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Case Report

Pseudo Precocious Puberty Caused By Block of 21-Hydroxylase of Late Manifestation

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Abstract: Precocious puberty is defined as the onset of secondary sexual characteristics in children at an unusually early age; When *puberty* begins before age 9 in boys, it is considered *precocious puberty*. Congenital adrenal hyperplasia (CAH) refers to a group of inherited diseases, due mostly to a deficiency in 21 hydroxylase, an enzyme involved in steroid hormone synthesis. All forms of CAH are transmitted in *autosomal* recessive mode. Partial 21-hydroxylase deficiency is most often asymptomatic among male subjects, but may be associated with shorter stature, precocious pubarche and prepubertal gyncomastia. We report the case of a male child with isosexuel pseudo precocious puberty revealing late-onset congenital adrenal hyperplasia with partial 21 hydroxylase deficiency.

Keywords: Pseudo precocious puberty, congenital adrenal hyperplasia, block of 21 hydroxylase.

INTRODUCTION

Non-classic congenital adrenal hyperplasia (NCAH) is an autosomal recessive disorder, caused by a deficiency of one of the enzymes involved in adrenal steroid synthesis: the 21-hydroxylasebeing the most common.

The enzyme deficiency may lead to a mild cortisol deficiency and, subsequently, to a reduced feedback inhibition on the pituitary with increased ACTH production and excess androgen synthesis as the result (New, M. (2007; & FIET, J. *et al.*, 1989). The increased ACTH drives adrenocortical growth and hyperplasia of the adrenals. Accumulation of the steroid precursors before the enzymatic block, as described above or because of enzyme kinetics, and their metabolism in the different androgen pathways result in the increased androgen synthesis and the clinical symptoms.

NCAH typically has 20–70% residual 21-hydroxylase enzyme activity (Tusie-Luna, M. T. *et al.*, 1990) and therefore results in a less severe phenotype than classic CAH.

CASE REPORT

A 9 years old male child born of a first degree consanguineous marriage, no notion of neonatal pain or psychomotor retardation; the family history revealed a 20 years old sister with primary amenorrhea, hirsutism and acne.

At the age of 6 years old, the child is presented with pubic and axillary hair, testicles and penis enlargement, rapid rate of statural growth. The infant also presented some behavioral disorder such as nervousness and school failure.

On clinical examination: HR = 60 bpm, RR = 16 bpm, statural and weight advance: weight = 41 kg (+3SD), length = 149 cm (+3SD) with a target height = 171 cm, BMI = 18,4 kg/m2, ophthalmological examination was normal. Tanner stage: P4, G2 (6ml), penis length = 8 cm (figure1).

Folstein Mini–Mental State Examination with a total of 21/30 showed a vigil patient with slight intellectual deterioration.

Laboratory investigation showed: Bone age at 15 of a chronological age of 9, Risser IV.

FSH = 0,7 (1) ng/ml, LH = 0,5 (1,1)ng/ml, high testosterone level at 2,88 ug/l, *estradiol = 36,1 ng/ml.*

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Baseline cortisol = 3,09 ug/dl, cortisol levels after synacthen test = 3,6 ug/dl, 17 OHP level after synacthen test = 1500 nmol /l (600 pg/l).

Glycemia = 0,78 g/l, natremia = 143 mmol/l, kalemia = 4,6 mmol/l, calcemia = 95 mg/l, albumin = 47 g/l. Prolactin = 12.49, TSH = 0.99 mUi/l, T4 = 14.4 pmol/l.

Beta-hCG = 0, alpha fetoprotein = 17 Ui/ml.

Testicular ultrasound: normal sized testicles, they are ovoid in shape and measure 1,8*0,7*1,98 cm on the right 1,84*0,8*1,79 cm on the left, with a regular outline and a homogeneous echogenicity ; no evidence of mass was seen bilaterally. A cyst-like mass located at the head of the right epididymis was found, measuring 1.5*0.5 cm, thin walled with anechoic contents and no internal septations = Right epididymal cyst.
Bone X-ray *showed no* significant abnormality.
Adrenal gland CT scan: bilateral hyperplasia.

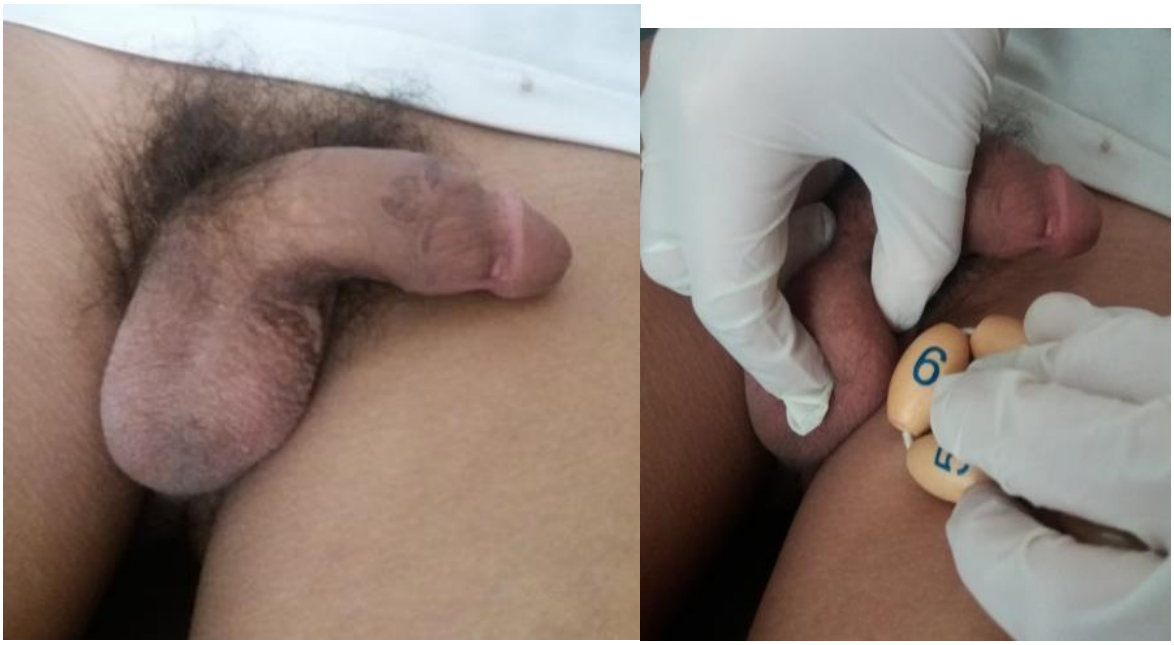

Figure 1: 9 years old male child with a Tanner stage: P4, G2 (6ml), penis length = 8 cm.

The diagnosis of pseudo precocious puberty due to 21 hydroxylase block was established based on the high level of 17-hydroxyprogesterone (17 OHP) after synacthen test at 1500nmol/l (600 pg/l) with cortisol level at 3.6 ug/dl. The same diagnosis was been considered in the case of the sister given the amenorrhea, virilization symptoms and 17 OHP level at 300 pg/l.

This disorder's management was based on glucocorticoid; the patient was put on 20 mg hydrocortisone. The patient and his parents were provided with adequate psychological support and education to improve their knowledge about the disease, its treatment and surveillance modalities (dose variation in case of stress, intramuscular injection of Hydrocortisone hemisuccinate).Genetic counseling was requested as a screening strategy for the family members.

DISCUSSION

21-hydroxylase partial deficiency results in a *decrease cortisol secretion* and an increased ACTH levels leading to adrenal hyperplasia. This *enzyme* deficiency also leads to an *accumulation* of *precursors upstream of the block* (17OHP) and excessive androgen production (New, M. *et al.*, 1981). The diagnosis of « the enzymatic block » is made based on the increasing in 17OHP level (>10ng/ml) after stimulation, and thus leading to a molecular analysis of 21 hydroxylase enzyme and a family screening (parents, siblings, children).

CAH is characterized by its great polymorphism, and besides the so-called "classic" early form, due to a complete or major block and which results in a sexual ambiguity at birth with or without loss of salt, there are forms labeled "Non-classic" that are milder and later onset form of a genetic condition, sometimes even asymptomatic (cryptic), and therefore diagnosed in the context of a family survey (Decourt, J. *et al.*, 1957; & Moran, C. *et al.*, 1998). In these forms - that appear in the literature under many labels- the enzymatic deficiency is only partial and cortisol production may be sufficient at the cost of an adrenal hyperplasia. The clinical presentation is most often that of a para pubertal or post pubertal late virilization (Decourt, J. *et al.*, 1957; & Moran, C. *et al.*, 1998).

In Non-classic congenital adrenal hyperplasia (NCAH)**,** the variations in phenotype depend on the severity of the enzyme deficiency and vary with age and gender. Homozygous patients with two mild mutations have less symptoms compared to those patients who are compound heterozygous with a classical mutation that are seen with early and more severe symptoms (Livadas, S. *et al.*, 2015 ; & Weintrob, N. *et al.*, 2000). .

Late-onset, non-classic CAH is usually diagnosed later on during childhood or adolescence or even in adulthood (Falhammar, H., & Nordenström, A. 2015). The symptoms may develop anytime during childhood or later in life. The degree of symptoms related to androgen excess is variable and related to age (Turcu, A. F., & Auchus, R. J. 2015 ; & Witchel, S.F. 2017).

In children aged younger than 10 years, the most common symptom was premature adrenarche (87%). adolescents and adults typical presenting symptoms are acne, hirsutism, oligo-menorrhea or infertility, While female adolescents may present with severe acne, hirsutism, androgen alopecia, clitoromegaly (11%), irregular menstruation (56%) or even primary amenorrhoea (9%) (Moran, C. *et al.*, 2000 ; & Carmina, E. *et al.*, 2017).

The symptoms at presentation are often indistinguishable from adrenarche, so that the diagnosis requires investigations. Studies in children with premature adrenarche have shown that 4–25% were diagnosed with CAH (Armengaud, J. B. *et al.*, 2009 ; & Skordis, N. *et al.*, 2015).

In adolescence and adulthood, males are diagnosed considerably less often than females, possibly owing to the fact that they are less prone to seek medical attention due to symptoms of androgen excess (Falhammar, H., & Nordenström, A. 2015). Hence, studies in men with NCAH are scarce. In one report on 45 males, 13 (29%) had premature pubarche before 9 years of age or hirsutism or acne (11%) (Livadas, S. *et al.*, 2015; & Wieacker, I. *et al.*, 2015). Gynaecomastia has been reported as the presenting symptom in two male adolescents with NCAH (Wasniewska, M. *et al.*, 2018).

According to literature, the pubertal age and peak velocity have been reported to start earlier in the group of patients with NCAH that had not been treated, by 2.3 years, on average (Weintrob, N. *et al.*, 1997). These patients may enter puberty earlier than the average population which affects final height and results in short stature (Bretones, P. *et al.*, 2016 ; & Bonfig, W. *et al.*, 2009). Individuals with compound heterozygous for both a mild and a severe allele had a significantly shorter final height (Eyal, O. *et al.*, 2013). Age at diagnosis was negatively correlated with final height SDS corrected for parental height; those who had bone age advancement at diagnosis had a significantly shorter corrected height than those who did not (Eyal, O. *et al.*, 2013). When treatment was started before bone age of 9 years, all were able to reach their target height (Weintrob, N. *et al.*, 1997). Hence, an early diagnosis and start of treatment may improve final height. Unfortunately, our patient only consulted at the age of 9, with a very advanced bone age at 15 years and Risser at 4, thus the patient will keep a final short stature.

Our patient was put on hydrocortisone 20 mg divided into two doses daily. Treatment for 21-hydroxylase deficiency with hydrocortisone is essential in early-onset CAH and remains the standard treatment for late-onset; with a low dose of 15 to 20 mg. it is a treatment that is both a substitute for potential cortisol deficiency and a disincentive for ACTH secretion and adrenal hyperplasia. It must therefore be able to lower adrenal androgens secretion and release the gonadotropic axis of the feedbacks exerted by the secretion of adrenal androgens, Growth velocity, weight and bone age are normally employed to guide glucocorticoid treatment in children, while in adults there is no consensus (Eyal, O. *et al.*, 2013).

CONCLUSION

Non classic CAH is a less severe form of CAH in which 20–50% of 21-hydroxylase activity is retained; the diagnosis is based on the high level of 17OHP leading to further investigations.

Late onset NCAH is usually found at puberty, sometimes later in life. When revealed before puberty, the consequences are more consistent with a very important impact on the final height, as well as the psychological state of mind, with the risk of sexual assaults in front of the sexual precocity, hence the important of an adequate psychological support, education and surveillance.

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