Growth Parameters and Insulin Like Growth Factor-1: Comparison between Cyanotic and Acyanotic Congenital Heart Disease and Normal Children

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Abstract: Children with congenital heart disease (CHD) have been reported show significant growth retardation. Also it seems that low insulin-like growth factor-1(IGF-1) levels could in CHD patients cause growth retardation, but the etiology of growth retardation in the patients with CHD is still unclear. In this study we aim to compare IGF-1 levels in cyanotic and acyanotic CHD patients and evaluate its correlation with growth parameters. sixty children with congenital heart disease (30 cyanotic and 30 acyanotic patients) and 30 healthy children were studied. Demographic findings, blood oxygen saturation, left ventricle ejection fraction (LVEF) and IGF-1 levels were compared between groups. LVEF was significantly higher in control group than other groups ($p=0.04$) and blood oxygen saturation and IGF-1 was significantly lower in cyanotic group than other groups (both, $p<0.001$). There was significant positive correlation between IGF-1 and blood oxygen saturation ($r=0.45$, $p<0.001$), IGF-1 and age ($r=0.63$, $p<0.001$), IGF-1 and BMI ($r=0.40$, $p<0.001$), IGF-1 and height ($r=0.37$, $p<0.001$) and IGF-1 and head circumference ($r=0.44$, $p<0.001$). The positive correlation between IGF-1 and growth parameters as well as low IGF-1 levels in cyanotic patients in comparison to acyanotic patients and healthy children are indicative of malnutrition and growth retardation in these patients which could be due to chronic hypoxemia considering lower blood oxygen saturation in these patients.

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1. Introduction

Insulin-Like growth factor-1 (IGF-1) is synthesized mainly in liver and kidney and is important in mediating of anabolic and growth promoting effects of growth hormone (GH) (Castellano et al., 2009). Both protective and harmful effects of IGF-1 on the cardiovascular (CV) system have been reported (Chisalita et al., 2011). Children with congenital heart disease (CHD) have been reported show significant growth retardation both prenatally and postnatally. Retardation in height as well as weight seems most pronounced in children with cyanotic heart disease (Siliman et al., 2012).

Hypoxia results from imbalances between oxygen demand and supply. It has been shown that chronic hypoxia has many effects on the endocrine system, mainly on growth (Eren et al., 2013). Growth retardation (GR) is a common and serious complication in children with cyanotic CHD (Linde etal., 1967; Weintraub and Menahem, 1993; Norris and Hill, 1994). Decreased energy intake, increased energy requirements, or malabsorption would be related to malnutrition and GR in children with cyanotic CHD (Venugopalan et al., 2001; Venugopalan et al., 2007). Growth retardation has been associated with hypoxemia which has effects on nutrition and growth of children with CHD (Venugopalan et al., 1999). There is shown to be a correlation between chronic hypoxia and IGF-1 in CHD patients, especially cyanotic CHD (Venugopalan et al., 2000; Dinleyici et al., 2007). Decreased levels of IGF-1 are seen in nutritional deficiencies (Soliman et al., 1986; Jones and Clemmons, 1995), as well as CHD patients (Dinleyici et al., 2007; Kerpel-Fronius et al., 1977). Also it seems that low IGF-1 levels could in CHD patients cause growth retardation, but the etiology of growth retardation (GR) in the patients with CHD is still unclear (Eren et al., 2013). In this study we aim to compare IGF-1 levels in cyanotic and acyanotic CHD patients and evaluate its correlation with growth parameters.

2. Materal and Methods

The study was conducted on 30 children with acyanotic CHD, 30 children with cyanotic CHD (without any surgical corrections), and 30 healthy children. CHD patients were selected from the pediatric cardiology outpatient clinic of Children's Hospital of Tabriz during years 2011 and 2012. All patients' cardiac diagnoses were made on the basis of clinical and laboratory examinations, echocardiography and, if needed, angiography. Healthy children were randomly chosen among patients with no heart disease visiting children general

clinic of the same hospital. All children were free from other malformations, pulmonary hypertension or signs of other disease. Patients with a history of prematurity, intrauterine growth retardation, known genetic malformations, dysmorphic features, and neurologic disability were excluded. The study protocol was approved by local ethical committee and informed consents were obtained from the parents of the subjects.

True history taking was done. Anthropometric measurements including weight, height and body mass index (BMI) were recorded. Anthropometry measurements were performed according to standard WHO procedures (WHO, 1995). Body mass index (BMI) was calculated as the ratio of body weight (kg) and squared height (m). Oxygen saturation in the blood (SO2) was measured using pulse oximetery. PO2 was measured using peripheral arterial blood gas analysis. All blood samples were drawn at 08-09 am and stored at $-20^{\circ C}$ until the procedure. Serum IGF-1 levels were analyzed with ELISA kit (Mediagnost, Reutlingen, Germany).

Data analysis: All data were analyzed using SPSS statistical package version 16.0 (SPSS Inc. Chicago, IL, USA). Continuous data with normal distribution are given as mean ± standard deviation, otherwise as median. Categorical variables were compared by x^2. The given data were compared between groups using one-way ANOVA. Student's t-test was used for comparisons between the two groups (cyanotic and acyanotic, cyanotic and control and acyanotic and control). The correlations between the groups were assessed by Pearson correlation. A p-value of 0.05 or less was considered significant.

3. Results

Data of 30 patients with cyanotic CHD (age: 3.05±2.67 yr), 30 patients with acyanotic CHD (age: 5.87±3.93 yr), and 30 healthy children (age: 3.67±2.23 yr) were analyzed. Patients' baseline findings are shown in Table 1. Cyanotic patients were significantly younger than acyanotic and control group because we selected cases of CHD before surgical interventions and most children with cyanotic CHD underwent surgical corrections in upper ages. Cyanotic and acyanotic patients had significantly lower BMI, height and head circumference. Mean left ventricle ejection fraction (LVEF) was %58.66±5.40 in cyanotic CHD, %58.86±6.81 in acyanotic CHD and %61.86±3.95 in control group (p=0.04). Control group had significantly higher LVEF than cyanotic (p=0.01) and acyanotic (p=0.04) group, but the difference between cyanotic and acyanotic groups was not significant (p=0.9).

Table 1: Patients' baseline findings in three groups.

		Cyanotic CHD	Acyanotic CHD	Control	P- Value
Gender (male)		16 (53.3%)	17 (56.7%)	14 (46.7%)	0.73
Age		3.05±2.67	5.87±3.93	3.67±2.23	0.001*
BMI (percentile)	3-25	22 (73.3%)	20 (26.7%)	2 (6.7%)	<0.001*
	25-50	4 (13.3%)	4 (13.3%)	17 (56.7%)	
	50-75	2 (6.7%)	3 (10%)	10 (33.3%)	
	75-90	2 (6.7%)	3 (10%)	1 (3.3%)	
Height (percentile)	3-25	19 (63.3%)	17 (56.7%)	1 (3.3%)	<0.001*
	25-50	4 (13.3%)	7 (23.3%)	14 (46.7%)	
	50-75	3 (10%)	2 (6.7%)	9 (30%)	
	75-90	4 (13.3%)	4 (13.3%)	6 (20%)	
Head circumference (percentile)	3-25	13 (53.3%)	10 (33.3%)	2 (6.7%)	0.03*
	25-50	9 (30%)	14 (46.7%)	18 (60%)	
	50-75	8 (26.7%)	6 (20%)	9 (30%)	
	75-90	0	0	1 (3.3%)	

There was significant difference between groups in SO2 (74.33±7.10 in cyanotic vs. 94.70±2.18 in acyanotic vs. 93.16±1.89 in control group, p<0.001). Cyanotic group had significantly lower SO2 in comparison to acyanotic (p<0.001) and control group (p<0.001). The difference between acyanotic and control group was also significant (p<0.001). PO2 was evaluated in cyanotic and acyanotic CHD patients. Mean PO2 in cyanotic CHD patients was significantly lower than acyanotic CHD patients (52.76±15.39 vs. 65.13±9.15, p<0.001).

Mean IGF-1 was 61.17±48.54 ng/ml in cyanotic CHD patients, 126.75±106.33 ng/ml in acyanotic CHD patients and 141.22±67.00 ng/ml in healthy subjects. Mean IGF-1 was significantly different between groups (p<0.001). Cyanotic CHD patients had significantly lower IGF-1 levels than acyanotic CHD patients (almost half the value of

acyanotic) (p=0.003) and healthy subjects (p<0.001). The difference between acyanotic and healthy subjects in IGF-1 levels was not significant (p=0.53). There was significant positive correlation between IGF-1 and SO2 (r=0.45, p<0.001), IGF-1 and age (r=0.63, p<0.001), IGF-1 and BMI (r=0.40, p<0.001), IGF-1 and height (r=0.37, p<0.001) and IGF-1 and head circumference (r=0.44, p<0.001).

4. Discussion

Children with CHD have lower height and weight in comparison to normal children in that age (Vaidyanathan et al., 2008). Growth impairment is most pronounced in infants with cyanotic CHD. Also it is reported that acyanotic CHD patients in comparison to normal children at the same age, were shorter and had lower BMI (Soliman et al., 1986). In the present study, cyanotic CHD patients had lower weight, BMI and head circumference in comparison to acyanotic CHD patients. As well it is shown that among CHD patients, children with acyanotic heart disease had a greater growth deficit in weight, and those with cyanotic heart disease had a greater growth deficit in stature as demonstrated by both decreased height and weight (Yilmaz et al., 2007). However, in the study of Barton and colleagues (Barton et al., 1996) despite lower height in cyanotic CHD patients, weight, BMI and head circumference parameters were similar to acyanotic CHD children.

Although cyanotic heart defects in particular are associated with poor growth, cardiac surgery results in increased IGF-I, increased growth velocity and increased BMI (El-Sisi et al., 2009). IGF-1 is a growth hormone-dependent peptide that plays an important role in tissue growth and differentiation (Cittadini et al., 1996). Correlation between IGF-1 and malnutrition especially in CHD patients are well documented (Dinleyici et al., 2007; Soliman et al., 1986; Jones and Clemmons , 1995; Kerpel-Fronius et al., 1977). It has even shown that the severity of congenital heart defects (shunt size, cyanotic/acyanotic) as an indicator of peripheral resistance also influenced IGF-I levels (Dündar et al., 2000; Dinleyici et al., 2007; Soliman et al., 1986).

In this study IGF-1 levels in cyanotic CHD patients were significantly lower than acyanotic CHD and normal subjects; but the difference between acyanotic CHD and normal subjects was not significant. There was also lower SO2 in cyanotic CHD patients than other two groups indicative of chronic hypoxia in these children. We also found positive correlations between IGF-1 and SO2, age, BMI, height and head circumference.

Results of other studies were similar to our findings, with few differences; in some studies the IGF-1 levels had significant differences between acyanotic CHD and healthy children (Dinleyici et al., 2007; Surmeli-Onay et al., 2011; Wei and Lu, 2007); in some other studies IGF-1 values were not different between cyanotic and acyanotic CHD patients (Barton et al., 1996). Interestingly, in the study of Surmeli-Onay and colleagues (Surmeli-Onay et al., 2011) this was acyanotic CHD patients that had lower IGF-1 levels than cyanotic CHD and normal subjects. These differences between studies could be due to differences in study population selection and different ages in each study, however, these differences needs to be more evaluated.

These findings support the possible correlation between IGF-1 and chronic hypoxia, especially in cyanotic CHD patients which was reported previously (Dündar et al., 2000; Dinleyici et al., 2007). Chronic hypoxia could reduce IGF-1 levels which could be a cause for increased growth failure in cyanotic CHD patients and would be a main cause for malnutrition. The positive correlation between IGF-1 and growth factors as well as low IGF-1 levels in cyanotic patients in comparison to acyanotic patients and healthy children are indicative of malnutrition and growth retardation in these patients which could be due to chronic hypoxemia considering lower blood oxygen saturation in these patients.

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