A HIV-infected adolescent with polycystic ovary syndrome

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Abstract. We report a case of polycystic ovary syndrome in a 15-year-old human immunodeficiency virus-infected female on highly active antiretroviral therapy who developed hypertriglyceridemia, hyperinsulinemia due to insulin resistance, and hyperandrogenism. Ultrasonography showed multiple small follicles at the right ovary and lobulated follicles at the left ovary. Treatment of polycystic ovary syndrome included insulin sensitizing agents (metformin, pioglitazone) and a contraceptive for hyperandrogenism. We also encouraged lifestyle modification including regular exercise and dietary fat restriction. She attained menarche 1 month after initiation of treatment.

Keywords: PCOS, HIV, HAART

1. Introduction

Polycystic ovary syndrome (PCOS) has multiple possible etiologies and clinical presentations, and is considered to be a multifactorial disorder that is characterized by several features: unexplained clinical or biochemical signs of hyperandrogenism, oligo-amenorrhea, and/or the presence of polycystic ovaries. Pathophysiologic mechanisms that are thought to be responsible for PCOS include: firstly, the increased release of luteinizing hormone (LH) from the pituitary, which leads to increased androgen production; secondly, insulin resistance, which leads to hyperinsulinemia (insulin itself then acts with LH to increase androgen production in the ovarian cells and additionally also decreases sex hormone-binding globulin levels, resulting in increased levels of active androgens and free testosterone); and thirdly, increased androgen which potentially originate from an increase in ovarian enzymatic activity engaged in the synthesis of testosterone precursors. In addition, among obese women PCOS may lead to hypertriglyceridemia [1–3].

The metabolic dysfunctions found in PCOS are similar to those in human immunodeficiency virus (HIV)-infected individuals receiving highly active antiretroviral therapy (HAART). HAART has been long associated with insulin resistance, lipodystrophy, and hypercholesterolemia [4–7]. Due to the overlapping features of the adverse effects of HAART and PCOS, a question remains as to whether HAART may therefore predispose development of PCOS.

2. Case report

We report a 15-year-old female with perinatal HIV infection. She was diagnosed with HIV at 1 year of
age, and was started on antiretroviral drugs at the age of four with zidovudine and abacavir. When she was 12 years old, the antiretroviral regimen was switched to tenofovir, efavirenz, and lamivudine because at that time this HAART regimen had become available to HIV-infected children free of charge under the Thai government scheme. Her viral load and immunity were within normal limits. At the age of 14, she presented with acne, darkening of skin near the neck and axilla, oily skin and hirsutism (11–13 according to the modified Ferriman-Gallwey score), and she had not attained menarche yet. She had no other known underlying conditions.

2.1. Physical examination

She was a well appearing non-obese female. Her height was 162 cm and her weight 51 kg, with a BMI of 19.4 (the 50th percentile). She had facial acne, slightly prominent nasolabial folds, loss of facial fat (sunken cheeks), and marked acanthosis nigricans at the neck and axilla. She also had thinner limbs with no prominent veins, with atrophy of buttocks without a buffalo hump and lipomas. The sexual maturity rate of her breasts was II and that of her pubic hair IV. No clitoromegaly was present.

2.2. Laboratory studies

The laboratory results showed a marked elevated level of triglycerides (5900 mg/dL; normal: 140 mg/dL) and serum cholesterol (550 mg/dL; normal: 180 mg/dL). Her high-density lipoprotein (HDL) level was within normal limits (51 mg/dL; normal: 40–60 mg/dL). An oral glucose tolerance test demonstrated diabetes and insulin resistance, with an elevated fasting blood sugar level (118 mg/dL; normal: <100 mg/dL) and high insulin level (132 uU/mL; normal: 0–17 uU/mL). In addition, she had an elevated 2-h post-prandial blood sugar level (245 mg/dL; normal: <140 mg/dL) with a high insulin level (1686 uU/mL; normal: 15–53 uU/mL). Her hemoglobin A1C level was normal (5.8%; normal: 4.2–5.9%). The testosterone level was elevated (178 ng/dL; normal: 13–35 ng/dL) with a decreased sex hormone-binding globulin level (6.4 nmol/L; normal: 18–114 nmol/L) and a decreased LH level (9.31 IU/L; normal: 0.4–11.7 IU/L) and follicle-stimulating hormone (FSH) (5.2 mU/L; normal: 1.0–9.2 mU/L), with a normal LH/FSH ratio (1.7/1). Her thyroid stimulating hormone level was normal (1.423 uU/mL; normal: 0.4–4 uU/mL) and her free thyroxine level (1.1 ng/dL; normal: 0.8–2.3 ng/dL). The Prolactin level was normal (6.66 ng/dL; normal: <20). Her levels of aspartate aminotransferase (25 U/L; normal: 5–45 U/L) and alanine aminotransferase (31 U/L; normal: 5–45 U/L) were normal. The adrenocorticotropic hormone (ACTH) stimulation test was performed and revealed normal rising of cortisol levels from 14.52 to 33.77 ng/dL and normal 17-OHP levels of 58 ng/dL at 0 min, and 236 ng/dL at 60 min. The allele specific amplification for the CYP21 gene for 21-hydroxylase deficiency was performed and neither heterozygous nor homozygous mutation was found.

Ultrasonography showed multiple small follicles at the right ovary and lobulated follicles at the left ovary. The adrenal glands appeared normal. The liver was diffusely enlarged with a fatty change (Fig. 1).

The diagnosis of lipodystrophy, diabetes, insulin resistance, hypertriglyceridemia and PCOS was made. The patient was started on metformin (2,500 mg/d), fenofibrate (320 mg/d) and fish oil (6 g/d), to control her metabolic disturbance. At 3 months of treatment, her laboratory results improved, such as the levels of fasting blood sugar (84 mg/dL), insulin (61 uU/mL), cholesterol (251 mg/dL), triglycerides (851 mg/dL), and HDL (34 mg/dL). Pioglitazone was added to improve glucose level control. Treatment for PCOS included insulin sensitizing agents (metformin, pioglitazone) and a transdermal contraceptive for hyperandrogenism (a patch form was applied to avoid systemic effects which might worsen lipid and liver abnormalities). We also encouraged life style modification including regular exercise and dietary fat restriction. The patient later attained menarche 1 month after treatment.

3. Discussion

We report a case of PCOS in a 15-year-old HIV-infected female who developed hyperinsulinemia and lipodystrophy potentially induced by nucleoside reverse transcriptase inhibitor (NRTI)-based HAART regimen. She fulfilled two of the three signs specified in the Rotterdam criteria for PCOS, including the presence of polycystic ovaries and biochemical signs consistent with hyperandrogenism. She had hirsutism and acanthosis nigricans along with insulin resistance, which were symptoms consistent with PCOS. Her basal
morning and after ACTH stimulation 17-OHP values were normal suggesting that a non-classical congenital adrenal hyperplasia condition could be ruled out [8]. Moreover, the molecular study did not show any heterozygous mutations of the CYP21 gene in this patient. We also excluded the presence of androgen-producing tumors because her testosterone and DHEAS level were within the normal range [2].

We proposed that long-term NRTI-based HAART regimen and the HIV infection itself potentially caused her condition of lipodystrophy. Previous studies have shown that the prevalence of lipodystrophy in HIV-infected children on HAART usually ranges between 25–30 percent; in addition, this condition can cause dyslipidemia and insulin resistance in a pediatric group similarly as in adults [9–13]. Recent surveillance data obtained by a European Study Group [11] demonstrated that the use of efavirenz is associated with lipatrophy. Moreover, a previous study further identified that HIV-infected children on HAART are most likely to develop lipodystrophy during puberty [14].

Hyperinsulinemia is an increasing recognized complication of HAART in HIV-infected women with lipodystrophy. The mechanisms of insulin resistance in this population are still debated: they could be related both to the inhibition of insulin-mediated glucose disposal by protease inhibitors (PI) as well as to the visceral adiposity. In this case the former hypothesis should be excluded since the patient was not taking a PI-based HAART regimen. Even though the patient presented lipoatrophy with no signs of lipohypertrophy, neither a computed tomography scan, nor a dual energy x-ray absorptiometry scan, nor an abdominal magnetic resonance imaging were performed to evaluate the visceral adiposity; so the latter mechanism could be even partially responsible for the occurrence of insulin resistance. Furthermore Hadigan et al. [15] showed significant fasting hyperinsulinemia and an increased insulin-to-glucose ratio even among significantly wasted HIV-infected women, as well as patients not receiving PI-based HAART regimens. On the other hand, insulin resistance accompanied by compensatory hyperinsulinemia is one of the major features and a pathogenic key factor of PCOS. We also propose that the possible mitochondrial toxicity of non-nucleoside reverse transcriptase inhibitor (NNRTI) and NRTI-based HAART regimens could eventually be responsible for the condition of insulin resistance in our patient [16–18].

To the best of our knowledge, this is the first report of PCOS in an HIV-infected patient treated with NNRTI/NRTI-based HAART regimens. Two previous case reports on this topic exist in the literature, both involving patients on PI-based HAART regimens. The first was a 37-year-old patient who was on a ritonavir plus saquinavir-based regimen [19], and the second a 14-year-old patient on an indinavir-based regimen [20] (Table 1). PI-based HAART regimens have long been reported to be associated with metabolic abnormalities and lipodystrophy, including insulin resistance, hypertriglyceridemia, and central obesity [4]. The mechanisms of action of insulin resistance attributed to PI-based HAART regimens are inhibition of GLUT4-
mediated glucose transport resulting in the inhibition of glucose uptake and defective insulin signaling [21].

The question as to whether or not HAART regimens may predispose young women to PCOS has not been extensively studied. It has been well recognized that lipodystrophy, insulin resistance and dyslipidemia are metabolic complications of antiretroviral treatment. Hyperinsulinism also plays an important role in the pathogenesis of PCOS development. However, one previous study [22] examining risk factors of PCOS in HIV-infected women taking various kinds of antiretroviral agents and healthy age- and body mass index-matched control subjects demonstrated that despite increased abdominal fat accumulation and hyperinsulinemia, signs characteristic of PCOS, including increased ovarian follicle numbers, irregular menses, hirsutism, and increased LH/FSH were not seen among HIV-infected women. This might indicate that the development of PCOS in HIV-infected women is not the consequence of HAART inducing hyperinsulinism. From our review of the literature, no studies exist examining whether or not such an exposure to HAART does indeed increase the risk of PCOS. In this case, we did not know whether our patient had a long-term hyperinsulinemia preceding clinical and sonographic signs of PCOS. The question whether PCOS developed as an additional metabolic complication of HAART or was not related to it therefore remains unsolved.

In general, treatment of PCOS mainly includes the improvement of metabolic abnormalities (such as the use of insulin-sensitizing agents for insulin resistance), weight reduction for obese patients, hormonal therapy for menstrual irregularity, hirsutism and acne. Hormonal contraceptives are considered for the regulation of menses and treatment of hirsutism and acne. Alternatively, antiandrogen can be added for the treatment of severe hirsutism and acne [2]. Some women may experience infertility due to oligo-anovulation. Clomiphene citrate has been proven effective in ovulation induction and should be considered the first-line therapy. Additionally, metformin combined with clomiphene citrate may increase ovulation rates and pregnancy. Gonadotropin should be considered second-line therapy for fertility in anovulatory women with PCOS [23].

In this case, we prescribed insulin-sensitizing agents and a transdermal contraceptive for her amenorrhea, hirsutism and acne conditions. We used a transdermal contraceptive in this patient because she had a fatty liver. Transdermal contraceptives are not metabolized in the liver and do not worsen lipid abnormalities. In general, treatment with contraceptives normalizes androgen levels within 1 month, improves acne within 3 months, and arrests progression of hirsutism [24].

The patient attained menarche 1 month after treatment and clinically responded to contraceptives within 3 months. If she wishes to have children in the future, control of her viral load to decrease the chance of vertical transmission and ovulation induction are mandatory. Ovulation can be induced by either clomiphene citrate alone or with metformin. After the concepbus has formed, metformin should be stopped and switched to insulin to control diabetes.

In conclusion, this issue will be of increasing importance as the number of available HAART regimens for children increases, allowing HIV-infected children to spend more years on these drugs that potentially contribute to metabolic syndrome and perhaps PCOS. We suggest that further studies explore cases of PCOS more fully in a pediatric population.

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