

# Impact of Chronic Hypoxia on Neurodevelopment of Children with Cyanotic Congenital Heart Disease

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## Abstract

**Background:** Children with cyanotic Congenital Heart Disease (CHD) are at higher risk for delay in their growth and development due to more energy consumption during their activities. In addition, they are more prone to respiratory infection and hospitalization. Due to the nature of disease, these patients suffer from a chronic hypoxia and its impact on growth and development is not well investigated. This study was designed to find out which physical growth and neurodevelopmental parameters of these patients are affected by chronic hypoxia in comparison with acyanotic disease.

**Methods:** 81 children with CHD (34 cyanotic and 47 acyanotic), aged between 6 months to 3 years from Children's Medical Center affiliated to Tehran University of Medical Sciences in Tehran were recruited from January 2013 to January 2014. Growth parameters including weight, height, and head circumference were checked and then these indices were categorized into three groups of Failure To Thrive (FTT). Functional development was assessed by using modified Denver Developmental Screening Test (DDST II).

**Results:** In acyanotic group, Ventricular Septal Defect (VSD) and in the cyanotic group, tetralogy of fallot (TOF) were the most prevalent disorders. Growth indices were low in 52% of patients (70% of cyanotic and 38.2% acyanotic), and also weight and height parameters were significantly lower in the cyanotic group ( $p=0.009$  and  $p=0.05$ ). 62% of cyanotic patients and 17% of acyanotic patients had delay at least in one of their neurological development indices (Gross motor, fine motor, speech or psychosocial behavior). This study also demonstrates an association between neurodevelopment delay and FTT in cyanotic patients, but not in acyanotic ones.

**Conclusion:** Results in this study suggest that children with cyanotic CHD are more prone to delay in their development besides their growth possibly due to the nature of their disease. Therefore, chronic hypoxia can be a risk factor influencing neurodevelopment of the patients and appropriate intervention is required to gain better outcome.

**Keywords:** Chronic hypoxia, Congenital heart disease, Cyanosis, Neurodevelopmental delay

## Introduction

Congenital Heart Defect (CHD) with an estimated incidence of 8-12 cases per 1000 live births is a major leading cause of infant deaths due to congenital anomalies (1,2). This frequency has increased over time to 7.93 and 17.51 in 1000 live births in Iran (3). Due to impending cardiac failure and/or pulmonary vascular resistance, early surgical intervention is often necessary in these patients despite all risks (4). Although advances in medical and surgical techniques have reduced mortality rates in these cases, surviving infants following surgical repair have a greater risk of comorbidities including neurodevelopmental disabilities (5,6). Therefore, improvement in outcomes has led to a gradual shift in focus from cardiac morbidity and mortality toward brain integrity, developmental and neurological outcomes (7).

The etiology of neurologic injury in patients with CHD is multifactorial and involves a complex interplay among fetal, preoperative, intraoperative, and postoperative factors (8). There are few studies that point out neurobehavioral and neurologic abnormalities in patients with CHD (9,10); these abnormalities have been presumed as significant risk factors in neurodevelopment of these patients (11,12). The congenital cardiac abnormalities are classified into two broad groups; those with cyanosis and acyanotic ones. Neonates and young children with CHD have long been known to be at risk for developmental delay. The frequency and severity of these abnormalities tend to be more apparent in children with cyanotic CHD compared with acyanotic ones (13). Altered cerebral blood flow with impaired cerebral oxygen delivery may affect brain development (14). Recently, studies suggest hypoxia may play a significant role in the pathogenesis of malnutrition, growth failure (15,16), and subsequent neurodevelopment (17).

Dalili *et al* found significantly lower body weights and heights in all Iranian CHD patients in comparison to the normal population (18). This difference was greater in cyanotic ones. However, to our knowledge, sufficient information is not available on neurodevelopmental status of children with CHD, with or without cyanosis in literature. Therefore, this study was carried out to evaluate the neurodevelopmental status of these children before corrective or palliative surgery to detect any possible relationship between chronic hypoxia and their developmental milestones.

## Materials and Methods

This cross-sectional descriptive study was conducted in Children's Medical Center affiliated to Tehran University of Medical Sciences from April 2013 to June 2014.

Children aged 6 months to 3 years with congenital heart disease who had not undergone corrective surgery were recruited in this study. The diagnosis of CHD was done by academic cardiologist based on physical examination, echo-cardiogram and pulse oximetry. Exclusion criteria were clinically recognizable genetic syndromes, metabolic disorders, immune deficiencies, CNS developmental anomaly or any acquired perinatal insult such as hypoxic ischemic encephalopathy, stroke, prematurity, and sepsis.

All cases were assessed for body weight, height, and Occipitofrontal Circumference (OFC) measured by anthropometric techniques. The children's growth was evaluated according to height, weight, and age using growth chart curves which were standardized for Iranian population (19). By using these curves, FTT severity in patients was categorized into three groups of type I (poor weight), type II (poor height and weight) and type III (poor height, weight, and OFC).

Furthermore, modified Denver Developmental Screening Test II was used for assessment of developmental milestones in these children in three consecutive months. Validity and reliability of this test have been already confirmed and considered standard for Iranian population in previous studies (20). Gross motor, fine motor, speech (language), and psycho-social aspects were assessed in all cases and were categorized as normal or delayed (impaired) if passing red flag in one aspect or falling in yellow zone in two aspects based on definition and subsequently confirmed when approved through neurological examination done by expert child neurologist. The analysis was carried out by employing statistical package for Social Science (version. 10) and EPI Info (version 3.5.1) of Microsoft Windows software package. Comparisons were made between the two main study groups (Acyanotic group and cyanotic group). The chi-square tests were used for categorical variables. Differences were considered significant at  $p < 0.05$ . Parents were informed about the purpose of the study and a written informed consent was obtained for their collaboration in this study. The

study protocol was approved by the hospital ethics committee in charge and investigation was executed based on adherence to the World Medical Association Declaration of Helsinki.

### Results

Eighty-one patients (Forty-six males and thirty-five females) with congenital heart diseases were recruited in this study. Thirty four of them were cyanotic and 47 were acyanotic. The male to female ratio was 1.31:1. Age of the patients was in the range of 6 months to 3 years, and mean age for cyanotic was 18 months and 3 weeks and the acyanotic 21 months and 3 weeks, respectively.

In acyanotic group, Ventricular Septal Defect (VSD) and in cyanotic group Tetralogy of Fallot (TOF) were the most common disorders. In cyanotic group, 18 cases were TOF, 2 Dextro-Transposition of the Great Arteries (D-TGA), 1 case with total anomalous pulmonary venous return, 13 had mixed anomalies including 5 cases with VSD and Pulmonary Stenosis (PS), 4 cases with tricuspid atresia, 2 cases with complete AtrioVentricular Septal Defects (AVSD), PS and Levo-Transposition of the Great Arteries (L-TGA), and 2 cases with Double Outlet Right Ventricle (DORV) and PS; and in acyanotic group, abnormalities were VSD in 21 of the cases, Patent Ductus Arteriosus (PDA) in 5, ASD in 2 cases, partial AVSD in 2, congenital pulmonary stenosis in 2, congenital aortic

stenosis in 4, mixed anomalies in 11 cases comprising 4 cases with Coarctation of the Aorta (CoA), mitral stenosis and bicuspid aortic valve, 3 cases with aortic stenosis and PDA, 3 cases with Atrial Septal Defect (ASD) and small VSD, and 1 case with PS and PDA.

Weight and height parameters were lower than the mean standard in 52% of patients (70% cyanotic and 38.2% acyanotic). Considering the weight curve, 23 (67.6%) patients with cyanotic and 18 (38.3%) cases with acyanotic CHD were under the 5<sup>th</sup> centile (p=0.009). Likewise, height parameter in 13 (38.2%) and 9 (19.1%) cases of cyanotic and acyanotic groups, respectively was under the 5<sup>th</sup> centile (p=0.05). But head circumference curve was similar in both groups and 5 (14.7%) and 5 (10.6%) cases of cyanotic and acyanotic groups, respectively were under the 5<sup>th</sup> centile (p=0.7). 76 % of all the patients showed FTT with different grading and this parameter was relatively more common in the cyanotic group (Table 1).

Developmental assessment of the patients is summarized in table 2. 62% (21) of cyanotic patients and 17% (8) of acyanotic patients had a delay in at least one of neurological developmental parameters (Either fine or gross motor, psychosocial or speech indices).

### Discussion

Neurodevelopmental delay after and even before surgery is a matter of great debate. Recent studies indicate possible

**Table 1.** Distribution of different types of Failure To Thrive (FTT) and development assessment of children based on FTT types in cyanotic and acyanotic patients

FTT Type	Group No. (%)	Language	p	Gross Motor	p	Fine Motor	p	Personal-Social	p
FTT Type 1	Cyanotic 18 (56.3)	12	P.S	11	P.S	12	P.S	4	-
	Acyanotic 23 (57.5)	2		1		1		0	
FTT Type 2	Cyanotic 9 (28)	7	P.S	7	P.S	8	-	3	-
	Acyanotic 12 (30)	2		1		0		0	
FTT Type 3	Cyanotic 5 (15.6)	3	P.NS	3	P.S	4	-	1	-
	Acyanotic 5 (12.5)	2		1		0		0	

Data presented as N (%), P value as significant (P.S) = ≤0.05 and no significant (P.NS) = >0.05

**Table 2.** Development assessment of studied children (n = 81)

Development Domains	Cyanotic CHD n = 34	Acyanotic CHD n = 47	p value
Gross Motor			
Impaired	11	1	0.0001
Normal	23	46	
Fine Motor			
Impaired	14	7	0.0007
Normal	20	40	
Language			
Impaired	13	3	0.0003
Normal	21	44	
Personal Social			
Impaired	4	0	0.002
Normal	30	47	

role of hypoxia in the pathogenesis of malnutrition, growth failure and neurodevelopment (15-17). The aim of our study was assessment of neurodevelopment of children with CHD before corrective operation to find out possible relationship between chronic hypoxia and neurodevelopmental impairment in these patients. In this descriptive hospital-based study, 81 children with CHD, 34 cyanotic and 47 acyanotic CHD cases were enrolled. The results of this study confirmed that neurodevelopmental delay is a common problem in children with CHD (36%), especially in those with cyanosis (62%). Furthermore, it demonstrates an association between neurodevelopmental delay and FTT in cyanotic group, but not acyanotic one (Table 1). Although the growth failure and FTT are well recognized morbidities in infants with CHD, but the aetiology of them is multifactorial and poorly understood (21,22). Like previous studies (23,24), nearly half of our patients (52%) had stunted growth indices, significantly in cyanotic ones (70% cyanotic vs 38.2% acyanotic), with major impact on their weight index. Pulmonary Hypertension (PH) has been mentioned in literature as a risk for growth failure in patients with cyanotic heart disease (16,25). Although this subject was not among the principal aims of our study, it is an important issue that needs to be considered and prevented by appropriate intervention in these patients.

In 1996, van Houten *et al* reported cranial ultrasound abnormalities in 59% of CHD patients which was higher (71%) in acyanotic CHD cases (26); likewise,

Limperopoulos *et al* found neurobehavioral and neurologic abnormalities in more than half of the patients in acyanotic CHD group with neurological abnormality of 79% than those with cyanotic defects (47%) (12). In contrast, our study showed a higher prevalence of developmental delay in cyanotic patients (62%) in comparison to acyanotic ones (17%). In another study, neurodevelopmental abnormalities were observed in 38% of infants before surgery, although abnormality was significantly associated with arterial oxygen saturations <85% (10). There is a direct link between reduced cerebral oxygenation and impaired brain growth in fetuses with CHD (27). Altogether, more developmental delay was expected from cyanotic CHD cases due to chronic hypoxia caused by underlying CHD.

Most of the studies investigated neurodevelopmental outcomes after surgery and they suggest that impairment is common in survivors with complex CHD (14). In agreement with previous studies, our results confirm prominent motor delay in the cyanotic group in comparison to acyanotic groups (23,28-30). Also, speech function but not personal-social function showed significant impairment in group with cyanotic CHD.

The high rate of developmental delay among children with CHD, especially cyanotic ones in this study, demonstrates important implication for practice and research purposes. This study used acyanotic group as control; however assigning non-CHD as the control group, doing follow-ups after surgery/ considering role of medication in these patients, and

other psychosocial factors that may have a negative/positive impact on these children can be considered as limitations of this study or subjects for future studies. For a better understanding of changes in growth and development in children with cyanotic CHD, a longitudinal study with bigger sample size and higher age of population is also recommended.

## Conclusion

This cross-sectional study showed that the children with congenital heart disease are prone to growth and developmental delay, and chronic hypoxia could play

a major role in impairment of neurodevelopment in patients with cyanotic CHD. So, neurodevelopmental monitoring is highly recommended for infants and children with congenital cyanotic heart disease and can be an indicator for appropriate interventions.

## Ethical consideration

This study was elicited from a research proposal and general pediatrics thesis conducted at Tehran University of Medical Sciences (TUMS) and was ethically approved by ethics committee and supported by research deputy of TUMS.

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