

Unusual presentation with polymenorrhagia and markedly high 17-hydroxy progesterone levels in a lady with Non-Classic Congenital Adrenal Hyperplasia

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Abstract

Congenital adrenal hyperplasia is generally associated with oligo-amenorrhea, and its presentation with polymenorrhagia is rare. Here we present a case of an Asian female who presented with polymenorrhagia since menarche, increased body hair growth and enlargement of clitoris for 7-8 years. Examination revealed a normal Body Mass Index, moderate hirsutism, Tanner 5 breasts and significant clitoromegaly. Serum testosterone and 17-hydroxyprogesterone levels were elevated. Ultrasonography revealed normal adrenal glands and polycystic ovaries. adrenocorticotrophic hormone stimulation test uncovered borderline cortisol deficiency. Oral dexamethasone was commenced and six months later, she showed improvement though there was no change in hirsutism or clitoromegaly. The case is unique because it presented with polymenorrhagia. Also, such phenomenally high 17-hydroxyprogesterone levels are not expected in non-classic congenital adrenal hyperplasia.

Keywords: Non-classic congenital Adrenal hyperplasia, Polymenorrhagia, 17-hydroxyprogesterone.

Introduction

Oligomenorrhoea has long been known to be present in patients with congenital adrenal hyperplasia (CAH),¹ but CAH presentation with polymenorrhagia is rare. Here we present a case of a young woman which was presented first at the 13th European Congress of Endocrinology, Rotterdam. The patient presented with polymenorrhagia, and was later diagnosed as having non-classic congenital adrenal hyperplasia (NC-CAH). Her serum level of 17-hydroxyprogesterone (17-OHP) was unusually high for this variety of CAH.

Case Report

After obtaining written informed consent from the patient for the publication of this report, we present a case of a 23-year-old, unmarried, female medical student,

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Table: Summary of Investigations.

Investigations	Result	Normal Range
Testosterone	145.8	6-82 ng/dl
Estradiol	32	0-160 pg/ml
Prolactin	21.64	4.79-23.3 ng/ml
Fasting glucose	78	65-110 mg/dl
LH (follicular)	8.35	1.1-11.6 mIU/ml
FSH (follicular)	4.89	2.8-11.3 mIU/ml
17-OH Progesterone (follicular)	170.0	0.19-1.82 ng/ml
Dehydroepiandrosterone sulfate	375	35-430 µg/dl
Thyroid Stimulating Hormone	2.54	0.17-4.05 µIU/ml
Free T4	17.51	11.5-23.0 pmol/L
Total cholesterol	107	< 200 mg/dl
Low Density Lipoprotein	58	<150 mg/dl
Triglycerides	57	35-135 mg/dl
Sodium	134.25	136-148 mmol/L
Potassium	4.07	3.6-5.0 mmol/L
Baseline cortisol	9.5	> 18 g/dl
30 min post-ACTH cortisol	15	>18 g/dl
60 min post-ACTH cortisol	17	> 18 g/dl

LH: Luteinizing hormone

FSH: Follicle-stimulating hormone

ACTH: Adrenocorticotrophic hormone.

who was an Urdu-speaking Pakistani, and presented in December 2009 with polymenorrhagia since menarche (10 years), clitoromegaly noticed since 8 years and hirsutism since 7 years. She reported having frequent menstrual cycles, every 15-20 days, with a heavy flow for 5 days, along with significant dysmenorrhoea. She had noticed some enlargement of clitoris for the preceding 8 years. Five years earlier, during anatomy classes at medical school, she realised that this clitoral enlargement was not normal. Subsequently, she further realised that thick hair growth over her body, especially around the chin area was also abnormal. She had previously been labelled as a case of polycystic ovarian syndrome (PCOS) and had been placed on Diane 35 (ethinyl estradiol + cyproterone acetate) by a gynaecologist. This had resulted in some regularisation of her menstrual cycles, but after using it for a certain period, she stopped taking it as she noted no improvement in the hirsutism or clitoromegaly. She had no history of ambiguous genitalia or salt-wasting crisis at

birth. Her 16-year-old Australian-born cousin was diagnosed to have classic CAH at birth. Subsequently, he had developed diabetes, which had been attributed to over-treatment with steroids. There was no history of diabetes or hormonal dysfunction relevant to her condition in any other first-degree relatives.

On clinical examination, she had normal height (158cm), built and weight (52kg; body mass index [BMI]: 21kg/m²). Waist and hip circumferences were normal (72cm and 88cm respectively). Vitals were within normal ranges (pulse: 80 beats/min, blood pressure: 110/70mmHg, temperature: 37°C, respiratory rate: 18 breaths/min). She had moderate hirsutism, most marked over the chin area (Ferriman Gallway [FG] score 20/36). She had no acne, frontal alopecia, or increased muscularity. No abnormal pigmentation or striae were present. Breast examination revealed Tanner stage 5 breasts (adult stage) without any discharge or galactorrhoea. Examination of genitalia revealed significant clitoromegaly, with clitoral index 50mm² [normal range: <35mm²]. Vaginal and urethral orifices were present.

Her hormonal profile was investigated (Table) and on the basis of all evidence possible, she was diagnosed as a case of NC-CAH with hyper-androgenism and subclinical adrenal insufficiency. Oral dexamethasone 0.5mg was commenced in reverse rhythm (at bed time), with advice to double the dose in times of stress. At follow-up after 6 months of therapy, her menstrual cycle had regularised, serum testosterone had gone down to 2.5ng/dl (from 145.8 ng/dl) and 17-OHP had decreased to 0.5ng/ml (from 170.0ng/ml). The patient reported no improvement in hirsutism or clitoromegaly. She was using local methods like waxing for hirsutism. Subsequently, the dose of dexamethasone was decreased to 0.25mg at bed time. For hirsutism she was advised to continue local depilatory methods, or to undergo laser therapy. Reconstructive plastic surgery was advised for managing the clitoromegaly, which she subsequently underwent in 2012.

Discussion

CAH due to 21 hydroxylase deficiency is one of the most common autosomal recessive hereditary diseases.²⁻⁴ In Caucasians, 1-2% of hyperandrogenism syndromes are due to late onset NC-CAH.^{5,6} In NC-CAH, about 20-50% of 21-hydroxylase activity is preserved, and it usually presents with a mild androgen excess in late childhood or during adolescence.

In adult women, NC-CAH may manifest with signs of virilisation, including hirsutism, acne, frontal alopecia, clitoromegaly, male pattern hair growth or deepening of

voice. Other presentations include oligomenorrhoea and primary amenorrhoea. Fertility issues are experienced by 13% of women with this condition.⁷ At times, the condition may be subclinical. In adult males, the condition is mainly asymptomatic, but some men may present with adrenal rest tumour and/or fertility problems.⁸

CAH is an entity that must be excluded prior to making a diagnosis of PCOS, which this patient had previously been labelled with. PCOS can also present with hirsutism and menstrual irregularities. Ultrasonographic appearance of polycystic ovaries can coexist with congenital adrenal hyperplasia,² as in the case of our patient. This further delayed her work-up, by gynaecologists and general physicians, for other hormonal abnormalities responsible for her presentation (hirsutism, clitoromegaly and menstrual irregularity). In addition to CAH, other conditions, such as cushing's syndrome/disease, androgen secreting tumours, acromegaly, hyperprolactinemia and thyroid disease, need to be considered in the differentials of PCOS. A complete hormonal evaluation, including her 17-OH progesterone levels were requested for, only when the patient had been referred to an endocrinologist following months of non-responsiveness to treatment with Diane 35.

This case is interesting because our patient had presented with polymenorrhagia (frequent menstrual cycles with heavy flow). To the best of our knowledge, all cases in the literature report oligo/amenorrhoea in association with CAH. There was a case report describing a hirsute lady with menorrhagia (heavy but regular menstrual cycles), who was subsequently found to have increased 17-OH progesterone levels.⁹

The other interesting aspect of our case is that this lady presented with a phenomenally high 17-OHP level (170.0ng/ml, unstimulated level). NC-CAH is usually associated with mildly elevated levels of 17-OHP, often requiring ACTH stimulation for confirmation of the disorder.¹⁻⁹ Levels of this degree are usually expected in the classic variety of CAH, usually diagnosed at birth.

Despite such high levels of 17-OHP, our patient displayed only borderline adrenal insufficiency, as evidenced by the short synacthen test. The results prompted us to counsel the patient about the importance of doubling the dose of steroid (dexamethasone) in times of stress.

In order to ensure optimal outcomes in adult patients with CAH, a multidisciplinary approach should be employed at specialist centres involving endocrinologists, gynaecologists, urologists, geneticists and psychologists.¹⁰

Conclusions

Prior to labelling a subject with hirsutism and menstrual irregularity as a case of PCOS, other hormonal dysfunctions require exclusion. Polycystic ovaries can co-exist with CAH which is an important consideration in the differentials. Clinicians need to be aware of the possibility of NC-CAH presenting with unusual findings of polymenorrhagia, and/or exceptionally high 17-OHP levels.

Written informed consent was obtained from the patient for publication of this case report.

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