Journal of the Endocrine Society, 2021, Vol. 5, No. 1, 1–2
doi:10.1210/jendso/bvaa163
Letter to the Editor

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Letter to the Editor: "Glucocorticoid Resistance in Premature Adrenarche and PCOS: From Childhood to Adulthood"

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Abbreviations: GR, glucocorticoid resistance; DST, dexamethasone suppression test; PCOS, polycystic ovary syndrome.

Received: 18 September 2020; Editorial Decision: 2 October 2020; First Published Online: 7 November 2020; Corrected and Typeset: 18 December 2020.

Abstract

The conclusion of Panayiotopoulos *et al.* that glucocorticoid resistance accounted for 57% to 67% of their premature adrenarche and polycystic ovary syndrome cases cannot be accepted from the data presented. This is because proper validation of their method for determining glucocorticoid sensitivity is not presented. Furthermore, the method seems insensitive to physiologic glucocorticoid concentrations.

The conclusion of Panayiotopoulos et al. that glucocorticoid resistance (GR) accounted for 57% to 67% of their premature adrenarche and polycystic ovary syndrome (PCOS) cases [1] cannot be accepted from the data presented. This is because proper validation of their method for determining glucocorticoid sensitivity is not presented.

The foundations on which all assays stand are accuracy, specificity, precision, and sensitivity. This paper fails to present most of these validating criteria.

(1) Demonstration of assay accuracy requires comparing a new assay with a gold standard assay. This is not done: rather than comparing assays, they dismiss all existing assays as "requir(ing) the use of radioactive agents, … more time consuming and expensive".

(2) Demonstration of specificity might be demonstrated by determining whether their "GR" patients had mutated glucocorticoid receptors or defects in glucocorticoid signaling. Specificity should have been sought by performing dexamethasone suppression tests (DSTs) to determine whether their GR groups were significantly less dexamethasone suppressible than normal. Serum cortisol of children with premature adrenarche is typically normally suppressible by dexamethasone, including doses as low as 1 mg/m^2 at bedtime [2, 3]. PCOS cortisol levels are normally suppressible by dexamethasone 0.25 mg/m^2 midday [4]. Their excuse for not testing for in vivo GR by DST is because it gives misleading results in rare putative adrenal hyperplasia patients. Demonstration of clinically significant GR should be essential for the diagnosis. Such data are lacking. Their only

ISSN 2472-1972

supporting evidence for specificity is that their GR premature adrenarche group—and not the PCOS group—had significant, slight increases in serum cortisol (within normal limits) and adrenocorticotropin. However, no evidence is presented that diurnal variation was controlled for.

(3) Precision (9.6%) seems good since the normal glucocorticoid sensitivity index was 325 ± 30.6 (standard deviation) and "reproducible when measured on different days with (peripheral blood monocytes) from the same or different control donors" (the determination of reproducibility of the standard curves used to generate the glucocorticoid sensitivity index data is what the authors term "accuracy"). However, there are no specific data on interassay or intraindividual variation.

(4) The test sensitivity (limit of detection) is poor: it seems to be ≥800 nM fluorescein-labeled dexamethasone (F-dex), judging from the overlap of standard curve standard deviations with the 0 point.

Furthermore, a physiologic point about test sensitivity. The F-dex binding curve standards range from 400 to 6400 nM F-dex. For comparison, a 1.0 mg overnight DST yields an average plasma dexamethasone concentration of about 10 nM [5]. Furthermore, since dexamethasone's gram molecular weight is 392.5, their standards range from 157 000 to 2 512 000 ng/L (=157-2512 µg/L) dexamethasone. Consider that dexamethasone 157 µg/L in a 70 kg adult represents 10 990 µg (10.9 mg) total body dexamethasone, assuming whole-body dexamethasone volume of distribution [6]. Thus, the assay is conducted with unphysiological glucocorticoid doses unlikely to be pertinent to glucocorticoid potency.

In conclusion, the data are based on a low-sensitivity assay of unvalidated accuracy and specificity, so do not justify the conclusion that most patients with premature adrenarche and PCOS have GR.

Additional Information

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Disclosure Summary: No conflicts of interest to disclose.

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