Female pseudohermaphroditism due to classical 21-hydroxylase deficiency and insulin resistance in a girl with Turner syndrome

M. Emre Atabek, Selim Kurtoğlu, Mehmet Keskin

Department of Pediatrics, Erciyes University Faculty of Medicine, Kayseri, Turkey

SUMMARY: Atabek ME, kurtoğlu S, Keskin M. Female pseudohermaphroditism due to classical 21-hydroxylase deficiency and insulin resistance in a girl with Turner syndrome. Turk J Pediatr 2005; 47: 176-179.

We report five-year-old girl with female pseudohermaphroditism due to classical form of 21-hydroxylase deficiency associated with Turner's syndrome (45,X/46,XX) and insulin resistance. She had clitoromegaly since birth, but Turner's syndrome and 21-hydroxylase deficiency were diagnosed incidentally at one and five years of age, respectively. Moreover, we determined insulin resistance, which resolved following corticosteroid therapy for disease. We regard the rare combination as a coincidental occurrence. We stress that adrenal function should be assessed, at least in the presence of clitoral enlargement, in patients with Turner's syndrome, particularly if their karyotype does not contain a Y chromosome. We conclude that chronic hypersecretion of androgen precursors due to an inborn error of metabolism can induce a reduction in insulin sensitivity. Improvement in insulin resistance after treatment of hyperandrogenism has not been previously reported.

Key words: congenital adrenal hyperplasia, insulin resistance, Turner's syndrome.

Turner's syndrome (TS) is a condition involving total or partial absence of one X chromosome in all or part of the body's cells, reduced final height, absence of female sex hormones, reduced amounts of male sex hormones, and infertility in most cases. Adrenal function should be assessed, at least in the presence of clitoral enlargement, in patients with TS, particularly if their karyotype does not contain a Y chromosome[1]. Congenital adrenal hyperplasia (CAH), an autosomal recessive condition, is due to an enzyme defect leading to excessive androgen production. It may present with hirsutism, acne, increased oiliness of the skin, increased libido, clitoromegaly, or masculinization. Deficiencies in 21-hydroxylase, 11β-hydroxylase, and 3β-hydroxysteroid dehydrogenase account for most enzymatic deficiencies from cholesterol to cortisol, although only the former results in androgen excess[2].

To our knowledge, this is the first case report of an association of TS with CAH due to 21-hydroxylase deficiency and with improved insulin resistance after treatment of hyperandrogenism.

Case Report

The patient, known to have a mosaic form of TS (45,X/46,XX), was referred to the endocrinology service at five years of age because of clitoral enlargement (Fig. 1). Her history revealed diagnosis as mosaic TS at one year of age, and she had ambiguous genitalia at birth. There was second-degree consanguinity between mother and father. There was no history of ambiguous genitalia. Our patient was the third child. The initial two pregnancies had resulted with abortion at three and seven months of age, respectively, and the reason for abortion was unknown in both cases. At five years of age, the patient's height was 105 cm (25^{th} percentile) and weighted 20 kg (50^{th}-75^{th} percentile). Blood pressure was 90/60 mmHg. Her clitoral length was 2 cm and clitoral width 1 cm. She experienced adrenarche at age four, but no thelarche or menarche. The degree of the ambiguity was consistent with Stage 3 according to Prader's five stages. Examination of her external genitalia revealed a single perineal

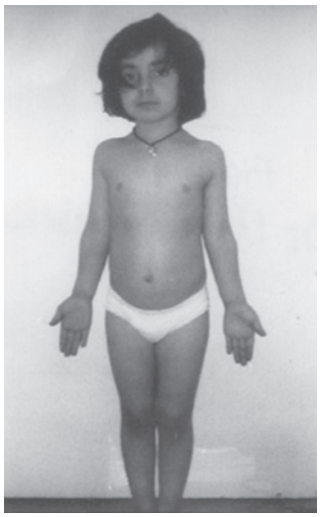

Fig. 1. General appearance of patient with female pseudohermaphroditism due to classical 21-hydroxylase deficiency and mosaic form of Turner's syndrome.

orifice giving access to a urogenital sinus, with the labia majora partially fused. Her bone age was eight years according to Greulich-Pyle Atlas. The simple virilizing form of 21-hydroxylase deficiency (21-OHD) was confirmed by high levels of basal serum 17α-hydroxy progesterone (17-OHP) and an exaggerated response of 17-OHP to adrenocorticotropic hormone stimulation (Table I). CAH due to 21-OHD was diagnosed according to published criteria[2]. A diagnosis of CAH was made, and prednisolone 5 mg/m^2/24h was prescribed. Repeat 17-OHP two weeks later had decreased to 0.5 ng/ml, progesterone was 0.2 ng/ml, and estradiol was 8 pg/ml. Urogenital sinus anomaly and low vaginal atresia were detected at endoscopic examination. Fasting insulin and glucose were measured. The fasting glucose (mg/dl) to insulin (μU/ml) ratio (FGIR9 and fasting insulin (μU/ml) x fasting glucose (mg/dl)/405 (HOMA, homeostasis model assessment) calculated as a measure of insulin ressitance were 5.8 and 4.1, respectively (normal value, ≥7 for FGIR[3] and <2.7 for HOMA[4]). After two weeks of treatment, the FGIR and HOMA were 14 and 1.29, respectively. Serum total cholesterol, triglyceride, low density lipoprotein (LDL)-cholesterol and high density lipoprotein (HDL) cholesterol levels were in normal range according to age and sex. Only one gonad with a few cysts of 2 mm in diameter and prepubertal uterus, including the absence of an endometrial echo, were seen at pelvic ultrasound.

Table I. Response of Steroids to Adrenocorticotropic Hormone in Our Patient

Minutes	17-OH (ng/ml)	DHEAS (ng/ml)	Androstenedione (ng/ml)	Testosterone (ng/dl)
0	67.6	1132	3.5	83
60	99.9	1133	4.2	91
Normal values for age	0.5-3.5	22.1-199.9	0.06-0.15	2.02-4.04

17-OHP; 17 hydroxy progesterone; DHEAS: dehydroepiandrosterone sulfate.

Discussion

Turner's syndrome is a condition involving total or partial absence of one X chromosome in all or part of the body's cells, reduced final height, absence of female sex hormones, reduced amounts of male sex hormones[1], and infertility in most cases. Abnormal glucose tolerance, hyperinsulinemia, and reduced insulin sensitivity are found with increased frequency in adolescents with TS[5,6] and in adults[7,8]. Naeraa et al.[9] recently found increased mortality in TS, where diabetes was reported as an underlying cause of death in 25% of the cases, as well as increased morbidity with increased frequency of ischemic heart diseases,

hypertension, and type 2 diabetes[10]. Thus, women with TS are prone to develop facets of the metabolic syndrome (syndrome X), in which hypertension, dyslipidemia (high triglycerides and low HDL cholesterol), type 2 diabetes, obesity, hyperinsulinemia, and hyperuricemia are all seen as different manifestations of the same disease[11]. Insulin resistance (IR) is an important risk factor for cardiovascular disease and type-2 diabetes mellitus. Therefore, simple measures of IR have been proposed to screen the at-risk patient. A FGIR <7 and HOMA of ≥3.8 were recently suggested as a screening tool for IR in certain pediatric patients[3,4]. In this article, we describe the effect of hyperandrogenism on glucose and insulin levels in girls with TS associated with CAH. We show that FGIR and HOMA, after an increase during hyperandrogenemia, returned to normal after two weeks' corticosteroid treatment for CAH. Moreover, we found normal levels of lipid parameters in the patient. Therefore, we speculated that the hyperandrogenism was contributing to insulin resistance and that TS associated with CAH can be characterized as prediabetic.

One of the main clinical features of TS is short stature. Although girls with TS are not growth hormone (GH) deficient[12], GH treatment has been proven to lead a considerable height gain in girls with TS in whom treatment with GH was started at a young age with supraphysiological dosages[13]. However, because GH treatment increases insulin levels, several authors have expressed concern regarding the long-term effect of GH treatment in children with a predisposition for diabetes mellitus[14,15]. Several reports, however, have shown an increased prevalence of insulin resistance and impaired glucose tolerance in untreated women with TS[6,16]. Our patient was not receiving GH treatment at the time of diagnosis. Moreover, after corticosteroid treatment for CAH, FGIR returned to normal level. Therefore, the insulin resistance might also have been a result of having CAH. We suggest that chronic hypersecretion of androgen precursors due to an inborn error of metabolism can induce a reduction in insulin sensitivity.

The baseline 17-OHP was in the range of the classical 21-OHD in our patient with TS who had clitoral enlargement since birth, but the diagnosis of CAH was incidental at five years of age. The diagnosis of CAH in TS is often difficult because the features of short stature, infertility, and amenorrhea are common to both. Signs of androgen excess are also seen in TS mosaics in the presence of a Y chromosome. The patient had mosaic form of TS and presented with evidence of clitoromegaly or androgen excess. However, she had no Y chromosome. Her 17-OHP level clearly established the diagnosis of homozygous classical form of 21-hydroxylase deficiency. Classical CAH has been previously reported in patients with TS[17]. Larizza et al.[18] sampled 51 patients with TS and found that 11 were heterozygous 21-OHD carriers. This was much higher than would be expected in the sampled population. We surmise that the elevation of androgen seen in this patient may have negatively impacted insulin sensitivity. The possible increased frequency of abnormal 21-hydroxylase metabolism in patients with TS may account four impaired carbohydrate metabolism.

REFERENCES

1. Gravholt CH, Sevnstrup B, Bennett P, Christiansen JS. Low androgen levels in adult Turner syndrome: influence of female sex hormones and growth hormone status. Clin Endocrinol Oxf 1999; 50: 791-800.
2. New MI, Lorenzen F, Lerner AJ, et al. Genotyping steroid 21-hydroxylase deficiency: hormonal reference data. J Clin Endocrinol Metab 1983; 57: 3320-3325.
3. Burgert TS, Vuguin PM, DiMartino-Nardi J, Attie KM, Saenger P. Assessing insulin resistance: application of a fasting glucose to insulin ratio in growth hormone-treated children. Horm Res 2002; 57: 37-42.
4. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-419.
5. Stoppoloni G, Prisco F, Alfano C, Iafusco D, Marrazzo G, Paolisso G. Characteristics of insulin resistance in Turner syndrome. Diabetes Metab 1990; 16. 267-271.
6. Caprio S, Boulware S, Diamond M, et al. Insulin resistance: an early metabolic defect of Turner's syndrome. J Clin Endocrinol Metab 1991; 72: 832-836.
7. Holl RW, Kunze D, Etzrodt H, Teller W, Heinze E. Turner syndrome: final height, glucose tolerance, bone density and psychosocial status in 25 adult patients. Eur J Pediatr 1994; 153: 11-16.
8. Gravholt CH, Naeraa RW, Nyholm B, et al. Glucose metabolism, lipid metabolism, and cardiovascular risk factors in adult Turner syndrome: the impact of sex hormone replacement. Diabetes Care 1998; 21: 1062-1070.
9. Naeraa RW, Gravholt CH, Hansen J, Nielsen J, Juul S. Mortality in Turner syndrome. In. Albertsson-Wikland K, Ranke MB (eds). Turner Syndrome in a Life Span Perspective: Research and Clinical Aspects. Amsterdam: Elsevier; 1995: 323.

10. Gravholt CH, Juul S, Naeraa RW, Hansen J. Morbidity in Turner syndrome. J Clin Epidemiol 1998; 51: 147-158.
11. Reaven GM. Banting lecture 1988: role of insulin resistance in human disease. Diabetes 1998; 37: 1595-1607.
12. Wit JM, Massarano AA, Kamp GA, et al. Growth hormone secretion in patients with Turner's syndrome as determined by time series analysis. Acta Endocrinol 1992; 127: 7-12.
13. Sas TC, de Muinck Keizer-Schrama SM, Stijnen T, et al. Normalization of height in girls with Turner syndrome after long-term growth hormone treatment: results of a randomized dose-response trial. J Clin Endocrinol Metab 1999; 84: 4607-4612.
14. van Teunenbroek A, de Muinck Keizer-Schrama SM, Aanstotoot HJ, Stijnen T, Hoogerbrugge N, Drop SL. Carbohydrate and lipid metabolism during various growth hormone dosing regimens in girls with Turner syndrome. Dutch Working Group on Growth Hormone. Metabolism 1999; 48. 7-14.
15. Cutfield WS, Wilton P, Bennmarker H, et al. Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. Lancet 2000; 355: 610-613.
16. Polychronakos C, Letarte J, Collu R, Ducharme JR. Carbohydrate intolerance in children and adolescents with Turner syndrome. J Pediatr 1980, 96: 1009-1014.
17. Maciel-Guerra AT, Guerra G Jr, Marini SH, Baptista MT, Marques-de-Faria AP. Female pseudohermaphroditism due to classical 21-hydroxylase deficiency in a girl with Turner's syndrome. Clin Genet 1997; 51: 351-353.
18. Larizza D, Cuccia M, Martinetti M, et al. Adrenocorticotropin stimulation and HLA polymorphism suggest a high frequency of heterozygosity for steroid 21-hydroxylase deficiency in patients with Turner's syndrome and their families. Clin Endocrinol (Oxf) 1994; 40: 39-45.