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Child Health

Case Report: "Precocious Puberty in a Child with Cortisone Reductase Type 2 Deficiency"

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Abstract **Case Report**

Cortisone reductase type 2 (CRD2) deficiency causes a failure in the regeneration of active cortisol from cortisone via the enzyme 11-beta-hydroxysteroid dehydrogenase (11β-HSD1), a deficiency that stimulates adrenal hyperandrogenism mediated by the increase in adrenocorticotropin (ACTH) causing peripheral precocious puberty in males. We present the first case in our setting of a 5-year-old boy carrying a rare pathogenic variant in *11β-HSD1* gene, who due to prolonged exposure to adrenal androgens developed central precocious puberty (CPP). We describe his evolution after 36 months of management, adding to the very small number of patients reported in the world, and drawing attention to the importance of an early diagnosis.

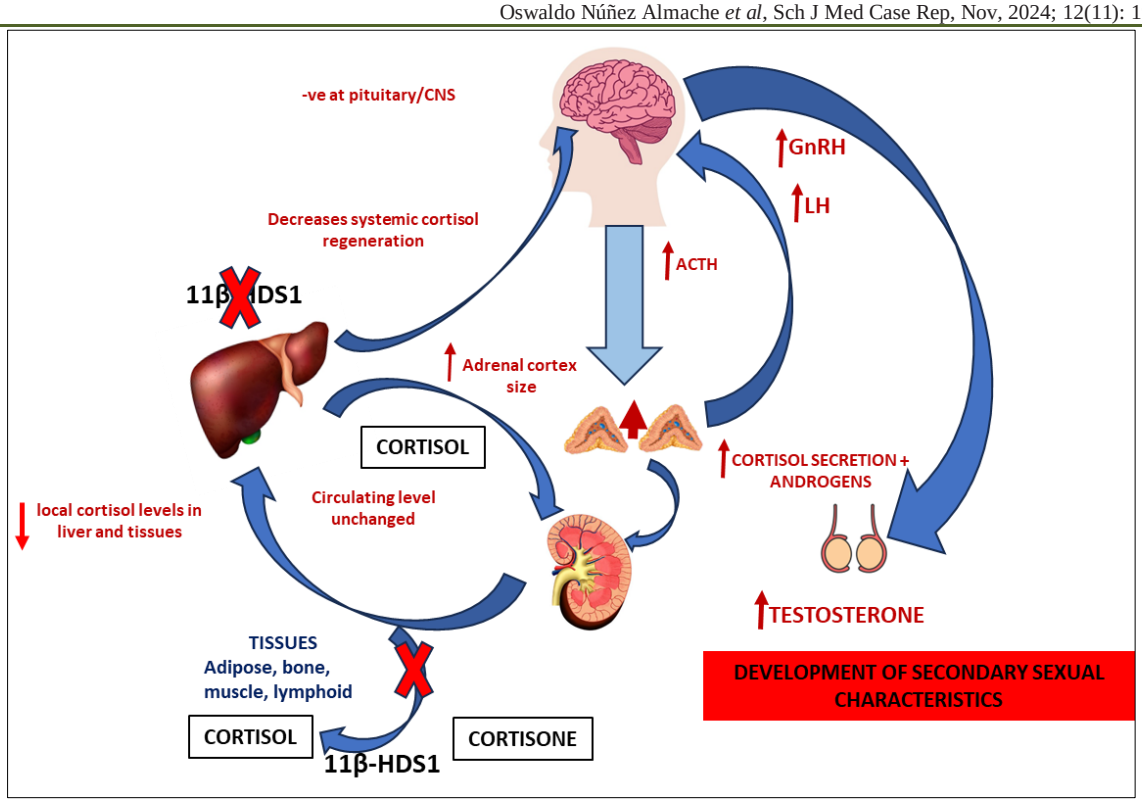
Keywords: Precocious Puberty, Hyperandrogenism, Cortisone Reductase Deficiency.

INTRODUCTION

CRD2 deficiency is characterized by the lack of regeneration of the active glucocorticoid cortisol from cortisone through the action of 11β-HSD1 [1]. CRD2 deficiency was described 40 years ago [2], but it was not until 14 years ago that the first heterozygous mutations (pathogenic variant) in the coding sequence of the *11β-HSD1* gene were described in two boys with hyperandrogenism, pseudopremature puberty and biochemical characteristics indicative of CRD2 deficiency[3]; however, they were unable to establish a metabolic phenotype, but they did establish the need for clinical studies to define the relevance of the genetic finding [3].

When 11β-HSD1 is deficient, the generation of hepatic and/or peripheral cortisol is reduced; to avoid a possible reduction in circulating cortisol, ACTH synthesis will be increased, which in turn will act on the adrenal gland to increase cortisol synthesis and maintain circulating serum levels; however, this process occurs at the expense of adrenal hypertrophy with an undesirable generation of excessive amounts of adrenal androgens [4]. The production of androgens, independent of the activation of the hypothalamus-pituitary-gonadal (H-H-G) axis, leads to peripheral precocious puberty and the delay in its identification leads to overexposure of sexual steroids in the brain and hypothalamus, for a sustained period, causing the activation of the H-H-G axis[5]. The final result will be the development of central precocious puberty, making clinical identification and subsequent management difficult (graph 1).

We present a case of precocious puberty due to CRD2 deficiency due to a mutation of the *11β-HSD1* gene, which is novel due to the lack of information on its population frequency.



Graph 1: The role of 11-HSD1 in abnormal HPA axis activity and subsequent androgenic action on the HPG axis. Adapted from: Cooper MS *et al*., [4]

CASE PRESENTATION

We present the case of a 5 -and- 4/12-year-old boy from Lima, Peru, whose parents complained that since the previous year he had presented accelerated linear growth, increased penile size, presence of pubic hair, hyperactivity, irritability, facial acne, scalp eczema, and a deep voice. He was a third-gestation child, born by vaginal delivery with a weight of 3200 g, a length of 49 cm, and a head circumference of 34.0 cm; with normal psychomotor development; and a history of chickenpox at one year of age. At the age of 2-and-10/12-years-old, his weight was 14 kg and his height was 93 cm. His parents denied a family history of consanguinity; however, a second-degree maternal uncle presented precocious sexual development. The physical examination revealed: weight 29.0 kg (>95p), height 127.8 cm (>95p, +3.04 SD); and BMI 17.7 Kg/m2 (>95p). Target height of 166.75 (± 6.5 cm). Preauricular appendage, sparse facial acne; penis greater than the 90th percentile for age; Tanner stage (G3 and VP3); no "café au lait" macules were evident. In his first evaluation, auxiliary tests showed 17OHP 1.0 ng/mL (VR= 0.03-2.85); Androstenedione < 0.3 ng/mL (VR=0.7 – 3.6); DHEA-S 15.8 ug/dL (VR=6-30); normal thyroid function; LH= 0.3 mIU/mL (VR= 0.7-2.3); FSH= < 0.1 (VR= 0.67-3.3); total testosterone 94 ng/dL (VR= Tanner 3: 15-280), normal renal and adrenal ultrasound, bone age (BA) of 10.6 years; and, normal pituitary CT scan. Subsequent increase in testicular volume and growth velocity suggests a diagnosis of central precocious puberty and starts GnRH analogue (triptorelin) 11.25 mg IM/84 days.

At 6-and-4/12-year-old follow up consult: weight 31 kg and height 134.4 cm (SD +3.18); growth velocity (GV) 8.9 cm/year; and, G3, VP3-4; laboratory: total testosterone 306 ng/dL (VR = 10-30); BHCG = <1.0 mIU/mL (VR = <2.5); Normal transaminases; BA = 12.8 years; normal chest and lumbar spine X-ray; a diagnosis of central precocious puberty triggered by a peripheral cause (testicular or cortisol metabolism) is proposed; complete exome sequencing (WES) analysis is requested and a third-generation nonsteroidal aromatase inhibitor (letrozole) and a nonsteroidal selective antiandrogen (bicalutamide) are added to the treatment.

At 6-and-9/12-year-old consult): weight 35.9 Kg, height 136.8 cm (SD +3.05); VC 5 cm/year; total testosterone 193 ng/d; BA= 14 years. WES: Variant HSD11B1:c.513delG:p. (Ala172Leufs*47), frameshift type, located at position 183 of exon 4/6, confirming the diagnosis of CRD2 deficiency. Dexamethasone was added to the treatment and bicalutamide was removed from the therapeutic regimen; in a later evaluation due to the development of Cushing's signs, dexamethasone was replaced by hydrocortisone and the same regimen was maintained until the time of this report. The anthropometric, hormonal and imaging evolution are shown in Table 1 and Graph 2.

Table 1: Clinical, laboratory and imaging response to treatment of patient with CRD2

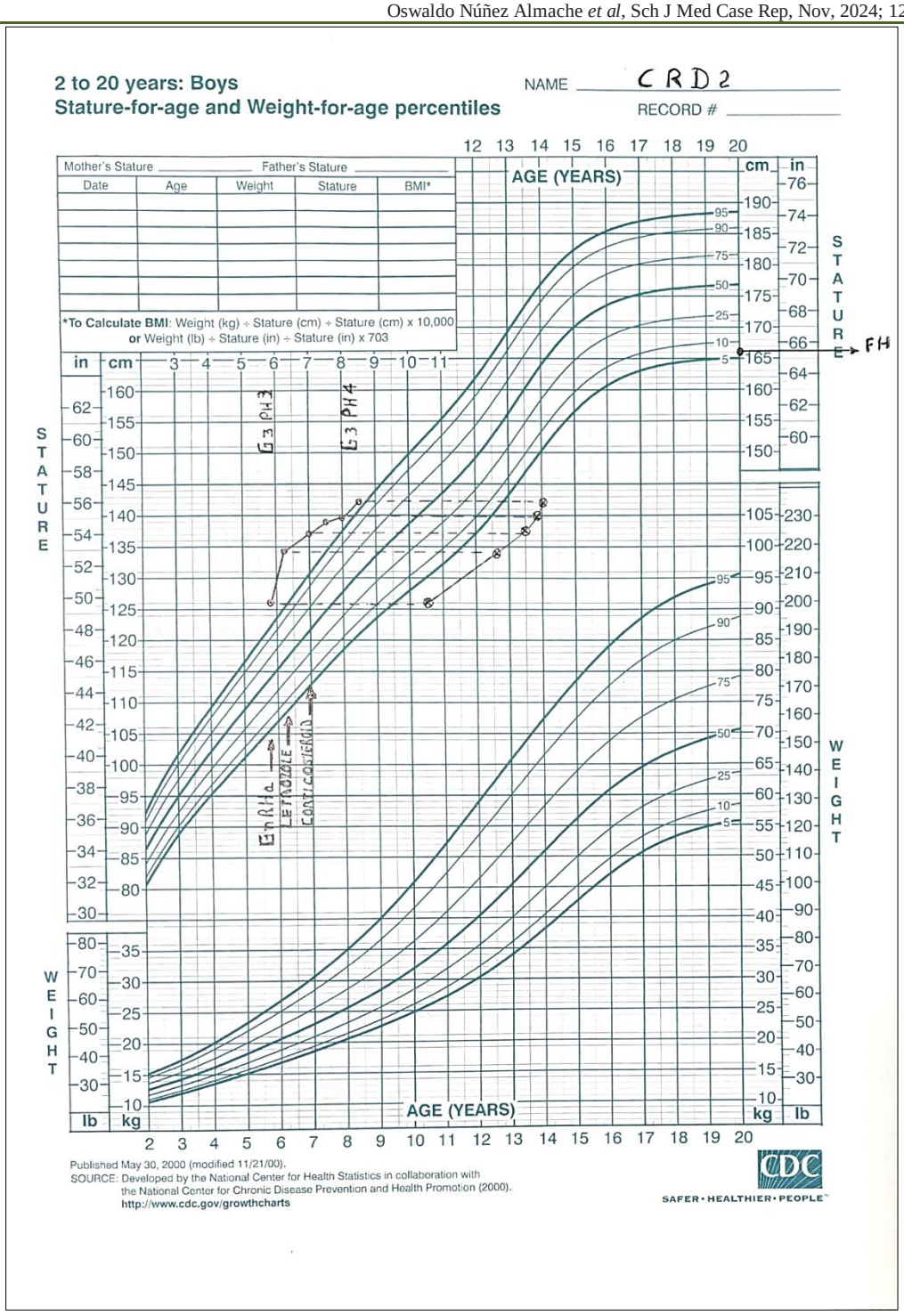
Control (months)	Height (DS)	BMI (Kg/T^2)	Tanner	Bone age (TW2)	LH (mUI/mL)	FSH (mUI/mL)	Testos-terone (ng/dl)	RX Backbone	CT scan Pituitary	Metab. Orina*
0	127.8 (3.04)	17.7 (>95p)	TV=8 ml PH= 3	10.6	0.3	< 0.1	94	-----	Normal	-----
9	134.4 (2.5)	17.2 (95p)	TV=8-10 ml PH=3-4	12.8	-----	-----	306	-----		-----
15**	136.5 (2.29)	19.8 (>95p)	TV=8-10 ml PH= 4	-----	0.31	< 0.1	193	Normal		-----
21	137.3 (2.36)	21.5 (>95p)	TV=10 ml PH= 4	13.8	1.0	0.1	364	-----		---
28	139.5 (2.04)	21.3 (95p)	TV=10 ml PH= 4	14.0	0.6	< 0.3	128	-----		---
34	141.5 (1.65)	22.4 (>95p)	TV=10 ml PH=4	14.2	0.37	<0.1	340	Normal	-----	---

* No urine metabolite measurements were performed.
** Start time of current therapeutic regimen
TV= Testicular volume. PH= pubic hair

DISCUSSION

CRD2 deficiency is a rare cause of peripheral precocious puberty, resulting from a pathogenic variant in the *11β-HSD1* gene. At the time, Lawson *et al*., reported the first 2 cases of heterozygous mutations (pathogenic variants) in the coding sequence of the *11β-HSD1* gene in two patients with hyperandrogenism and peripheral precocious puberty, eleven individuals with CRD2 deficiency had been reported and analyzed for *11β-HSD1* gene pathogenic variants; however, no patient had pathogenic variants in the *11β-HSD1* gene and, consequently, they were called "apparent" cortisone reductase deficiency (ACRD) [6], a situation different from that of our patient who has a true *11β-HSD1* gene pathogenic variant and the same clinical expression as the cases described by Lawson *et al*., [3].

The participation of 11β-HSD1 in various tissues has led authors such as Copper *et al*., to review its physiology and pathophysiology regarding the consequences on the Hypothalamus-Pituitary-Adrenal (HPA) axis, metabolic syndrome and inflammatory response; pointing out that patients with genetic defects in the action of 11β-HSD1 show abnormal responses of the HPA axis, with hyperandrogenism being an important consequence [4]. In this regard, in the case we present, the involvement of the HPA axis is evident; however, no evidence of metabolic syndrome or involvement in the inflammatory response has been observed, but, given the short observation time, its presentation in the future is not ruled out.



Graph 2: Growth curve of the patient during treatment. FH = Familial height or target height. G = Gonad. PH = Pubic hair. GnRHa = GnRH analogue

The very rare pathogenic variant identified in the present case [HSD11B1:c.513delG:p.(Ala172Leufs*47)] is located on chromosome 1 (1q32.2), with phenotype MIM#614662, autosomal dominant inheritance, gene/locus HSD11B1 and is added to those reported by Lawson, contributing to facilitate the genotype-phenotype association as there is no information on its population frequency [7].

Early identification of changes in sexual characteristics in children is necessary to enable early diagnosis. If the patient's changes would have been detected earlier, the differentiation between central precocious puberty (CPP) and peripheral precocious puberty (PPP) could have been established more easily since the gonads would have had prepubertal characteristics; however, the delay caused prolonged exposure to sexual steroids and as indicated in the

literature [8], this led to CPP, especially in our patient with significant bone age advancement.

In the present case, the main therapeutic objectives were to slow the progression of sexual characteristics and bone maturation; to this end, we sought to inhibit the production of adrenal androgens by maintaining adequate levels of cortisol and gonadal androgens with the use of GnRH analogues. On the one hand, in order to inhibit the increased activity of ACTH due to cortisol deficiency, the use of systemic corticosteroids is required, and although the use of dexamethasone has been described [4], in the present case we have observed a good response with the use of hydrocortisone. On the other hand, to block the aromatization of testosterone to estradiol and prevent the action of the latter on the epiphyseal growth cartilage with the use of letrozole, a third-generation non-steroidal aromatase inhibitor, which at a dose of 2.5 mg/PO/day has demonstrated good safety [9]. We consider that, despite the late diagnosis, the stated objectives are being achieved.

With the presentation of this first case of CRD2 deficiency, we wish to highlight: the importance of WES in the identification of this rare pathology, considering it´s vital in patients with CPP with inadequate response to GnRHa; the importance of monitoring growth and development in identifying rapid increases in height or body characteristics; the contribution to the establishment of genotype-phenotype association; and, the proposal of a therapeutic scheme.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and NO text-to-image generators have been used during writing or editing of this manuscript.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the Instituto Nacional de Salud del Niño.

Ethical Approval

As per international standards or university standards written ethical approval has been collected and preserved by the author and the Instituto Nacional de Salud del Niño (Reg. CIEI 196-2024).

Competing Interests: Authors have declared that no competing interests exist.

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