A Case of Primary Amenorrhea Presenting with Hypokalemic Paresis and Hypertension

K Sumana[1], KM Suryanarayana[2], Chitra Selvan[3], Nagaraj HK[4]

ABSTRACT

Introduction: 17α hydroxylase deficiency, an autosomal recessive disorder is a rare cause of Congenital Adrenal Hyperplasia (CAH) with an estimated incidence of around 1 in 70,000. Only a very few cases have been reported so far from India.

Case report: We present here a 19 year old patient reared as female, born out of consanguineous marriage who presented with symptoms of sudden onset generalized weakness, quadriparesis, hypertension and with an additional history of primary amenorrhea and lack of secondary sexual characteristics. Basic evaluation revealed severe hypokalemia, metabolic alkalosis and low basal serum cortisol suggesting a likely possibility of 17α hydroxylase deficiency. Further evaluation revealed high FSH (follicle stimulating hormone) and LH (leutinizing hormone) elevated ACTH (adrenocorticotropic hormone) and progesterone, low plasma renin activity (PRA), 17-OH progesterone and testosterone. MRI (magnetic resonance imaging) revealed absent uterus with bilateral atrophic gonads lying at superficial inguinal rings. Blood karyotyping studies showed 46,XY. All these features and investigations were consistent with the diagnosis of CAH due to 17α hydroxylase deficiency in a phenotypically female which was confirmed by genetic analysis. Glucocorticoid and aldosterone antagonist treatment was initiated after potassium correction. As patient wished to continue as female, bilateral gonadectomy was performed after counseling which on histopathology revealed atrophic testes. Estrogen therapy has been initiated for the development of secondary sexual characters.

Conclusion: We suggest considering 17α hydroxylase deficiency in the differential diagnosis in a patient presenting with a triad of symptoms of hypertension, hypokalemia, delayed puberty or primary amenorrhea so that appropriate early therapy can be initiated.

Keywords: 17α Hydroxylase Deficiency, CAH, Hypertension, Delayed Puberty, Hypokalemia

INTRODUCTION

17α-hydroxylase/17,20-lyase deficiency, an autosomal recessive (AR) disorder is an uncommon cause of CAH. The human 17α-hydroxylase (CYP17A1) gene is a single copy gene located on chromosome 10q24.3-q25. This protein is an enzyme expressed in the adrenal cortex and the gonads. Genetic abnormalities in the CYP17A1 gene affect both adrenal and gonadal steroidogenesis. The 17α-hydroxylase/17,20-lyase deficiency leads to impaired production of cortisol and sex steroids with an associated elevation of plasma ACTH and overproduction of mineralocorticoids, other than aldosterone, resulting in hypertension, hypokalemia, and bilateral adrenal hyperplasia. In addition, due to deficiency of sex steroids, males present with an undervirilized state (female phenotype) or ambiguous genitalia at birth and females present with delayed puberty. Only a few cases have been reported from India. We report here one such case of 17α-hydroxylase deficiency in a 46,XY phenotypic female which had been confirmed by genetic analysis.

CASE REPORT

A nineteen years old phenotypically female patient with parental consanguinity reported to emergency with severe generalized weakness, quadriparesis and hypertension. Neither she had attained menarche nor had any secondary sexual characters. She was 163.5 cm tall, weighing 55 kg, BP of 150/110 mm Hg with grade 3 power in all muscle groups, generalized hyporeflexia and with A1B1P1 Tanner's staging, infantile female external genitalia and blind vagina (figure 1). Investigations revealed hypokalemia (serum k+:1.5 mEq/L), metabolic alkalosis (pH : 7.5, HCO_3^- : 30 mmol/L) and low serum cortisol (4.25 µg/dL). Values of other investigations outlined as in table 1. Uterus and gonads were not visualized on ultrasonogram and karyotyping study showed 46,XY. MRI revealed both gonads at superficial inguinal rings. Genetic studies revealed a homozygous missense mutation in exon 6 of CYP17A1 gene [variation: chr10:104592323G>A c.1084C>T p.Arg362Cys in the redox partner interaction domain (347-447 amino acids)].

Patient became asymptomatic after treatment with intravenous and oral potassium, spironolactone-100mg (potassium sparing diuretic to control hypertension) and prednisolone – 10 + 5mg. In view of 46 XY genotype, after due counseling, as per her wish to continue as a female, prophylactic bilateral gonadectomy (figure 1) was done, as gonads left unattended could turn malignant and can present as malignant mixed germ cell tumor[1]. On discharge she was prescribed dexamethasone 0.5mg in the night, spironolactone 100mg and conjugated equine estrogen 0.625mg and advised further follow up for titration of medication.

DISCUSSION

17α-hydroxylase deficiency, an uncommon cause of CAH with AR inheritance was first described by Biglieri et al. The estimated incidence is around 1 in 70,000[2]. It occurs due to mutations in the CYP17A1 gene which encodes p450c17, a microsomal enzyme located on chromosome 10q24-q25 and mediates both

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Hormonal invesigations	Result	Reference interval
Serum Testosterone (ng/dL)	<2.5	65-800
Serum FSH (mIU/mL)	77.15	1.4 – 15.4
Serum LH (mIU/mL)	33.38	1.2 – 7.8
Serum 17-OHProgesterone (ng/mL)	0.17	0.6 – 3.42
Serum Progesterone (ng/mL)	2.68	1.2 -3
Plasma ACTH (pg/mL)	44.6	0-46
PRA (ng/mL per hour)	0.59	Upright:1.6 – 7.4
Serum Aldosterone (ng/dL)	22.3	Upright: 2.52- 39.2

Table-1: Showing results of hormonal investigations

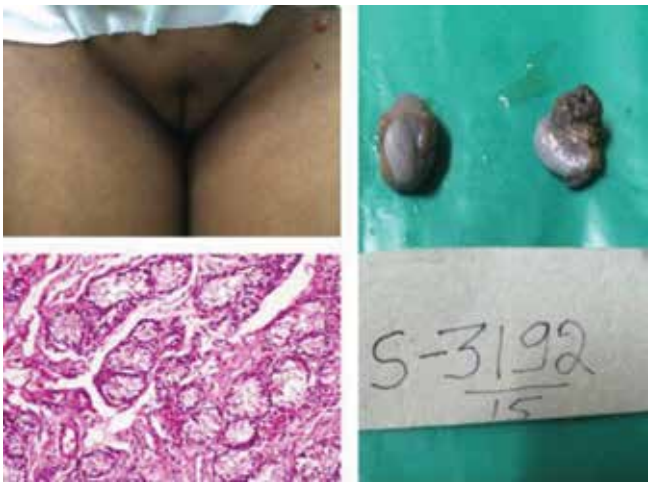

Figure-1: Showing infantile female external genitalia, Gross anatomy of removed gonads, Histopath at 40x showing immature seminiferous tubules

17α-hydroxylase and 17,20-lyase activities. 17α-hydroxylase catalyzesconversionofpregnenolonetо17-hydroxypregnenolone and progesterone to 17-hydroxyprogesterone. The 17,20-lyase action catalyzes conversion of 17-hydroxypregnenolone to DHEA (dehydroepiandrosterone) and 17-hydroxyprogesterone to androstenedione (figure 2). Defects in CYP17A1 gene can rarely cause isolated 17,20-lyase deficiency and more commonly combined 17αhydroxylase/17,20lyase deficiency. Most mutations result in the loss of both catalytic activities and cause impaired gonadal and adrenal steroidogenesis with mineralocorticoid excess. The severity of the phenotype variations depend upon whether the activities of these enzymes are completely or partially lost and the type and localization of the mutation in the CYP17A1 gene. The classic phenotype of complete combined 17α-hydroxylase/17,20-lyase deficiency consists of phenotypic female (46,XX or underandrogenized 46,XY) presenting with absence of secondary sexual characteristics (hypergonadotropic hypogonadism) at puberty and is associated with low renin hypertension and hypokalemic alkalosis. It is one of the types of CAH that is associated with hypertension and the other being 11βhydroxylase deficiency[3]. A defect in 17α-hydroxylation in the adrenal cortex and gonads results in impaired synthesis of 17-hydroxyprogesterone and 17-hydroxypregnenolone and therefore of cortisol, androgens and estrogens. Decreased cortisol synthesis causes increased ACTH production which results in excessive secretion of steroids proximal to the block, like 11deoxy-corticosterone (DOC), corticosterone, and 18-hydroxycorticosterone. Excess DOC secretion leads to sodium retention, hypertension,

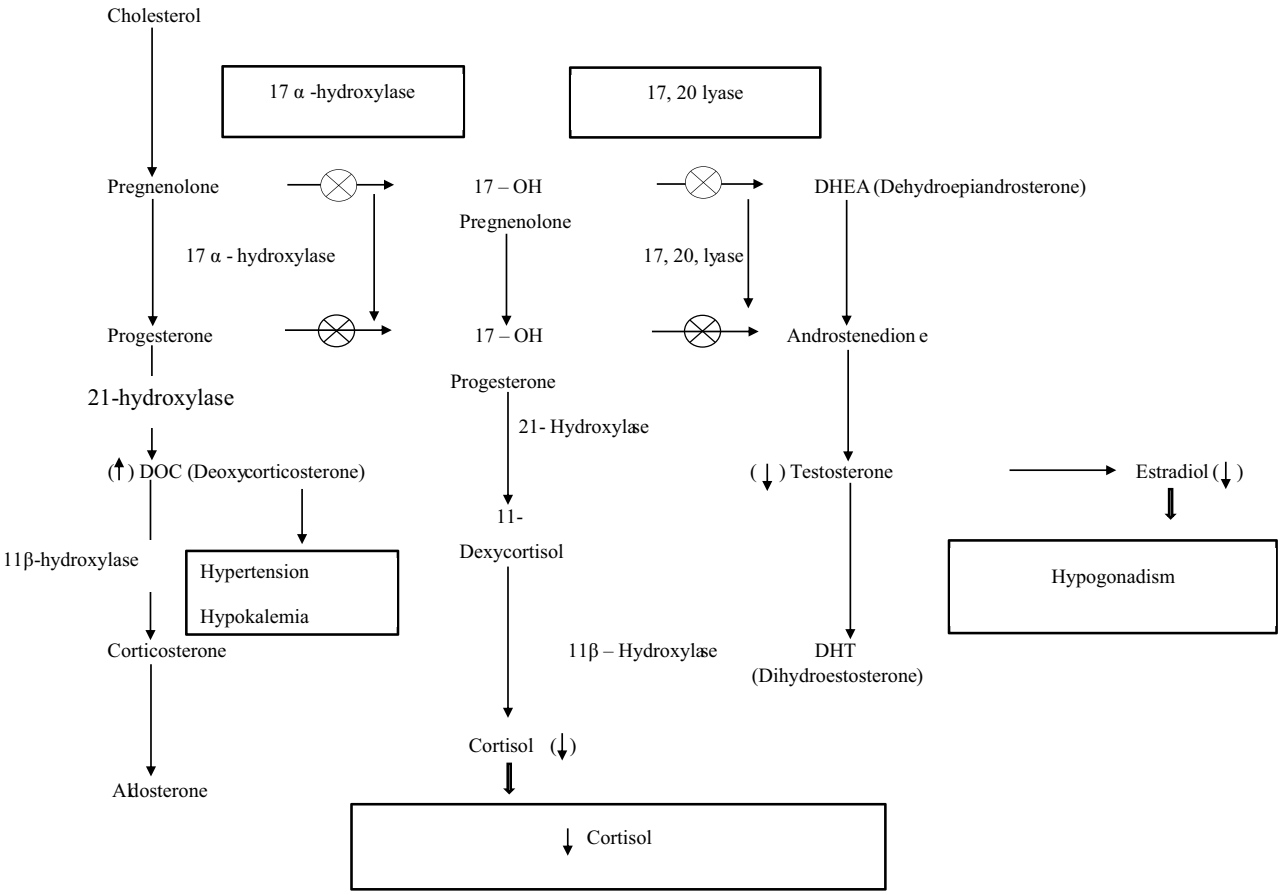

Figure-2: Showing steroidogenesis pathway and deficiencies that occur with 17 hydroxylase deficiency

kalliuresis, hypokalemic alkalosis and suppression of renin angiotensin system. Aldosterone levels are usually suppressed or normal due to the salt retaining and volume expanding effects of the high levels of DOC, with consequent transcriptional downregulation of aldosterone synthase, but sometimes aldosterone level could be increased. Inadequately treated or untreated CAH can rarely transform to adrenal cortical adenoma or carcinoma due to long-term overproduction of ACTH. Corticosterone in high concentrations prevents the signs and symptoms of cortisol deficiency like hypoglycemia due to its weak glucocorticoid activity. Elevated ACTH levels can lead to hyperpigmentation. With no exposure to testosterone in utero, patients with 17α-hydroxylase deficiency have female external genitalia regardless of male (XY) or female (XX) karyotype.

XX individuals have uterus and ovaries with atretic follicles and they do not develop any secondary sexual characteristics, nor attain menarche. However spontaneous menarche and menstrual cycles have been reported with incomplete 17α-hydroxylase deficiency and assisted reproductive techniques have been tried with poor results, although recently viable pregnancy in a female with compound heterozygous mutation has been reported[4]. XY individuals do not have uterus or fallopian tubes as the anti mullerian hormone produced by testes in utero causes their regression. Prostrate, seminal vesicles and vas deferens are usually absent due to lack of testosterone.

The constellation of features like hypertension, hypokalemic alkalosis, decreased testosterone and estradiol, increased progesterone, corticosterone, deoxycorticosterone, low PRA (plasma renin activity) and high FSH and LH levels usually suggest the diagnosis of 17hydroxylase deficiency. Definitive diagnosis is established by molecular analysis, as in this case.

Replacement with minimal physiological doses of glucocorticoids suppresses ACTH driven DOC excess and thereby normalizes potassium level and controls hypertension. As our patient initially presented with severe hypokalemia with associated quadriparesis, she was treated with iv potassium followed by oral potassium and also with spironolactone 100 mg/day (aldosterone antagonist) for the control of hypertension. Usually all patients are raised as girls regardless of genotypic sex, (with rare exceptions in XY patients with partial deficiencies and ambiguous genitalia). As our patient was phenotypic female (but 46,XY) and wished to continue as female, bilateral gonadectomy was performed. Sex steroids appropriate for phenotypic sex of the patient should be started at the expected time of puberty. Genotypic males rearing as females usually require estrogen replacement therapy to promote the development of breasts and to prevent osteoporosis. Our patient was started with 0.625 mg of conjugated equine estrogen. In case of phenotypic and gentotypic females, initially estrogen therapy is given and followed by sequential addition of medroxyprogesterone to promote withdrawal bleeding.

CONCLUSION

We suggest considering 17hydroxylase deficiency in the differential diagnosis of primary amenorrhea especially when associated with hypertension and hypokalemia. However, normally it is diagnosed during early adulthood when patients present with a hypokalemic episode. It is important to record BP and measure serum potassium in all patients being evaluated for delayed puberty with primary amenorrhea so as to arrive at an early correct diagnosis and institute appropriate therapy and to prevent complications of severe hypokalemia, and uncontrolled hypertension. This is especially so in a case of 46,XY, so that sex rearing can be decided early in life.

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