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Childhood Metabolic Syndrome and Its Components in Premature Adrenarche

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Context: Premature pubarche (PP), the main clinical manifestation of premature adrenarche (PA), has been associated with insulin resistance and dyslipidemia in selected populations.

Objectives: Our aim was to determine the prevalence of childhood metabolic syndrome (cMBS) and to study its components in prepubertal Northern European girls with PA.

Design and Patients: We conducted a cross-sectional study on 63 prepubertal girls with PA (32 with PP = PP-PA, 31 without PP = nonPP-PA) and 80 healthy age-matched control girls. A standard 2-h oral glucose tolerance test with insulin sampling was performed. Plasma lipids and serum SHBG were analyzed, and blood pressure and weight-for-height were recorded. cMBS was defined by modified criteria of the U.S. National Cholesterol Education Project Adult Treatment Panel III and the World Health Organization.

Setting: The study was performed at University Hospital.

Results: The mean weight-for-height ($P = 0.002$) and the prevalence of cMBS by the modified Adult Treatment Panel III (24 *vs.* 10%) and World Health Organization definitions (16 *vs.* 5%) ($P < 0.05$ for both) were higher in the PA than control girls. The weight-for-height adjusted serum insulin concentrations during the oral glucose tolerance test were elevated in the whole PA group, whereas the fasting insulin concentrations were increased and SHBG was decreased only in the PP-PA subgroup. The weight-for-height adjusted blood pressure, lipid, or glucose levels did not differ between the study groups.

Conclusions: Prepubertal Northern European PA girls have increased prevalence of cMBS mainly due to being overweight and their hyperinsulinism. Among the PA children, the nonPP-PA girls have milder metabolic changes than the PP-PA girls. **(*J Clin Endocrinol Metab* 92: 4282–4285, 2007)**

IDIOPATHIC PREMATURE ADRENARCHE (PA) is defined as the appearance of androgenic signs before the age of 8 yr in girls or 9 yr in boys in the absence of central puberty, steroidogenic enzyme defects, or virilizing tumors. It was previously regarded as a benign variant of normal sexual development (1). Premature pubarche (PP), the main clinical manifestation of PA, has recently been connected with an increased risk of developing ovarian hyperandrogenism in Spanish girls and with hyperinsulinism in a few study populations (reviewed in Ref. 2). Both abnormal (3, 4) and normal (5) lipid profiles have been reported in PP girls. As PP has been associated with some components of the metabolic syndrome (MBS) in selected populations, we studied the prevalence of "childhood MBS" (cMBS) in girls with the whole clinical spectrum of PA in a homogenous Northern European population with low prevalence of nonclassical congenital adrenal hyperplasia (6).

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Abbreviations: ATP III, Adult Treatment Panel III; BMI, body mass index; BP, blood pressure; BW, birth weight; cMBS, childhood MBS; DHEAS, dehydroepiandrosterone sulfate; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; IS, insulin sensitivity; LDL, low-density lipoprotein; MBS, metabolic syndrome; OGTT, oral glucose tolerance test; PA, premature adrenarche; PP, premature pubarche; WC, waist circumference.

Subjects and Methods

Subjects

We examined 63 prepubertal Finnish girls with PA and 80 age-matched control girls. For the PA group, the inclusion criterion was the appearance of any clinical sign(s) of adrenarche (pubic/axillary hair, oily hair/skin, adult-type body odor) before 8 yr of age and the evaluation age less than 9 yr. All eligible children in our hospital district were invited to the study, and 63 of 65 (97%) were willing to participate. Steroidogenic enzyme defects and virilizing tumors were excluded biochemically and by adrenal ultrasonography. PA subjects were divided into two subgroups: those with PP (PP-PA; n = 32) and those with other PA symptoms only (nonPP-PA; n = 31). The control group was a random sample of girls from the same district, obtained from the Finnish population register. Girls with central puberty, endocrine disease, or long-term medication were excluded in all groups. The study protocol was approved by the Research Ethics Committee of the Kuopio University Hospital. An informed written consent was obtained from the parents and assent was obtained from the children.

Clinical evaluation

Height was measured with a calibrated Harpenden stadiometer (Holtain Ltd, Crymych, UK) and recorded to the nearest 0.1 cm as the mean of three repeated measurements. Weight was measured after an overnight fast, recorded to the nearest 0.1 kg, and converted to a percentage in relation to median weight-for-height using the Finnish reference values (Pediator V6.7.6; Pediatric Research Foundation, Helsinki, Finland). Body mass index (BMI) [weight (kg)/height^2 (m)] was calculated, and girls exceeding the 75th BMI percentile for age were recorded using the national children's BMI charts based on previously published growth data (7). Birth weight (BW) and gestational age data were obtained from the hospital records. BW was converted to SD score according to growth charts adjusted for duration of gestation and gender. Blood pressure (BP) was measured with a standard sphygmomanometer

from the left arm in supine position after a 30-min rest in bed and recorded as the average of three repeated readings.

Blood sampling and standard 2-h oral glucose tolerance test (OGTT)

The basal samples for plasma glucose and lipids, blood glycosylated hemoglobin (HbA_{1c}), and serum insulin, SHBG, and dehydroepiandrosterone sulfate (DHEAS) were drawn between 0900 and 1000 h, after an overnight fast. An OGTT was performed by administering 1.75 g/kg glucose (max 75 g) to each subject with samples for glucose and insulin analyses taken at 30, 60, 90, and 120 min. Glucose, HbA_{1c}, and lipids were analyzed on the same day. After separation, serum samples were immediately frozen and stored at −70 C until assayed.

Laboratory methods

Plasma glucose concentrations were analyzed by a glucose oxidase method (Clarke Electrode, Rapidlab 865/1265; Bayer, Tarrytown, NY) and blood HbA_{1c} was analyzed with liquid chromatography (Tosoh G7; Tosoh Corporation, Tokyo, Japan). Serum insulin and SHBG concentrations were analyzed with specific time-resolved fluoroimmunoassays by AutoDelfia (PerkinElmer Life and Analytical Sciences Wallac Oy, Turku, Finland) and DHEAS was analyzed with RIA (Diagnostic Products Corporation, Los Angeles, CA). Plasma total cholesterol and triglyceride concentration and cholesterol in high-density (HDL) and low-density (LDL) lipoproteins were determined using enzymatic methods (Thermo Electron Co., Vantaa, Finland). To determine insulin sensitivity (IS), homeostasis model assessment for insulin resistance (8) and IS index (9) were calculated.

Definition of cMBS

cMBS was assessed by two definitions: modified U.S. National Cholesterol Education Project Adult Treatment Panel III (ATP III) MBS criteria for adolescents (10, 11) and those of the World Health Organization with child-specific cutoff values (11, 12) (Table 1). In our modified ATP III definition, BMI (>75th percentile) was used instead of waist circumference (WC) (>75th percentile of the U.S. reference values in the original ATP III) due to the lack of national WC reference measures.

Statistical analyses

All statistical analyses were performed with the SPSS 14.0 software (SPSS Inc., Chicago, IL). The frequencies of cMBS and each cMBS component were compared using the χ^2 test. All continuous parameters were tested for normality with the Kolmogorov-Smirnov test. The one-way ANOVA was performed to analyze the differences between the study groups, in the case of the non-normally distributed parameters after logarithmic (ln) transformation. A *post hoc* correction (least significant difference with two comparisons) was applied when comparing each PA subgroup separately with the controls. The comparisons were repeated by incorporating weight-for-height as a covariate in the univariate linear model. For parameters remaining non-normally distributed after ln-transformation, the nonparametric Mann-Whitney test was used. $P < 0.05$ was considered significant. Values are presented as mean (95% confidence interval).

Results

The characteristics and main findings of the study groups are depicted in Table 2.

BW, current weight, and prevalence of cMBS

There were no significant differences in the mean BW SD score between the PA, PP-PA, or nonPP-PA and control girls (Table 2). The mean BMI (18.3 *vs.* 16.8, $P = 0.002$) and weight-for-height (114 *vs.* 106%, $P = 0.002$) were higher in the PA than control group and in the PP-PA subgroup compared with the controls (Table 2). cMBS was more common in the PA than control children by both the World Health Organization (16 *vs.* 5%, $P = 0.030$) and modified ATP (24 *vs.* 10%, $P = 0.028$) definition. In the subgroup analyses, statistical significance was reached only between the PP-PA and control girls (Table 2). Of the cMBS components (definitions in Table 1), high fasting serum insulin (28 *vs.* 10%, $P = 0.016$) and high BMI (66 *vs.* 41%, $P = 0.016$) were more frequent in the PP-PA than control group, whereas there were no other significant differences in the prevalence numbers of the cMBS components between the study groups.

Glucose metabolism

Adjusted for weight-for-height, stimulated serum insulin concentrations during the OGTT were higher in the PA than

TABLE 1. cMBS definitions: modified U.S. National Cholesterol Education Project ATP III MBS criteria for adolescents and those of the World Health Organization (WHO)

Definition	Risk factor	Defining level
Modified ATP III (cMBS = any three criteria met)[a]	BMI	>75th percentile for age/gender[b]
	Plasma TG (mmol/liter)	>1.1
	Plasma HDL cholesterol (mmol/liter)	<1.3
	Systolic or diastolic BP (mm Hg)	>90th percentile for gender, age, and height[c]
	Fasting plasma glucose (mmol/liter)	>5.6[d]
WHO (cMBS = high fasting serum insulin + any two other criteria met)	BMI	>75th percentile for age/gender[b]
	Plasma TG (mmol/liter)	>90th percentile of the control group (>0.97 mmol/liter)
	Plasma HDL cholesterol (mmol/liter)	<10th percentile of the control group (<1.1 mmol/liter)
	Systolic or diastolic BP (mm Hg)	>90th percentile for gender, age and height[c]
	Fasting serum insulin (mU/liter)	>90th percentile of the control group (>7.81 mU/liter)

TG, Triglycerides.

[a] BMI percentile instead of WC measure.

[b] Finnish national BMI charts (Childhood obesity, Current Care Summary 26.10.2005. Working group appointed by the Finnish Pediatric Society; BMI chart based on growth data in Ref. 7).

[c] U.S. normative BP tables by the National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents (Ref. 11).

[d] Corresponding blood glucose > 6.1 mmol/liter.

TABLE 2. Characteristics, cMBS frequencies, BP values, and metabolic findings in PA children with (PP-PA) and without pubarche (nonPP-PA), and in control children.

	PP-PA (n = 32)	P^1	Control (n = 80)	P^2	nonPP-PA (n = 31)
Age (yr)	7.7 (7.5–8.0)	0.396	7.5 (7.3–7.7)	0.086	7.1 (6.8–7.5)
Weight-for-height (%)	117 (110–123)	0.004	106 (103–109)	0.374	111 (104–117)
BMI (kg/m^2)	18.8 (17.8–19.9)	***<0.001***[a]	16.8 (16.2–17.3)	0.287[a]	17.7 (16.5–18.8)
BW SDS	−0.13 (−0.56 to 0.26)	0.482	0.14 (−0.99 to 0.38)	1.000	0.11 (−0.33 to 0.55)
cMBS ATPm (%)	28	***0.017***[b]	10	0.191[b]	19
cMBS WHO (%)	19	***0.021***[b]	5	0.149[b]	13
		One-way ANOVA/ weight-for-height corrected[c]		One-way ANOVA/ weight-for-height corrected[c]	
S-DHEAS (mmol/liter)	2.4 (1.9–2.8)	***<0.001/<0.001***	0.9 (0.79–1.00)	***<0.001/<0.001***	1.7 (1.2–2.2)
Systolic BP (mm Hg)	105 (102–108)	***0.004***/0.224	99 (97–101)	0.132/0.428	103 (97–106)
Diastolic BP (mm Hg)	66 (63–69)	***0.014***/0.456	61 (59–63)	1.000/1.000	62 (58–65)
fP-Glucose (mmol/liter)	4.8 (4.73–4.97)	1.000/1.000	4.8 (4.75–4.91)	1.000/1.000	4.8 (4.73–4.96)
2-h-Glucose (mmol/liter)	5.6 (5.2–5.9)	0.320/0.222	5.9 (5.6–6.1)	***0.048***/0.064	6.4 (6.0–6.8)
fS-Insulin (mU/liter)	6.5 (5.7–7.2)	***<0.001/0.012***	4.6 (4.0–5.1)	0.822/1.000	5.0 (4.0–6.0)
Mean S-Insulin (mU/liter)	39 (34–45)	***<0.001/0.002***	27 (24–30)	***0.012/0.042***	38 (27–49)
HbA1c (%)	5.3 (5.2–5.4)	1.000/1.000	5.3 (5.2–5.3)	0.106/0.110	5.2 (5.1–5.3)
fP-TC (mmol/liter)	4.2 (3.9–4.5)	1.000/1.000	4.3 (4.1–4.4)	1.000/1.000	4.3 (4.1–4.5)
fP-TG (mmol/liter)	0.72 (0.60–0.84)	0.232/0.832	0.63 (0.56–0.70)	0.506/0.808	0.68 (0.57–0.79)
fP-HDL C (mmol/liter)	1.35 (1.24–1.46)	0.104/0.598	1.48 (1.41–1.56)	0.844/1.000	1.43 (1.30–1.55)
fP-LDL C (mmol/liter)	2.54 (2.30–2.77)	1.000/1.000	2.52 (2.39–2.65)	0.876/1.000	2.62 (2.43–2.81)
S-SHBG (nmol/liter)	67 (58–76)	***<0.001/<0.001***	103 (97–110)	0.170/0.464	92 (76–107)
HOMA-IR	1.41 (1.27–1.56)	***0.002***/0.060	1.17 (1.06–1.28)	0.232/0.512	1.29 (1.11–1.47)
ISI_{comp}	0.73 (0.64–0.82)	***<0.001/0.002***	1.07 (0.99–1.16)	0.084/0.278	0.91 (0.74–1.07)

Values are expressed as mean (95% confidence interval). S, Serum; f, fasting; P, plasma; B, blood; Mean S-Insulin, mean serum insulin concentration during the OGTT; TC, total cholesterol; TG, triglycerides; C, cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; ISI_{comp}, insulin sensitivity index. HOMA-IR = [fasting insulin (μU/ml) × fasting glucose (mmol/liter)]/22.5. ISI_{comp} = 10,000/ $\sqrt{}$[fasting glucose (mg/dl) × fasting insulin (μU/liter) × mean glucose (mg/dl) × mean insulin (μU/liter)]. P^1, Comparison between PP-PA and controls; P^2, Comparison between nonPP-PA and controls by one-way ANOVA with *post hoc* correction [least-significant difference (LSD) with two comparisons]. *Bold and italic* data indicate statistically significant differences ($P < 0.05$) in the results between the two study groups.

[a] Mann-Whitney test.

[b] χ^2 test.

[c] Univariate linear model; weight-for-height as covariate.

control girls (38.5 *vs.* 27.2 mU/liter, $P = 0.001$), whereas there were no significant differences between the PA subgroups ($P = 0.411$; Table 2). The PP-PA girls had higher weight-for-height adjusted fasting insulin and lower SHBG concentrations compared with the nonPP-PA ($P = 0.031$ and 0.013, respectively) and control girls (Table 2). Only one of the 26 non-obese (BMI < 75th percentile) PA subjects exceeded the 90th percentile of the controls in fasting/OGTT insulin concentrations.

Lipids and BP

There were no significant differences in the plasma triglyceride or HDL or LDL cholesterol concentrations between the PA and control group (0.70 *vs.* 0.63, 1.39 *vs.* 1.48, and 2.58 *vs.* 2.52 mmol/liter; $P = 0.09$, 0.09, and 0.58) or between the PA subgroups (Table 2; $P = 0.72$, 0.33, and 0.59, respectively). There was a trend for lower mean plasma HDL cholesterol concentration in the PP-PA than control group. Mean BP did not differ between the study groups when adjusted for weight-for-height (Table 2).

Discussion

The present work shows increased prevalence of cMBS in prepubertal Northern European girls with PA. Our results agree with previous findings of decreased IS in PP girls of selected populations (2), but they also reveal for the first time that hyperinsulinism is present throughout the whole clinical spectrum of PA.

In line with previous reports (13, 14), our PA girls had higher mean weight than the population-based controls of the same age. Adjusted for weight, OGTT-stimulated insulin concentrations were higher and IS was lower in the PA than control girls, while fasting insulin concentrations were significantly increased only in the PP-PA subgroup. SHBG was lower in the PP-PA than nonPP-PA children. High serum insulin concentrations were rare in lean PP-PA and nonPP-PA subjects. Hence, overweight seems to increase the risk of hyperinsulinism more than PA in prepubertal girls. Overall, hyperinsulinism was less pronounced in our non-selected PA subjects than in the Spanish/American-Hispanic PP girls with amplified adrenarche in previous studies (2, 15). As all our study subjects were prepubertal, the physiological decrease in IS during puberty (16) should not affect our results. Previous observations of insulin resistance (17) and ovarian hyperandrogenism (2) in adolescent girls with the history of PP suggest that disturbances in insulin metabolism persist through puberty.

Our PP-PA, nonPP-PA, and control children had similar triglyceride, total and LDL cholesterol concentrations. Slightly, although not statistically significantly lower HDL cholesterol in the PP-PA girls associated with their increased weight. These findings differ to some extent from those of Spanish girls with a history of PP (4). The controversy may

reflect different inclusion criteria, ethnic differences in lipid metabolism or PA manifestations, or suggest that unfavorable lipid profiles do not fully develop before puberty. BP did not differ between the study groups if adjusted for weight, agreeing with one study on lean PP children (4) but disagreeing with another (3). Although low BW has been connected to PP (18), we found no difference in the mean BW SD score between our PA and control girls.

By including all girls presenting with clinical signs of PA, not only those with pubarche or with high serum androgen concentrations, we were able to examine the whole clinical spectrum of PA and to avoid selection bias. The slightly younger mean age in our nonPP-PA than PP-PA subjects means that some of the nonPP-PA children may develop PP. They had similar but milder abnormalities in insulin metabolism compared with PP-PA girls, indicating a continuum of metabolic features from mild to more pronounced PA.

A limitation in our cMBS definitions is that we did not measure WC, but used BMI percentiles as a marker of body composition. The WC measures would have better reflected the harmful abdominal fat. Still, BMI associates with the risk of MBS, correlates strongly with WC (19, 20), and is used as a criterion in MBS definitions in children (21).

Our control group was not matched for weight, because we found the community-based random sample of healthy controls more appropriate in our study setting. If BMI-matched controls had been used, we would not have been able to compare the prevalence of overweight or cMBS between the PA and control children.

To conclude, prepubertal girls with PA have an increased prevalence of cMBS, mostly because of their increased weight and decreased IS. NonPP-PA girls show less pronounced metabolic features than PP-PA girls. Our findings suggest that determination of IS in the PA girls with high BMI (>75th percentile) might be justified already in prepuberty.

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