Cardiovascular risk factors and increased carotid intima-media thickness in young patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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ABSTRACT

Objective: Increased arterial intima-media thickness has been observed in adults with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD). CAH has also been associated with obesity, insulin resistance, and hypertension. The aim of the present study was to compare youths with CAH with healthy, normal-weight individuals, evaluating carotid intima-media thickness (CIMT) and indicative factors of cardiovascular risk to seek for abnormalities in the CAH group.

Subects and methods: Clinical, biochemical, and ultrasonographic evaluations, according to published criteria, were performed in 113 subjects (5 to 20 years old): 40 patients with 21-OHD and 73 healthy individuals matched for gender, pubertal status, and age.

Results: Most CAH patients were female (80%), salt-losers (72.5%), and pubescent (80%); 10 (25%) patients were overweight. An increase in CIMT was observed both on the right (p = 0.0240) and left (p = 0.0003) sides in 38 CAH patients compared with the healthy individuals. The body mass index, BMI/age Z score, and systolic blood pressure (SBP) were higher in patients compared with controls (p < 0.000 and p = 0.0219, respectively).

Conclusions: Findings of increased CIMT, BMI, and SBP in young patients with 21-OHD indicate the need for early identification and intervention regarding cardiovascular risk. Validating these findings might result in improved therapeutic approaches for children with 21-OHD in the future.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is a common autosomal recessive disorder associated with significant morbidity. Obesity, hypertension, and insulin resistance have been associated with 21-OHD, and these comorbidities may begin in childhood (1,2). It is not known whether these metabolic abnormalities can be linked to the disease itself, its treatment, or both (3). As these metabolic abnormalities are related to the pathogenesis of atherosclerosis (4), increased cardiovascular risk might be expected for 21-OHD patients. Increased artery intima-media thickness (IMT) has also been reported in adults with the classical form of 21-OHD (5). Carotid intima-media thickness (CIMT) is an independent predictor of future cardiovascular risk (6,7), and its increase has been reported in children with chronic diseases, suggesting early vascular injury in the paediatric group (8). CIMT also is positive correlated with body mass index (BMI) and systolic blood pressure (9). Presently, there is limited knowledge of comorbidities in children with 21-OHD, and it is uncertain whether they have increased cardiovascular risk.

The aim of the present study was to identify abnormalities indicative of cardiovascular risk, evaluating...
CIMT, clinical and biochemical parameters in youths with 21-OHD.

SUBJECTS AND METHODS

This cross-sectional study was approved by the Research Ethics Committee of Federal University of Minas Gerais, Brazil (ETIC302/08). All of the children, adolescents and legal guardians signed an informed written consent after receiving information concerning the study.

One-hundred-thirteen individuals were evaluated, including 40 patients diagnosed with classical CAH due to 21-OHD (29 of which were salt losers) and 73 healthy, normal-weight children and adolescents.

All 21-OHD patients, 5 to 20 years old, who were followed-up at the Pediatric Endocrinology Division of the Hospital das Clínicas, Federal University of Minas Gerais were selected to participate, based on the evaluation of medical records.

The diagnosis of 21-OHD was based on clinical and biochemical assessment and confirmed in 72.5% of the cases by genetic analysis of the CYP21A2 gene. All females presented with ambiguous genitalia at birth (n = 32). No participant had other chronic disease or regularly received medication, aside from hormone replacement therapy for CAH.

The healthy children were recruited from a public school located in Belo Horizonte, Minas Gerais, Brazil, and matched to the CAH group for age and gender. The inclusion criteria consisted of being in good health. The exclusion criteria were the presence or a history of any chronic disease, continuous use of medication, and being obese or overweight according to the World Health Organization (WHO) established criteria (body mass index for age and gender over the 85th percentile) (10). The control group was not matched for weight because we found the community-based random sample of healthy children more appropriate in our study setting.

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All participants underwent clinical, biochemical, and nutritional evaluation. A complete physical examination was conducted. The anthropometric parameters assessed according to the WHO criteria were measured using portable digital scales (G-Tech®) to the nearest 0.1 kg for weight, and a wall-mounted stadiometer to the nearest 0.1 cm for height. Blood pressure was analysed following the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, according to age and height (11). Pubertal staging for females breast development and for testes size/genitalia for males were evaluated using the Tanner criteria (12). To analyze the pubertal status the participants were classified as prepubescent (Tanner 1), early puberty (Tanner 2 and 3), and late puberty (Tanner 4 and 5).

Following overnight fasting, blood samples were collected between 7 and 8 a.m. for the biochemical assessment. Serum glucose, total cholesterol and fractions, and triglycerides were measured by colourimetric methods (VITROS® 5.1 FS Chemistry System, Buckinghamshire, UK). Insulin and androstenedione levels were measured by chemiluminescence assay (IMMULITE® 1000 Immunoassay System, Los Angeles, CA, USA), and 17α-hydroxyprogesterone was measured by radioimmunoassay (Siemens Healthcare Diagnostics Inc., Los Angeles, CA, USA).

Insulin resistance was assessed by the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) according to the formula: insulin (µU/mL) x glucose (mmol/L)/22.5 (13).

High-resolution B-mode ultrasonography was performed by a single experienced specialist in radiology and diagnostic imaging blinded to the status of the participants to measure the intima-media layer thickness and evaluate the colour Doppler flow characteristics of the carotid arteries. The recommendations of the Consensus Statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force were followed (14).

The exams were conducted using a Toshiba Xario device model SSA-660A with a high-resolution multifrequency linear transducer adjusted to 12 MHz. B-mode colour photographic and Doppler velocimetry documentation was performed using image-acquisition software Image Explorer 3.1 for Windows.

After resting for 10 min, the subjects were evaluated in the supine position with the neck slightly extended and inclined to 45°. Longitudinal and transverse sections of the right and left common carotid arteries (CCA), carotid bulbs, internal carotid arteries, and external carotid arteries were obtained using B-mode and colour Doppler ultrasound.

The ultrasound evaluation was conducted focusing on the identification of the intima-media layer and distinction of focal atherosclerotic plaques. Three measurements of the IMT of each right and left common carotid arteries were obtained in the 15 mm stretch below the
bulb region, free from focal plaques, where the double lines pattern of the IMT can be clearly observed. Multiple measurements were averaged to report a mean IMT value for each artery. Colour Doppler flow examination of the internal and external common carotid arteries was conducted using technical parameters specific to the carotid arteries. Pulsed Doppler ultrasound was performed in the most distal segments of the internal and external common carotid arteries accessible to the exploratory probe with an insonation angle less than or equal to 60° to obtain quantitative information through spectral analysis. The equipment settings used were the same as the ones used for the qualitative analysis.

**Statistical analysis**

Comparisons between cases and controls data were adjusted for pubertal status and were performed in two sets: all CAH patients versus controls and normal weight CAH patients versus controls.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 19.0 (SPSS Corporation, Chicago, IL, USA) and EPI INFO version 6.04. The WHO AnthroPlus software version 1.0.4. (10) was used to calculate BMI. Normal distribution for the variables was tested using the Kolmogorov-Smirnov test. Descriptive statistics were performed, and data are presented as measures of central tendency and dispersion (median and mean ± SD) for continuous variables and as proportions for categorical and quantitative variables. The Student’s t-test was used to compare means, and the Mann-Whitney test was used to compare medians. The Chi-square test was used for group analysis. The Pearson correlation coefficients (r) between CIMT and other variables were calculated. Statistical significance was defined as a p value < 0.05.

**RESULTS**

Patients with 21-OHD were mostly salt-losers (72.5%), females (80%), and pubertal individuals (80% Tanner stages 4 and 5). Both CAH patients and healthy control groups were similar as to gender (p = 0.55), age (p = 0.45), and pubertal status (p = 0.80). CAH patients were 14.3 ± 4.4 years old, were diagnosed with CAH at a median age of two months (0-120 months), and were three months old (0-120 months) when they began follow-up at the University Hospital. They reported good adherence to treatment according their medical records. The clinical characteristics of the subjects are presented in table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 40)</th>
<th>Controls (n = 73)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>32/08</td>
<td>52/21</td>
<td>0.55</td>
</tr>
<tr>
<td>Age*</td>
<td>14.1 (5.11-20.1)</td>
<td>14.9 (7.61-20.06)</td>
<td>0.453</td>
</tr>
<tr>
<td>BMI/age Z-score†</td>
<td>0.30 ± 0.90</td>
<td>-0.53 ± 0.85</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pubertal status (n)</td>
<td>40</td>
<td>73</td>
<td>0.80</td>
</tr>
<tr>
<td>Prepubescent</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Early puberty</td>
<td>6</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Late puberty</td>
<td>32</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>WC/H ratio</td>
<td>0.44 (0.38-0.57)</td>
<td>0.41 (0.36-0.55)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SBP &lt; P90†</td>
<td>27</td>
<td>58</td>
<td>0.219</td>
</tr>
<tr>
<td>SBP &gt; P90†</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>DBP &lt; P90†</td>
<td>22</td>
<td>49</td>
<td>0.1695</td>
</tr>
<tr>
<td>DBP &gt; P90†</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

* Median (minimum-maximum); † n ≤ 18 years old. WC/H: waist circumference/height ratio. SBP: systolic blood pressure; DBP: diastolic blood pressure.

At their last visit, CAH patients were receiving a daily dose of 14.6 ± 3.6 mg/m² of hydrocortisone. The salt-losers received fludrocortisone at an average dose of 100 µg/day. CAH patients were shorter than controls with height/age Z-scores of -0.36 ± 1.41 and 0.16 ± 1.01, respectively (p = 0.033).

Twenty-five percent of the patients with 21-OHD were overweight (n = 10), but none was obese. The BMI/age z score of the whole CAH patients group (n = 40) was significantly higher than the z score of the control group (p < 0.001). The BMI/age z score of normal weight CAH patients (n = 30) was also significantly greater than that of controls (−0.12 ± 0.71 vs. −0.53 ± 0.85; p = 0.029).

When CAH patients under 18 years old (n = 33) were compared with control individuals of the same age group (n = 60) higher systolic blood pressure (SBP) levels (≥ 90 centiles) were found in CAH patients (p = 0.0219). Although there were also more patients (33%) presenting with diastolic blood pressure (DBP) levels ≥ 90 centiles when compared with the controls (18%), the difference was not statistically significant (p = 0.1695). No difference was found in systolic (p = 0.34) and diastolic blood pressure (p = 0.13) between the salt-losing CAH patients and those exhibiting the simple virilising form.

The results of the biochemical evaluations of the investigated subjects are presented in table 2. The serum lipid and insulin levels were similar in patients and controls, except for high-density lipoprotein cholesterol (HDL-c), which was lower in the CAH group. The CAH patients also exhibited significantly lower glucose concentration than controls, but the values of HOMA-IR were similar in both groups.
Table 2. Biochemical characteristics of patients with CAH and healthy controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 40)</th>
<th>Controls (n = 73)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>17α-hydroxyprogesterone (nmol/L)*</td>
<td>130.59 (1.36-1215.03)</td>
<td>2.84 (0.24-18.18)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Androstenedione (nmol/L)*</td>
<td>20.46 (0.73-34.92)</td>
<td>6.00 (0.73-20.95)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Glucose (mmol/L)**</td>
<td>4.16 ± 0.44</td>
<td>4.50 ± 0.33</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Insulin (pmol/L)*</td>
<td>27.98 (14.35-150.67)</td>
<td>34.72 (14.35-116.95)</td>
<td>0.322</td>
</tr>
<tr>
<td>HOMA-IR**</td>
<td>1.07 ± 0.90</td>
<td>1.13 ± 0.77</td>
<td>0.25</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)*</td>
<td>0.85 (0.28-2.19)</td>
<td>0.76 (0.37-2.52)</td>
<td>0.931</td>
</tr>
<tr>
<td>Total-c (mmol/L)**</td>
<td>4.03 ± 0.88</td>
<td>4.19 ± 0.86</td>
<td>0.316</td>
</tr>
<tr>
<td>HDL-c (mmol/L)**</td>
<td>1.22 ± 0.32</td>
<td>1.35 ± 0.29</td>
<td>0.046</td>
</tr>
<tr>
<td>LDL-c (mmol/L)**</td>
<td>2.39 ± 0.81</td>
<td>2.44 ± 0.68</td>
<td>0.745</td>
</tr>
</tbody>
</table>

* Median (minimum-maximum); ** Mean ± SD.
HOMA-IR: Homeostatic Model Assessment for Insulin Resistance.

Ultrasonography of the carotid arteries was performed in 60 adolescents, 38 21-OHD patients and 22 healthy individuals. Both CAH patients and healthy children were similar as to age (p = 0.286), and pubertal status (p = 0.992). CAH patients had significantly increased CIMT (RC = 0.47 ± 0.05; LC = 0.48 ± 0.04) compared with the control group (RC = 0.42 ± 0.09; LC = 0.41 ± 0.10) both in the right (p = 0.0240) and left (p = 0.0003) sides. The subset of normal weight CAH patients also showed significantly increased CIMT when compared with the control group, as shown in figure 1. Among female patients, both RCIMT (0.50 ± 0.07 x 0.42 ± 0.07) and LCIMT (0.50 ± 0.06 x 0.42 ± 0.08) were significantly greater in CAH patients when compared with controls (p = 0.0021 and p = 0.0006, respectively). No difference was observed for males.

During the last four years before CIMT evaluation, cumulative hydrocortisone dosis data from 29 of the 40 CAH patients (72%) was retrieved. According to the medical records these children received a mean daily dose of 13.38 ± 2.84 mg/m² of hydrocortisone over 41.83 ± 10.44 months of follow-up. No significant association between hydrocortisone dose and CIMT could be demonstrated in these patients (right carotid: r = -0.05 r² = 0.00 p > 0.05; left carotid: r = -0.24 r² = 0.06 p > 0.05).

No significant associations were also demonstrated between CIMT and BMI, between CIMT and blood pressure, and between CIMT and all metabolic parameters, including serum androstenedione, total cholesterol and fractions, triglycerides, and HOMA-IR.

Doppler assessment of the carotid arteries did not show signs of obstruction of the blood flow, which maintained its laminar pattern and normal velocity.

DISCUSSION

Young patients with 21-OHD in this study had increased CIMT when compared with the healthy children.

A significant increase in CIMT, a surrogate marker of atherosclerosis, has been reported in adult CAH patients suggesting increased cardiovascular risk (5). It is known the process of atherosclerosis starts during infancy (6). Two recent reports showed an increased CIMT in children and adolescents with classical CAH (15,16), as was found in the present study. Findings of increased CIMT in childhood suggest that vascular lesions might be amenable to early detection, and that CAH patients may benefit from specific interventions to address their cardiovascular risk (1).

Table 3. Carotid intima-media thickness (mean ± DP) in patients with CAH and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 38)</th>
<th>Controls (n = 22)</th>
<th>p-value</th>
<th>Normal weight patients (n = 29)</th>
<th>Controls (n = 22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCIMT</td>
<td>0.47 ± 0.05</td>
<td>0.42 ± 0.09</td>
<td>0.0240</td>
<td>0.47 ± 0.05</td>
<td>0.42 ± 0.09</td>
<td>0.0168</td>
</tr>
<tr>
<td>LCIMT</td>
<td>0.48 ± 0.04</td>
<td>0.41 ± 0.10</td>
<td>0.0003</td>
<td>0.48 ± 0.04</td>
<td>0.41 ± 0.10</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

RCIMT: right carotid intima-media thickness; LCIMT: left carotid intima-media thickness.
Another study showing brachial artery dysfunction on ultrasound without carotid disease in 14 young CAH patients, when compared with obese or healthy individuals, lends further support to such early and targeted intervention (17).

Ultrasoundographic assessment of CIMT is a well-established examination for screening individuals at cardiovascular risk (7). A hindrance to the wider use of CIMT measurements in the paediatric population is the lack of standardisation of CIMT values in this age group. Values above the 95th percentile of the control group (CIMT > 0.475 mm) were considered abnormal in a study of children with high cardiovascular risk (6). However, one should take into consideration that a slight linear increase in CIMT with age is observed among healthy children, preventing the use of a single reference value in childhood (9). Comparison with healthy controls in studies increases the reliability of the results, but this comparison is not feasible in everyday clinical practice.

Chronic diseases in children such as dyslipidaemia, type 1 diabetes mellitus, and chronic renal failure have been associated with increased CIMT (8). The relationships of obesity and high blood pressure with increased CIMT have also been reported in adolescents (18). Notwithstanding the previously mentioned difficulties, a systematic review concluded that despite heterogeneous methodology in ultrasonographic assessment, a significant increase in CIMT could be demonstrated in 55 out of 67 studies in the paediatric population (8). Therefore, screening for cardiovascular risk in several chronic diseases including CAH during childhood might be achieved using CIMT measurements.

The reasons for the presumably increased cardiovascular risk in 21-OHD patients remain unknown. Due to the current inability to replace the physiological secretion of cortisol perfectly, children with CAH may present with periods of endogenous hyperandrogenism and iatrogenic hypercortisolism during treatment. The difficulty of devising an ideal treatment for those patients is widely agreed upon (3). Glucocorticoid replacement may increase the risk of cardiovascular disease through multiple pathways, resulting in a trade-off between benefit and harm. In a recently published report, children and adolescents with CAH were observed to be obese, have a higher BP, demonstrate impaired glucose tolerance with reduced insulin sensitivity, and have an increased CIMT compared with their healthy counterparts. The authors did not find a correlation between these variables and mean daily hydrocortisone dose, but they hypothesized that there might be a cumulative effect of glucocorticoid therapy over years (16). The greater risk of metabolic complications in patients with CAH might also be related to the pharmacogenetics of an individual response to glucocorticoids (19). The greater sensitivity to glucocorticoids of some patients results in a therapeutic overdose that is not necessarily related to improved control but exposes patients to developing metabolic complications (20).

We found glucocorticoid replacement in the studied group was uniform and appropriate, following the current recommendations and consistent with previous findings of therapeutic efficacy in the same group of children (21,22). Follow-up was performed systematically at the same medical facility, and patients had no clinical signs of glucocorticoid excess or suppressed levels of serum steroids. Contrary to what would be expected in glucocorticoid excess, they showed lower mean glucose levels than controls. Furthermore, we could not demonstrate a correlation between mean hydrocortisone dose and CIMT. Taken together these findings suggest that the increased CIMT should not be attributed to treatment-related effects, however, this possibility cannot be ruled out.

Twenty-five percent of the patients with 21-OHD were overweight. Increased body fat in childhood is an early risk factor for morbidity and mortality in adult life (8) and has already been reported in CAH children (23). Possible metabolic consequences of increased body fat are dyslipidaemia and reduced insulin sensitivity, both of which are more common in CAH patients (24). Increased body fat in 21-OHD patients might reflect general population trends, as is currently occurring in Brazil, where a prevalence of 20.5% of overweight and 4% of obesity for children 10 to 19 years old has been reported, according to data from Instituto Brasileiro de Geografia e Estatística (IBGE) (25). Nonetheless, the BMI in the studied CAH group was higher than in the control group, even when normal weight CAH patients were compared with healthy controls.

Obesity and familial predisposition were reported as significant determining factors of an adverse metabolic profile in young patients with CAH (26). On the other hand, it has been suggested that increased body fat in classical CAH children could reflect the effects of lifetime glucocorticoid therapy (27,28), as stated before.

The association between increased CIMT and higher androgen levels reported in obese female adolescents (29)
notes another aetiology in increased cardiovascular risk, namely, hyperandrogenism, which is a frequent finding in CAH patients. This possibility cannot also be ruled out in the present study. However, serum androstenedione levels did not show a significant association with CIMT.

Another relevant previously reported finding was the increased SBP in CAH patients in both obese and normal weight individuals (30). Increased SBP has been associated with increased CIMT. In a longitudinal evaluation of nearly 100 Latin-American children diagnosed with metabolic syndrome, SBP and 2-h postprandial glucose were the best predictors of CIMT, even when taking into consideration other components of the syndrome (31). This association could not be proven in the present study. Although such increases in blood pressure have been associated with obesity and increased CIMT in adolescents (18), it is difficult to assess the relative contribution of each variable. Again, the treatment regimen has been implicated in the increase of blood pressure in children with CAH (32). Further studies are needed to achieve a better understanding of these associations and to assess other possibilities in the development of hypertension in patients with CAH.

It was observed that cardiovascular risk factors detected in childhood such as elevated LDL-c, SBP, and BMI were associated with increased CIMT and that progression to atherosclerosis may be predicted in childhood independent of risk factors identified later in adulthood (33). Most studies show normal lipid profiles in CAH patients (24). On the other hand, a higher HDL-c may independently predict a lower cardiovascular risk (34). Therefore, the lower levels of HDL-c among patients with CAH, as was found in this study, may represent an additional cardiovascular risk factor for these children. These findings give support for intervention programmes intended to reduce cardiovascular risk factors during childhood (35).

This cross-sectional study presents some limitations. The most important of these limitations is that the sample size is small for ascertaining associations. This small sample size did not permit drawing conclusions regarding the causes of increased CIMT. However, an increased CIMT in CAH children, as shown in this study, has also been recently reported by two other research groups (15,16), which indicates that these findings will likely be confirmed through further trials.

Although the physiopathology of the metabolic abnormalities occurring in CAH is currently unknown, early detection of these abnormalities may be of great relevance. Reversibility of early atherosclerotic alterations has been reported in obese prepubescent children with increased CIMT who showed a significant reduction in carotid lesion size with weight loss (35).

We conclude that increased CIMT might be an early indication of greater cardiovascular risk in children and adolescents with CAH, as previously reported in adults. Abnormal SBP and BMI may also represent independent risk factors for these children. These findings of increased CIMT, BMI, and SBP in young patients with CAH require confirmation and might lead to improved therapeutic approaches for children with CAH in the future.

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