Cardiometabolic Risk Factors in Pediatric Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency: Evidence for Insulin Resistance

Fatores de Risco Cardiometabólico na Hiperplasia Congénita da Suprarrenal Pediátrica por Deficiência de 21-Hidroxilase: Evidência de Resistência à Insulina

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This work was developed in: Unidade de Endocrinologia Pediátrica do Serviço de Pediatria, Hospital de Braga, Braga, Portugal.

Abstract

Background: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is associated with an increased cardiometabolic risk profile in adult life. The aim of this work was to evaluate cardiometabolic risk factors in patients with CAH due to 21-hydroxylase deficiency in pediatric age.
Methods: Clinical records of patients with CAH evaluated in a Pediatric Endocrinology Unit were reviewed. Data regarding anthropometric parameters, arterial blood pressure and lipid profile was collected. Patients ≥ 6 years-old were submitted to an oral glucose tolerance test (OGTT).
Results: Eight patients (5 females), with a mean age of 11.4 ± 4.5 years-old were included. Four patients presented the salt wasting form, 3 patients the simple virilizing form and 1 patient the non-classic form. Currently, 2 patients are prepubertal, 3 pubertal and 3 postpubertal, with a mean time of follow-up of 7.62 ± 0.2 years. Half of the patients had normal-weight, 1 had low weight, 1 had weight excess and 2 had obesity. Mean fasting glucose and insulin was 78.12 ± 5.11 mg/dL e 15.58 ± 11.4 µIU/mL, respectively. Patients presented a mean HOMA-IR of 2.56 ± 1.5 and 3 patients evidenced insulin resistance. The OGTT evidenced no dysglycemic cases and the mean Matsuda index was 5.89 ± 2.2.
Conclusion: Half of the patients presented ≥ 1 cardiometabolic risk factor and insulin resistance was present at a very young age. Our results highlight the importance of evaluating cardiometabolic profile in patients with CAH and the necessity to promote healthy life styles in order to reduce the prevalence of cardiovascular disease in the adult life.

Keywords: cardiovascular risk; congenital adrenal hyperplasia; insulin resistance; obesity; pediatric

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> INTRODUCTION

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency, an autosomal recessive condition in which deletions or mutations of the cytochrome P450 21-hydroxylase (CYP21) gene result in glucocorticoid deficiency. [1] This condition leads to increased secretion of adrenocorticotropic hormone (ACTH), adrenal hyperplasia, and increased production of androgens and steroid precursors upstream to the enzymatic defect. [1] 21-hydroxylase deficiency accounts for 90–95% of all CAH cases and it has been demonstrated that the type

Resumo

Introdução: A hiperplasia congénita da suprarrenal (HCSR) por défice de 21-hidroxilase está associada a um aumento do risco cardiometabólico na vida adulta. O objetivo deste trabalho foi avaliar fatores de risco cardiometabólico na idade pediátrica em doentes com HCSR por défice de 21-hidroxilase.
Métodos: Os processos clínicos de doentes com HCSR avaliados em uma Unidade de Endocrinologia Pediátrica foram analisados. Foram colhidos dados referentes a parâmetros antropométricos, pressão arterial e perfil lipídico. Doentes com ≥ 6 anos foram submetidos a uma prova de tolerância à glicose oral (PTGO).
Resultados: Foram incluídos 8 doentes (5 do sexo feminino), com idade média de 11,4 ± 4,5 anos. Quatro doentes apresentaram a forma perdedora de sal, 3 doentes a forma virilizante simples e 1 doente a forma não clássica. Atualmente, 2 doentes são pré-púberes, 3 púberes e 3 pós-púberes, com tempo médio de seguimento de 7,62 ± 0,2 anos. Metade dos doentes apresentou peso normal, 1 apresentou baixo peso, 1 apresentou excesso de peso e 2 apresentaram obesidade. A média de glicemia e insulina em jejum foi de 78,12 ± 5,11 mg/dL e 15,58 ± 11,4 µIU/mL, respetivamente. O HOMA-IR médio foi de 2,56 ± 1,5 e 3 doentes evidenciaram critérios de insulinorresistência. A PTGO não evidenciou disglicemia e o índice de Matsuda médio foi de 5,89 ± 2,2.
Conclusão: Metade dos doentes apresentou ≥ 1 fator de risco cardiometabólico e a insulinorresistência foi demonstrada em idade muito jovem. Este estudo destaca a importância da avaliação do perfil cardiometabólico em doentes com HCSR e a necessidade de promover estilos de vida saudáveis, visando a redução da doença cardiovascular na vida adulta.

Palavras-chave: risco cardiovascular; hiperplasia congénita da suprarrenal; insulinorresistência; obesidade; pediatria

of mutation within the CYP21 gene correlates well to the phenotype. [2] Depending on the extent of enzyme impairment, classic CAH is subdivided into salt wasting type (SW) with deficiency in both aldosterone and cortisol and simple virilizing type (SV) mainly with cortisol deficiency. In both conditions androgen excess results in neonatal virilization of external genitalia and postnatal virilization in girls, while in boys it leads to isosexual precocious puberty. [1, 3] In the SW form severe enzymatic deficiency additionally impairs aldosterone synthesis resulting in hyponatremic dehydration, hyperkalemia and subsequent shock during the first weeks of life. [3] Glucocorticoid treatment and, when necessary, mineralocorticoid replacement, prevents adrenal crisis and suppresses the elevated adrenocortical secretion of androgen steroid precursors from the adrenal cortex. [1,3] A third form of CAH due to 21-hydroxylase deficiency is nonclassic congenital adrenal hyperplasia (NCAH), when the clinical features predominantly reflect androgen excess rather than adrenal insufficiency. [4] Glucocorticoid treatment can be necessary for children and adolescents with significantly advanced skeletal maturation or severe hyperandrogenism. [4]

In patients with CAH there is heterogeneity in respect to the age of diagnosis, forms of presentation and treatment options. Glucocorticoid therapy has a very narrow security spectrum and patients are often at risk for developing iatrogenic Cushing's syndrome or hyperandrogenism. [3] Supraphysiological doses, often needed to control the hyperandrogenism can impair growth, decrease bone mineral density and result in the development of metabolic abnormalities. An increased prevalence of cardiovascular risk factors has been described in patients with CAH due to 21-hydroxylase deficiency in adulthood. [5] These cardiometabolic comorbidities may result from the disease itself, from the excessive circulating androgens, but also due to glucocorticoid therapy. Nevertheless, data regarding pediatric age is limited and few studies have addressed the consequences of CAH and glucocorticoid therapy on metabolic and cardiovascular risk factors in the pediatric age.

The aim of the study is to evaluate the prevalence of metabolic abnormalities that increase cardiovascular risk in patients with CAH due to 21-hydroxylase deficiency in pediatric age.

> METHODS

Between January 2004 and April 2018, 8 children with CAH due to 21-hydroxylase deficiency were diagnosed in the Pediatric Endocrinology Unit of a tertiary hospital in the north of Portugal.

We collected data regarding age and form of presentation of CAH, type of CYP21A2 gene mutation and other comorbidities. Anthropometric measures, blood pressure and pubertal Tanner stage were obtained in all patients. BMI was calculated as weight (kg)/height (m)^2.

17-Hydroxyprogesterone (17-OHP) was determined as a measure of hormonal control. It was measured in the morning, before the first hydrocortisone dose.

A lipid profile analysis was performed in each patient after a minimum 12-hour overnight fast, before the morning hydrocortisone dose and it included: total cholesterol, LDL-cholesterol (LDL-c), HDL-cholesterol (HDL-c), triglycerides and calculated non-HDL cholesterol (non-HDL-c).

Carbohydrate Metabolism

Patients older than 6 years underwent an oral glucose tolerance test (OGTT) according to the standard protocol. Patients received 1.75 g of glucose/kg of body weight with a maximum of 75 g. Venous blood samples were obtained at fasting, 60 and 120 min for determination of plasma glucose and serum insulin concentrations. For definitions of impaired glucose tolerance and diabetes, we used the American Diabetes Association (ADA) criteria. [6] The homeostatic model assessment for insulin resistance (HOMA-IR) index was estimated using the following formula: HOMA-IR = insulin (µIU/mL) × fasting glucose (mg/dL) /405 [7] and considered positive if ≥3.5. Data from the OGTT was used to assess the insulin sensitivity index (ISI or Matsuda Index) to evaluate insulin resistance: [8, 9] 10,000/ √ [fasting glucose (mg/dL) X fasting insulin (µIU/mL) X OGTT glucose at 120' (mg/dl) X OGTT insulin 120' (µIU/ mL)] and considered positive if ≤ 2.5.

Statistical Analysis

The collected data was analyzed using the software IBM SPSS® version 25.0 and statistical significance was set at p <0.05. For continuous quantitative variables, the existence of normal distribution was tested through histogram observation and kurtosis and skewness analysis. To describe variables, we used central tendency measures (mean and median) and dispersion measures (standard-deviation and percentiles 25-75) for quantitative variables and absolute numbers and percentages for qualitative variables. To compare continuous variables with normal distribution between groups, an Independent Samples t Test was used. Due to the number of patients included, only comparisons between patients with SW and SV forms were performed.

This study has been approved by the ethical committee of our hospital.

> RESULTS

Patients Characteristics

This study included 8 patients, 5 females and 3 males, with a mean age of 11.4 ± 4.5 years-old (min 3.8, max 16.7 years-old). Four patients presented the SW form, all diagnosed with salt losing crises in the neonatal period. Three patients presented the SV form, diagnosed at a mean age of 83.3 ± 10.5 months-old (6.9 ± 0.9 years--old). One patient was diagnosed with non-classic CAH at 5.8 years-old, during evaluation for precocious pu-

barche. Diagnosis was based on clinical evidence, elevated basal 17-OHP concentrations, 17-OHP levels after ACTH stimulation test and sequencing analysis of the CYP21A2 gene in all patients. There was no familiar consanguinity. Two patients were sisters and both parents were carriers of a CYP21A2 gene mutation. The youngest of the sisters had the diagnosis during the pre-natal period and the mother was submitted to dexamethasone treatment during pregnancy.

All patients were treated since the time of diagnosis. Seven patients were on glucocorticoid replacement treatment with hydrocortisone (all except the patient with NCAH) with a mean dose of 11.41 ± 1.8 mg/m^2/day. Five patients were treated with fludrocortisone and no patient was under supplementation with sodium chloride tablets. Two patients were submitted to genital reconstructive surgery and 2 patients were under treatment with an anti-androgenic drug.

At the time of the evaluation, 2 patients were prepubertal, 3 patients were pubertal and 3 postpubertal. All patients presented systolic and diastolic blood pressure <90th percentile for age, sex and height. No patient had smoking habits. Four patients had normal weight, 1 patient had low weight, 1 patient had pre-obesity and 2 patients presented with obesity. Median 17-OHP concentration was 12 ng/mL (P25 4 ng/mL, P75 27 ng/mL). The mean follow-up time was 7.62 ± 0.2 years (min 2, max 14 years). The patients' characteristics and clinical form`s specificities are presented in Table I.

Lipid Parameters

Patients presented mean total cholesterol, LDL-c, HDL-c and non-HDL-c levels of 138.0 ± 31.9, 72.71 ± 24.2, 59.86 ± 12.1 and 78.43 ± 26.7 mg/dL, respectively. Mean triglycerides were 55.0 ± 14.4 mg/dL. Comparing patients with SW and SV forms, no significant differences were observed regarding HDL-c and triglycerides. Nevertheless, patients with SV form presented statistically significant elevated levels of total cholesterol, LDL-c and non-HDL--c than patients with the SW form (Table II).

Carbohydrate Metabolism

Patients presented a mean fasting glucose level of 78.12 ± 5.11 mg/dL and mean insulin level of 15.58 ± 11.4 µIU/ mL. Mean HOMA-IR was 2.56 ± 1.5 and mean ISI was 5.89 ± 2.2. Glucose and insulin mean levels during the OGTT were 103.83 ± 24.9 mg/dL and 60.82 ± 27.7 µIU/ mL, respectively at 60 minutes and 82.17 ± 19.2 mg/dL and 38.78 ± 18.0 µIU/mL respectively at 120 minutes.

Three patients evidenced positive criteria for insulin resistance: 1 patient with SV form, obesity and with Tanner 3 and 2 patients with SW form, 1 with Tanner 5 and obesity and the other with Tanner 4 and normal-weight (Table III).

> DISCUSSION

There has been increasing evidence that patients with CAH have multiple vascular risk factors that may enhance the risk of cardiovascular disease in adulthood. We found a prevalence of 37.5% of excessive weight or obesity in our cohort. These results are in agreement with the US National Institutes of Health study where 35% of children with CAH were obese, with no differences between the classic and the non-classic groups [10] and with a European study were the prevalence of overweight and obesity in pediatric CAH patients was 25.9% and 14.8%, respectively. [11] In fact, children and adolescents with CAH have a greater risk of obesity evidenced by having a higher BMI and truncal fat mass. [12] Moreover, it has been suggested that leptin axis dysregulation may contribute to the increased risk of overweight and obesity in CAH. [13] Children with CAH due to 21-hydroxylase deficiency have been described with higher fasting serum insulin levels and increased HOMA-IR. [14] In our study, the mean HOMA-IR was 2.56, similar to the findings of d'Annuzio et al., that evidenced a HOMA-IR of 1.49 ± 0.91 in a cohort of healthy Italian children and adolescents. [15] Three patients (37.5%) had HOMA-IR ≥3.5, which is the cut-off used at our laboratory for insulin resistance. Some studies investigated insulin resistance indexes in pediatric age. [15] A European study defined the HOMA-IR cut-off value for non-obese and obese individuals in pediatric age. HOMA-IR ≥ 1.68 in normal-weight individuals was considered abnormal, whereas considering overweight and obese individuals, the cut-off rises to 3.42. [16] Comparing these cut-off values, the 3 patients with positive criteria for insulin-resistance would still present a positive HOMA-IR. There seems to be a decrease in insulin sensitivity during puberty, causing an increased insulin secretion after glucose load. [17] In fact, d'Annuzio et al. demonstrated that there is an increase in HOMA-IR during Tanner stages

Tabel I - Clinical, hormonal and molecular characterization of patients with classic 21-hydroxylase deficiency.

Parameters	SW (n=4)	SV (n=3)	P	NCAH (n=1)
Age, years	9.0 ± 5.35	14.0 ± 3.5	0.222	10
Gender (F/M)	03/jan	01/fev	NA	1/0
Weight (kg)	48.7 ± 35.1	55.8 ± 1.9	0.712	38.5
Height (cm)	139.1 ± 32.4	153.5 ± 12.9	0.509	150.7
BMI (kg/m²)	21.7 ± 8.5	23.9 ± 3.1	0.657	16.9
BMI				
Low weight (n)	1	0	NA	0
Normal-weight (n)	1	2	NA	1
Weight excess (n)	1	0	NA	0
Obesity (n)	1	1	NA	0
Tanner (for each patient)	1, 1, 4, 5	3, 5, 5	NA	4
SBP (mmHg)	115.0 ± 3.6	110.7 ± 7.4	0.412	108
DBP (mmHg)	55.33 ± 11.1	58.33 ± 2.1	0.668	67
Follow-up, years	9.0 ± 5.3	7.0 ± 4.3	0.621	4
Mean HC dose, mg/m²/day	12 ± 1.9	10.3 ± 1.2	0.339	0

SW = Salt wasting; SV = Simple virilizing; NCAH = nonclassic congenital adrenal hyperplasia; F = Female; M = Male; BMI = Body mass index; SBP = Systolic Blood pressure; DBP= Diastolic blood pressure; HC = hydrocortisone
Data are presented by mean ± standard-deviation, unless otherwise indicated. Statistical analysis performed using Independent Samples t Test

Tabel II - Lipid parameters in patients with classic 21-hydroxylase deficiency.

Parameters	SW (n=3)	SV (n=3)	P	NCAH (n=1)
Total cholesterol (mg/dL)	108.0 ± 16.4	166.3 ± 14.3	0.010	145
LDL-c (mg/dL)	52.3 ± 8.1	93.7 ± 20.2	0.030	71
HDL-c (mg/dL)	50.7 ± 8.5	65.7 ± 11.8	0.149	70
Non-HDL-c (mg/dL)	57.33 ± 8.1	100.7 ± 25.7	0.049	75
Triglycerides (mg/dL)	54.3 ± 3.5	56.0 ± 24.6	0.918	54

SW = Salt wasting; SV = Simple virilizing; NCAH = nonclassic congenital adrenal hyperplasia; LDL-c = Low-density lipoprotein cholesterol; HDL-c = High-density lipoprotein cholesterol; Non-HDL-c = Non-high-density lipoprotein cholesterol
Data are presented by mean ± standard-deviation, unless otherwise indicated. Statistical analysis performed using Independent Samples t Test

and found mean HOMA-IR of 1.26 ± 0.61, 1.58 ± 1.09 and 1.99 ± 1.08 in Tanner 1, 2-3 and 4-5, respectively. There are no established cut-off values for Portuguese pediatric individuals. Nevertheless, Portugal and Italy are both Mediterranean countries, and in comparison, 3 of our patients presented HOMA-IR higher than the superior limit of these cut-off values, even after adjusting for Tanner stage. There are no studies reporting normal insulin levels in healthy patients during OGTT, but some studies have evaluated glucose-stimulated indexes in the pediatric age in some pathologies such as obesity. Ozhan *et al.* studied, in Turkish obese pediatric patients, OGTT`s insulin levels at minute 120 and found mean insulin levels of 60.00 ± 40.28 µIU/mL and 93.17 ± 76.73 µIU/mL in prepubertal children and pubertal adolescents, respectively. Maggio *et al.*, in a Switzerland cohort of obese adolescents, found mean insulin levels in OGTT of 47.0 ± 37.6 µIU/mL at minute 120. [18] Our results are similar to Maggio *et al.*, but comparing to the obese population included in their study, only 2 of our patients had obesity, thus we highlight the abnormal insulin levels found in this study, that are similar to levels typically encountered in obese pediatric individuals. No patient had insulin resistance according to the Matsuda Index (mean 5.89) and our results were similar to those found by Maggio *et al.* (6.4 ± 3.1) and Ozhan *et al.* (5.0 ± 0.32). Similarly, Mooij *et al.* found in their cohort of 27 CAH pediatric patients, a mean HOMA-IR of 2.64 and a 29.6% prevalence of HOMA-IR above the 90th percentile. [11] Unfavorable changes in glucose profile in CAH children, compared to healthy controls, seems to be related mainly to higher fasting insulin concentrations. [19] In fact, we found that the mean levels of fasting insulin were elevated in all forms of CAH. Additionally, several patients presented very high insulin levels after glucose exposure during the OGTT. Interestingly, two out of three patients with an HOMA-IR ≥ 3.5 were obese and the other one was normal-weight, indicating that the relation between insulin resistance is not only mediated by weight. Two factors, like intermittent iatrogenic hypercortisolism may contribute to hyperinsulinism and insulin resistance, and intermittent hyperandrogenism in states of

inadequate hormonal control seems to increase insulin resistance after glucose exposure. [20]

Mooij *et al.* found that 18.5% of CAH patients had systolic hypertension and 14.8% were pre-hypertensive. [11] In our study, no patient presented with hypertension (evaluated by measuring systolic and diastolic blood pressure at a specific moment). Some studies have demonstrated that children with CAH due to 21-hydroxylase deficiency have elevated 24-hour ambulatory blood pressure and absence of the physiological nocturnal dip. [21] De Vries *et al.* have suggested that the treatment, rather than the CAH itself, is responsible for the enhanced systolic blood pressure and other blood pressure abnormalities. [22] We found in our patients a hydrocortisone daily dose according to the guidelines (10–15 mg/m^2/day) so, we believe that, by avoiding overtreatment with glucocorticoids, our patients present a favorable blood pressure profile. [23]

Mooij *et al.* found a normal lipid profile in the vast majority of their cohort, with 63%–78% of the population having triglycerides levels, total cholesterol, and/or LDL-c levels below the 50th percentile. [11] Furthermore, LDL-c, HDL-c and triglyceride levels were not associated with 17-OHP, hydrocortisone dose, BMI or HOMA-IR. (11) Harrington *et al.* found mean levels of total cholesterol, LDL-c, HDL-c and triglycerides of 158.5, 88.9, 54.1 and 70.8 mg/dL in a group of adolescents with CAH, [24] which are in accordance with our results that evidenced mean total cholesterol, LDL-c, HDL-c and triglycerides of 138.0 ± 31.9, 72.71 ± 24.2, 59.86 ± 12.1 and 55.0 ± 14.4 mg/dL,

Tabel III - Parameters of insulin resistance/sensitivity, derived from oral glucose tolerance tests.

Parameters	SW (n=3)	SV (n=2)	NCAH (n=1)
Tanner (for each patient)	1, 4, 5	3, 5	4
BMI (for each patient)	Normal-weight, weight excess, obesity	Normal-weight, obesity	Normal-weight
G 0 min, mg/dL	77.7 ± 5.8	76.0 ± 4.24	82
G 60 min, mg/dL	91.0 ± 24.1	113.0 ± 29.7	124
G120 min, mg/dL	75.7 ± 26.5	83.5 ± 4.5	99
I 0 min, µIU/mL	19.18 ± 13.8	11.9 ± 13.6	12.2
I 60 min, µIU/mL	58.33 ± 37.4	69.6 ± 27.8	50.6
I 120 min, µIU/mL	29.23 ± 9.3	43.1 ± 27.4	58.7
HOMA-IR	2.87 ± 1.5	2.15 ± 2.4	2.47
HOMA-IR ≥3.5 (n)	2	1	0
ISI	5.59 ± 0.3	7.07 ± 4.3	4.43

SW = Salt wasting; SV = Simple virilizing; NCAH = nonclassic congenital adrenal hyperplasia; G = Glucose; I = Insulin
HOMA-IR = Homeostatic model assessment for insulin resistance; ISI = Insulin sensitivity index
Data are presented by mean ± standard-deviation, unless otherwise indicated.

respectively. Although Sartorato *et al*. did not find differences regarding total cholesterol, HDL-c and triglycerides in a group of 19 young patients with CAH, [25] Zimmermann *et al*. found that HDL-c was statistically significant lower and LDL-c was statistically significant higher in patients with CAH versus controls. [26] We did not find statistically significant differences in HDL-c and triglycerides levels between patients with the SW and SV form, although absolute mean concentrations of these parameters were higher in patients with SV form. Nevertheless, patients with the SV form presented statistically significant higher levels of total cholesterol, LDL-c and non-HDL-c, indicating a worse lipid profile and a prevalence of more atherogenic particles in this particular CAH subtype. These results, not previously reported in the literature remain unclear, however, aldosterone may play a role in these differences. It has been suggested that aldosterone is positively associated with LDL-c and non-HDL-c and inversely associated with HDL-c in the general population. [27] Thus, the decreased aldosterone production in the SW form can be possibly protective regarding lipid profile comparing to patients with the SV form.

Our study has limitations, namely the relatively small size (CAH is a rare disease and NCAH is usually diagnosed later in life) and the lack of a control group. We could not include a control group with healthy matched controls, due to regulations of the medical ethical committee in our center. Nevertheless, this study also has strengths. First, we highlight the relatively long follow--up of the cohort attending a single tertiary medical center and patients were evaluated always by the same team. Second, most literature data report the presence of insulin resistance based on basal fasting measurements of glucose and insulin, but we performed OGTTs and calculated indexes of insulin resistance to further characterize potential abnormalities in the carbohydrate metabolism. This study provides first evidence for discrete alterations in lipid metabolism between CAH SW and SV forms and further characterizes the state of insulin resistance in a group of pediatric age with CAH due to 21-hydroxylase deficiency.

Current knowledge of metabolic consequences in subjects with NCAH are limited and longitudinal follow up data of these patients regarding either the natural course of the disease or the outcomes of therapeutic regiments mainly based on glucocorticoids are missing. [28] In children with both classical CAH and NCAH prevalence of obesity exceeds obesity rates in children and adolescent in the general population. Moreover, these children are frequently hyperinsulinemic and hyperleptinemic, espe-

cially in those with classical form of CAH. In our study, the patient with NCAH had normal weight but presented an HOMA-IR of 2.47 and insulin levels > 50 µIU/mL during the OGTT.

Taken together, literature data suggests that patients with CAH due to 21-hydroxylase deficiency may present with a constellation of metabolic abnormalities similar to those observed in the metabolic syndrome that are independent risk factors for cardiovascular disease. [10-13] The present study confirms that these patients display traits of the metabolic syndrome. We evidenced the presence of a high rate of overweight or obesity and insulin resistance evaluated by HOMA-IR and an hyperinsulinemic profile in the dynamic response to an OGTT. We also have shown that CAH patients with SV form have a significant increase in atherogenic particles compared to the SW form, namely LDL-c and non-HDL-c. It is noteworthy that all these metabolic abnormalities were present already early in life. Larger studies with a higher number of patients are needed in order to confirm these findings. Based on our data we propose that regular controls of cardiometabolic parameters should be performed early in those patients. Future studies should focus on nonpharmacologic and pharmacologic interventions targeting dyslipidemia and insulin resistance in order to improve the outcomes of atherogenesis and cardiovascular morbidity in patients with CAH due to 21-hydroxylase deficiency.

> CONCLUSIONS

CAH due to 21-hydroxylase deficiency is a lifelong condition that seems to be associated with multiple cardiovascular risk factors. In this study, 4 patients (50%) had at least one cardiovascular risk factor. Although hypertension and obesity are described in the literature as more prevalent in patients with CAH due to 21-hydroxylase deficiency, we highlight the high prevalence of insulin resistance in our patients. Hyperinsulinism may contribute to an increased production of androgens, both by the ovary and the adrenal gland. Reduced efficacy of the glucocorticoid treatment, may also contribute to the future development of polycystic ovary syndrome and metabolic syndrome. Despite the young age, these patients seem to present already different cardiovascular risk factors. In addition to optimal hormonal replacement treatment of CAH, according to current guidelines, all children should have assessment of potential cardiovascular risk factors. Monitorization of central adiposity, hypertension and insulin resistance, as well as the use of the minimum effective dose to adequately su-

ppress androgens in adolescence, may have an important role in decreasing future cardiovascular disease. <

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