Original Article

Linear growth in relation to the circulating concentration of insulin-like growth factor-I in young children with acyanotic congenital heart disease with left to right shunts before versus after surgical intervention

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ABSTRACT

Objectives: The aim was to determine the degree of linear growth retardation of patients with congenital acyanotic heart disease at presentation and the magnitude of catch-up growth, if any, in relation to their echocardiographic changes and insulin-like growth factor- I (IGF-I) concentration before versus after surgical intervention. **Materials and Methods:** This prospective study recorded the anthropometric data and measured the circulating IGF-I, free thyroxin (FT4), and thyrotropin (TSH) of 27 infants and children with congenital acyanotic heart disease with left to right shunt (10 with VSD, 8 with ASD, 9 PDA) without heart failure, or severe pulmonary hypertension, before and 12 months or more after surgical or catheter intervention. Eighty normal age and sex- matched normal siblings of these patients were included as controls for the auxologic data. **Results:** At presentation, patients' mean age = 35.6 ± 26 months, height SDS (HtSDS) = -1.6 ± 1.1, and body mass index (BMI) = 15.1 ± 2.5. They were significantly shorter and with lower BMI compared to normal controls (HtSDS = 0.25 ± 0.3, BMI = 16.4 ± 1.5). One year or more after catheter or surgical treatment, the HtSDS and BMI increased significantly in patients to –0.55 ± 0.9 and 15.9 ± 1.5, respectively). IGF-I levels increased from 46.8 ± 29 mcg/L before to 77.3 ± 47.6 mcg/L after intervention. No significant change has been detected in circulating FT4 or TSH concentrations. The HtSDS after treatment was correlated with the IGF-I concentration ($r = 0.804$, $P < 0.001$). The change in the HtSDS after intervention was correlated significantly with BMI ($r = 0.594$, $P < 0.001$) and negatively with age ($r = -0.52$, $P < 0.01$). The shunt size was correlated negatively with BMI and HtSDS before intervention ($r = -0.35$, $P < 0.01$ and $r = -0.461$, $P < 0.05$, respectively). GVSDS after intervention surgery was correlated with BMI after intervention ($r = 0.495$, $P < 0.001$) and negatively with the age at operation ($r = -0.683$, $P < 0.001$). **Conclusions:** In congenital acyanotic heart diseases, early surgical interference and weight gain have beneficial effect on postoperative growth spurt. This catch-up growth appears to be mediated through activation of the GH/IGF-I system and suggests an important role of increasing BMI (an indicator of nutrition) as an imperative factor.

Key words: Atrial septal defect, catch-up growth, insulin-like growth factor-I, patent ductus arteriosus, ventricular septal defect

Introduction

Children with congenital heart disease (CHD) have been reported to show significant growth retardation both prenatally and postnatally.[1-8] Retardation in height as well as weight seems most pronounced in children with cyanotic and acyanotic heart disease.[3,4] Medical therapy has been associated with little improvement of their slow growth. Although different degrees of catch-up growth after successful surgical repair has been reported in different forms of CHD,[8-11] none of the studies has simultaneously compared the degree of catch-up growth in these different forms of congenital acyanotic heart diseases after surgical correction. Advances and recent developments in surgical approach and enteral nutrition have improved the care

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of these patients.[1,11-13] In addition, the degree of growth retardation at presentation and the magnitude of catch-up growth and their relation to the change, if any, to important hormones controlling growth (insulin-like growth factor-I (IGF-I), free T4 (FT4), and thyrotropin (TSH) needs further clarification.

The aim of the present prospective study was to evaluate long-term growth of infants with acyanotic CHD and to look for a possible relationship between echocardiographic parameters at the moment of surgical correction and the degree of post-surgical catch-up growth.

Materials and Methods

Growth parameters for 27 children with acyanotic CHD (8 with patent ductus arteriosus (PDA), 10 with ventricular septal defect (VSD), and 9 with atrial septal defect (ASD), without heart failure or severe pulmonary hypertension) were recorded prospectively. These data represent all patients followed up in the department of Pediatric Cardiology, HMC, between January 2006 and January 2008. Patients with multiple CHDs, associated chromosomal malformations, peculiar syndromes, or prematurity were not included in the present study. Our patients were 12 females and 16 male patients. The mean operation ages of our patients are given in Table 1. The mean birth weight and length were normal for all patient groups and did not differ among the three patient groups. Eighty age and sex-matched normal siblings of our patients with congenital heart diseases were randomly selected to use as controls for growth parameters.

All patients were examined thoroughly with special emphasis on:

1. Detailed history taking including nutritional intake.
2. Anthropometric measurements included weight and length.
3. Height standard deviation score (HtSDS), linear growth velocity standard deviation scores (GVSDS), and body mass index (BMI) were calculated prospectively before and at least 12 months or more after treatment. Annual GV was calculated from length measurements taken 12 months apart. Length was measured with an infant/child height/length measuring board. This board has 130 cm capacity (collapses to 75 cm) and has 0.1 cm increments, with the sliding head-foot piece (Shorr Productions; 17802 Shotley Bridge Place; Olney, MD 20832, USA). The standard deviation of the difference between blind triplicate height measurements of 20 children was 0.15 cm. Weight (child lightly clothed) was measured using an electronic Baby scale with Digital Display. The height was measured by Seamen Stadiometer Standard deviation scores (SDS) calculated for length, height, length/height velocity, and BMI using WHO standards.[14-16]
4. Investigations included measurement of circulating IGF-I, FT4, and TSH.
5. During each clinic visit (every 3-4 months for at least 12 months), the anthropometric parameters were reassessed and recorded and the laboratory tests repeated.

IGF-I, TSH, and FT4 were measured by radioimmunometric assay using reagents purchased from Mediagnost; (Reutlingen, Germany). Intraassay coefficient of variation (CVs) was 7.6%, 6.9%, and 5.9% respectively, and interassay CVs were 7.9%, 7.9%, and 8.2%, respectively. Results are expressed as the mean ± SD and analyzed by paired Student's *t*-test to compare growth parameters and analyte concentrations before versus after surgical treatment. A non-paired Student's *t*-test was used to compare growth parameters and analyte concentrations between patients with CHD and control group. Correlation and linear regression analysis were used to investigate the relation between growth parameters and the other variables. For

Table 1: Anthropometric and hormonal data of patients with CHD before versus after surgery

		All Data		PDA Data		VSD Data		ASD Data		Controls	
		Before *n* = 27	After *n* = 27	Before *n* = 8	After *n* = 8	Before *n* = 10	After *n* = 10	Before *n* = 9	After *n* = 9	Before *n* = 80	After *n* = 80
Age	Mean	35.6	46.0	24.8	32.8	21.2	35.6	48.8	61.1	29.5	45.5
(mon)	SD	26.8	27.9	27.0	27.0	15.0	4.2	25.0	3.7	12.5	15.8
BMI	Mean	15.3 #	15.9*	16.4	16.8*	15.3	15.9*	14.3 #	15.1*	16.4	16.7
kg/m^2	SD	2.5	1.5	2.0	1.5	3.5	0.9	-2.4	1.1	1.5	1.4
HtSDS	Mean	-1.55#	-0.55*#	-1.54# -0.1*		-2.03#	-0.6*#	-1.1#	-0.35*#	0.25	0.42
	SD	1.1	0.9	1.5	1.7	2.0	2.0	1.0	1.1	0.3	0.27
IGF-I	Mean	46.8	77.3*	23.7	77.0	50.0	68.0	66.6	87.0	ND	ND
mcg/L	SD	29.0	47.6	9.2	56.5	15.2	23.6	24.7	40.5		
Free T4	Mean	15.7	14.6	16.4	16.2	16.2	15.6	15.5	13.5	ND	ND
	SD		2.3	2.0	1.6	1.6	1.2	0.9	2.1	0.2	
TSH	Mean	3.0	1.9	4.6	2.1	2.3	3.1	0.1	1.6	ND	ND
uIU/ml	SD	2.1	0.9	1.1	1.1	0.5	0.8	1.4	0.6		

PDA: Patent ductus arteriosus, VSD: Ventricular septal defect, ASD: Atrial septal defect, BMI: Body mass index, IGF-I: Insulin-like growth factor-I, TSH: Thyrotropin, #P < 0.05 patients versus controls, *P < 0.05 patients before versus after 1 year of intervention

ethical reasons, hormonal and analyte concentrations for normal controls were not measured.

None of the included patients were subsequently excluded. For age periods, three measurements were used in the first year of life. For postoperative periods, three measurements were taken for every patient. Preoperative measurements were taken in the preoperative 2 weeks closest to operation. Three measurements each year were used in the first year after operation. The relationship between catch-up growth and the severity of preoperative growth failure was evaluated by correlating GVSDS after operation with the growth parameters before surgery. The relationship between catch-up growth and age at time of surgical intervention was also evaluated. Measurement of circulating IGF-I, free thyroxine (FT4) and TSH was done before and 6 months or more after surgery. IGF-I standard deviation scores were calculated using published data using the same type of assay.[17] Hormonal data are correlated with anthropometric and echocardiographic data.

Ethical approval

Research Ethics Board, Hamad Medical Centre, Doha, Qatar, has approved the protocol of the study and informed consents were obtained from all the parents of the children included in this study.

Statistical analysis

Usual parametric statistics were used for calculation of the mean values and confidence intervals. A significant difference was considered to exist between the reference population and our patient data if the mean value of the data set differed from 0 at the 0.05 confidence level. The Pearson correlation coefficient was used for studying the relationships between catch-up growth and the severity of initial growth retardation. The Excel statistical package was used for data management.

Results

Anthropometric and hormonal data [Table 1] showed preoperatively patients' mean age = 35.6 ± 26.8 months, length SDS (LSDS), HtSDS = -1.55 ± 1.1 and body mass index (BMI) = 15.3 ± 2.5. They were significantly shorter compared to normal controls. One year after catheter/surgical intervention, the HtSDS increased significantly in patients to –0.55 ± 0.9 with a significantly increased growth velocity SDS (GVSDS) = 2.35 ± 0.85. They significantly had higher GVSDS compared to normal controls (0.34 ± 0.25). Circulating concentrations of IGF-I and IGF-I SDS increased significantly from 46.8 ± 29 mg/L and -1.01 ± 0.44, respectively, before surgical treatment to 77.3 ± 47.3 and -0.72 ± 0.34, respectively, after treatment. No significant change has been detected in circulating FT4 or TSH concentration after versus before surgery.

The HtSDS of PDA, VSD, and ASD groups increased by 1.5, 1.4, and 0.74 SD, respectively, 1 year after surgery [Figure 1]. Significant catch-up growth occurred in all patient groups (mean = 1SD/year). After a year of surgical correction, the HtSDS of patients with PDA, VSD, and ASD were within ±0.5 SD of their MPHtSDS. However, they were still significantly shorter than the control group. One year after intervention, patients had significantly increased BMI versus before therapy and their BMI did not differ than those for controls.

The HtSDS after treatment was correlated with the IGF-I concentration (r = 0.804, $P < 0.001$). After surgery, the percent change in IGF-I was correlated significantly with GV (r = 0.589, $P < 0.01$) and BMI (r = 0.82, $P < 0.001$). The change in the HtSDS after intervention was correlated significantly with BMI (r = 0.594, $P < 0.001$) and negatively with the age (r = -0.52, $P < 0.01$).

Before surgery, the shunt size was negatively correlated with BMI (r = -0.35, $P < 0.01$) and with HtSDS (r = -0.461, $P < 0.05$). GVSDS after surgery was correlated with the BMI before and after intervention surgery (r = 0.339, $P < 0.02$ and r = 0.495, $P < 0.001$, respectively) and negatively with the HtSDS before surgery (r = -0.461, $P < 0.05$) and the age at operation (r = -0.683, $P < 0.001$).

Discussion

In this study, infants and young children with acyanotic CHD (n = 27, below 4 years of age) presented with short stature (LSDS/HtSDS = -1.55 ± 0.55). Marked improvement in their HtSDS was achieved 1 year after surgical correction with a period of significant catch-up growth evidenced by GVSDS = 2.35 ± 0.85 during the

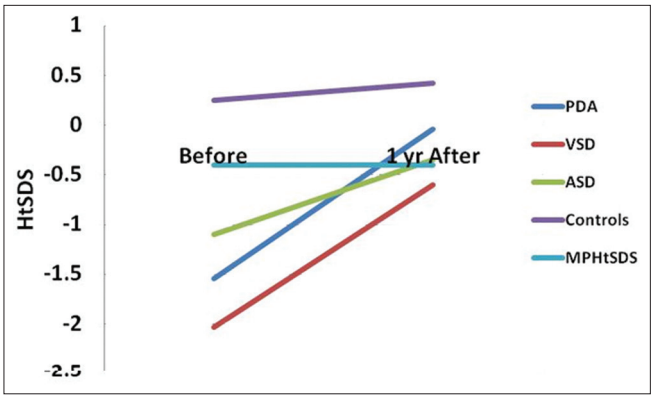

Figure 1: Height Standard deviation score before versus after surgical intervention. PDA: Patent ductus arteriosus, VSD: ventricular septal defect, ASD: atrial septal defect. MPHtSDS: mid-parental height standard deviation score

year after intervention. This growth spurt appeared to compensate adequately for the period of the previous growth retardation in most of the patients.

Many factors can contribute to impaired linear growth in these infants including: (1) hypoxia and defective perfusion to the growing tissues including the epiphyseal growth plate, (2) increased metabolic rate inducing a hypermetabolic state, (3) malnutrition due to decreased appetite and/or malabsorption and (4) possible effect on GH/IGF-I axis.[1,5,13,18-21]

In our patients with acyanotic CHD, circulating IGF-I concentrations increased significantly after versus before surgical intervention. After surgery, the percent change in IGF-I was correlated significantly with GV and BMI. These findings supported the view that the attained growth spurt after treatment is mediated through increased IGF-I synthesis (stimulation of GH-IGF-I axis). The GVSDS after treatment was also significantly correlated with the BMI before surgery and negatively with the HtSDS before surgery. It appeared that higher BMI preoperatively was associated with better growth spurt. In support of our results, underweight patients with CHD who received nutritional counseling showed increased dietary intake and improved anthropometric measurements on follow-up.[14]

Significantly accelerated linear growth after surgical treatment of acyanotic CHD appears to be mediated through activation of the IGF-I synthesis. The correlation between GV after surgery with the BMI before surgery and the significant correlation between percent increase of IGF-I and the BMI after surgery pointed out to the importance of intensive nutritional support to increase BMI and IGF-I secretion before and after surgery as an essential factor determining growth spurt after the operation.

GV after surgery was correlated negatively with the age at operation (r = -0.639, $P < 0.001$) denoting that early surgical interference was associated with better growth spurt. Delay in surgical repair of congenital heart lesions can lead to worsening of nutrition and growth status of patients. Several reports have documented encouraging results of early repair of critical congenital heart defects in symptomatic neonates and infants rather than palliative operations and of primary surgical closure of large VSDs.[8,22,23]

In conclusion, an intensive nutritional treatment and early corrective surgery should be considered to optimize growth outcome in patients with CHD.

References

1. Varan B, Tokel K, Yilmaz G. Malnutrition and growth failure in cyanotic and acyanotic congenital heart disease with and without pulmonary hypertension. Arch Dis Child 1999;81:49-52.
2. Mehrizi A, Drash A. Growth disturbance in congenital heart disease. J Pediatr 1962;61:418-29.
3. Weintraub RG, Menahem S. Growth and congenital heart disease. J Paediatr Child Health 1993;29:95-8.
4. Norris MK, Hill CS. Nutritional issues in infants and children with congenital heart disease. Crit Care Nurs Clin North Am 1994;6:153-63.
5. Abad-Sinden A, Sutphen J. Growth and nutrition, in Moss and Adams heart disease in infants, children and adolescents. In: Allen HD, Gutgesell P, Clark EB, Driscoll D, editors. Chapter 17. Philadelphia: Lippincott Williams & Wilkins 2000. p 326.
6. Silove ED. Assessment and management of congenital heart disease in the newborn by the district paediatrician. Arch Dis Child Fetal Neonatal Ed 1994;70:F71-4.
7. Strangeway A, Fowler R, Cunningham K, Hamilton J. Diet and growth in congenital heart disease. J Pediatr 1976;57:57-86.
8. Vogt KN, Manlhiot C, Van Arsdell G, Russell JL, Mital S, McCrindle BW. Somatic growth in children with single ventricle physiology. Impact of physiologic state. J Am Coll Cardiol 2007;50:1876-83.
9. Leitch CA, Karn CA, Peppard RJ, Granger D, Liechty EA, Ensing GJ. Increased energy expenditure in infants with cyanotic congenital heart disease. J Pediatr 1998;133:755-60.
10. Jacobs EG, Leung, MP, Karlberg, J. Birthweight distribution in southern Chinese infants with symptomatic congenital heart disease. J Paediatr Child Health 2003;39:191-6.
11. Reddy VM, McElhinney DB, Sagrado T, Parry AJ, Teitel DF, Hanley FL. Results of 102 cases of complete repair of congenital heart defects in patients weighing 700 to 2500 grams. J Thorac Cardiovasc Surg 1999;117:324-31.
12. Page RE, Deverall PB, Watson DA, Scott O. Height and weight gain after total correction of Fallot's tetralogy. Br Heart J 1978;40:416-20.
13. Forchielli ML, McColl R, Walker WA, Lo C. Children with congenital heart disease: A nutrition challenge. Nutr Rev 1994;52:348-53.
14. WHO Child Growth Standards: Methods and development growth velocity based on weight, length and head circumference. Geneva: World Health Organization; 2009.
15. WHO Child Growth Standards: Methods and development: Head circumference-for-age, arm circumference-for-age, triceps skinfold-for-age and subscapular skinfold-for-age. Geneva: World Health Organization; 2007.
16. WHO Child Growth Standards: Methods and development: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age. Geneva: World Health Organization; 2006.
17. Yüksel B, Özbek MN, Mungan NÖ, Darendeliler F, Budan B, Bideci A, *et al*. Serum IGF-1 and IGFBP-3 Levels in healthy children between 0 and 6 years of age. J Clin Res Pediatr Endocrinol 2011;3:84-8.
18. Gilger M, Jensen C, Kessler B, Nanjundiah P, Klish WJ. Nutrition, growth, and the gastrointestinal system: Basic knowledge for the pediatric cardiologist. In: Ganson A, Bricker JT, McNamara PG, editors. The science and practice of pediatric cardiology. Philadelphia: Lea & Febiger; 1990. p. 2354-70.
19. Krieger I. Growth failure and congenital heart disease. Am J Dis Child 1970;120:497-502.
20. El-Sisia A, Khella A, Numan M, Dilwar M, Bhat A, Soliman A. Linear growth in relation to the circulating concentration of insulin-like growth factor-i and free thyroxine in infants and children

with congenital cyanotic heart disease before vs. after surgical intervention. J Trop Pediatr 2009;55:302-6.
21. Salzer HR, Haschke F, Wimmer M, Heil M, Schilling R. Growth and nutritional intake of infants with congenital heart disease. Pediatr Cardiol 1989;10:17-23.
22. Hardin JT, Muskett AD, Canter CE, Martin TC, Spray TL. Primary surgical closure of large ventricular septal defects in small infants. Ann Thorac Surg 1992;53:397-401.
23. Meijboom F, Szatmari A, Utens E, Deckers JW, Roelandt JR, Bos E, *et al*. Long-term follow-up after surgical closure of ventricular septal defect in infancy and childhood. J Am Coll Cardiol 1994;24:1358-64.

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