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RESEARCH ARTICLE

Lipid profiles in Children and Adolescents with Classic Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (CAH)

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Abstract

Background: Cardiovascular risk factors such as obesity, insulin resistance, and hypertension are common in children and adolescents with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH), whereas data ondyslipidemia is inconsistent.

Objective: To investigate lipid profiles in children with CAH.

Patients and Methods: We studied 43 CAH patients (24 females, 19 males) aged 6.9 to 17.9 years. Diagnosis was confirmed by genetic tests in all subjects. Blood was taken during a routine follow-up visit from all patients between 8-9 am after a 12-hour overnight fasting period. Plasma concentrations (mg/dL) of total cholesterol (TC), HDL-cholesterol, and triglycerides (TG) were measured, and the levels of LDL-cholesterol and non-HDL-cholesterol were calculated. The data was collected with the approval of the ethics committee of the University Hospital of Erlangen. The threshold values of increased lipid concentrations were taken from the current Guideline of the German Working Group for Pediatric Disorders of Metabolism (AWMF-Registry No.: 027-068). The quality of therapy control was evaluated through the 24 h-urinary excretion of pregnanetriol and pregnanetriolone.

Results (Mean ± SD): The concentration of TC was 178.7 ± 35, TG 74.4 ± 34.1, HDL-cholesterol 64.7 ± 13.5, LDL-cholesterol 98.9 ± 29.3 and non-HDL-cholesterol 114.2 ± 32.2. The ratio of TG/HDL was 1.25 ± 0.79. Compared with data from a reference population, TC and non-HDL-cholesterol levels were elevated in 8 patients (18.6 %), TG in 4 (9.3 %), LDL-cholesterol in 6 (13.9 %), and the TG/HDL-ratio in 5 patients (11.6 %). In all patients, HDL-cholesterol concentrations were in the normal range. We found no differences between boys and girls, and between clinical forms or genotype. The lipid profile was not correlated to body weight or the hydrocortisone equivalent dose. Patients with good therapy control had even higher lipid values than patients who were badly controlled.

Conclusion: Dyslipidemia was found in a fraction of our CAH patients. The prevalence rate of elevated TC levels was markedly higher than in reference populations. Our data reflect the situation at only one follow-up visit. We have no data documenting dyslipidemia in CAH children over a longer period. We recommend regular assessment of lipid profiles in patients with CAH.

Abbreviations: CYP21A2: Cytochrome P450 Family 21 Subfamily A Member 2; CAH: Congenital adrenal hyperplasia; BMI: Body mass index; SDS: Standard deviation score; TC: total cholesterol; DDL-C: HDL-cholesterol; TG: triglycerides; LDL-C: LDL-cholesterol; non-HDL-C: non-HDL-cholesterol 17-OHP: 17-Hydroxyprogesterone; CA: chronological age; BA: bone age; ANOVA: Analysis of variance

Keywords: CYP21A2; Dyslipidemia; Cholesterol; Lipoproteins; Co-Morbidity; Cardiovascular Risk

Introduction

Classic congenital adrenal hyperplasia with 21-Hydroxylase defect (CAH) is caused by mutations in the active 21-Hydroxylase gene (CYP21A2). Two forms, one form with salt loss and one without salt loss, characterize classic CAH clinically. CAH is a life-long chronic disease, requiring adequate therapy with glucocorticoids. Precision in substitution therapy is very important since both under and overdosing can result in harmful side effects. Chronic underdosing can lead to hyperandrogenemia, which usually necessitates an increase in the glucocorticoid dose. Hyperandrogenemia and hypercortisolism are associated with long-term complications. Overweight CAH patients demonstrate insulin resistance, reduced insulin sensitivity and impaired glucose tolerance [1,2]. Arterial hypertension and insulin resistance have been described in children and adolescents with CAH co-morbidities such as overweight/obesity [2-5]. These co-morbidities contribute to an increased cardiovascular risk profile in adults with CAH [6].

Dyslipidemia which occurs in childhood and adolescence is also a relevant risk factor for cardiovascular disease [7]. Data on dyslipidemia in children with CAH are inconsistent. Both normal lipid profiles [8] as well as hyperlipidemia [9] have been reported in CAH children. However, in adolescents and young adults with CAH, an increased intima media thickness of the carotid arteries as a marker for atherosclerosis has been reported [10,11]. In one study, intima media thickness correlated positively with the triglyceride concentrations and the triglyceride/HDL ratio [12].

The primary aim of this study was to investigate the lipid profile in pediatric patients with classic CAH who were followed regularly in the outpatient department of our hospital. We analyzed also possible relationships between the lipid concentrations and the genotype, sex, weight, steroid dosage and quality of disease control. The secondary aim was to compare our data with results in the literature and to assess the clinical necessity of regular lipid measurements.

Patients and Methods

Patients

Forty-three CAH patients (24 females, 19 males), aged 6.9 to 17.9 years (median: 13.6 years) were enrolled in the study. All patients had classic CAH, 37 with the salt-wasting form and six with the simple virilising form. Diagnosis was confirmed in all subjects through genetic tests. The mutations which result in classic CAH are classified internationally according to the residual activity of 21-hydroxylase in the mutation groups Null, A, and B. There were 18 patients in mutation group Null, 16 patients in group A and 9 patients in group B. The patients were examined every 4-6 months in the children and adolescents endocrinology outpatients' clinic of the University Hospital Erlangen. With the exception of the primary disease, they were all healthy. No additional chronic diseases, and in particular no lipometabolic disorders were known in the families (42 German, 1 Turkish). The substitution therapy consisted of hydrocortisone (72.1 %), prednisolone (18.6 %) or dexamethasone (9.3 %). The hydrocortisone was administered by t.i.d. dosing (50 % in the morning and 25% each at midday and in the evening). 93 % of the patients received fludrocortisone therapy (Table 1). The prednisolone and dexamethasone doses were converted to hydrocortisone equivalent doses (prednisolone x 4, dexamethasone x 30).

	Male	Female	Total
N	19	24	43
Age [years]	12.6 ± 3.0 (7.7 – 17.9)	13.6 ± 3.3 (6.9 – 17.9)	13.2 ± 3.2 (6.9 – 17.9)
Height-SDS	0.1 ± 1.3 (-2.3 – 3.1)	-0.9 ± 1.2 (-3.5 – 1.5)	0.5 ± 1.3 (-3.5 – 3.1)
BMI-SDS	0.94 ± 1.42 (-2.15 – 3.13)	0.64 ± 1.16 (-1.17 – 3.36)	0.79 ± 1.29 (-2.15 – 3.36)
Hydrocortisone equivalent dose (mg/m²)	14.4 ± 5.1 (3.8 – 25.0)	15.9 ± 4.3 (7.5 – 23.5)	15.2 ± 4.7 (3.8 – 25.0)
Fludrocortisone (µg/m²)	47.7 ± 12.3 (26.3 – 62.5)	42.8 ± 17.8 (16.7 – 89.3)	45.0 ± 15.6 (16.7 – 98.3)

Table 1: Clinical data of patients with classic CAH; Mean ± SD (Min~– Max.)

Study Design

The data was collected over a 4-month period during check-ups in the out-patient's clinic. The patients attended between 8 and 9 o'clock in the morning after fasting for 12 hours, whereby 93 % of patients had already taken their morning glucocorticoid dose. At presentation, patients brought along a 24-hour urine sample collected at home. Blood samples were taken with a venous indwelling cannula; the serum/plasma was frozen at -20° C until it was analyzed. The ethics committee of the medical faculty of the University of Erlangen approved the study (No: 4014). The parents provided written consent. Since well-documented normative values for healthy children were available, we had no permission to study a control group of healthy children and adolescents. Anthropometric data were expressed as standard deviation scores (SDS) using the reference data of Kromeyer-Hauschild, *et al.* [13]. Puberty was assessed according to Marshall and Tanner [14,15].

Biochemical Data

Plasma concentrations of total cholesterol (TG), HDL-cholesterol (HDL-C) and triglycerides (TG) were measured using a Cobas c501 Clinical Chemistry analyser (Roche, Germany). The concentrations of LDL-cholesterol (LDL-C) and non-HDL-cholesterol (non-HDL-C) were calculated: LDL-C= TG minus HDL-C minus (tri-glycerides x 0.2); non-HDL-C = TG minus HDL-C. Adverse lipid concentrations were defined as follows: Total cholesterol (TC) concentration ≥ 200 mg/dL; HDL-C concentration < 40 mg/dL; LDL-C concentration ≥ 130 mg/dl, and non-HDL-C con-centration of ≥ 145 mg/dL. To convert TC, HDL-C, and non-HDL-C to mmol/L, multiply by 0.0259 [16,17]. The ratio of LDL cholesterol to HDL cholesterol (LDL/HDL-ratio) was calculated in order to assess the risk of arteriosclerosis. The risk is considered to be increased in values > 3.5. A ratio of triglyceride to HDL cholesterol (TG/HDL ratio) of ≥ 2 was judged to be pathological [18].

The hormones 17-hydroxyprogesterone, androstenedione and testosterone were measured by liquid chromatography tandem mass spectrometry, and the urine steroids were measured by gas chromatography mass spectrometry in the laboratory in the children's hospital. Quality of therapy was monitored through biochemical checks on the concentration of pregnanetriol and pregnanetriolone in the 24-hour urine sample.

Statistics

All statistical analyses were performed using SPSS 21.0 software (IBM Inc., USA). Normality of the sample was examined by the Shapiro-Wilk test. Normally distributed data are expressed as mean and SD. Mean data were compared between groups using Student's t-test or Mann-Whitney-U-Test. Differences in biochemical variables between the different mutation groups were analyzed using one-way ANOVA, followed by the post hoc comparisons using Tukey's test. Linear regression analyses were performed to explore relationships between BMI-SDS and steroid doses. Statistical significance was considered with a 2-sided P value of < 0.05.

Results

Clinical Data (Mean ± SD)

The patients were 13.2 ± 3.2 years old. The height SDS was -0.5 ± 1.3 and the BMI-SDS was 0.79 ± 1.29 (Table 1). BMI in 9 patients (20.9 %) (5 m, 4 w) was > 2 SDS. Nine patients were prepubertal, 15 were pubertal, and in 19 patients, puberty was completed. The daily hydrocortisone equivalent dose was 15.2 ± 4.7 mg/m^2 BSA and the fludrocortisone dose was 45.0 ± 15.6 µg/m^2 BSA. No significant differences were seen between sexes.

Laboratory Data (Mean ± SD)

Hormones

According to the urinary steroid hormone concentrations, we assigned 30 patients as well-controlled, and 13 patients as poorly controlled. In the well-controlled patients the urinary concentration of pregnanetriol was 1.92 ± 1.40 mg/d (min. – max.: 0.37-4.7) and pregnanetriolone was 0.63 ± 0.47 mg/d (0.16 – 1.6). In the poorly controlled patients the concentration of pregnanetriol was 23.9 ± 33.8 mg/d (4.0-127) and pregnanetriolone was 4.99 ± 6.03 mg/d (0.55-20.7). The serum concentrations of 17OHP, androstenedione and testosterone were significantly elevated in the patients where therapy was poorly controlled (Table 2).

	Disease control*		
	"sufficient" (n=30)	"bad" (n=13)	Level of significance
17-OHP (ng/ml)	6.1 ± 6.4 (4.4)	42.3 ± 39.3 (45.0)	P = 0.01
Androstenedione (ng/dl)	53 ± 35 (43)	205 ± 201 (147)	P = 0.01
Testosterone** (ng/dl) (sufficient: n=16, bad: n=8)	15 ± 5 (12.5)	58 ± 52 (43)	P = 0.03

Table 2: Serum steroid concentrations in CAH patients in relation to disease control*; Mean ± SD (Median)
* assessed according to the excretion of pregnanetriole and pregnanetriolone (24-hour urine samples)
** testosterone (girls)
conversion factors to SI: 17OH-progesterone ng/ml x 3 = nmol/L; androstenedione ng/dl x 0.03 = nmol/L; testosterone ng/dl x 0.03 = nmol/L

Lipids

Parameter	Acceptable	Borderline	Elevated
Total Cholesterol	< 170 mg/dl	170 - 199 mg/dl	≥ 200 mg/dl
Patients N (%)	21 (48.8)	14 (32.6)	8 (18.6)
LDL-Cholesterol	< 110 mg/dl	110 - 129 mg/dl	≥ 130 mg/dl
N (%)	30 (69.8)	7 (16.3)	6 (13.9)
non-HDL-Cholesterol	< 123 mg/dl	120 – 144 mg/dl	≥ 145 mg/dl
N (%)	30 (69.8)	6 (13.9)	7 (16.3)
HDL-Cholesterol	> 45 mg/dl	35 – 45 mg/dl	-
N (%)	41 (95.4)	2 (4.6)	-
Triglycerides Children Adolescents	 < 75 mg/dl < 90 mg/dl	 75 – 99 mg/dl 90 -129 mg/dl	 ≥ 100 mg/dl ≥ 130 mg/dl
N (%)	33 (76.8)	6 (13.9)	4 (9.3)

Table 3: Lipid concentrations in CAH patients according to reported threshold values from the literature [17]
conversion factors to SI: Total Cholesterol, LDL-Cholesterol, non-HDL-Cholesterol, HDL-Cholesterol: mg/dl x 0.0259 = mmol/l; Triglycerides mg/dl x 0.01 = mmol/l

Plasma concentration of total cholesterol was 178.7 ± 35 mg/dl, triglyceride concentration was 74.4 ± 34.1 mg/dl and HDL cholesterol concentration was 64.7 ± 13.5 mg/dl. The calculated concentrations of LDL- and non-HDL cholesterol were 98.9 ± 29.3 mg/dl and 114.2 ± 32.2 mg/dl. The lipid concentrations did not differ between boys and girls. According to the standards in the S2k guidelines on diagnosis and therapy of hyperlipidemias in children and adolescents [17], 8 patients (18.6 %) had increased levels of total cholesterol and non-HDL cholesterol; in 4 patients (9.3 %) the TG level was increased and the LDL cholesterol level was raised in 6 patients (13.9 %) (Table 3). The concentrations of HDL cholesterol were > 45 mg/dl in 41 patients (95.4%); 2 patients had marginally low levels. The mean LDL/HDL ratio was 1.59 ± 0.66 (SD). The mean triglyceride/HDL ratio was 1.25 ± 0.79 (SD). In 5 patients (11.6 %) the TG/HDL ratio was increased > 2.

In patients in whom laboratory findings indicated poor therapy control, the concentrations of cholesterol, non-HDL and -LDL cholesterol were significantly lower ($p<0.01$) than in patients where therapy was well controlled (Table 4). In 3 boys (age: 14.9 -17.9 years) the plasma concentrations in cholesterol, non-HDL cholesterol, LDL-cholesterol, triglyceride as well as the TG/HDL ratio were increased. Two of these patients were obese (BMI-SDS 2.5 and 3.1) and one had normal weight (BMI-SDS 0.12). No significant correlations were found between the lipid plasma concentrations and the variable genotypes, sex, BMI-SDS and the hydrocortisone equivalent doses.

	Total	**Disease Control**	
	N = 43	"sufficient" (n=30)	"bad" (n=13)
Total Cholesterol	178.7 ± 35.0 (171.0)	187.3 ± 36.5 (182)	157.3 ± 18.7 (152)
LDL-Cholesterol	98.9 ± 29.3 (91.6)	107.7 ± 29.9 (97.9)	79.9 ± 16.7 (76.9)
non-HDL-Cholesterol	114.2 ± 32.3 (103.2)	122.1 ± 33.7 (110.1)	95.8 ± 19.4 (91.0)
HDL-Cholesterol	64.7 ± 13.5 (63.7)	65.5 ± 14.5 (64.1)	62.8 ± 11.1 (61.3)
Triglycerides (TG)	74.9 ± 33.9 (64.0)	75.9 ± 37.8 (62.5)	72.6 ± 23.6 (65.0)
LDL/HDL-Ratio	1.59 ± 0.61 (1.48)	1.71 ± 0.63 (1.66)	1.32 ± 0.42 (1.15)
TG/HDL-Ratio	1.25 ± 0.79 (0.98)	1.25 ± 0.86 (0.98)	1.23 ± 0.62 (0.96)

Table 4: Lipid plasma concentrations (mg/dl) and lipid ratios in patients with classic CAH in relation to disease control; Mean ± SD (Median)
Conversion factors to SI: Total Cholesterol, LDL-Cholesterol, non-HDL-Cholesterol, HDL-Cholesterol: mg/dl x 0.0259 = mmol/l; Triglycerides mg/dl x 0.01 = mmol/l

Discussion

Co-morbidities such as overweight/obesity, arterial hypertension and insulin resistance in children and adolescents with classic CAH have been related to an increased cardiovascular risk profile in adults [6,19]. Dyslipidemia is known to be a relevant cardiovascular risk factor [7,16,20]. Dyslipidemias are generally defined in terms of increased levels of cholesterol or triglycerides or lower HDL cholesterol levels in a circulating blood sample. Lipid levels in children and adolescents are assessed on the basis of age-related reference data from different populations without known abnormalities of lipid metabolism [21-23]. In adults with CAH both a normal [11,24,25] as well as and increased prevalence [26,27] for dyslipidemia was found. In a meta-analysis of 14 studies with 437 CAH patients aged from 14 months to 63 years, no difference was found in the lipid concentrations compared with healthy controls [28].

Only a few studies of children and adolescents with CAH compare lipid profiles with data of healthy controls or with data derived from a healthy population. In the majority of CAH children, the lipid profile was normal and did not differ from controls [5,8,12,29-31]. Neither total cholesterol nor triglyceride levels differed significantly; patients with classic CAH exhibited even higher levels of HDL cholesterol [5]. However, alterations in the lipid metabolism have been reported in small cohorts of children with CAH. Botero, *et al.* [32] found significantly elevated mean serum levels of triglycerides in 14 prepubertal Colombian children with CAH compared with a control group, and the percentage of elevated triglycerides > 1.0 mmol/L also differed statistically significantly from the controls [32]. Higher triglycerides were also found in a group of CAH patients from the UK [9], and higher small-dense low-density lipoprotein sub-fractions together with lower HDL-cholesterol concentrations were reported in a group of German CAH patients [33].

When categorizing lipid levels as low, borderline or elevated according to the National Cholesterol Education Program guidelines for children and adolescents [7], only 3.7 % of 27 CAH children had elevated total cholesterol, LDL-cholesterol, and triglycerides [34]. These results confirm recently published data by Vijayan, *et al.* [35] who used the same references. Total cholesterol was elevated in 5 %, LDL-cholesterol in 11 %, and triglycerides in 3 % of the 36 CAH patients studied [35]. The prevalence of lower HDL-cholesterol levels of 22 % in CAH patients from India was markedly higher than that of 3.7 % in Dutch patients [34].

The prevalence rate of dyslipidemia found in CAH children has to be compared with prevalence rates of healthy children. Data from the National Health and Nutrition Examination Survey (NHANES) showed in 2011-2012 that 7.8 % of youths aged 8 to 17 years had adverse total cholesterol, 12.8 % had an adverse HDL-C, and 8.4 % had an adverse non-HDL-C concentration [36]. The prevalence rate of dyslipidemia was 11.1% in children from China [37], and an adverse total cholesterol was found in 10.2 % of the German boys aged 10 to 13 years studied in KiGGS, the German Health Interview and Examination Survey for Children and Adolescents [23].

In our cohort, 18.6 % of the CAH patients had elevated total cholesterol concentrations. This value was markedly higher than the reported prevalence rate for CAH patients and even higher than the prevalence rate of healthy children. In addition, triglycerides in CAH patients were also higher in our cohort than the values reported in the literature (9.3 % vs. 3 to 3.7 %) but comparable to data in the NHANES study [21]. Our results of normal HDL-cholesterol concentrations in CAH patients both confirm [5] and contradict other results [33,35]. When assessing the cardiovascular risk with parameters such as non-HDL-cholesterol [38] or by the ratio of LDL-cholesterol to HDL-cholesterol, we found that 16.3 % had elevated non-HDL-cholesterol concentrations, whereas the LDL/HDL-ratio was in an uncritical range [39].

Dyslipidemia has be discussed as a possible consequence of increased body fat [40]. In our cohort, 20.9 % were obese (BMI SDS >2), but we found no correlation between BMI and lipid levels which is in line with previously reported results from the UK [9]. However, a positive correlation between fasting lipids and visceral abdominal adiposity determined by CT imaging was reported in a group of CAH patients [41]. In an epidemiological Swedish registry study, an increased rate of dyslipidemia was found particularly in male CAH patients with a null genotype [19]. Our data do not confirm this result. Surprisingly, CAH patients with a sufficient metabolic control showed a relatively adverse lipid profile. This is in contrast to the data of Mooiji, *et al.* [34] who found that cholesterol and triglyceride levels were not associated with therapy control [34].

In summary, some of our CAH patients exhibited abnormalities in lipid metabolism, with two adolescents already fulfilling the criteria of a metabolic syndrome. The strength of this study is that the data presented is derived from a single center, using a consistent, relatively homogenous treatment approach in a decently sized pediatric CAH cohort. However, our study has several limitations. Our data reflect the situation at only one follow-up visit; we have no data documenting dyslipidemia in CAH children over a longer period. We therefore recommend regular longitudinal assessment of lipid profiles in CAH patients. Moreover, the prevalence of co-morbidities such as obesity and hypertension might lead to an increase in the percentage of children and adolescents with CAH who qualify for lipid screening. Patients with recurring abnormalities should be adequately treated according to current guidelines [17]. Further studies are needed to better address the potential association of dyslipidemia and atherosclerosis in children and young adults with CAH.

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