Original Article

Utility of a Commercially Available Blood Steroid Profile in Endocrine Practice

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Abstract

Background: A blood steroid profile has recently become available on commercial basis in India. In this study, we report our initial experience with the use of steroid profile in the evaluation of disorders of sex development (DSD) and suspected cases of congenital adrenal hyperplasia (CAH) and discuss the potential scenarios in endocrine practice that may benefit from this steroid profile. **Materials and Methods:** The study included six subjects. Patient 1 was a 46, XX girl who presented with peripubertal virilization, patient 2 was a girl who presented with normal pubertal development, secondary amenorrhea, and virilization, and patient 3 was a girl who presented with primary amenorrhea and virilization. These three patients were suspected to have CAH but had non-diagnostic serum 17 OH-progesterone levels. Patient 4 and 5 were 46, XY reared as girls who presented with primary amenorrhea alone and primary amenorrhea and virilization, respectively, and sixth subject was a heathy volunteer. All subjects were evaluated with blood steroid profile by Liquid chromatography tandem mass spectrometry (LC-MS/MS). **Results:** Patient 1 and 2 were diagnosed to have 11 β-hydroxylase deficiency by using the steroid profile. Patient 3 was suspected to have CAH, but the steroid profile excluded the diagnosis and helped to confirm the diagnosis as polycystic ovary syndrome. In patient 4 and patient 5, although steroid profile ruled out the possibility of steroidogenesis defects, it did not help to reach at the specific diagnosis. **Conclusion:** The blood steroid profile used in this study is most useful for the diagnosis of 11 β-hydroxylase deficiency. The utility of this test is limited in the evaluation of 46, XY patients with under-virilization.

Keywords: Blood steroid profile, congenital adrenal hyperplasia, disorder of sex development

Introduction

Congenital adrenal hyperplasia (CAH) is the cause of virilization of the external genitalia in majority of 46, XX infants. 21α-hydroxylase deficiency is the most common cause of CAH, and serum/plasma 17α-hydroxyprogesterone (17-OHP) is the most useful test to confirm or exclude the condition.[1] However, 17-OHP may not help in the diagnosis of rarer forms of CAH. Steroid profile that comprises quantification of multiple steroids in blood or urine is a useful test to detect rare forms of steroidogenesis defects. The recent position statement on steroid profile suggests it as an important first-line approach to the diagnosis of disorders of sex development (DSD).[2] The steroid profile provides fast and comprehensive results and thus allows for a rapid differential diagnostic orientation. Moreover, it has good phenotype-genotype correlation in CAH cases.[3] In the evaluation of 46, XY DSD, next generation sequencing has been proven to be the most useful test and steroid profile may not be as useful in 46, XY DSD as in 46, XX DSD.[4] Nevertheless, the steroid profile remains an essential test for holistic understanding of individual DSD cases.

These steroid profiles provide the levels of multiple intermediate molecules in the steroidogenesis and their metabolites, the latter especially in urine steroid profile.[5] However, in India no steroid profile testing was available on commercial basis. A blood steroid profile has recently become available on commercial basis in India.[6] In this study, we report our initial experience with the use of steroid profile in the evaluation of DSD and suspected cases of CAH and discuss the potential scenarios in endocrine practice that may

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benefit from this steroid profile. We also suggest the areas for improvization of the steroid profile.

Materials and Methods

This retrospective study was conducted at Narayana Medical College and Hospital, Nellore, Andhra Pradesh. The study was approved by the institutional ethics committee and a written informed consent was obtained from all the participants. Patients who were evaluated with steroid profile between January 2017 and June 2018 were included in the study.

The details of clinical, biochemical, and hormonal evaluation at the institute and that of steroid profile were collected in a pre-structured format. Initial hormonal evaluation for testosterone, 17-OHP, and dehydroepiandrosterone sulphate (DHEAS) was performed at the institute by chemiluminescence assay (CLIA) using Access 2 Beckman Coulter.

For steroid profile, 5 ml of EDTA blood was collected from all the participants. In patient 1, the sample was collected at Bangalore, Karnataka, whereas in all other participants sample was collected at Nellore, Andhra Pradesh by one of the authors, and plasma was separated by centrifugation at the respective institution. The samples were collected within half an hour of collection by the Thyrocare technicians and were transported at 4–8°C to Mumbai within 12–24 h of sample collection. The blood steroid profile (except aldosterone, which was measured by CLIA) was performed using LC MS/MS at Thyrocare laboratory, Mumbai. The blood steroid profile included measurement of hormones included in Table 1 in addition to 25-OH vitamin D.

Results

The steroid profile was tested in six subjects.

Patient 1

An 11-year-old girl presented with enlargement of the clitoris for 4 years and deepening of the voice for 2 years. Pubic hair was noticed at the age of 7 years, whereas breast development noticed at 10 years. She measured 149 cm (+3 SD), and blood pressure was 120/80 mmHg. Sexual maturity was B3P3. She had dark complexion, acne, muscular appearance, and clitoromegaly (24 mm *15 mm) but no posterior labial fusion (anogenital ratio: 0.44). Bone age was 16 years. Evaluation revealed elevated serum total testosterone (201 ng/dl), slightly elevated DHEAS (314.2 µg/dl), and pubertal LH (8.83 mIU/ml). Karyotype was 46XX. Serum 8:00 am cortisol was normal (8.1 µg/dl) but under the effect of high adrenocorticotropic hormone (ACTH) (395 pg/ml). ACTH stimulated cortisol was low (8.69 µg/dl), whereas ACTH stimulated 17-OHP (6.11 ng/ml) and DHEAS (309.4 µg/dl) were normal. The plasma renin activity was normal (2.1ng/ml/h). Although exact cause of CAH was not identified, she was initiated on oral prednisolone 5 mg/day with stress doses of glucocorticoids being recommended during periods of illness. Three months later, her total testosterone had reduced to 42 ng/dl, DHEAS to 52 µg/dl, and acne improved. She was continued on prednisolone 5 mg/day. At the age of 12 years, she attained menarche. At the age of 14 years, despite the counseling not to stop prednisolone, patient had stopped prednisolone for 2 weeks during her 10th standard final exams. At this point, blood steroid profile was performed at baseline and 1 h after subcutaneous injection of 25 units of acton prolongatum, the results of which are summarized in Table 1. The results revealed the diagnosis of 11 β-hydroxylase deficiency. The patient was restarted on oral prednisolone and was counseled to adhere to therapy.

Patient 2

An 18-year-old girl attained menarche at 13 years of age, had regular menstrual cycles during the first post-menarchal year, once in 2–3 months during the next 2 years, and secondary

Table 1: Summary of steroid profile of study participants and their final diagnosis

	Patient 1 (Basal)	Patient 1 (ACTH stimulated)	Patient 2 (ACTH stimulated)	Patient 3 (Basal)	Patient 4 (Basal)	Patient 5 (Basal)	Control (Basal)
Testosterone (ng/dl)	79.77	106.6	222	91.6	46.12	49.31	42.86
Cortisol (µg/dl)	6.8	6.1	8.4	6.9	3.1	8.8	18.47
17-OHP (ng/dl)	86.19	139.2	290.1	182.3	96.8	52	56.77
Androstenedione (ng/dl)	468.8	604.43	2337.2	482.4	100.4	67.76	141.86
DHEAS (µg/dl)	43.53	32.3	345	326.6	403	57.68	100.46
DHEA (ng/ml)	10.5	9.61	69.5	63.1	72	31.7	26.46
Progesterone (ng/ml)	0.1	0.1	0.5	0.2	0.2	0.1	0.16
11-deoxycortisol (ng/dl)*	2133.4	3445	5326.2		32.48	31.09	214.94
Corticosterone (ng/dl)	6491.4	12488	24103	78.32	135.54	79.92	448.75
Estradiol (pg/ml)	33	44	47	56	<10		127
Aldosterone (ng/dl)	2	2.6	1	6.87	16.3	17.01	12.6
Final diagnosis	11 β-OHD		11 β-OHD	PCOS	46 XY GD	AIS	Normal

11β-OHD: 11β-hydroxylase deficiency, AIS: Androgen insensitivity syndrome, ACTH: Adrenocorticotropic hormone (actonprolongatum), Basal: Unstimulated sample between 8:00 am and 9:00 am, GD: Gonadal dysgenesis, PCOS: Polycystic ovary syndrome. *Mentioned as "deoxycortisol" in the reports, but it was confirmed to represent "11-deoxycortisol" by personal communication with Dr A Kalai Selvan

amenorrhea for the last 2 years. She also had hirsutism for 2 years and complained of short stature. On examination, she had knuckle hyperpigmentation, mild deepening of the voice, temporal hair loss, and clitoromegaly (13 mm *9 mm). Serum total testosterone was 203 ng/dl, serum 17-OHP was 3.62 ng/ml, and serum DHEAS was 354 μg/dl. Hence, she was suspected to have androgen secreting neoplasm, and computed tomography (CT) abdomen-pelvis was done that revealed bilateral adrenal hyperplasia. Hence, the diagnosis of CAH other than 21 α-hydroxylase deficiency was considered, and the steroid profile was ordered, which revealed the diagnosis of 11 β-hydroxylase deficiency [Table 1].

Patient 3

An 18-year-old girl presented with primary amenorrhea, hirsutism for 4 years, clitoral enlargement for 4 years, and worsening of dark complexion for 3 years. She was lean (BMI: 20.44 kg/m^2). She had elevated testosterone (0.98 ng/ml) with polycystic ovary morphology on ultrasound pelvis. She was suspected to have nonclassical CAH, but DHEAS (211.8 μg/dl), serum 8:00 am cortisol (8.0 μg/dl), adrenocorticotropic hormone (ACTH) stimulated cortisol (22.8 μg/dl), and ACTH stimulated 17-OHP (3 ng/ml) were normal. The steroid profile was done, which was not suggestive of defective steroidogenesis but was consistent with polycystic ovarian syndrome (PCOS)[Table 1]. She had normal fasting plasma glucose (72 mg/dl) but elevated corresponding serum insulin (52.2 μIU/ml) and anti-mullerian hormone (AMH) (11.7 ng/ml), which corroborated with the diagnosis of PCOS.

Patient 4

A 14-year-old girl presented with primary amenorrhea. She was eunuchoid (US: LS = 0.87), and Tanner's sexual maturity rating was B4P3 with normal female external genitalia and two separate openings in the introitus. Hormonal evaluation revealed elevated gonadotropins with low estradiol and normal testosterone. Initial ultrasound revealed nonvisualization of Mullerian structures and ovaries. Karyotype was 46XY. Another profile from the same laboratory "Infertility profile B" was done, which revealed very low AMH and no defects in adrenal steroidogenesis. The findings were consistent with complete gonadal dysgenesis [Table 1].[6] Subsequent ultrasound identified a hypoplastic uterus.

Patient 5

A 14-year-old reared as girl presented with complaints of absent secondary sexual characters and primary amenorrhoea. She was born full-term and of a consanguineous marriage. There was no history suggestive of salt wasting. There were no symptoms of virilization at puberty. She had eunuchoid habitus, normal blood pressure (110/70 mmHg), prepubertal sexual maturity rating (B1A1P1), clitoromegaly (clitoral index; 200 mm^2), and bilateral palpable gonads in the respective inguinal regions. MRI pelvis revealed masses with testes, epididymis, and vasa deferens in the bilateral inguinal region and urethra of male configuration. Uterus and ovaries were not visualized. Karyotyping was 46XY. Gonadotropins (FSH: 2.51 mIU/ml; LH: 3.38 mIU/ml) were inappropriately normal with serum testosterone of 1.20 ng/ml. Hence, steroid profile was performed but was not suggestive of any defects in testosterone biosynthesis [Table 1]. Clinical exome sequencing was performed, which revealed a homozygous missense variation in exon 1 of the androgen receptor (AR) gene (chrX: 66766162C > T; c. 1174C > T) that results in the amino acid substitution of serine for proline at codon 392 (p. Pro392Ser) was detected. Both parents were heterozygous for the mutation. Bilateral laparoscopic gonadectomy was done; biopsy showed testicular tissue.

Discussion

We report our initial experience with the use of a new commercially available blood steroid profile in the diagnosis of endocrine conditions in India. We found that the blood steroid profile was useful, especially in patients with suspected CAH but normal or slightly elevated 17-OHP, which is incongruent with the diagnosis of 21-hydroxylase deficiency. In our study, both the CAH cases evaluated by blood steroid profile were diagnosed to have 11 β-hydroxylase deficiency.

The presence of hypertension is often a good clinical clue to suspect CAH where single biochemical test such as 11-deoxycortisol can be ordered which helps to confirm the diagnosis. However, the onset of hypertension is variable in 11 β-hydroxylase deficiency, making it a less reliable clue.[7] Although suppressed plasma renin can be another useful clue, it may not be helpful always (as observed in patient 1). However, as documented in the steroid profile of patient 1 and 2, a suppressed plasma aldosterone can be a useful clue. The measurement of serum 11-deoxycortisol is the most useful test in the diagnosis of 11 β-hydroxylase deficiency. However, at present only very few laboratories in India are offering 11-deoxycortisol as a single test, and steroid profile/panels that comprise 11-deoxycortisol are becoming a more widely available option.[6,8-12] Hence, the ordering a blood steroid profile comprising 11-deoxycortisol may be a more feasible option in patients with suspected 11 β-hydroxylase deficiency.

When we have a suspected case of 46, XX virilizing CAH but normal or only slightly elevated 17-OHP, the common differential diagnoses in addition to 11 β-hydroxylase deficiency include 3 β-hydroxysteroid dehydrogenase (HSD) deficiency and P450 (POR) oxidoreductase deficiency.[13] The diagnosis of POR deficiency is best performed using urinary steroid profile, whereas the use of blood steroid profile may only lead to its misdiagnosis.[13] However, although elevated progesterone, 17-OHP with low DHEAS, and androstenedione are useful clues toward POR deficiency, these findings overlap with those of 17 α-hydroxylase deficiency.[13] 17-OH-pregnenolone and pregnenolone, the most useful tests for the diagnosis of 3 β-HSD deficiency are not part of this profile.[14] Nevertheless, ratio of DHEAS to androstenedione may be a useful alternative parameter to confirm 3 β-HSD

deficiency and can be obtained from the blood steroid profile used in this study.

PCOS is a diagnosis of exclusion, and testing serum 17-OHP is recommended in all or at least in hyperandrogenic PCOS women.[15] Testing steroid profile is approximately two times costlier than serum 17-OHP and is less cost-effective in PCOS patients with hyperandrogenemia. However, steroid profile has advantages of accurate measurement of 17-OHP by LC MS/MS and potential to diagnose rarer forms of CAH such as 11 β-hydroxylase deficiency or 3 β-HSD deficiency.[16] However, the routine use of steroid profile cannot be recommended in all PCOS women with hyperandrogenemia at present.

The most commonly recommended situation for steroid profile is to use it as second tier tier test in patients with elevated 17-OHP during neonatal screening. 17-OHP in the heel prick has high false positive rate with very low PPV.[17] Recalling all these, infants may not be a cost-effective approach and may have psychological impact on the parents. Hence, the measurement of second tier tests on the filter paper to reduce recall rates would be beneficial.[18] Although initial studies suggested ratios comprising 21-deoxycortisol which is not part of the steroid profile used in this study, recent studies have demonstrated the utility of ratios using 11-deoxycortisol as well.[19,20] However, at present, the laboratory is not offering measurement 17-OHP or 11-deoxycortisol by LC MS/MS in a filter paper sample.

The monitoring of CAH owing to 21α-hydroxylase deficiency includes steroids such as total testosterone, 17-OHP, and androstenedione.[21] Although 17-OHP and/or testosterone are the most commonly used tests, additional testing of androstenedione may be useful. In such cases, the cost of ordering the steroid profile is comparable to or less than that of ordering all the three hormones separately.[6,22-26]

The utility of the blood steroid profile is limited in the evaluation of 46, XY DSD.[2] It is not useful to differentiate androgen insensitivity syndrome (AIS) from 5 α-reductase deficiency because the profile does not include dihydrotestosterone (DHT).[27] However, the inclusion of DHT in the profile would be inferior to urinary steroid profile, which provides the ratio of 5α to 5β metabolites.[28] However, the profile would be useful to differentiate testosterone biosynthetic defects (high steroidogenesis defects, 17 α-hydroxylase deficiency, and 17 β-HSD deficiency) from each other and from Leydig cell hypoplasia and gonadal dysgenesis.[2] However, it may not be useful to differentiate the latter two conditions. AMH is a useful test to differentiate the two conditions and as done in our patient 4.

Normal gonadotropin levels with very low-normal testosterone and estradiol at the age of 14 years were surprising findings in patient 5. This could be because of the constitutional delay in puberty or concomitant hypogonadotropic hypogonadism. The steroid profile was not confirmatory for any specific diagnosis. However, it suggested against the possibility of testosterone biosynthetic defect because there was no increase in any of the testosterone precursors. The diagnosis on clinical exome sequencing was AR mutation that was again surprising owing to low-normal testosterone but may be because of the reasons explained earlier. The reported AR mutation has been previously reported as pathogenic and has been associated not only with all forms (minimal, partial, and complete) of AIS but also with testicular cancer.[29,30] However, functional studies to demonstrate the pathogenicity of the mutation are lacking.

Conclusion

The blood steroid profile used in this study is most useful for the diagnosis of 11 β-hydroxylase deficiency. It may be a useful adjunctive test to diagnose 3 β-HSD deficiency. It will be a useful test to diagnose 17 α-hydroxylase deficiency and 17 β-HSD deficiency. However, utility of this test is limited in the evaluation of 46, XY patients with under-virilization (except for few testosterone biosynthetic defects).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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