Complete androgen insensitivity syndrome in a young woman with metabolic disorder and diabetes

A case report

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Abstract

Rationale: Androgen insensitivity syndrome (CAIS) is a rare X-linked recessive androgen receptor disorder characterized by complete resistance to the actions of androgens in an individual with 46,XY karyotype. Metabolic disorder and diabetes has been rarely reported in these patients.

Patient concerns: A 22-year-old female patient was admitted to our center for the evaluation of high blood sugar. The central obesity, lipid dysfunction, and diabetes were found in the patient. The patient also presented as primary amenorrhea and poor secondary sex characteristics after puberty.

Diagnoses: The diagnosis of CAIS in this patient was established by infantile female genitalia, absence of ovary and uterus, history of gonadectomy, 46,XY karyotype, and carried a mutation c.2751C>G (p.917F>L) in androgen receptor gene.

Intervention: The patient was treated by insulin, metformin, statins and estrogen.

Outcomes: After 6 months follow-up, blood sugar and lipid profiles were normal, but breast development and weight loss were not obvious.

Lessons: We report a case of CAIS in a 22-year-old female accompanying central obesity, dyslipidemia, and diabetes mellitus. It is extremely important to recognize special type diabetes among the young-onset diabetic patients, and this case will provide further evidence of a link between impaired androgen receptor signaling and metabolic regulation.

Abbreviations: ACTH = adrenocorticotropic hormone, AIS = androgen insensitivity syndrome, AR = androgen receptor, CAIS = complete androgen insensitivity syndrome, GADA = glutamic acid decarboxylase antibody, HbA1c = glycosylated hemoglobin, HDL-c = high-density lipoprotein cholesterol, HOMA-IR = Homeostasis model assessment-insulin resistance, IAA = insulin autoantibody, ICA = islet cell autoantibodies, LDL-c = low-density lipoprotein cholesterol, PPARα = proliferator activated receptor alpha.

Keywords: androgen receptor, complete androgen insensitivity syndrome, diabetes, gene mutation, metabolic syndrome

1. Introduction

Androgen insensitivity syndrome (AIS) is a rare X-linked recessive androgen receptor (AR) disorder in an individual with 46,XY karyotype. According to the degree of androgen insensitivity, AIS could be classified as complete, partial, or mild AIS. Complete AIS (CAIS) is characterized by complete resistance to the actions of androgens and presented as female appearance and normal breast development, absence of uterus and ovaries, bilateral undescended testis, and elevated testosterone levels. Many studies proved that AR signaling was associated with glucose homeostasis and lipid metabolism.1–3 Our case provides the association between CAIS and metabolic disorder, which may contribute to the understanding of the role of AR in metabolic regulation.

2. Case report

A 22-year-old female patient was admitted to our center for the evaluation of high blood sugar in December 14, 2016. She was diagnosed as diabetes by routine examination last year. The fasting glucose at that time was 7.0 mmol/L. However, the patient did not pay any attention to the disease and did not take any oral hypoglycemic agent. One month ago, the patient presented with polyuria, polydipsia, and lost 10 kg of her body weight. Her casual plasma glucose was 20 mmol/L and ketone bodies were negative. The patient was raised as a girl at birth. At 2 years of age, testicles were found in the groin in the course of herniotomy,
and then she underwent gonadectomy. The patient has primary amenorrhea and poor secondary sex characteristics after puberty. No further evaluation was conducted for her. The patient was adopted by her foster parents, whereas the information about her biological parents is not available. On physical examination, she had body mass index 26.8 kg/m², waist circumference 100 cm, and hip circumference 92 cm. The patient presented with infantile female genitalia, absence of ovary and uterus, history of gonadectomy, 46,XY karyotype, and detected a mutation in AR gene. The mutation c.2751C>G (p.917F>L) detected in this patient has been described in an Austrian patient with CAIS. It should be noticed that early gonadectomy could explain the absence of breast development and low levels of testosterone in our patient.

The patient had never received hormone replacement during puberty and post-puberty. At the age of 21 years, she was diagnosed as diabetes. Her diabetes was characterized by no ketoacidosis and negative antibodies for IAA, ICA, and GADA. Her blood glucose levels gradually decreased after a daily dose of insulin of 0.8 U/kg, suggesting an insulin resistance. Considering the patient had central obesity, diabetes, and lower levels of HDL-c, the patient can also be diagnosed with metabolic syndrome according to 2005 International Diabetes Federation Criteria. Those information support the type of diabetes in the patient, which might be type 2 diabetes.

Our data are in agreement with the previous study, which claimed that in women with CAIS, disruption of AR signaling may increase body fat and lead to abnormal values of cholesterol (total and LDL-c) and HOMA-IR. The underlying mechanism might be explained by reduced P38 activity and PPARα gene in the skeletal muscle and the liver, and increased expression of genes that stimulate hepatic glucose production, late adipocyte differentiation, and lipid accumulation.[3,4] Moreover, AR also plays significant roles in central nervous system, which was not only related to various masculine behaviors but also associated the role of neuronal AR in metabolic regulation.[3]

For therapy, the patient was treated by insulin, metformin, and statins. Besides the treatment for diabetes and metabolic disorder, estrogen replacement is also required for the patient, which can help in development of secondary sexual characteristics, maintain metabolic health, and promote general wellbeing. After 6 months follow-up, the patient had a good control of blood sugar and lipid profiles. However, the breast development and body weight change were not obvious. Further follow-up should be conducted in the patient.

### Table 1. Laboratory findings on admission.

| Items                      | Normal range |
|----------------------------|--------------|
| Blood biochemistry         |              |
| Alanine transaminase, U/L  | 43.7 <45     |
| Aspartate transaminase, U/L| 27.8 <32     |
| Albumin, g/L               | 45 34-48     |
| Creatinine, μmol/L         | 42.6 45-84   |
| Triglyceride, mmol/L       | 4.44 <1.7    |
| Total cholesterol, mmol/L  | 5.99 <5.2    |
| LDL-c, mmol/L              | 3.67 0.1-3.35|
| HDL-c, mmol/L              | 0.98 0.9-1.68|
| Fasting plasma glucose, mmol/L| 17.3 3.9-6.1 |
| Hemoglobin A1c (%)         | 12.8 4.5-6.3 |
| Glucose, mmol/L            | 5.5 4.0-6.1  |
| Hemoglobin A1c (%)         |              |
| Fasting plasma glucose, mmol/L| 17.3 3.9-6.1 |
| Hemoglobin A1c (%)         | 12.8 4.5-6.3 |

ACTH = adrenocorticotropic hormone, FSH = follicle-stimulating hormone, HDL-c = high-density lipoprotein cholesterol, LDL-c = low-density lipoprotein cholesterol, LH = luteinizing hormone, sTSH = sensitive thyroid-stimulating hormone. T3 = triiodothyronine, T4 = thyroxine.

### 3. Discussion

Both epidemiological studies and experiment have demonstrated that AR signaling plays a role in glucose homeostasis and lipid metabolism.[1–3] It was reported that male AR knockout mice showed a risk factor for the development of obesity and metabolic abnormalities.[4] In addition, androgen deficiency in men was associated with increased body fat and impaired insulin sensitivity.[4] Recently, some disorders of sex development are reported to be associated with increased risks of diabetes and metabolic syndrome as well.[5,6] But there were few data on the components of metabolic syndrome in young women with CAIS.

The diagnosis of CAIS in this patient was established by infantile female genitalia, blind end of the vagina, absence of ovary and uterus, history of gonadectomy, 46,XY karyotype, and detected a mutation in AR gene. The mutation c.2751C>G (p.917F>L) detected in this patient has been described in an Austrian patient with CAIS.[8] It should be noticed that early gonadectomy could explain the absence of breast development and low levels of testosterone in our patient.

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### 4. Conclusion

We reported a case of CAIS with diabetes mellitus and metabolic syndrome, which would imply that to recognize special type diabetes among the young-onset diabetic patients is extremely important. Moreover, this case will provide further evidence of a link between impaired AR signaling and metabolic regulation.

### Author contributions

Conceptualization: Manna Zhang, Xiang Liu.
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