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International Journal of Reproductive Research
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ISSN: 2836-2225 REVIEW ARTICLE

Value of Increasing the Reliability of Diagnosis of Nonclassical Congenital Adrenal Hyperplasia with Use of LC- MS/ MS in escalating the Diagnostic Capacity of Women with Clinical hyperandrogenism-A Short Communication

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Received: 15 September 2022; **Accepted:** 26 September 2022; **Published:** 03 November 2022.

Citation: Kulvinder K. K., (2022). Value of Increasing the Reliability of Diagnosis of Nonclassical Congenital Adrenal Hyperplasia with Use of LC- MS/ MS in escalating the Diagnostic Capacity of Women with Clinical hyperandrogenism-A Short Communication. International Journal of Reproductive Research. 1(1).

Abstract

Congenital adrenal hyperplasia (CAH) represents a disorder that takes place secondary to the deficiency of the adrenal enzymes, most commonly 21 hydroxylases (21OH) along with the commonest autosomal recessive condition in humans. In case of milder non canonical type (NCCAH), normal quantities are generated at the cost of adrenocorticotropic hormone quantities that in turn results in Clinical hyperandrogenism that gets presented from childhood via early adult period. A remarkable resemblance of signs along with symptoms with those of Polycystic ovary syndrome (PCOS). Hence NCCAH constitutes a significant differential diagnosis, in case of women manifesting acne, hirsutism, menstrual aberrations along with infertility.

Keywords: *diagnosis, in case of women manifesting acne, hirsutism, menstrual aberrations*

Introduction

Congenital adrenal hyperplasia (CAH) represents a disorder that takes place secondary to the deficiency of the adrenal enzymes, most commonly 21 hydroxylases(21OH) along with the commonest autosomal recessive condition in humans [1]. In case of milder non canonical type (NCCAH), normal quantities are generated at the cost of adrenocorticotropic hormone quantities that in turn results in Clinical hyperandrogenism that gets presented from childhood via early adult period [2]. A remarkable resemblance of signs along with symptoms with those of Polycystic ovary syndrome (PCOS). Hence NCCAH constitutes a significant differential diagnosis, in case of women manifesting acne, hirsutism, menstrual aberrations along with infertility [3].

The diagnosis of NCCAH is basically dependent on escalated basal in addition to cosyntropin stimulated quantities of the 21OH substrate 17 hydroxy progesterone (17 OHPg) in addition to 21deoxy cortisol(21DF), both of which are biochemical markers of 21OH deficiency [4,5]. Nevertheless, the present basal in addition to cosyntropin stimulated quantities of the 17 OHPg cut-off values are dependent on old method that is no standardized immunological approach that is considered outdated now [6]. In the ideal conditions the basal blood sample is required to be drawn at the time of early menstrual follicular phase, however in case of irregular along with scanty occasional menstruation it becomes tough to collect accurately timed sample.

In recent decade liquid chromatography, which is coupled with tandem mass spectrometry (LC- MS/ MS) is utilized for quantitative estimation of steroid hormones whose implementation is being done escalating, being advocated in the form of gold standard [7]. LC- MS/ MS provides superior analytic specificity in contrast to immunoassays along with possess the capacity of reproducibility in addition to traceability depending on one accuracy (i.e., international reference materials) that aids in

contrasting the outcomes across approaches, time as well as place. its having multiplexing capacities aids in evaluation of various steroid hormones in a single analytic run for the generation of a single ‘’steroid fingerprint ‘’ that is the other main benefit. Newer reference ranges in addition to cut-off values as well as validation is the need of the hour as appreciated by the Endocrine Society [8] on introducing the newer analytic approaches.

Cosyntropin test gets utilized for the diagnosis of partial enzymes abnormalities in NCCAH. An escalation of serum 17 OHPg>30-45nmol/L(10-15ng/ml)60’ subsequent to Cosyntropin stimulation is believed to be diagnostic for CAH/ NCCAH [9], when immunoassay is used. Ueland et. al [10]. earlier observed that cosyntropin stimulated quantities of 17 OHPg<9nmol>

Corroboration of diagnosis of NCCAH is required with the utilization of CYP21A2 genotyping.The etiology of CAH/ NCCAH syndrome is deletions, macroconversions, microconversions or variants of a pseudogene for the area CYP21A2 on chromosome .Large variations in adrenal steroidprofiling despite the same genotype that highlights the variations amongst the genotype along with phenotype of these diseases[10]. Heterozygous carriers might illustrate mild hyperandrogenism, with this condition being frequent a risk of carriers of transmitting the disease to their offspring. The precise risk correlated with fertility, pregnancy, along with delivery as well a offsprings in Heterozygous carriers is not clear.

Lesser frequent enzymes deficiencies, In the adrenal steroid generation might be thought off by escalated quantities of precursors that are upstream in the steroid pathways. Adrenal steroid profiling might reveal such rare aberrations.

Thus, Ueland et. al [11]. Conducted a **prospective** cohort evaluation of 121 healthy adults along with 65patients assessed for probable NCCAH (Corroboration cohort). The cut-off values for11 steroids as estimated by LC- MS/ MS (basal in addition to cosyntropin stimulated quantities had a definition of 2.5% and 97.5% percentile in healthy individuals. Corroboration cohort was utilized for contrasting. They observed that of the 65PCOS like patients assessed for probable NCCAH,8 (12.5%) was observed besides corroborated genetically with 2 having classic Congenital adrenal hyperplasia. Maximum provision of diagnostic precision for NCCAH was offered by cosyntropin stimulated quantities of the 21OH substrate 17 hydroxy progesterone (17 OHPg) in an area of curve of 0.95(0.89—1.0) with a sensitivity of 86% as well as specificity of 88%. 21hydroxycortisol along with 17 OHPg were escalated in homozygote patients, whereas in heterozygote patients just 17 OHPg(be it basal or stimulated were enhanced .(see figure1 and2)4 patients , In the Corroboration cohort had 17 OHPg above the basal cut-off. Thus, concluding that NCCAH syndrome is common amongst patients where PCOS is speculated along with needs to be taken into account in the form of a routine screening while evaluating for infertility. They advocated serum steroid profiling inclusive of 21deoxy cortisol in addition to Cosyntropin stimulation test with 17 OHPg .As per there data, a 17 OHPg cutoff of 8.5nmol/L(2.8ng/ml)60min subsequent to Cosyntropin stimulation on estimation with LC- MS/ MS, that is significantly lesser in contrast to European Guidelines [11].

Hence this article by Ueland et al. [11], needs to switch the pattern of for assessment of women with speculated PCOS or NCCAH.As outlined before. Ueland et. al. [10], had earlier provided the cut-off values for ruling out the diagnosis of NCCAH with the utilization of LC- MS/ MS, ACTH stimulated 17OHP quantities under 3ng/ml that was a quantity much lesser in contrast to 10-15ng/ml earlier believed to be diagnostic for in Classic Congenital adrenal hyperplasiaor NCCAH on use of immunoassays. In the present study Ueland et al.[11], obtained a reference range regarding besides17OHP quantities, 21deoxy cortisol, 11deoxy cortisol, corticosterone, 17 hydroxy pregnenolone, cortisol, cortisone ,androstenedione, testosterone (T) in addition to Dehydroepiandrosterone sulphate (DHEAS).Of the 63 women with hirsutism, infertility as well as /or atypical manifestation of PCOS were evaluated as Corroboration cohort which were inclusive of 2 cases with Classic CAH along with 8(12.6%)having genetically corroborated NCCAH,3 homozygotes along with 5 heterozygous carriers. None of the remaining 55cases had NCCAH. 17 OHPg proved to be the marker possessing maximum accuracy; nevertheless, stimulated 21deoxy cortisol escalated the diagnostic precision.

Conclusion

Taking into account the outcomes of this publication is significant for reproductive endocrinologists to realize the assay that their local laboratory utilizes for determination of 17 OHPg along with 21deoxy cortisol. In case LC- MS/ MS assay used ,these new standards documented by Ueland et al.[11], for

prevention of under diagnosis of NCCAH. In view of the present commercial investigations do not possess the capacity of differentiating amongst the pathological CYP21A2 gene aberrations along with the pseudogene, hormonal evaluation continues to be significant in the current time where expanding carriers screening is in vogue.

Despite, regenerating the diagnostic criteria of NCCAH is of considerable significance, there might be broader Clinical importance for NCCAH along with PCOS in view of the overlapping manifestations clinically. While PCOS diagnosis is made by excluding NCCAH, NCCAH diagnosis needs particular criteria. By altering these diagnostic criteria changes both groups. Like having 90 cases in one group awa 10 in other, shifting 5 from the group of 90 along with addition of these 5 to the group of 10 would alter both groups. Although depleting 5 from the group of 90 would apparently not cause an appreciable alteration; nevertheless, this alteration might become significant regarding escalation from 10 to15.By altering the classification for NCCAH, our insight for both the disorders would alter, which will be much greater for those diagnosed with NCCAH.

Hence it is mandatory to bother about this NCCAH prototype shift. Precise diagnosis of NCCAH might lead to a more advantageous insight along with treatment for women presenting with hirsutism or Clinical hyperandrogenism [12].

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