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


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.

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 (25th percentile) and weighted 20 kg (50th,75th 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...
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 criteria². A diagnosis of CAH was made, and prednisolone 5 mg/m²/24h 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 resistance were 5.8 and 4.1, respectively (normal value, ≥7 for FGIR³ and <2.7 for HOMA⁴). 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

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

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 hormones¹, and infertility in most cases. Abnormal glucose tolerance, hyperinsulinemia, and reduced insulin sensitivity are found with increased frequency in adolescents with TS⁵,⁶ and in adults⁷,⁸. 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\textsuperscript{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\textsuperscript{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 \( \geq 3.8 \) were recently suggested as a screening tool for IR in certain pediatric patients\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{14,15}. Several reports, however, have shown an increased prevalence of insulin resistance and impaired glucose tolerance in untreated women with TS\textsuperscript{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\textsuperscript{17}. Larizza et al.\textsuperscript{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 for four impaired carbohydrate metabolism.

REFERENCES


