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Evaluation of cardiac function in a group of small for gestational age school-age children treated with growth hormone☆

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ABSTRACT

Introduction and objectives: Small for gestational age (SGA) patients have an increased risk of developing a cardiovascular pathology, as well as a metabolic syndrome. Our objective is to evaluate the cardiac morphology and function of SGA children treated with growth hormone (GH), identifying changes that could potentially have long-term consequences.
Methods: We selected 23 SGA school-age patients and 23 healthy children. We measured their weight, height, blood pressure and heart rate. Using transthoracic echocardiography, we evaluated cardiac chamber size, ascending and abdominal aortic diameter as well as the systolic and diastolic function of both ventricles.
Results: SGA children have a higher systolic and diastolic blood pressure ($p < .05$) without significant changes in their heart rate. They also have a thicker interventricular septum (SGA *Z*-score 1.57 vs. 0.89; $p = .026$) and a worse right ventricular systolic function, with a lower TAPSE (SGA *Z*-score −0.98 vs. 0.95; $p = .000$), as well as a lower blood flow rate in the pulmonary artery (SGA 0.85 m/s vs. 0.97 m/s; $p = .045$). No significant difference was observed in the patients' left ventricular function. SGA patients' ascending aortic diameter was greater (SGA *Z*-score −1.09 vs. −1.93; $p = .026$), whereas the systolic abdominal aortic diameter was smaller (SGA *Z*-score−0.89 vs. −0.19; $p = .015$).
Conclusions: We found functional and morphological cardiac changes in SGA school-age patients treated with GH. It is important to follow-up this patient group in order to determine if these changes contribute to an increased cardiac morbidity in adulthood.

Evaluación de la función cardiaca en un grupo de niños pequeños para la edad gestacional en edad escolar en tratamiento con hormona de crecimiento

Palabras clave:
Ecocardiografía
Estructura
Hormonas
Pediatría
Ventrículo derecho

RESUMEN

Introducción y objetivos: Los pacientes pequeños para la edad gestacional (PEG) son población de riesgo para el desarrollo de enfermedad cardiovascular y síndrome metabólico. Nuestro objetivo es estudiar la morfología y la función cardiaca en un grupo de niños PEG en edad escolar en tratamiento con *growth hormone* (GH, «hormona de crecimiento»).
Métodos: Se han incluido en el estudio 23 pacientes PEG y 23 controles sanos. Se valoró peso, talla, presión arterial y frecuencia cardiaca. Mediante ecocardiografía transtorácica se evaluó el tamaño de las cavidades cardiacas, el diámetro de la aorta ascendente y abdominal y parámetros de función biventricular.

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Resultados: Los niños PEG presentan mayores percentiles de presión arterial sistólica y diastólica (p < 0,05), sin cambios significativos en la frecuencia cardiaca. Tienen un mayor diámetro del septo interventricular (Z-*score* 1,57 en PEG frente a 0,89; p = 0,026) y una peor función sistólica del ventrículo derecho, con un TAPSE inferior (Z-*score* −0,98 en PEG frente a 0,95; p = 0,000) y una menor velocidad sanguínea en arteria pulmonar (0,85 m/s en PEG frente a 0,97 m/s; p = 0,045). No se han encontrado diferencias en la función del ventrículo izquierdo. El diámetro de la aorta ascendente es mayor en PEG (Z-*score* −1,09 frente a −1,93; p = 0,026), mientras que el diámetro de la aorta abdominal en sístole es menor (Z-*score* −0,89 frente a −0,19; p = 0,015).

Conclusiones: Se han observado cambios significativos en la morfología y la función cardiaca en niños PEG en edad escolar tratados con GH. Es importante continuar en ellos un seguimiento para determinar si estas alteraciones contribuyen a un aumento de morbilidad cardiaca en la edad adulta.

Introduction

A small for gestational age (SGA) child is a new-born whose weight and/or size is below −2 standard deviations (SD) for his/her gestational age, according to data from the reference population.[1] This poor foetal growth affects 6–10% of new-borns and can be attributed to various factors (foetal, maternal, placental, etc.), although the cause is not identified in 40% of cases.[1] If it is SGA, this can determine these children's both, short and long term postnatal prognosis and morbidity. In this sense, associations between SGA children and many adult diseases have been observed in numerous studies.[2] SGA at birth is associated, among others, with an increased risk of cardiovascular disease and mortality from this cause. This association is explained because the SGA are a population at risk of developing metabolic syndrome, though recent studies show that delayed growth alone could also produce direct changes in the foetal cardiovascular system.[3] Foetal pathophysiological characteristics induce adaptive mechanisms in the form of haemodynamic redistribution in response to foetal malnutrition and chronic hypoxia, which results in subclinical cardiac dysfunction and vascular remodeling.[4] Recent reports have described these foetuses as having larger and more globular hearts and showing signs of both systolic and diastolic dysfunction, assessable by foetal echocardiography.[5]

So far, changes have been described in relation to the hearts of SGA fetuses,[4–6] but there are hardly any studies investigating whether these changes persist at a later stage in life. The aim of this study is to assess cardiac function and morphology of a group of school-age children diagnosed with SGA at birth, treated with *growth hormone* (GH), and compare them with those of healthy control subjects of the same age group to determine if there are changes in any of the parameters that are related to cardiovascular function, which could increase morbidity in adulthood.

Materials and methods

Patients

The study group consists of 23 children diagnosed with SGA at birth, controlled at the University Hospital of Zaragoza and treated with GH. They have been compared with 23 controls matched for age and sex.

The inclusion criteria for the SGA group have been established by the Human Growth Hormone Advisory Committee of the Ministry of Health, Social Services and Equality for SGA children:

- A birth weight and/or size lower than −2 SD as per reference standards (García-Dihinx tables and graphs, 2002).[7]
- A height from the age of 4 below −2.5 SD as per reference standards (Andrea Prader Center tables and graphs, Government of Aragon, Ferrández et al.).[8]
- Not having experienced growth recovery at the age of 4, taking into account the growth rate during previous years.
- Having previously ruled out any medical condition or treatment that could have caused a growth disorder, including GH deficiency.

Exclusion criteria were as follows:

- Non-compliance with the auxological inclusion criteria.
- Having a syndromic condition.
- Having been diagnosed with diabetes mellitus or other potentially serious carbohydrate metabolism disorders.
- Being born premature.
- Having a family and/or personal history of cardiomyopathy.
- Taking additional drug treatments that could affect cardiovascular function.

Methods

Before the start, the study particulars were explained in detail to the child's parents and their consent was requested.

The morphological and functional study was performed by a colour M-mode two-dimensional echocardiography, pulsed tissue Doppler, with a Philips ultrasound system, model EnVisor C HD, with 4–8 MHz transducer. The examination was carried out by the same observer in all children, taking the average of 3 cardiac cycles.

Echocardiographic variables identified were: left ventricular systolic and diastolic diameter (mm), thickness of the interventricular septum (IVS) and the posterior wall of the left ventricle during diastole (mm), left ventricle end-diastolic diameter (mm), left ventricular mass (g), ejection fraction (EF) (%) and fractional shortening (FS) (%), maximum transmitral velocity: wave *E* and *A* (m/s), *E*/*A* ratio, mitral annular tissue Doppler: wave *s*′, *e*′ and *a*′ (cm/s), *e*′/*a*′ ratio, *E*/*e*′ ratio, *tricuspid annular plane systolic excursion* (TAPSE) (mm) and maximum velocity across the aorta.

M-mode measures were taken following the recommendations of the American Society of Echocardiography.[9] Early transmitral flow (*E*) and late transmitral flow (*A*) velocity records were made using pulsed Doppler and localizing the sample volume at the mitral valve leaflet tip during diastole. A sample volume of 5 mm was placed in the lateral mitral annulus from the apical 4-chamber view to calculate the early diastolic velocity (*e*) and the late diastolic velocity (*a*) by tissue doppler. The ascending aorta diameter was measured from the suprasternal view, between the aortic root and the brachiocephalic trunk output in the aortic arch; and the abdominal aorta from a subcostal view, obtained with M mode, making measurements in systole and diastole, thus calculating the FS in the abdominal aorta.

Since no segmental wall motion abnormalities were evident, the EF was calculated by the Teichholz[10] method and the left ventricular mass with the Deveraux[11] formula. Sex, age, weight and