

Iron Deficiency and Behavioral Disorders in Children with Congenital Heart Disease

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DOI: [10.36348/sjm.2021.v06i07.005](https://doi.org/10.36348/sjm.2021.v06i07.005)

| Received: 03.06.2021 | Accepted: 07.07.2021 | Published: 15.07.2021

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Abstract

Introduction: Congenital heart disease (CHD) is the most common birth defect. Emotional and behavioral problems are among the most prevalent chronic health conditions of childhood and often have serious negative consequences for a child's academic achievement and social development. Iron deficiency is one of the most common nutrient deficiencies.

Aim of The Work: To determine the effect of iron deficiency and congenital heart disease on the behavior of children.

Subjects and Methods: This is a case control study of 90 children, 60 children had congenital heart disease they divided into two groups: 30 cyanotic and 30 acyanotic. All studied children subjected to the following: Assessment of behavioral disturbance using an adapted Arabic translation of Conners' PARENT rating scale and specific laboratory investigations including: serum ferritin, serum iron, total iron binding capacity, transferrin saturation capacity. **Results:** Behavior disorders were more frequent among congenital heart disease patients (33, 3%) compared to controls (13.3%) regardless the type of congenital heart disease either. Iron deficiency was more prevalent among children with congenital heart disease 25 (41.6 %) in comparison to control group 4 (13.3%) specially in cyanotic heart disease as we found 43.3% had iron deficiency in comparison to cyanotic heart disease (33%) . There was slight increase in behavioral disorder in children with iron deficiency specially in those with cyanotic heart disease. **Conclusion:** Children with CHD are at higher risk of behavioural disorder specially those how suffering from iron deficiency.

Keywords: Congenital heart disease-Iron deficiency -Behavioral disorder.

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INTRODUCTION

Congenital heart defects (CHD) are defined as abnormal cardiocirculatory structure or function present at birth, although they are often not detected until later in life. CHDs are the most frequent lethal malformation, affecting about 1% of newborns and causing significant morbidity and mortality in infants. These account for 30% of total congenital abnormalities, with a birth prevalence of 4–50 per 1000 (Hoffman *et al.*, 2002).

With the advancement of diagnostic techniques and corrective therapies for congenital heart disease (CHD), the percentage of individuals surviving to adulthood has increased over past few decades. While it is true that the majority of children with CHD today will survive, up to half of surviving children will have impaired neurodevelopmental outcome across a wide spectrum of domains (Van *et al.*, 2011).

As more children survive with congenital heart diseases, management of their behavioural problems are becoming increasingly important as children with congenital heart diseases have more behavioural problems compared to children without chronic illnesses (Beena *et al.*, 2015).

Emotional and behavioral problems are among the most prevalent chronic health conditions of childhood and often have serious negative consequences for a child's academic achievement and social development. (Turgeon *et al.*, 2002).

Negative iron balance can result in classic iron deficiency anemia as well as tissue level iron deficiency without accompanying anemia. The latter is particularly concerning, because models demonstrate that brain iron can be affected prior to the onset of anemia. Which have negative impact on cognitive function. (west *et al.*, 2010).

In the brain, iron is bound to ferritin, low ferritin levels in childhood have been reported to affect the development of the central nervous system, leading to mental retardation and behavioral disorders (Grantham-McGregor & Ani, 2001).

Since iron has a role as a cofactor of tyrosine hydroxylase, its decrease limits enzyme involvement in the synthesis of dopamine, and its deficiency may change the receptor density and the dopamine activity (Menegassi *et al.*, 2010). Therefore brain iron stores are expected to influence the monoamine-dependent functions that are altered in attention deficit hyperactivity disorder (Konofal *et al.*, 2008).

Serum ferritin is a reliable measure of iron stores in body tissues, including brain, and low level can detect an early iron deficiency sufficient to cause neurological or behavioral symptoms (Juneja *et al.*, 2010).

Aim of this work

The aim of this work is to determine the effect of iron deficiency and congenital heart disease on the behavior of children.

Subjects and Methods

This study conducted on 90 Egyptian children with ages ranging between 4 years and 18 years old. Sixty children had congenital heart disease they divided into two groups:

Group 1: consisted of 30 patients with cyanotic heart disease

Group 2: consisted of 30 patients with acyanotic heart disease.

In addition to 30 age and sex matched healthy children serve as a control group. They recruited from pediatric department in National Heart Institute.

Patient group

Inclusion criteria

- Both genders
- Age of the patients ranging from 4- 18 years
- Children with congenital heart disease (either cyanotic or acyanotic)

Exclusion Criteria

- Children with co-morbid severe chronic health problems (renal, hepatic, endocrinal, respiratory diseases)
- Children with rheumatic heart disease or cardiomyopathy
- Children with neurological disorder
- Children with chromosomal abnormalities
- Children with acute illness

Control Participants

Healthy children who had:

- No history of congenital heart disease
- No history of chronic illness.

METHODS

All studied children subjected to the following

1. Clinical history taking with special emphasis on

Demographic data ,detailed cardiac symptoms, detailed neurological symptoms detailed history of child behavior

2. Physical examination with special emphasis on

- a- Anthropometric measurements
- b. Full cardiac examination
- c. Full neurological examination

3. Routine Laboratory investigations including

- a. Complete blood count
- b. Renal and liver function test

4. Specific Laboratory investigations including

- a. Serum ferritin.
- b. Serum iron.
- c. Total iron binding capacity.
- d. Transferrin saturation capacity.

5. M mode, 2 dimensional Echocardiography

6. Assessment of behavioral disturbance using an adapted Arabic translation of. Conners' PARENT rating scale revised LONG version, (CPRS-R-L) introduced by professor Keith Conners in 1997.

RESULTS

This case control study included on 60 children with congenital heart disease (54%) was females and (46%) were males.

The studied groups were subdivided to acyanotic and cyanotic heart disease groups .In Acyanotic heart disease group there were 14 females (46.7 %) and 16 male (53.3%) while in the Cyanotic heart disease group there were 19 females (63.3%) and 11 males (37.3%).

A total of 60 patient with congenital heart disease 30 acynaotic patient and 30 cyanotic patients was diagnosed echocardiographically in acyanotic heart disease Atrial septal defect was the commonest with rate 43, 3% then Ventricular septal defect with rate 26, 7% then Congenital mitral regerge10, 0% then Subaortic memberane by a rate 10, 0% then Pulmonary stenosis by arate of 6, 7% then Coarctation of aorta with a rate 3, 3%, in cyanotic heart disease Fallot tetrolgy was 36, 7%, Double outlet right ventricle was 16, 7%, TGA was 16, 6%, Double inlet left ventricle 6, 7%, Truncus artrioues 6, 7%, Ebstien 6, 7%, Atrio

ventricular septal defect was 3, 3%, Esinmenger PDA3, 3%, Esinmenger VSD 3, 3%.

Behavior disorders were more frequent among congenital heart disease patients compared to controls. There was 33, 3% of patients with congenital heart disease had behavior disorder in comparison to 13, 3% of controls as shown in table 1 However no significance in the behavioural disorder between children with cyanotic and acyanotic heart disease except for ADHD as shown in table 2.

Iron deficiency was more prevalent among children with congenital heart disease in comparison to control group as we found 25 (41.6%) had iron deficiency, iron deficiency was more prevalent in acyanotic heart disease by 43.3% in comparison to cyanotic heart disease by 33%, however this difference was insignificant.

In our study cyanotic group had increased Hb, HCT which reflect the increase in cyanotic patient in response to hypoxia causing polycythemia as shown in table 3.

Table-1: Comparison between behavioural disorder in congenital heart disease and control

Variable		Congenital heart (N0.=60)		Control group (N0.=30)		Chi square test	
		No.	%	No.	%	X ²	P value
Presence of behavioral disorder	No	40	66, 7%	26	86, 7%	4.091	0.043*
	Yes	20	33, 3%	4	13, 3%		
Externalizing	No	24	40%	25	83, 3%	15, 14	<0, 001*
	Yes	36	60%	5	16, 6%		
Internalizing	No	25	41, 6%	23	76, 6%	9, 84	0, 02*
	Yes	35	58, 3%	7	23, 3%		
Internalizing subscales Cognitive problem	No	28	46, 6%	28	93, 3%	18, 52	<0, 001*
	Yes	32	53, 3%	2	6, 7%		
Anxious-shy	No	33	55%	28	93, 3%	13, 4	<0, 001*
	Yes	27	45%	2	6, 7%		
Perfectionism	No	32	53, 3%	23	76, 6%	11, 9	0, 001*
	Yes	28	46, 6%	7	23, 3%		
Psychosomatic	No	32	53, 3%	23	76, 6%	11, 9	0, 001*
	Yes	28	46, 6%	7	23, 3%		
Emotional liability	No	34	56, 6%	23	76, 6%	10, 17	0, 001*
	Yes	26	43, 7%	7	23, 3%		
Externalizing subscales oppositional	No	34	56, 6%	28	93, 3%	12, 54	<0, 001
	Yes	26	43, 3%	2	6, 6%		
Hyperactivity	No	32	53, 3%	27	46, 6%	11, 9	0, 01
	Yes	28	46, 6%	3	53, 3%		
Social problems	No	38	63, 3%	29	96, 6%	11, 68	0, 01
	Yes	22	36, 7%	1	3, 33%		
Restless –impulsive	No	40	66, 7%	27	90, 0%	5, 72	0, 17
	Yes	20	33, 3%	3	10, 0%		
Conner :ADHD	No	30	50%	25	83, 3%	9.351	0.002*
	Yes	30	50%	5	16, 7%		

Table-2: Comparison between behavioural disorder in acyanotic and cyanotic heart disease patients

Variable		Acyanotic heart (N0.=30)		Cyanotic heart (N0.=30)		Chi square test	
		No.	%	No.	%	X ²	P value
Presence of behavioral disorders	No	21	70, 0%	19	63, 3%	0.300	0.583
	Yes	9	30, 0%	11	36, 7%		
Externalizing	No	14	46.6%	10	33, 3%	1.111	0.292
	Yes	16	53.3%	20	66.6%		
Internalizing	No	13	43.3%	12	40%	0.069	0.793
	Yes	17	56.6%	18	60%		
Internalizing subscales	No	14	53, 3%	14	46, 7%	0.001	1.00
	Yes	16	46, 7%	16	53, 3%		
Cognitive problem	No	19	63, 3%	14	46, 7%	1.684	0.194
	Yes	11	37, 7%	16	53, 3%		
Anxious-shy	No	18	73, 3%	14	46, 7%	1.07	0.301
	Yes	12	26, 7%	16	53, 3%		
Perfectionism	No	16	53, 3%	16	53, 3%	0.001	1.00
	Yes	14	46, 7%	14	46, 7%		
Psychosomatic	No	18	60, 0%	16	53, 3%	0.27	0.602
	Yes	12	40, 0%	14	46, 7%		
Emotional lability	No	34	56, 6%	28	93, 3%	12, 54	<0, 001
	Yes	26	43, 3%	2	6, 6%		
Externalizing subscales	No	32	53, 3%	27	46, 6%	11, 9	0, 01
	Yes	28	46, 6%	3	53, 3%		
oppositional	No	38	63, 3%	29	96, 6%	11, 68	0, 01
	Yes	22	36, 7%	1	3, 33%		
Hyperactivity	No	40	66, 7%	27	90, 0%	5, 72	0, 17
	Yes	20	33, 3%	3	10, 0%		
Social problems	No	19	63, 3%	11	36, 7%	4.267	0.038*
	Yes	11	36, 7%	19	63, 3%		
Restless –impulsive	No	19	63, 3%	11	36, 7%	4.267	0.038*
	Yes	11	36, 7%	19	63, 3%		
Conner :ADHD	No	19	63, 3%	11	36, 7%	4.267	0.038*
	Yes	11	36, 7%	19	63, 3%		

Table-3: Iron profile in acyanotic, cyanotic and control

	Acynotic heart (N0.=30)		Cyanotic heart (N0.=30)		Control group (N0.=30)		One way ANOVA	
	Mean	SD	Mean	SD	Mean	SD	F	P value
TLC	10, 32	1, 28	9, 97	1, 21	10, 25	1, 06	0, 753	0, 474
HG	11, 76	1, 33	17, 54	2, 24	11, 96	0, 67	134, 308	<0.001
HCT	35, 18	4, 00	57, 69	9, 43	36, 10	6, 40	100, 090	<0.001
MCV	77, 17	3, 35	76, 09	13, 57	74, 04	5, 01	1, 034	0, 360
MCH	26, 71	1, 60	26, 31	1, 72	24, 48	2, 36	11, 541	<0.001
McHC	34, 71	2, 28	33, 55	1, 27	34, 46	1, 64	3, 549	0, 033
RDW%	13, 58	0, 92	15, 09	1, 46	15, 25	0, 86	20, 476	<0.001
RDWa	75, 35	111, 29	60, 78	6, 93	58, 48	6, 47	0, 604	0, 549
RBC	5, 69	0, 63	6, 18	0, 78	5, 31	0, 66	11, 929	<0.001
PLT	249, 40	70, 58	267, 53	55, 14	266, 70	53, 26	0, 869	0, 423
IRON	79, 73	64, 70	90, 93	57, 08	88, 30	65, 54	0, 263	0, 769
TIBC	532, 37	334, 63	416, 47	126, 26	379, 37	152, 39	3, 793	0, 026
Ferritin	33, 13	52, 76	37, 87	54, 55	50, 43	80, 85	0, 585	0, 559
Transferring saturation capacity	17, 94	13, 45	24, 17	16, 56	24, 96	16, 40	1, 835	0, 166

Table-4: Comparison between behavioural disorder in congenital heart disease patient with and without iron deficiency

congenital heart disease group		Iron deficient (N0.= 25)		Non iron deficiency (N0.=35)		Chi square test	
		No.	%	No.	%	X ²	P value
Presence of behavioral disorders	No	17	68%	23	65.7%	0.034	0.853
	Yes	8	32%	12	34.2%		
congenital heart disease group Conner :ADHD	No	6	24%	24	68.5%	11.589	0.001*
	Yes	19	76%	11	31.5%		
acyanotic heart disease group Externalizing	No	6	46.1%	8	47%	0, 02	0.961
	Yes	7	53.8%	9	53%		
Internalizing	No	8	61.5%	5	29.4%	3.096	0.078
	Yes	5	38.4%	12	70.5%		
cyanotic heart disease group Externalizing	No	5	41.6%	5	27.7%	1.714	0.190
	Yes	7	58.3%	13	72.2%		
Internalizing	No	5	41.6%	7	58.3%	0.023	0.879
	Yes	7	58.3%	11	61.1%		
Externalizing subscales in Acyanotic heart disease Oppositional	No	8	61.5%	11	65%	0.858	<0, 032*
	Yes	5	38.5%	6	35%		
Hyperactivity	No	7	54%	11	65%	0.547	0.362
	Yes	6	46%	6	35%		
Social problems	No	9	69%	11	65%	0.794	0.068
	Yes	4	31%	6	35%		
Restless –impulsive	No	9	69%	12	70%	0.936	0.006*
	Yes	4	31%	5	30%		
Internalizing subscales In acyanotic heart disease Cognitive problem	No	9	69%	5	29.5%	4.693	0.03*
	Yes	4	31	12	70.5%		
Anxious-shy	No	11	84.6%	8	47%	4.474	0.034*
	Yes	2	15.3%	9	53%		
Perfectionism	No	8	61.5%	10	59%	0.023	0.88*
	Yes	5	38.5%	7	41%		
Psychosomatic	No	10	77%	6	35%	5.129	0.024*
	Yes	3	23%	11	65%		
Emotional lability	No	8	61.5%	10	59%	0.023	0.88
	Yes	5	38.5%	7	41%		
Externalizing subscales in cyanotic heart disease oppositional	No	6	50%	9	50%	1.000	<0, 001*
	Yes	6	50%	9	50%		
Hyperactivity	No	6	50%	8	44%	0.765	0.089
	Yes	6	50%	10	56%		
Social problems	No	8	66%	10	56%	0.543	0.37
	Yes	4	34%	8	44%		
Restless –impulsive	No	9	75%	10	56%	0.279	1.172
	Yes	3	25%	8	44%		
Cognitive problem	No	5	42%	9	50%	0.201	0.654
	Yes	7	58%	9	50%		
Anxious-shy	No	7	58%	7	39%	1.094	0.296
	Yes	5	42%	11	61%		
Perfectionism	No	6	50%	8	44%	0.089	0.765
	Yes	6	50%	10	56%		
Psychosomatic	No	6	50%	10	56%	0.089	0.765
	Yes	6	50%	8	44%		
Emotional lability	No	6	50%	10	56%	0.089	0.765
	Yes	6	50%	8	44%		

DISCUSSION

Children with congenital heart disease are prone to hypoxia, repeated infection and frequent hospital admission that have several long term sequel including psychobehavioural aspects.

Behavioural problems in children can be classified into externalizing behaviours and internalizing behaviours. Externalizing behaviours are marked by defiance, impulsivity, hyperactivity, disruptiveness, aggression and antisocial features.

Internalizing behaviours are evidenced by withdrawal, dysphoria and anxiety. (Broberg *et al.*, 2001).

In our study, there was an increased percentage of behavior disorder among congenital heart disease patients compared to controls. There was 33, 3% of patients with congenital heart disease had behavior disorder in comparison to 13, 3% of controls .however no significance in the behavioural disorder between children with cyanotic and acyanotic heart disease.

Previous studies reported that children with chronic illnesses including congenital heart disease are more likely to suffer from Internalising problems and are likely to experience social competence problems. Parents in this study reported more social and attention problems (Fredriksen *et al.*, 2004).

In agreement with our study Spijkerboer, *et al.* (2007) showed that according to parents' reports of problem behaviours a significant proportion of congenital heart disease children scored in the deviant range (16.9%) compared to the control group (10.2%).

[Gupta *et al.*, 2001].reporting elevated levels of behavioural and emotional problems in congenital heart disease children and adolescents according to parents' reports.

Elevated somatic symptoms may reduce this kind of social activities for younger male with congenital heart disease patients. It can be speculated that parents reported more social problems for their congenital heart disease children due to parental perceptions of reduced physical ability in their children interfering with peer relationships (Fredriksen *et al.*, 2004).

Another study found that boys with CHD scored higher regarding somatic complaints than healthy children. A similar trend, however not significant, was displayed for attention score. These results were more in line with what would be expected, as patients do have more somatic problems that may hinder daily life activity. No such tendency was found among girls (Fredriksen *et al.*, 2008).

Another study showed Children with congenital heart disease were more likely to demonstrate 'emotional symptoms' and 'hyperactivity/inattention' symptoms. The rate of total scores in the abnormal range was higher in patients than in the test norms Emotional symptoms 15.8% and control by 7.7% Conduct problems 7.4% and control 6.6% Hyperactivity/inattention 12.6% and control 9.8% Peer relationship problems 10.5% and control by 7.0% Prosocial behaviour 6.3% and control 7.1% (Lane *et al.*, 2002).

LING-LING *et al.* (1993) found by comparison of subjects with congenital cardiac disease with normal controls revealed significantly greater behavioral disturbances among cardiacpatients. Parents rated their children as being more hyperactive, impulsive, aggressive, depressed, anxious, and hypochondriacal. Understanding the causes of the behavioral disturbances found among children with acyanotic heart disease is not known and would require longitudinal investigation.

Our study showed that there was statistically significant increase in ADHD in congenital heart disease in comparison to control group as 50% of congenital heart disease patient have ADHD in comparison to 16. %7 by p value 0.002 and there was statistically significant increase in cyanotic heart disease in comparison to acyanotic heart disease regarding Conner's ADHD scale.

Our study showed that there was statistically significant increase in inattentive disorder in congenital heart disease in comparison to control group.

Our study shows that there was increase statistically significant increase in hyperactive impulsive disorder in cyanotic heart disease in comparison to acyanotic heart disease.

In a study by McCusker *et al.* (2007) more than two thirds of children with hypoplastic left heart syndrome (HLHS) were considered to have the symptoms of inattention, hyperactivity, or both. Abnormal attention scores were present in 45% and abnormal hyperactivity scores in 39% of the children with HLHS according to the responses of parents and teachers on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Rating Scale and Behaviour Assessment System for Children. Kovacs *et al.* (2005) reported that 50% of children with total anomalous pulmonary venous return displayed abnormal hyperactivity, attention deficits, or both.

In the current study iron deficiency was more prevalent among children with congenital heart disease 25 (41.6%) in comparison to control group, we also found, iron deficiency was more pevelent in acyanotic heart disease by 43.3% in comparison to cyanotic heart disease by 33%, however this difference was insignificant

In agreement with our finding Olcay *et al.* (1996) reported iron deficiency in 52.2% of children with congenital heart disease Lang'o *et al.* (2009) found that 16.9% of children with cyanotic heart disease had low ferritin level and iron deficiency. Gaiha *et al.* (1993) reported a prevalence of 18.2% iron deficiency in cyanotic heart disease. The difference between the previous studies may be contributed to the underlying

nutritional and socio demographic difference between the studied populations.

In our study cyanotic group had increased Hb, HCT which reflect the increase in cyanotic patient in response to hypoxia causing polycyemia. However this hyperactive bone marrow increase the demand for iron to fulfill the increased requirement for erythropoiesis, if the iron intake is insufficient, these children will be more liable to iron deficiency.

Since iron has a role as a cofactor of tyrosine hydroxylase, its decrease limits enzyme involvement in the synthesis of dopamine, and its deficiency may change the receptor density and the dopamine activity (Buchowski *et al.*, 2010). Therefore brain iron stores are expected to influence the monoamine-dependent functions that affect the psychobehavioural development of such. (Cottrill *et al.*, 2008).

Our study showed slight increase in behavioral disorder in children with iron deficiency especially in those with cyanotic heart disease. This may be related to the combined effect of hypoxia and iron deficiency on the growing brain.

However our study showed that there was no statistically significant increase in behavioural disorders in children with iron deficiency in comparison to noniron deficiency group in congenital heart disease group except for ADHD disorder.

Our study showed that there was statistically significant increase in Cognitive problem Anxious-shy, Perfectionism and Psychosomatic, internalizing subscales in acyanotic heart disease with iron deficiency in comparison to acyanotic heart disease without iron deficiency, and there was statistically significant difference in oppositional and Hyperactivity externalizing disorder subscales in congenital heart disease with iron deficiency in comparison to congenital heart disease without iron deficiency.

Our study showed that there was statistically significant difference in oppositional and Restless – impulsive disorder subscales in cyanotic heart disease with iron deficiency in comparison to cyanotic heart disease without iron deficiency, and there was statistically significant increase in oppositional disorder subscale in cyanotic heart disease with iron deficiency in comparison to cyanotic heart disease without iron deficiency.

CONCLUSION AND RECOMMENDATION

Children with CHD have more behavioral problems than their healthy peers. Children born with CHD are at increased risk of suffering from ADHD symptoms. Externalizing and internalizing disorders are more common in congenital heart disease children more than healthy children behavioral disorder is more

common in children with cyanotic heart disease with iron deficiency more than children with cyanotic heart disease without iron deficiency. ADHD is more common in children with congenital heart disease with iron deficiency more than children congenital heart disease without iron deficiency. So assessment and management of behavioural problems should be an integral component of the comprehensive treatment of children with CHD and those who found to have iron deficiency should be treated accordingly.

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