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Study on Bone Age in Pediatric Patients with Congenital Heart Disease and its Relation with Cyanosis and Pulmonary Artery Pressure

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Abstract: The aim of this study is to evaluate the growth failure in children with Congenital Heart Diseases (CHD) associated with the Pulmonary Hypertension (PH) and cyanosis. Growth parameters including weight, height and head circumference of 120 cases with congenital heart defects aged 6 months to 14 years were compared with standard growth curves (50th percentile) between November 2007 and November, 2008. Of all, sixty five (54.1%) were male and 55 (45.8%) were female. The patients were classified into four groups based on the presence or absence of PH and cyanosis. The gap between chronological age and bone age (BA) for all subjects was determined. Growth disturbance in weight, height and head circumference was detected in 80 (66.7%), 79 (65.8%) and 41 (34.2%) of the patients, respectively. Bone age delay was seen in fifty five percent of the cases. Generally, delay in all parameters was more seen in acyanotic patients with pulmonary hypertension. In subjects with cyanosis whether in addition to PH or not, bone age was significantly retarded. Etiology of growth failure in children with CHD is multifactorial. Further studies are required to assess the role of different factors in this field.

Key words: Congenital heart disease, cyanosis, pulmonary hypertension, bone age, growth failure

INTRODUCTION

Children with Congenital Heart Disease (CHD) have an increased prevalence of malnutrition and growth failure. Malnutrition widely ranges from mild undernutrition to severe failure to thrive (FTT). (Avitzur *et al.*, 2003; Yilmaz *et al.*, 2007; Varan *et al.*, 1999). On the basis of multifactorial etiology for growth retardation in these patients, some causes are presumed. Decreased energy intake, increased energy requirements and recurrent respiratory infections may all contribute. Current evidences strongly suggest that pre-operative malnutrition is a major factor affecting the outcome of cardiac surgery (Nydegger and Bines, 2006; Vaidyanathan *et al.*, 2008). Different types of cardiac malformations can affect nutrition and growth to various degrees. Presence of cyanosis and/or Pulmonary Hypertension (PH), which are frequently seen in many patients with CHD, appears to influence the growth pattern of affected children (Nydegger and Bines, 2006; Vaidyanathan *et al.*, 2008; Avitzur *et al.*, 2003; Da Silva *et al.*, 2007). Congenital cardiac lesions are classified into two large groups based on the presence or absence of cyanosis, which can be revealed by physical examination applying the pulse oximeter. These two groups are further subdivided considering the

pattern of their chest radiography showing evidence of increased, normal, or decreased pulmonary vascular markings. Acyanotic defects can be divided into two major groups on the basis of their dominant load abnormally imposed on the heart. These two categories are the lesions leading to volume overload and the defects resulting in pressure overload (Weeks and Friedman, 2004; Chowdhury, 2007; Allen *et al.*, 2008; Bernstein, 2007).

Likewise, it has been previously proposed that the Bone Age (BA) may be delayed in children with CHD (White *et al.*, 1972; Danilowicz, 1973; Pelargonio *et al.*, 1975). Chronic hypoxemia has a direct or indirect effect on serum insulin like growth factor I (IGF-I) concentrations leading to its reduced level and this may be a cause of increased growth failure in patients with cyanotic congenital heart disease (Dündar *et al.*, 2000; Dinleyici *et al.*, 2007). It is suggested that patients with increased pulmonary blood flow and pulmonary hypertension are more prone to develop malnutrition and growth retardation and cyanotic patients with pulmonary hypertension are the ones most severely affected. In a study growth retardation was related to the size of intra cardiac left to right shunts. However, available data are conflicting (Varan *et al.*, 1999; Cameron *et al.*, 1995; Leite *et al.*, 1995; O'Brien and Smith, 1994).

The separate influences of hypoxemia and pulmonary hypertension on the growth of these patients have been widely studied but the additive effects of cyanosis and pulmonary hypertension on the prognosis of these children have rarely been assessed. This study was designed to investigate the effect of several types of cardiac malformations on the nutrition and growth status including delayed bone age, weight, height and head circumference and determine their relation with cyanosis and pulmonary artery pressure.

MATERIALS AND METHODS

In a cross-sectional study performed from November, 2007 to November, 2008 in Tabriz Shahid Madani Hospital, 120 children with the diagnosis of CHD were investigated. These patients were admitted for surgical correction, medical management or cardiac catheterization. Patients with a history of intrauterine growth retardation, prematurity, known genetic syndromes and dysmorphic features were excluded. The diagnosis of CHD was made through medical history, clinical examinations and laboratory investigations including chest X-ray and electrocardiography confirmed by echocardiography or cardiac catheterization together with echocardiography.

Echocardiographic and angiographic evaluations were done by an expert pediatric cardiology subspecialist. In order to be able to assess chronic effects of CHD on growth parameters, patients younger than 6 month old were excluded. Eligible subjects were allocated to 4 strata based on the presence of cyanosis and/or pulmonary hypertension:

- **Group A/PH:** Acyanotic patients with pulmonary hypertension (patients with left to right shunt and pulmonary hypertension)
- **Group A/No PH:** Acyanotic patients without pulmonary hypertension
- **Group C/No PH:** Cyanotic patients without pulmonary hypertension
- **Group C/PH:** Cyanotic patients with pulmonary hypertension

Growth parameters including body weight (kg), height (cm) and head circumference (cm) were measured by a nurse. Anteroposterior wrist X-ray was done as part of a bone-age study. The graphics were reported by a radiologist blinded to the type of CHD and patients' age, only informed about their sex. The gap between reported bone age and the chronological age was determined and any delay was detected. Weight (kg), height (cm) and head circumference (cm) values were plotted on standard

growth curves. The values of 50th percentile were assigned as standard measures and any differences between the growth parameters and standard values were determined. Growth retardation and bone-age delay were assessed regarding the presence of cyanosis and/or PH. The research ethics committee of Tabriz University of Medical Sciences approved the study and informed consent was obtained from all parents.

Data were analyzed by SPSS ver15 considering the simultaneous effects of cyanosis and pulmonary hypertension on growth parameters. The descriptive values were stated as percent, mean and prevalence. Chi-square, Mann-Whitney U-test and independent samples t-test were used as required (Neely *et al.*, 2003; Rosner and Grove, 1999; Conover, 1999). A p-value less than 0.05 was considered statistically significant.

RESULTS

A total of 120 children with CHD aged 6 months to 14 years were investigated over the one year period. The mean age of patients was 39.74 ± 34.78 months. Of these cases, 65 (54.1%) were male and 55 (45.8%) were female. The subjects were categorized into four groups on the basis of presence or absence of cyanosis and pulmonary hypertension. Among these cases, 46 (38.4%) were acyanotic without pulmonary hypertension (A/No PH); 33 (27.5%) were acyanotic with pulmonary hypertension (A/PH); 33 (27.5%) of patients were in cyanotic without pulmonary hypertension group (C/No PH) and 8 (6.6%) were in cyanotic with pulmonary hypertension group (C/PH).

Bone age delay compared with chronological age and weight, height and Head Circumference (HC) disturbance to reach standard percentile of growth curves were evaluated.

Overall, 80 (66.7%), 79 (65.8%) and 41 patients (34.2%) were below 50th percentile for weight, height and head circumference, respectively. Delay in bone age was detected in 67 patients (55.8%). Total number and percent of different types of growth failure in four studied categories are presented in Table 1.

Table 1: Total number and percent of different types of growth failure in four studied groups

Groups	Delay in bone age	Weight deficient	Height deficient	Delay in head circumference
A/No PH	15 (32.6)	22 (47.8)	24 (52.2)	15 (32.6)
A/PH	24 (72.7)	31 (93.9)	27 (81.8)	18 (69.2)
C/No PH	21 (63.6)	21 (63.6)	21 (63.6)	10 (41.7)
C/PH	7 (87.5)	6 (75.0)	7 (87.5)	6 (75.0)

A/No PH: Acyanotic patients without pulmonary hypertension, A/PH: Acyanotic patients with pulmonary hypertension, C/No PH: Cyanotic patients without pulmonary hypertension, C/PH: Cyanotic patients with pulmonary hypertension. Values in brackets are percentages

Assigning acyanotic patients without PH as standard, we compared the parameters in other three categories with this group. There was significant differences in all measured factors (delay in BA, weight, height and head circumference) between A/PH and A/No PH group ($p < 0.001$, $p < 0.001$, $p = 0.007$, $p = 0.014$, respectively). The delay in all growth parameters was significantly more frequent in A/PH group. For C/No PH group the only significant finding was delay in bone age ($p = 0.006$). The differences in weight ($p = 0.164$), height ($p = 0.310$) and HC (0.565) were not significant.

In C/PH group delay in bone age was significant ($p = 0.006$). There was no significant disparity in other three parameters ($p = 0.253$ for weight, $p = 0.119$ for height and $p = 0.092$ for head circumference).

DISCUSSION

Here, we aimed to assess the adverse effects of Congenital Heart Diseases (CHD) on various aspects of growth and evaluate the additive role of cyanosis and pulmonary hypertension. There are not enough studies assessing this concomitance, so, further studies are needed to fulfill these goals.

This study shows that the delay in bone age was significantly more in both cyanotic patients with pulmonary hypertension and cyanotic subjects without PH compared to standard group (the patients without PH and cyanosis). For the patients with PH and without cyanosis there was significant disparity in terms of all growth parameters including weight, height and head circumference as well, bone age compared to those with none of PH and cyanosis.

Patients with CHD and cyanosis, pulmonary hypertension and congestive heart failure appear to have an increased prevalence of growth failure and malnutrition compared to normal population (Da Silva *et al.*, 2007). It is well known that malnutrition accompanies and contributes to morbidity in CHD. Optimizing nutritional status improves surgical outcome and is associated with reduced morbidity (Shrivastava, 2008; Ardura Fernández *et al.*, 2003; Leitch, 2000; Varan *et al.*, 1999).

In the research done by Jacobs *et al.* (2000), 40% of patients with CHD had subnormal weight and height values.

Varan *et al.* (1999) studied 89 children with proven CHD and showed that 65% of patients were below the 5th percentile for weight and 41% were below the 5th percentile for both weight and height.

In a large study by Mehrizi and Drash (1962) 890 children with CHD were enrolled. Of these cases, 55% had short stature, 52% had poor weight gain and 27% had delayed values of both weight and height for age.

Malnutrition and growth failure were more prevalent in present study. There are several factors that may explain this finding such as the severity of congenital heart defect, difference in definition and interpretation of growth failure and socioeconomic status of the family. The recent one may be the most significant factor in the patients. Delay in medical refers and inappropriately postponed surgical interventions seem to be another reason for increased prevalence of growth retardation in this study.

Any earlier study evaluating the rate of growth failure on the basis of head circumference was not found.

Present data suggest that growth retardation is more relevant to pulmonary hypertension than cyanosis except for bone age. It may be attributed to the role of hypoxemia in reducing serum levels of IGF-I and as a result, delay in appearing bony centers. There are various results about the pathophysiology and the effect of cyanosis in children with CHD (Da Silva *et al.*, 2007; Himeno, 2001; Himeno *et al.*, 2003).

Tambic-Bukovac and Malčić (1993) on 223 children with CHD showed that growth failure was significantly more prevalent in cyanotic cases compared to noncyanotic ones. In the earlier studies by Cameron *et al.* (1995) and Leite *et al.* (1995) cyanotic congenital heart diseases in children cause more pronounced growth retardation compared to acyanotic ones.

In some studies in children there was no significant correlation between physical growth parameters and the presence of cyanosis (Vaidyanathan *et al.*, 2008; Linde *et al.*, 1967). Even in some reviews acyanotic patients had more prevalence of growth failure than cyanotic ones (Jacobs *et al.*, 2000; Salzer *et al.*, 1999).

Considering the role of factors other than cyanosis altering the results is important in explanation of these disparate findings.

The effect of pulmonary hypertension on the status of growth parameters and skeletal maturation is evaluated in some reviews. Varan *et al.* (1999) suggested that pulmonary hypertension was the most prominent factor associated with failure to thrive (FTT) in patients with CHD. In the review done by Vaidyanathan *et al.* (2008) congestive heart failure and pulmonary hypertension were significant predictors of growth disturbance consistent with the findings of present study.

In present study, both cyanosis and pulmonary hypertension were associated with significantly more prevalence of bone age retardation. We did not find any recent review relating the bone age with CHD. Plargonio *et al.* (1975) showed the adverse effects of congenital heart diseases on the appearance and development of ossification centers in roentgenograms.

In another study by Damilowicz (1973) cyanosis was put forward to be a risk factor for delay in bone age. The findings of these two studies are consistent with the results of present survey. Considering the lack of recent studies assessing the role of CHD and the separate effects of cyanosis and pulmonary hypertension on the appearance and growth of bony centers, further reviews should be designed.

According to the results of this study, bone-age delay and growth retardation are common findings in children with CHD. Presence of cyanosis and/or PH may further deteriorate these conditions and should be promptly managed. Considering the significance of growth failure in patients with PH. The results of present study underline the importance of referring patients with CHD and PH for early corrective surgery. This is important to emphasize that in children with congenital heart disease and increased pulmonary blood flow, timely corrective intervention remains the most important factor in improving the growth and nutritional status. In the present era most of the congenital heart defects can be corrected if diagnosed early. This study reports a significantly high prevalence of delayed bone age in hypoxemic patients, suggesting that correction of the cardiac anomaly in cyanotic patients may favorably influence the skeletal maturation.

Considering the positive correlation between chronic hypoxemia and reduced level of serum IGF-I and the role of this factor in growth retardation, further studies are needed to assess the relationship between IGF-I levels and growth status.

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