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Original Article

Prevalence of metabolic syndrome according to different metabolic syndrome definitions in children and adolescents with congenital adrenal hyperplasia: a single center study

Konjenital adrenal hiperplazi tanılı çocuk ve adolesanlarda farklı metabolik sendrom tanı kriterlerine göre metabolik sendrom sıklığı: tek merkez çalışması

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ABSTRACT

Aim: The aim of this study was to investigate the prevalence of metabolic syndrome according to different metabolic syndrome definitions in children and adolescents with congenital adrenal hyperplasia due to 21-hydroxylase deficiency.

Material and Methods: A total number of 45 patients (31 patients with classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency and 14 patients with non-classical congenital adrenal hyperplasia) were enrolled to the study. The anthropometric, clinical, hormonal findings and the dose of hydrocortisone were analyzed starting from the initial day of diagnosis until the beginning of our study and the metabolic controls (good-bad) were evaluated in the follow-up period. At the last visit, systemic and anthropometric examinations (involving measures of height, weight, waist circumference and blood pressure) was performed by the same physician. Serum lipid levels were examined and oral glucose tolerance tests were performed. Metabolic syndrome prevalence in our patients was calculated with respect to the modified criteria of WHO, IDF and NCEP ATP III.

Results: Metabolic syndrome was diagnosed in only 1 (2.2%) of the 45 patients in the study according to modified WHO definition, 8 patients (17.8%) received a diagnosis of metabolic syndrome according to NCEP ATP III definition. Metabolic syndrome was diagnosed in 1 (3.3%) of 30 patients above 10 years of age according to IDF definition and 20% of patients aged 6-10 years were considered to be risky for development of metabolic syndrome.

Conclusion: It was found that the prevalence of metabolic syndrome was highest when NCEP ATP III definition was used.

Keywords: Metabolic syndrome, congenital adrenal hyperplasia, 21-hydroxylase deficiency, childhood

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ÖZ

Amaç: Çalışmanın amacı 21 hidroksilaz eksikliğine bağlı konjenital adrenal hiperplazi tanısı olan çocuk ve adolesanlarda farklı metabolik sendrom tanı kriterlerine göre metabolik sendrom prevelansını belirlemektir.

Gereç ve Yöntemler: Çalışmaya konjenital adrenal hiperplazisi tanısı olan toplam 45 hasta (21 hidroksilaz eksikliğine bağlı klasik konjenital adrenal hiperplazi tanısı olan 31 hasta, non klasik konjenital adrenal hiperplazi tanısı alan 14 hasta) dahil edildi. Hastaların antropometrik ölçümleri, klinik değerlendirmeleri, hormonal sonuçları ve hidrokortizon dozu tanı anından çalışmanın başladığı tarihe kadar incelendi ve izlemdeki metabolik durumları (iyi-kötü) belirlenen kriterlere göre değerlendirildi. Son vizitte, hastaların sistemik ve antropometrik değerlendirmeleri (boy, kilo, bel çevresi ve kan basıncı ölçümlerini içeren) aynı tecrübeli klinisyen tarafından yapıldı. Hastaların serum lipid düzeyleri ölçüldü ve hastalara oral glukoz tolerans testi uygulandı. WHO, IDF ve NCEP ATP III modifiye kriterlerine göre metabolik sendrom prevalansı hesaplandı.

Bulgular: Çalışmamızda modifiye WHO kriterlerine göre yalnızca 1 (2,2%) hastada, NCEP ATP III kriterlerine göre ise 8 (17,8%) hastaya metabolik sendrom tanısı konuldu. IDF kriterlerine göre 10 yaş üstü 30 hastadan 1'ine (3,3%) metabolik sendrom tanısı konulur iken 6-10 yaş arası hastaların 20%' sinin metabolik sendrom gelişimi için risk altında olduğu saptandı.

Sonuç: Konjenital adrenal hiperplazi tanılı çocuk ve adolesan hastalarda NCEP ATP III metabolik sendrom tanı kriterleri kullanıldığında en yüksek oranda metabolik sendrom sıklığı saptanmıştır.

Anahtar Kelimeler: Metabolik sendrom, konjenital adrenal hiperplazi, 21-hidroksilaz eksikliği, çocukluk dönemi

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder associated with inborn errors of steroid metabolism. 21-hydroxylase enzyme deficiency occurs in 90 to 95% of all cases of CAH. Glucocorticoid and/or mineralocorticoid replacement is applied individually in the treatment of CAH. It is aimed to maintain glucocorticoid replacement, to prevent excess androgen production, salt-wasting and avoid adrenal crisis. The glucocorticoid dose should be optimum level to suppress the excessive production of sex steroids and minimize its'side effects (1,2).

Adults patients with classical CAH have a higher frequency of obesity, visceral obesity, hyperinsulinism, insulin resistance and hyperandrogenism compared with normal individuals (3). Adrenomedullary dysfunction and intermittent hypercortisolism are linked to these abnormalities, which predispose these patients to a higher risk of metabolic syndrome and atherosclerosis (4). There are no adequate studies investigating the prevalence of metabolic syndrome parameters in children and adolescents with CAH. Moreover, different definitions (modified NCEP ATP III, modified Weiss, modified IDF definition) were used in evaluation of MS in the limited number of studies and different results were obtained (5-7).

In our study; it was aimed to investigate the prevalence of MS according to WHO, IDF and NCEP ATP III definitions and to determine factors that affect development of MS in children and adolescent patients with CAH due to 21-hydroxylase deficiency.

Material and Methods

Our study involved 45 patients with a diagnosis of CAH due to 21-hydroxylase deficiency at Dr. Sami Ulus Obstetrics, Gynaecology and Pediatrics Training and Research Hospital. Age range was between 6 and 18 years. The diagnosis of 21-hydroxylase deficiency was made on the basis of clinical and hormonal findings as well as the mutations in the 21-hydroxylase gene. The study was approved by Clinical Research Ethics Committee and started prospectively after informed consent was obtained from all subjects.

Patients with the diagnosis of classical CAH and non-classical CAH with the symptoms of virilization (including premature pubarche and cliteromegaly) and advanced bone age were administered a hydrocortisone therapy optimized for their CAH sub-type profiles. For our study, we only included patients with non-classical CAH who were in need of a hydrocortisone treatment. Hydrocortisone doses were adjusted to physiologically optimum levels in accordance with the anthropometric, clinical and laboratory findings in follow up. The fludrocortisone treatment was added in the patients with salt-wasting type.

Body weight was measured by platform scale with 50 grams sensitivity, height was measured in an upright position with Harpenden stadiometer. Waist circumference was measured at level of the umbilicus by using rigid tape measure. Body mass

index (BMI) was calculated by the formula of "Body weight (kg) / [height (m)]^2". Body weight, height and BMI percentiles were determined using growth curves for Turkish children (8). The patients with BMI of over 95 percentile were considered as obese. Turkish children's waist circumference percentile values were used in the evaluation of waist circumference percentiles (9).

Systolic and diastolic blood pressures were measured 2 times with 5 minute intervals with a mercury sphyngomanometer using appropriately sized cuff for blood pressure measurement after a rest period of 10-15 minutes and the average of these values was obtained. Arterial pressure measurements were evaluated by using hypertension percentile values according to gender, age and height (10).

All patients included in the study were controlled with intervals of 3-4 months. Anthropometric assessment of the patients (height, weight, BMI, waist circumference, growth rate) were made in every control and bone age assessment was made once a year. Bone age was determined according to the Greulich-Pyle method (11).

The levels of basal serum 17-hydroxyprogesterone, ACTH, testosterone, androstenedione and in the patients with salt-wasting type plasma renin activity were measured for metabolic control. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen (E2), dehydroepiandrosteronesulphate (DHEA-SO4) and total testosterone levels were all measured via the chemiluminescence technique (Advia Centaur XP, Siemens AG, Munich, Germany). 1.4-Androstenedione and 17-OHP levels, on the other hand, were measured by using liquid chromatography/tandem mass spectrometry (LC/MS/MS). ACTH levels were evaluated by an immunoassay analysis (Immulite 2000, Siemens AG, Munich, Germany), where renin levels were evaluated via radioimmunoassay procedure (Berthold Gamma Counter, CA, USA). The target levels have been checked by making measurement of serum 17-OHP and ACTH at least 3 times per year under glucocorticoid and/or mineralocorticoid treatment. The target levels were considered as <10 nmol/L (3.3 ng/ml) for17-OHP and <70 pg/ml for ACTH. At all controls, the patients who provide target metabolic control values at 70% and higher for ACTH and 17-OHP levels were interpreted as in good metabolic control, the others were interpreted as in poor metabolic control (12,13). Moreover, testosterone and androstenedione levels were paid attention to remain in the normal range in good metabolic control. Blood samples were taken from the patients at 08:00 in the morning after 8 hours of fasting. Levels of insulin, glucose, lipid levels (cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride), 17-OHP, ACTH, PRA, androstenedione, testosterone were measured. Then, oral glucose tolerance test (OGTT) was performed. Fasting plasma blood glucose level of 100-126 mg/dl was defined as impaired fasting glucose. Impaired glucose tolerance was interpreted as blood glucose level of 140-199 mg/dl at second hour on OGTT. Fasting plasma blood glucose level of ≥126 mg/dl and blood glucose level of ≥200mg/dl at second hour on OGTT were defined as diabetes. In prepubertal patients fasting insulin level of ≥15 µIU/ml, in pubertal patients fasting insulin level of ≥30 µIU/ml and in postpubertal patients fasting insulin level of ≥20 µIU/ml were evaluated as fasting hyperinsulinism. Total insulin level of ≥300µIU/ml on OGTT were evaluated as hyperinsulinism (14). Insulin resistance was determined by calculating HOMA-IR. HOMA-IR was calculated by formula of FPG (nmol/L) x fasting insulin (µIU/ml)/22.5 (15). HOMA-IR values >2.6 and >2.2 were interpreted as insulin resistance respectively in prepubertal boys and girls. HOMA-IR values >5.2 and >3.8 were interpreted as the level of insulin resistance for pubertal boys and girls, respectively (14).

Diagnosis of MS was made on the basis of modified WHO, IDF and NCEP ATP III definitions in CAH patients in this study (16).

Statistical Analysis

Statistical analyzes were performed in IBM SPSS for Windows Version 21.0 package program. Quantitative variables were summarized by mean±standard deviation, median [minimum-maximum] values. Categorical variables were demonstrated by the number and percent. The normality of quantitative variables was analyzed by Shapiro Wilks test and the homogeneity of variances was examined by Levene test. Whether the difference between the two groups in terms of quantitative variables was investigated using Mann-Whitney U test. Whether the difference between the two groups in terms of categorical variables was determined by chi-square test. The significance level was considered as $p<0.05$.

Results

Average age of the patients was 11.9 ± 3.9 years (6-18 years), 35 (77.8%) of 45 patients were female, patients with classical CAH were diagnosed in the newborn and infant periods. 40% of the patients were in salt-wasting type, 29% of them were in simple virilizing type and 31% of them were in non-classical type of CAH. Follow-up period of patients was 6 months-18 years (median 6±4.5 years), average dose of hydrocortisone was found as 15.5±5.4 mg/m^2/day in classical CAH group and 8.2±4.0 mg/m^2/day in non-classical CAH group.

Fludrocortisone treatment was used in 21 patients (46.7%) and the maximum dose of fludrocortisone was 0.1 mg/day except the neonatal period. 49% of patients with classical CAH were in good metabolic control and 51% of them in poor metabolic control. 80% of our patients were in pubertal and 20% of them were in prepubertal period.

In our cases, data obtained related to the MS components are summarized in Table 1. According to the modified IDF criteria 7 (46.7%) of 15 patients under 10 years of age were reassessed because waist circumference was ≥90th percentile. A history of risky disease for MS, type 2 diabetes, dyslipidemia, cardiovascular disease, hypertension and/or obesity were questioned in family. After this evaluation, 20% of patients aged 6-10 years were considered to be risky for development of MS and they were followed closely.

Table 1. The Data Related to Metabolic Syndrome Parameters

Metabolic Syndrome Parameters	WHO (n/%)	NCEP ATP III (n/%)	IDF (>10 year) (n/%)
Obesity	10 (%22.2)	31 (%68.9)	11 (%36.6)
Impaired glucose metabolism	5 /%11.1)	0	0
Dyslipidemia	6 (%13.3)	22 (%48.9)	7 (%23.3)
Hypertension	7 (%15.6)	16 (%35.6)	5 (%16.7)
Metabolic syndrome	1 (%2.2)	8 (%17.8)	1 (%3.3)

The characteristics of one patient who was diagnosed with MS according to modified WHO and IDF definitions were summarized in Table 2 and the characteristics of 8 patients who were diagnosed with MS according to the NCEP ATP III definition were summarized in Table 3.

Table 2. The Clinical Features of Patient Diagnosed MS According to WHO and IDF Criteria

Gender/ Age (Years)	HK dose (mg/m^2/ day)	KAH type	Metabolic control	Height cm/sds	BMI/Waist circumference percentile	Fasting/ postprandial blood sugar (mg/dl)	Fasting insülin (µIU/ml)	TG (mg/dl)	HDL (mg/dl)	Systolic/ diastolic BP MmHg/ percentile
Male/18	25.5	Salt-wasting	Poor	156 (-2.9)	>95/>97	90/142	16.5	158	44	145/90 (>99/99)

HK, hydrocortisone.KAH, congenital adrenal hyperplasia, BMI, body mass index.TG, triglyceride.HDL, High density lipoprotein.BP, blood pressure.

Table 3. The Clinical Features of Patient Diagnosed MS According to NCEP III Criteria

Gender/Age (Years)	KAH type	HK dose (mg/m^2/ day)	Metabolic control	BMI percentile	Waist circumference percentile	FBP (mg/dl)	TG (mg/dl)	HDL (mg/dl)	Systolic BP MmHg/ percentile	Diastolic BP MmHg/percentile
Female/14.5	NK	6	6	75	85	92	90	45	120 (90-95)	85 (95-99)
Female/10.2	SW	11.7	11.7	>95	>97	84	128	30	110 (50-90)	70 (50-90)
Female/6	SW	9.4	9.4	50	97	88	48	49	100 (50-90)	70 (90-95)
Male/13.3	SV	15.9	15.9	90	85	79	49	36	110 (50-90)	80 (95)
Female/17.5	SW	12.7	12.7	75	90	83	64	40	145/95 (>99)	95 (>99)
Female/8.3	NK	6.5	6.5	>95	>97	94	53	49	110 (50-90)	80 (95-99)
Female/8.2	SW	18	18	95	95	64	42	42	130 (>99)	90 (>99)
Male/18	SW	25.5	25.5	>95	>97	90	158	44	145 (>99)	90 (99)

KAH, congenital adrenal hyperplasia.HK, hydrocortisone.BMI, body mass index.FBG, fasting blood glucose.TG, triglyceride.HDL, High density lipoprotein.BP, blood pressure.NK, non-classical.SW, salt-wasting.SV, simple virilizing.

Parameters which affect development of MS were detailed in the patients diagnosed with MS according to the NCEP ATP III definition. MS was detected in 2 (20%) of 10 male and 6 (17.1%) of 35 female patients. A significant relationship was not observed between gender and prevalence of MS.

Mean follow-up time of 8 patients who were diagnosed with MS was 7.2±4.9 years, 7.1±4.5 years in 37 patients who were not diagnosed with MS. There was no difference between the follow-up time of both groups. When the patients were analyzed according to the types of CAH; MS was diagnosed in 5 (27.8%) of 18 patients with salt-wasting type, 1 (7.7%) of 13 patients with simple virilizing type and 2 (14.3%) of 14 patients with non-classical type.

From the perspective of mean HC dose; MS was diagnosed in 3 of 17 (17.6%) patients receiving ≥15 mg/m^2/day and in 5 (17.9%) of 28 patients receiving <15 mg/m^2/day. There was no statistically significant relationship between mean HC dose and prevalence of MS.

MS was diagnosed in only 1 (4.5%) of 22 patients with good metabolic control, and it was observed in 7 (30.4%) of 23 patients with poor metabolic control. A statistically significant relationship was found between metabolic control and MS ($p<0.05$). While MS was present in 3 (30%) of 10 obese patients, it was present in 5 (14.3%) of 35 non-obese patients. Although MS is more common in obese patients, relationship between body mass index and prevalence of MS was not statistically significant (p:0.349).

MS was diagnosed in 1 (11.1%) of 9 prepubertal and 7 (19.4%) of 36 pubertal patients. Although there was no statistically significant relationship because of the small number of patients, MS was observed to be higher in pubertal patients. All of 8 patients with diagnosis of MS had been born appropriate for gestational age. Contrary to the expectations, MS was not observed in patients who were small or larger for gestational age. While MS was detected in only 2 (8.7%) of 23 patients who have no family history of risky disease for MS, it was detected in 6 (27.3%) of 22 patients who have a family history of risky disease for MS. The prevalence of MS was observed to be increased in the patients who have a risky family history, but a statistically significance study could not be performed due to insufficient number of patients.

There was 23 (51.1%) patients with total insülin level of ≥300 µIU/ml and 22 patients (48.9%) with total insulin level of <300 µIU/ml on OGTT. When relationship between hyperinsulinism and prevalence of MS was examined, MS was presented in 3 (13.6%) of 22 patients with total insulin level <300 µIU/ml and 5 (21.7%) of 23 patients with total insulin level of ≥300 µIU/ml. This difference was not statistically significant.

HOMA-IR value was high in 5 (55.6%) of 9 prepubertal and 6 (16.7%) of 36 pubertal patients. While MS was diagnosed in only 1 (9.1%) of 11 patients with high HOMA-IR value, it was diagnosed in 7 (20.6%) of 34 patients with normal HOMA-IR value. This difference was not statistically significant.

Hyperandrogenism was detected according to total testosterone and/or 1,4-Δ-Androstenedione levels in 18 (40%) of 45 patients who were included in the study. MS was observed to develop in 5 (27.8%) of 18 patients with hyperandrogenism. The relationship between hyperandrogenism and development of MS was not statistically significant. Moreover, relationships between hyperandrogenism and glucose metabolism disorders, hypertension and dyslipidemia were examined. When it was evaluated separately for each of the 3 parameters, there was no significant relationship between these components and hyperandrogenism.

Discussion

Usage of glucocorticoids in the treatment of congenital adrenal hyperplasia and prolongation of survival time in CAH have brought up investigation of the long-term effects of chronic hyperandrogenism and/or glucocorticoid treatment (17-19). Even though there are numerous studies focusing on metabolic complications such as obesity, insulin resistance, dyslipidaemia and hypertension in children and adolescents with CAH, studies evaluating MS prevalence in this group of patients are rather limited in literature (20-27,28,29). Determination of prevalence of MS and comparison of studies are difficult because there is not any standard definition for MS in children and normal values of the parameters vary according to age groups (30).

In our study in contrast to the other studies in the literature, we used 3 different definitions in order to determine prevelance of MS in CAH. In our patients, MS was detected respectively in 2.2% and 17.8% according to the modified WHO and NCEP ATP III definitions. MS was observed in 3.3% of patients over 10 years of age according to the IDF definition. Because waist circumferences of 7 (46.7%) of 15 patients <10 years of age were ≥90th percentile according to the IDF definition, they were reevaluated. They were examined in respect to family history of risky disease for MS, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, hypertension and/or obesity. 20% of patients aged 6-10 years were in the risk group for development of MS and they were followed carefully.

In our study, only one patient was diagnosed to MS due to IDF criteria. Schnaider-Rezek et al. (3) found no MS diagnosis in any adolescent who had received a CAH diagnosis. This causes to question the appropriateness of this definition for the evaluation. The prevelance of MS was found to be significantly higher in compliance with the literature according to NCEP ATP III definition in our study. In the studies performed by Moreira et al. (6,31) using NCEP ATP III definition in pediatric and adult patients with CAH, MS was found in 12.1% and 7.3%, respectively. The reasons for determining higher MS prevelance with NCEP ATP III definition might be threshold values of criterias being lower than the other two classifications, and existence of any 3 of the 5 parameters (obesity, insulin resistance, high triglyceride level, low HDL level and hypertension) to be sufficient in order to make a diagnosis of MS. For each of the three definitions in our study, the most common component in MS parameters was obesity and the least common component was glucose metabolism disorder. The waist circumference was found to be higher according to NCEP ATP III and IDF definitions in patients who insulin resistance was detected by assessment of HOMA-IR. Therefore, it was concluded that patients with high waist circumference percentiles should be investigated in terms of insulin resistance which plays an important role in pathogenesis of MS.

The patients who were diagnosed with MS according to the NCEP ATP III definition were examined in detail. A significant relationship was not detected between age, gender, duration of follow-up, mean dose of HC, birth weight for gestational age, hyperinsulinemia, insulin resistance, hyperandrogenism and development of MS. Moreira et al. (31) observed MS was observed more frequently in those with family history of risky disease for the development of MS. Finkielstain et al. (5) found the development of MS in adults to be associated only with advanced age. In our study, the only statistically significant factor for development of MS was metabolic control status. While MS was observed in 4.5% of patients with good metabolic control, this rate was 30.4% in patients with poor metabolic control ($p<0.05$). In patients with and without hyperandrogenism, the incidence of MS was 28% and 11%, respectively. However, the difference was probably not statistically significant because of the insufficient number of patients.

Consequently, in this study, the prevalence of MS in patients with CAH due to 21-hydroxylase deficiency was found as 2.2% according to modified WHO definition, 3.3% according to IDF definition (in ≥10 years of age group) and 17.8% according to NCEP ATP III definition. MS should be carefully investigated especially in patients with poor metabolic control and children with family history of MS. Further studies are needed in order to investigate the presence of MS and to reveal the factors that affect the development of MS in children and adolescents with CAH.

Declaration of conflict of interest

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