A Curious Case of Primary Amenorrhea

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CASE DESCRIPTION

A 16-year-old phenotypic female presented with primary amenorrhea and lack of breast development, with no axillary or pubic hair. She had no previous medical history, aside from vitamin D deficiency and mild iron deficiency anemia as a child. There was no family history of endocrinopathy. On examination, she was normotensive, overweight, and noted to be tall in comparison to her nonconsanguineous parents.

Her baseline biochemical testing by immunoassay showed serum luteinizing hormone 28 IU/L (follicular phase 1.9–12.5), follicle-stimulating hormone 16 IU/L (follicular phase 2.5–10.2) in the presence of a low normal concentration of 17β-estradiol 0.026 ng/mL (0.019–0.144), consistent with ovarian dysfunction. Serum androgens were undetectable: dehydroepiandrosterone sulfate (DHEAS) <0.30 ng/mL (148–3852), androstenedione <0.29 ng/mL (0.29–3.29), and testosterone <0.09 ng/mL (0.14–0.74). The serum progesterone concentration of 17.1 ng/mL (prepubertal range 0–1.74) was increased, while a 9 AM serum cortisol was low at 44.6 ng/mL (49.3–221). Thyroid-stimulating hormone was within the reference interval.

Further investigations appeared to confirm adrenal insufficiency with respect to cortisol release, with the patient having an increased plasma adrenocorticotropic hormone (ACTH) of 143 ng/L (<50 ng/L), and no cortisol response to 250 μg synacthen: baseline serum cortisol was 43.2 ng/mL and 30 min serum cortisol 47.9 ng/mL. The patient's karyotype was 46 XX.

Serum was sent to a referral laboratory for liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis. The reported 17-hydroxyprogesterone (17-OHP) was normal at 1.36 ng/mL (follicular phase <2.9), but 11-deoxycortisol was markedly increased at 21.0 ng/mL (2.41–4.48).

A urinary steroid profile by gas chromatography mass spectrometry (GC-MS) (1) was then performed and showed high concentrations of corticosterone metabolites, while the concentrations of metabolites of androstenedione, DHEAS, and cortisol were all low, consistent with the previous results. However, metabolites of 11-deoxycortisol were low, and this was therefore not consistent with the increased serum 11-deoxycortisol result.

In order to resolve these discrepancies, the serum sample was sent for reanalysis at King's College Hospital, London, using an alternative LC-MS/MS assay. This method was designed to target intermediates and products of the major steroid biosynthetic pathways(2). 11-Deoxycortisol was now found to be below the detection limit, while corticosterone was markedly increased, and 11-deoxycorticosterone was also increased. Values provided by the first laboratory for 17-hydroxyprogesterone and cortisol were confirmed.

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QUESTIONS TO CONSIDER
• What are the most common forms of congenital adrenal hyperplasia (CAH)?
• What is the potential diagnosis of this case, as suggested by the increased progesterone and decreased 9 AM cortisol?
• In what form of CAH would an increase in 11-deoxycortisol be expected?

References

1. Taylor N. Urinary steroid profiling. Methods Mol Biol 2013;1065:259–76.

2. Taylor DR, Ghataore L, Couchman L, Vincent RP, Whitelaw B, Lewis D, et al. A 13-steroid serum panel based on LC-MS/MS: Use in detection of adrenocortical carcinoma. Clin Chem 2017;63:1836–46.

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the September 2020 issue of *Clinical Chemistry*. To view the case and comments online, go to https://academic.oup.com/clinchem/issue/66/9 and follow the link to the Clinical Case Study and Commentaries.

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