



Cyanotic congenital heart disease: Impact on growth and endocrine functions.

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Article received on:

07/07/2020

Accepted for publication:

08/09/2020

ABSTRACT... Objective: To find out the impact of Cyanotic Congenital Heart Disease (CCHD) on growth and endocrine functions at a tertiary care child healthcare facility of South Punjab. **Study Design:** Case Control study. **Setting:** Department of Pediatric Cardiology and Department of Pediatric Endocrinology, Institute of Child's Health (ICH), Multan, Pakistan. **Period:** December 2018 to March 2020. **Material & Methods:** During the study period, a total of 53 cases of Echocardiography confirmed CCHD were registered. Along with 53 cases, 50 controls during the study period were also enrolled. Height, weight, body mass index (BMI) along with hormonal and biochemical laboratory investigations were done. **Results:** There was no significant difference between gender and age among cases and controls (p value > 0.05). Most common diagnosis of CCHD among cases, 24 (45.3%) were Tetralogy of Fallot (TOF) followed by 9 (17.0%) transposition of the great arteries (TGA) with Ventricular Septal Defect (VSD) with Pulmonary Stenosis (PS). Mean weight of CCHD cases was significantly lower in comparison to controls (21.19+6.24 kg vs. 26.48+8.1 kg, p value=0.0003). Blood glucose was significantly lower among cases in comparison to controls (77.58+14.58 mg/dl vs. 87.25+11.82 mg/dl, p value=0.0004). No significant difference was found in between cases and controls in terms of various hormone levels studied (p value > 0.05) except Insulin-like Growth Factor-1 (IGF-1) levels (p value < 0.0001). **Conclusion:** Children with cyanotic congenital heart disease seem to have negative effects on nutrition and growth. Change in pituitary-adrenal axis is suspected while pituitary-thyroid axis seemed to be working fine among CCHD cases. Serum glucose and IGF-1 levels were significantly decreased among CCHD cases.

Key words: Body Mass Index, Growth, Height, Weight.

Article Citation: Arshad MS, Khan WI, Zulqarnain A, Anwar-ul-Haq HM, Adnan M. Cyanotic congenital heart disease: Impact on growth and endocrine functions. Professional Med J 2021; 28(10):1477-1483.
<https://doi.org/10.29309/TPMJ/2021.28.10.5471>

INTRODUCTION

Congenital heart disease (CHD) is known to be structural abnormalities related to the heart or intrathoracic great vessels taking place while fetus is developing.¹ CHD is recorded to be the commonest form of birth defect affecting 8-9 per 1000 live births and is described as the most frequent cause of mortality among children having congenital malformations.² CHD can be classified as either non-cyanotic CHD or cyanotic CHD (CCHD). CCHD is further divided in to three different forms of lesions like right heart obstructive lesions, left heart obstructive lesions or mixing lesions.^{3,4} Among CHD cases, around 25% are estimated to be CCHD cases.² Tetralogy of Fallot (TOF) and transposition of the great arteries (TGA) are noted to be the commonest

forms of CCHD.⁵ TGA is also known to be the commonest CCHD manifestation found in the 1st week following birth. In cases having congenital malformations, 35% of the deaths among infants are noted due to cardiovascular abnormalities.²

In infants having CCHD, 15-20% of the cases are due to known chromosomal abnormalities while majority of them are aneuploidies like trisomy 21, 13, 18 and Turner syndrome.² Environmental factors include maternal illness like diabetes mellitus or phenylketonuria. Maternal exposure to toxins, drugs or viral infections during pregnancy also contribute to CHD in the fetus.

As CCHDs are models of chronic hypoxia, these are known to impact endocrine system.^{6,7}

Effect of CCHDs on growth has been studied sparingly in the past. A study conducted by Eren E et al from Turkey⁸ evaluating endocrine functions among children with CCHD found that chronic hypoxia proved to have a negative effect on nutritional and growth parameters. Serum glucose was significantly decreased ($75+15$ mg/dl vs $83+12$) among cases in comparison to controls ($p=0.033$). Significantly low scores of height and weight among children with CCHD in comparison to controls were also reported in that same Turkish study.⁸ Growth retardation (GR) is a common and serious complication in children with CCHD. Underlying causes of GR among cases of CCHD is not fully understood. Chen CW and coworkers noted delayed growth as well as development in children having CCHD in comparison to normal children.^{9,10}

Not many studies have been conducted around the world to find out the impact of CCHD on growth and endocrine functions of the affected children. No work is found from Pakistan regarding these aspects. This study was planned to find out the impact of CCHD on growth and endocrine functions at a tertiary care child healthcare facility of South Punjab. Results of this study are thought to shed light on the extent of CCHD affecting individuals in terms of growth and normal endocrine functions.

MATERIAL & METHODS

This case control study was done at the Department of Pediatric Cardiology and Department of Pediatric Endocrinology of The Children's Hospital and The Institute of Child's Health (ICH), Multan, Pakistan from December 2018 to March 2020. Approval from the Institutional Ethical Committee was taken for this research (09/18/Ethical committee/CH&ICH). Informed consent was also sought from parents/guardians of all the study participants, either having CCHD or controls.

A sample size of a total of 92 cases (including 46 cases and 46 controls) was calculated considering 95% confidence interval (2-sided), with power of 80% and ratio of sample size (group 2/group 1) as 1 and $P1=75+15$ and

$P2=83+12$.⁸ During the study period, a total of 53 cases of Echocardiography confirmed CCHD were registered. Along with 53 cases, 50 controls during the study period were also enrolled. All cases were non operated children having age more than 5 years and presenting to cardiology outpatient department of The Children's Hospital and ICH, Multan. All post-operative cases who underwent cardiac surgery for CCHDs either palliative or corrective or patients having associated chromosomal disorders or syndromes were excluded. Patients having any other chronic systemic ailments, renal or hepatic failure, additional genetic or endocrinological abnormalities like congenital hypothyroidism, were also not enrolled. Controls were consisted of patients aged more than 5 years, presented to pediatric medicine outpatient department of The Children's Hospital & ICH with complaints like headache, abdominal discomfort or routine vaccination visits.

Height, weight and body mass index (BMI) were noted among all study participants. Complete blood count, serum sodium (Na), potassium (K), calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), urea, creatinine and phosphorus were measured using the blood samples drawn. Fasting glucose and insulin level were also assessed for carbohydrate metabolism. ACTH, cortisol for adrenal examination, TSH, T4 (fT4) for thyroid functions, and parathormone (PTH) level along with Vitamin D level for bone metabolism were assessed.

The statistical analysis was performed using SPSS 20.0. For qualitative variables, frequency and percentages were calculated. The Student's t-test was performed to compare the continuous variables while chi square test was applied to compare qualitative variables. P value of less than 0.05 was considered significant.

RESULTS

Among 53 cases, there were 30 (56.6%) boys and 23 (43.4%) girls while among 50 controls, 30 (60.0%) boys and 20 (40.0%) girls (p value=0.7268). Mean age among cases was noted to be 4.62 ± 3.27 years while among controls, it

was 4.28 ± 3.74 years (p value=0.6239).

Table-I showing that the most common diagnosis of CCHD among cases, 24 (45.3%) were TOF followed by 9 (17.0%) TGA with VSD with PS and 4 (7.5%) PA.

Table-II highlights that there was no significant difference between cases and controls in terms of Height or BMI (p value>0.05) whereas mean weight of cases was significantly lower in comparison to controls (21.19 ± 6.24 kg vs. 26.48 ± 8.1 kg, p value=0.0003).

Table-III showing comparison of various biochemical laboratory findings among cases and controls. Blood glucose was significantly

lower among cases in comparison to controls (77.58 ± 14.58 mg/dl vs. 87.25 ± 11.82 mg/dl, p value=0.0004) whereas uric acid was significantly raised among cases in comparison to controls (5.08 ± 2.31 mg/dl vs. 3.62 ± 0.67 mg/dl, p value<0.0001) while all other biochemical laboratory findings were statistically similar between cases and controls (p value>0.05).

Table-IV compares findings of various hormone levels between cases and controls. No significant difference was found in between cases and controls in terms of various hormone levels studied in the present research (p value>0.05) except IGF-1 (ng/ml) levels that were significantly decreased among cases in comparison to controls (p value<0.0001).

Diagnosis	Number of Patients (%)
Tetralogy of Fallot (TOF)	24 (45.3%)
TGA with Ventricular Septal Defect (VSD) with Pulmonary Stenosis (PS)	9 (17.0%)
Pulmonary Atresia	4 (7.5%)
Tricuspid Atresia	3 (5.7%)
Univentricular Heart with PS	2 (3.8%)
Complete Atrioventricular Septal Defect (AVSD) with PS	1 (1.9%)
Complex Congenital Heart Disease	8 (15.1%)
Ebstein Anomaly	2 (3.8%)

Table-I. Diagnostic findings among cases (n=53)

Characteristics	Mean + Standard Deviations		P-Value
	Cases (n=53)	Controls (n=50)	
Height (cm)	107.20+42.57	118.83+52.29	0.2175
Weight (kg)	21.19+6.24	26.48+8.1	0.0003
BMI	16.85+2.47	17.35+2.61	0.3202

Table-II. Characteristics of cases and controls

Biochemical Findings	Mean + Standard Deviations		P-Value
	Cases (n=53)	Controls (n=50)	
Blood Glucose (mg/dl)	77.58+14.58	87.25+11.82	0.0004
Urea (mg/dl)	20.15+6.75	22.07+6.82	0.1542
Creatinine (mg/dl)	0.62+0.10	0.57+0.80	0.6527
Uric Acid (mg/dl)	5.08+2.31	3.62+0.67	<0.0001
Alkaline Phosphatase (U/L)	242.74+80.81	214.14+71.54	0.0606
Sodium (mEq/L)	135.26+2.0	136.17+1.8	0.8112
Potassium (mEq/L)	4.48+0.62	4.42+0.58	0.6136
Calcium (mg/dl)	9.30+0.52	9.49+0.35	0.1142
Phosphorus (mg/dl)	5.3+1.1	5.0+0.8	0.1184

Table-III. Biochemical laboratory findings among cases and controls

Hormone Levels	Mean + Standard Deviations		P-Value
	Cases (n=53)	Controls (n=50)	
Free T4 (ng/dl)	1.32+0.18	1.25+0.21	0.0718
TSH (mIU/ml)	2.6224+0.782	2.2928+0.978	0.0610
Adrenocorticotrophic Hormone (pg/ml)	18.53+12.61	21.92+14.89	0.2144
IGF-1 (ng/ml)	84.6+74.8	198.2+135.4	<0.0001
Cortisol (mcg/dl)	12.24+6.6	10.0+5.2	0.0595
Insulin (mU/ml)	8.17+9.93	8.52+8.84	0.8257
Vitamin D (ng/L)	30.82+17.62	23.61+20.92	0.0612
Parathyroid Hormone (pg/ml)	74.35+68.52	56.37+26.47	0.0855

Table-IV. Findings of hormone levels among cases and controls

DISCUSSION

GR (Growth Retardation) is considered an important issue among children having CHD. It has also been highlighted by the previous researchers that children having CCHD have more pronounced growth impairment.^{11,12}

In the current study, although, mean height of cases in comparison to controls was much lesser (107.20+42.57 cm vs. 118.83+52.29cm) but it did not reach statistical significance (p value=0.2175). It was also observed that mean weight of cases was significantly lower in comparison to controls (21.19+6.24 kg vs. 26.48+8.1 kg, p value=0.0003). Hansen SR and Dorup I noted that incidence of GR was much higher among cases having CCHD while it hampered both weight and height.¹³ In another study, it was found that heights of 55% of the cases having CCHD, weights of more than half of the study participants was < 3 percentiles which is again correlating well with current findings where difference of weight among cases and controls reached statistical significance.¹⁴ A study from Turkey recorded weight, height, and both weight and height to be < 3 percentiles among 20%, 13.3% and 13.3% CCHD cases respectively.⁸ Lower levels of BMI among cases in the present study are also highlighting nutritional growth impairments. Children having CCHD are also found to have lower weight, BMI and head circumference when compared to children having cyanotic CHD.⁵

We have noted that there was no significant difference in levels of various hormones studied

between cases and controls. Researchers also noted that hormone levels of children having CCHD were similar to controls but they found that levels of IGF-1 and IGF binding protein 3 (IGFBP3) were significantly lower among cases in comparison to controls.⁸ Lower levels of IGF-1 found in our study and by other researchers among CCHD cases might be due to the inhibition of binding of growth hormone to its receptor during chronic hypoxia. Post-operative cases of CCHD when compared to pre-operative status have been found to have higher BMI so higher levels of IGF-1.¹⁵

It is widely accepted that hypoxia is known to have an effect on adrenal cortex and plays an important role during adrenal-steroid synthesis.^{8,16} Roles of acute and chronic hypoxia on the anterior-hypothalamus and adrenal cortex have been studied among rats and rabbits and it has been found that ACTH and cAMP secretions are higher because of acute hypoxia.^{17,18} Although, we did not find significant difference in terms of ACTH or cortisol levels between cases and controls but lower levels of ACTH along with normal levels of cortisol among 7 CCHD cases in the present study might be elaborated with the help of central ACTH inhibitor under stress. Similar findings have been reported by other researchers as well, showing increased disease severity among CCHD cases.⁸

Systemic hypoxia is known to be linked with insulin resistance. Cases having sleep apnea are noted to have much higher insulin resistance due to intermittent hypoxia.¹⁹ Although there was no significant difference between insulin

levels among cases and controls in the present study, but lower levels of plasma insulin were found among CCHD cases in the present study which could be because of impaired insulin secretions. CCHD cases are also more prone to have hypoglycemia so a special attention should be given to these cases in the post-operative period.²⁰ In the present study, significantly lower levels of glucose were recorded among CCHD cases in comparison to controls. These findings have been observed by other researchers as well. Lower glucose levels could be due to increased demand of energy for circulation and respiration among CCHD individuals. Higher levels of insulin resistance can also be explained as preventable mechanism against hypoglycemia. Our findings in terms of FT4 and TSH levels were quite similar to previous ones, showing no significant difference between cases and controls.²¹ This could also mean that pituitary-thyroid axis was intact and working normally. Pubertal delays are also suspected in patients with CCHD.²² Further studies in older age group survivors may be planned to elaborate this aspect.

In the present study uric acid was significantly raised among cases in comparison to controls (5.08+2.31 mg/dl vs. 3.62+0.67 mg/dl, p value<0.0001). The exact mechanism behind this phenomenon is not known but pediatric age groups with CCHD have been pointed out to have higher risk of kidney injury in the past.^{23,24}

There were few limitations to our study as well. As this was a single center study, in future, studies involving multi-centers and larger sample size will serve better. As we had only included children in preoperative status, future studies following children after corrective post-operative status for CCHD will give us insight about their endocrine functions as well.

CONCLUSION

Children with cyanotic congenital heart disease seem to have negative effects on nutrition and growth. Change in pituitary-adrenal axis is suspected while pituitary-thyroid axis seemed to be working fine among CCHD cases. Serum glucose and IGF-1 levels were significantly

decreased among CCHD cases. Better nutritional support and early corrective surgery can possibly avoid growth delay in these children. In third world countries like Pakistan, where the nutritional status of even otherwise healthy children is not up to the mark and such patients with CCHD are at greater risk for nutritional deficiencies. Moreover, delay in diagnosis and then delay in surgical corrective treatment of CCHD is another major problem.

ACKNOWLEDGEMENT

The authors would like to thank Muhammad Aamir (Research Consultant, Bahawalpur) for his volunteer support in statistical analysis of this research.





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2	Waqas Imran Khan	Data Analysis, Proof reading.	
3	Arif Zulqarnain	Methodology, Discussion.	
4	Hafiz M. Anwar-ul-Haq	Data collection, Drafting.	
5	Mudasser Adnan	Data Collection, Literature review.	