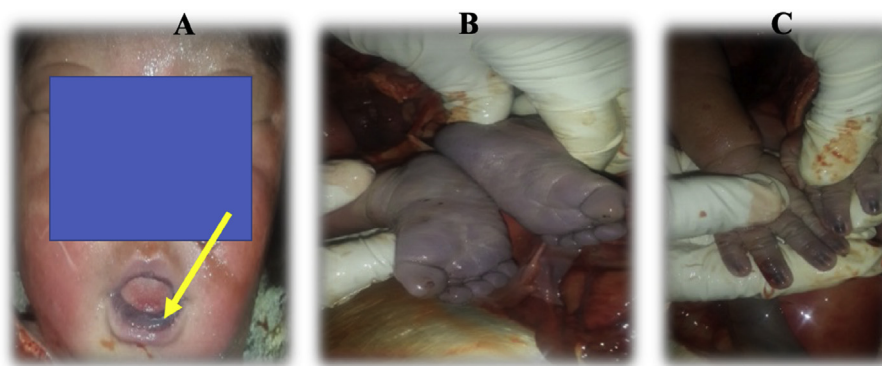


Figure 1. Gross appearance from autopsy depicting cyanosis in the Mouth (A), Feet (B) and Hands (C).

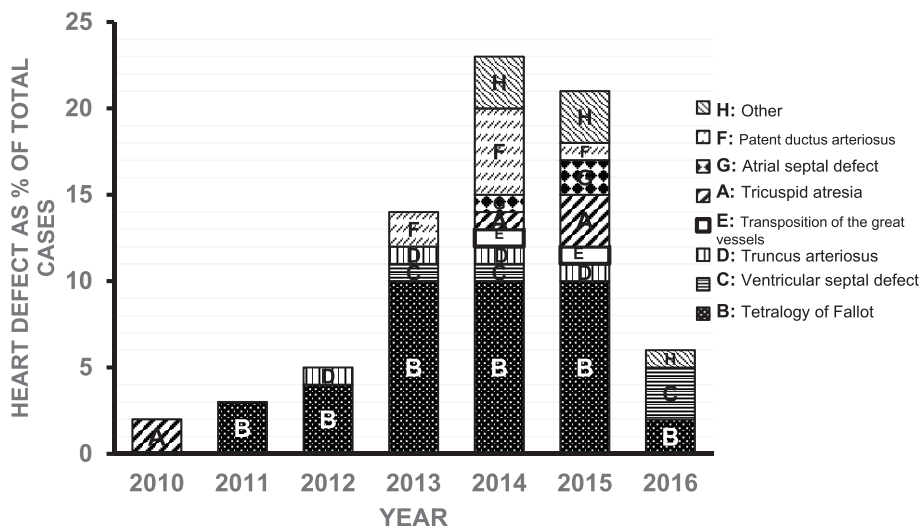


Figure 2. Frequency (expressed as percent of total cases), of the types of CHD (A: Tricuspid atresia; B: Tetralogy of Fallot; C: Ventricular septal defect; D: Truncus arteriosus; E: Transposition of the great vessels; F: Patent ductus arteriosus; G: Atrial septal defect and H: others) in children at KATH between January 2010 and March 2016. Tetralogy of Fallot was the most frequently encountered defect in all years.

4. Discussion

We have investigated the presence of congenital heart disease in children at KATH between January 2010 and March 2016. Use of iron supplements was also assessed in the same group. Eighty (80) cases of CHD were recorded within the study period. Our results indicate the presence of various categories of CHD ranging from simple defects like ventricular septal defects and persistence of ductus arteriosus through moderately complex defects like Tetralogy of Fallot and aortic stenosis to

more complex congenital heart disease that included double outlet right ventricle and truncus arteriosus. There appears to be an increase in number of cases from two in 2010 to a peak at 28 in 2015. We attribute the earlier low figures to missed diagnosis due to lack of expertise and poor record keeping. The higher numbers is due to factors including increased awareness of the condition resulting from the presence of paediatric cardiologists in the hospital and better record keeping as the hospital computerised its systems. Over the study period, the highest proportion of the cases (50%) was recorded in children below one year,

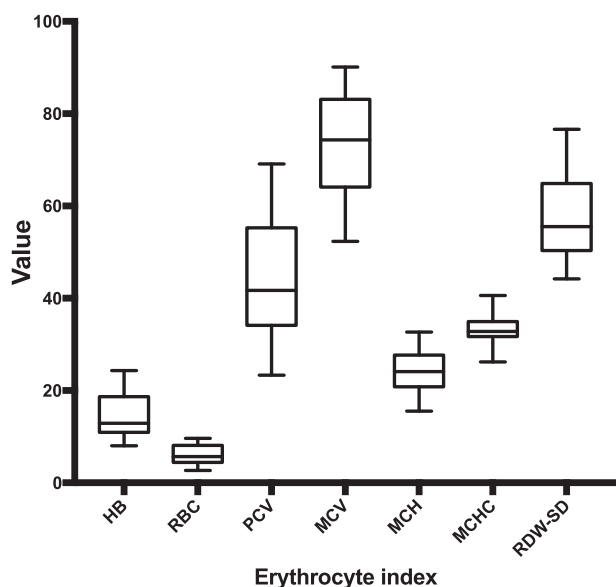


Figure 3. Erythrocyte indices of CHD patients. Each box represents the median, lower quartile (Q1), upper quartile (Q3), minimum and maximum values (n = 66) for each parameter. The details are provided in Table 2. HB – haemoglobin; RBC – red blood cell; PCV – packed cell volume; MCV – mean corpuscular volume; MCH – mean corpuscular haemoglobin; MCHC – mean corpuscular haemoglobin concentration; RDW-SD – red cell distribution width standard deviation.

declining to 38.8% in children of the age group 1–5 years and significantly lower proportion of 11.3% in children aged between 5 and 14 years. This observation confirms earlier reports of poor survival rates among children with CHD in resource constrained environments [6, 7].

Evidence of persistent missed diagnosis of CHD was provided from autopsy reports. This observation, though unfortunate is not unusual because even in better resourced settings with better diagnostic techniques, where standard practice requires clinical examination of the cardiovascular system at the routine newborn examination, it has been reported that routine cardiovascular examination misses nearly half the newborns with significant CHD [11, 12].

More recent reports show that in better-resourced settings, the diagnosis of CHD is currently established by one week of age in 40–50% of patients and by one month in up to 60% [13]. In such settings, prenatal diagnosis is often used to detect most cases of CHD before birth. However, in most developing countries and in our center for that matter, only a few children with CHD are detected, often at late stage, and few benefit from surgical treatment because most do not survive to meet surgical intervention. This is the result of delayed diagnosis, absence of highly skilled and competent personnel and lack of facilities for surgery. This situation leaves infants in poorly resourced countries with unrepaired or palliated CCHD or undetected septal defects resulting in suboptimal

management and unfavourable outcomes. The detection of undiagnosed cases from autopsy reports in our study is therefore not surprising.

Relative iron-deficiency was detected in most of the patients with some being cyanotic. A major consequence of cyanosis is increased tissue hypoxia resulting from iron-deficiency anaemia. The hypochromic, microcytic anaemia characteristic of iron deficiency in infants and young children is ordinarily accompanied by a moderate or severe decrease in the haemoglobin concentration below levels considered normal for the age of the patient. The low oxygen saturation present in the blood of these patients causes a compensatory increase in haemoglobin concentrations at abnormally high levels to prevent tissue anoxia. In response to tissue hypoxia, specialised sensor cells in the kidneys produce erythropoietin. When CHD is associated with hypoxia, erythropoietin levels increase and secondary erythrocytosis ensues. The increased erythrocyte mass may resolve the deficit in tissue oxygenation and establish a new equilibrium at higher haematocrit. Therefore, the extra demand on iron stores often results in iron deficiency in infants with cyanotic congenital heart disease without corresponding decreases in Hb and RBC. This observation is reflected in our results.

Paradoxically, the excessive increase in erythrocyte mass can impair tissue oxygen delivery because of increased blood viscosity [14]. These children commonly exhibit symptoms of anaemia like irritability, anorexia, poor weight gain or attacks of dyspnoea. They are more predisposed to developing metabolic acidosis, hyper-cyanotic attacks and thromboembolic events especially in those less than 4 years of age [15].

Thus, in the management of children with CHD, it is important to not only accurately diagnose iron deficiency in these patients but also appropriately manage it. Diagnosis of iron deficiency anaemia usually involves use of expensive resources not readily available in resource-constrained environments. Yet failure to diagnose this has dire consequences for patients. In this study, iron deficiency anaemia was largely diagnosed using Red Cell Distribution Width (RDW) and Mean Corpuscular Volume (MCV), affordable validated parameters for diagnosing iron deficiency [16, 17, 18]. When RDW and MCV are considered together, iron deficiency anemia could be diagnosed with 98% accuracy [15].

Iron deficiency may have been under-diagnosed in our study because there was evidence that some clinicians depended on the Hb and RBC counts. As indicated earlier Hb, Hct and RBC are unreliable parameters in diagnosing iron deficiency anaemia in CHD patients. In consonance with earlier studies, we reiterate that it is sufficient to use RDW, MCV and MCH values to diagnose iron deficiency in children with CCHD. Red cell distribution width picks up early iron deficiency before other tests. It indicates red cell size variation which is the earliest morphologic changes in iron deficiency anaemia. In pre-latent and latent stage of iron deficiency MCV are normal. Whereas in latent stage, Red Cell Distribution Width (RDW) increases because of a microcytic population of cells appearing in the blood [17]. The large median RDW values seen in our study represent this phenomenon. Additionally, the median values for MCH and MCV were significantly decreased indicating presence of microcytic cells due to iron deficiency. The absence of expensive additional diagnostic tests like SI, TIBC and serum ferritin do not therefore,

Table 2. Red cell indices of study sample the measures include Median, minimum and maximum values, lower quartile (Q1) and upper quartile (Q3) values for each haematological parameter.

Parameter	Group size (n)	Reference (Normal) value	Values from patients		First (lower) quartile (Q1)	3 rd (upper) quartile (Q3)
			Median	Min - Max		
Hb (g/dL)	66	11.0–14.0	14.6	8.0–24.3	11.7	18.5
RBC (10 ⁶ /μl)	65	3.8–5.4	7.8	2.7–9.9	4.7	5.8
MCH (pg)	65	31.0–36.0	25.1	14.1–35.9	22.3	27.7
MCHC (g/dL)	66	30.0–35.0	32.9	24.9–40.6	31.5	34.6
PCV (%)	65	30.0–40.0	44.2	16.3–69.1	34.9	52.6
MCV (fL)	66	85.0–97.0	74.6	52.3–98.0	67.7	82.3
RDW-SD (fl)	66	39.0 46.0	53.5	13.3–86.7	45.8	61.7

invalidate this simple approach of using RDW, MCH and MCV as reliable parameters for diagnosing iron deficiency anaemia.

Guidelines for iron supplementation recommend that in iron sufficient children with Hct below 60%, low dose iron supplements (3 mg/kg, ferrous sulphate three times daily for four weeks) should be given to prevent onset of latent iron deficiency. Adherence to this guideline should be monitored.

As we draw attention to the need for more routine screening for CHD in children, we do not under-estimate the complexity of diagnosing the condition and management. We therefore, present these findings with caution as several limitations confound our results. For example, patients with history of recent or current acute and chronic infection or vaccination or of renal disease should be excluded because of their known effects on bone marrow and iron metabolism. Similarly, patients with history or sign of liver disease or any genetic disorder, including Down syndrome or hypothyroidism should be excluded in these studies as these conditions cause macrocytosis. Other groups include children with leukemia or reticulo-cytosis and children already receiving iron supplements.

5. Conclusion

Although corrective surgery for CHD may be available in resource-constrained countries like Ghana, it must be linked to a strategy of early detection and creation of a network of trained health practitioners that could evaluate and allow for easy identification and informed referral from primary health care units in the health system to surgical/medical centres with the requisite personnel and resources to best manage the condition. Health care teams comprising pediatricians, surgeons and clinical pharmacists must collaborate in the design of locally relevant protocols, recognizing the constraints in terms of resources for diagnosis and management of patients with CHD. Early detection of relative iron deficiency is also advised as well as strict adherence to guidelines on management.

Declarations

Author contribution statement

I. Ossei: conceived and designed the experiments; performed the experiments; analyzed and interpreted the data; contributed reagents, materials, analysis tools or data; wrote the paper.

P. P. S. Ossei: conceived and designed the experiments; analyzed and interpreted the data; contributed reagents, materials, analysis tools or data; wrote the paper.

K. O. Buabeng, M. Duwieja: conceived and designed the experiments; analyzed and interpreted the data; wrote the paper.

S. B. Nguah: conceived and designed the experiments; performed the experiments; wrote the paper.

W. G. Ayibor, E. Agyemang-Duah: analyzed and interpreted the data; contributed reagents, materials, analysis tools or data; wrote the paper.

B.P. Anto: conceived and designed the experiments; wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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