17 alpha-hydroxylase deficiency as a cause of gonadal dysgenesis

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ABSTRACT

Introduction: Gonadal dysgenesis is a rare disorder caused by congenital adrenal hyperplasia due to a defect in cortisol and sexual steroid biosynthesis that results in an excess of mineralocorticoids, hypertension with hypokalemia, and sexual abnormalities such as pseudohermaphroditism in men and sexual infantilism in women. Its incidence is 1:50,000. It has an autosomal recessive pattern and is caused by mutations in the cytochrome gene P450c17 (CYP17) that mediates 17 alpha-hydroxylase and 17,20-lyase activity.

Objective: To report the experience at the Hospital General de México with gonadal dysgenesis secondary to 17alpha-hydroxylase deficiency, along with its diagnostic methodology, clinical symptoms, and management.

Conclusions: 17 alpha-hydroxylase deficiency is a rare condition and should be suspected in patients with hypokalemic hypertension and delay in the development of secondary sexual characteristics in order to implement appropriate therapy. It is usually managed by hormonal replacement with estrogens for the induction of secondary sexual characteristics. Prophylactic gonadectomy is indicated in genetic males due to the risk of malignization.

Key words: 17alpha-hydroxylase deficiency, gonadal dysgenesis, Mexico.

RESUMEN

Introducción: La disgenesia gonadal es un trastorno raro, causado por una hiperplasia suprarrenal congénita por defecto en la biosíntesis del cortisol y esteroides sexuales que resultan en exceso de mineralocorticoides, hipertensión hipokalémica y anormalidades sexuales, como seudohermafroditismo en hombres e infantilismo sexual en mujeres. Incidencia de 1:50 000. Tiene patrón autosómico recesivo y es causado por mutaciones en el gen de la citocromo P450c17 (CYP17) que media la actividad de la 17 alfa hidroxilasa y la 17,20-Liasa.

Objetivo: Informar la experiencia en el Hospital General de México sobre la disgenesia gonadal secundaria a deficiencia de 17α-hidroxilasa, su metodología diagnóstica, cuadro clínico y manejo empleado.

Conclusión: La deficiencia de 17 α-hidroxilasa es una condición rara que debe ser sospechada en pacientes con hipertensión hipokalémica y retardo en el desarrollo de los caracteres sexuales secundarios para lo que debe implementarse una terapia apropiada. Se suele manejar con reemplazo hormonal: estrógenos para la inducción de los caracteres sexuales secundarios. La gonadectomía profiláctica está indicada en hombres genéticos por el riesgo de malignizarse.

Palabras clave: Deficiencia de 17 α-hidroxilasa, disgenesia gonadal, México.
INTRODUCTION

Gonadal dysgenesis is a rare form of congenital adrenal hyperplasia with defect in cortisol and sexual steroid biosynthesis resulting in excess mineralocorticoids, high blood pressure, hypokalemia, and sexual abnormalities such as pseudohermaphroditism in men and sexual infantilism in women. Incidence is from 1:50,000 to 1:100,000 in newborns. There is a recessive autosomal pattern in 1% of cases caused by mutations in the cytochrome P450c17 (CYP17) gene found in the 10q24.3 chromosome. It is made up of eight exons that are expressed in the adrenal cortex, ovaries and testes. It also mediates 17 alpha hydroxylase and 17,20-lyase activity. It was first described in 1966 by Biglieri et al in a genetic female with high blood pressure, hypokalemia, and delayed puberty. In 1970 a genetic male presenting with pseudohermaphroditism was reported. There are little more than 150 cases reported in the literature.

The objective of this article is to report two cases of gonadal dysgenesis secondary to 17 alpha-hydroxylase deficiency, its clinical symptoms, diagnostic methodology, and management.

CASE PRESENTATION 1

Patient is an 18-year-old female with no important past medical history. She presented with primary amenorrhea; no pregnancies. Patient had never engaged in sexual activity. Her illness began three days prior to initial examination with bilateral sensation of weakness and heaviness of the lower limbs, stabbing pain principally in the thighs that increased with exercise, making walking impossible. She presented with tinnitus, predominantly frontal stabbing headache, and 2 episodes of epistaxis. Blood pressure was 170/80 upon examination. Patient had normal cardiopulmonary function, absence of breast development (Tanner I), no axillary hair, no pubic hair on external genitals, no abdominal alterations (Figure 1); vaginal examination was not done (virgin patient). Lower limbs presented with increased muscle tone, diminished strength, pain upon palpation of muscle groups, conserved tendon reflexes, negative Babinski, and conserved joint movement. Laboratory tests were in normal ranges with the exception of lactase dehydrogenase (LDH) 1213, potassium (K) 2.1, arterial blood gas (ABG) with pH 7.6, pCO₂ 36.2, pO₂ 58.5, HCO₃ 36.6, SO₂ 93.3%. Urinalysis reported density of 1.001 and 12-15 leukocytes per field. The remaining tests were normal.

Electrocardiogram: sinus rhythm, heart rate 60 beats per minute, left axis deviation, inverted T-wave in precordial leads. Hormone profile: luteinizing hormone (LH) 41.1, follicle-stimulating hormone (FSH) 67.9, prolactin 24.4, estradiol 10, adrenocorticotropic hormone (ACTH) 53, progesterone 4.1, testosterone 10.0, normal thyroid hormones. Magnetic resonance showed gonadal dysgenesis, bilateral adrenal hyperplasia, probable testicular feminization, absence of uterus and ovaries, and metabolic alteration in medulla of long bone (Figures 2 and 3). After evaluation in the Department of Genetics, polymerase chain reaction (PCR) typification for Y chromosome was suggested, finding patient to be genotypically XY. Study was complemented with syndromic diagnoses of hypogonadism, hyperaldosteronism, hypokalemia, and high blood pressure with diagnosis of 17 alpha-hydroxylase deficiency. Orchiectomy of 1 x 1 cm preperitoneal bilateral testicular remnants in deep inguinal orifice (Figures 4 and 5) was carried out together with treatment based on nifedipine, enalapril, spironolactone, and potassium salts. Finally, patient was given breast implants.

CASE PRESENTATION 2

Patient is a 15-year-old female with no important past medical history. She presented with primary amenorrhea; no pregnancies. She stated she had not begun sexual activity. Her disease began at birth with mother noting genital ambiguity but not giving it importance. Growth and development were apparently without alterations until patient presented with bronchial pneumonia at 2 years of age. She was interviewed and evaluated at a general hospital before being referred to the authors’ hospital.

Upon physical examination vital signs were normal. Phenotypically, biological age was greater
than chronological age without characteristic facies. There was important facial acne, large nose, neck with no alterations, normal anterior and posterior thorax, no breast growth, and abdomen with no alterations. Patient presented with genitals with android pubic hair distribution, both testes were identified at the superficial inguinal ring level. Testes were approximately 4 x 3 x 2 cm with well-defined epididymides and identifiable vas deferens. Penis was found and was approximately 3.5 x 1 x 1 cm. Corpora cavernosa were identified, meatus was not identified. Labia majora were identified but not labia minora. The equivalent of the introitus was found and canalized, observing urine exit. There were no other alterations apparent in the rest of the physical examination. Laboratory tests were normal. Ultrasound showed absence of uterus and ovaries, corroborating testes in inguinal canal. Testosterone: 2.16 ng/mL (H:0.2-0.8  M:3.7-9.5); dihydrotestosterone
or abnormal aldosterone production. Diagnosis is progesterone level is altered. Many patients have low Canadian Mennonites and Brazilians. Physiologically, a greater prevalence in certain ethnic groups such as mineralocorticoid synthesis. Its function is to hydroxylate pregnenolone and progesterone in position 17 and at the same time it acts as a lyase, breaking the bond between carbon 17 and 20, thus allowing for sexual androgen synthesis. When there is 17alpha-hydroxylase deficiency, cortisol masculinization of the external genitals to take place. When there is 17alpha-hydroxylase and 17,20-lyase activity. Enzymatic activity analysis shows that more than 25% of normal activity is necessary in order for normal masculinization of the external genitals to take place. When there is 17alpha-hydroxylase deficiency, cortisol secretion reduction causes an increase in ACTH production resulting in overproduction of 17-deoxy steroids by the adrenal cortex. Serum progesterone is a diagnostic marker. After ACTH stimulation the progesterone level is altered. Many patients have low or abnormal aldosterone production. Diagnosis is usually made at puberty with the presence of high blood pressure (although 10-15% of patients can have normal blood pressure), hypokalemia (with neuromuscular and intestinal symptoms), and hypergonadotrophic hypogonadism (primary amenorrhea and absence of secondary sexual characteristics in women and pseudohermaphroditism in men). There are usually no symptoms of adrenal insufficiency. The patient in Case Presentation 1 had the characteristic symptoms but the patient in Case Presentation 2 had no symptomatology. Female patients have external female genitals at birth but there is no sexual development at puberty. Male patients have external female genitals, a blind vaginal canal, and absence of uterus and Fallopian tubes, as observed in the cases presented here. Diagnosis can be established based on elevated levels of 17-deoxy-C21 steroids, progesterone, pregnenolone, serum deoxycorticosterone (DOC) and corticosterone and an increase in urinary excretion of their metabolites by means of radioimmunoassay (RIA) and chromatography/spectroscopy.

High blood pressure is generally resolved with glucocorticoids but persists if diagnosis is erroneous. Mineralocorticoid antagonists such as spironolactone can aid in better control of arterial pressure. Adding a calcium channel blocker is effective if hypertension persists. High blood pressure and hypokalemia in the first patient presented here were resolved after glucocorticoid replacement and treatment with potassium-saving diuretics. In these cases sexual steroids should be added to compensate deficit secondary to low gonadal production. In the two cases presented here sexual hormone replacement was carried out to induce sexual development. Genital surgery is one of the most controversial procedures in intersex management. It tends to be corrective surgery to resect or create reproductive organs appropriate for the sex of the child. Bilateral gonadectomy is recommended as soon as possible given that the defective gonad has a high malignization potential (approximately one third of patients develop gonadoblastoma between the first and fourth decades of life). For this reason prophylactic gonadectomy was performed on the patient presented in Case 1. Correct sex determination is important with respect to both treatment and emotional well-being of the child.

**DISCUSSION**

Congenital adrenal hyperplasia is a disorder resulting from deficiency of one of the five enzymes required for cortisol synthesis in the adrenal cortex. The most common form of the disease is the classic form due to 21 hydroxylase deficiency followed by 11 hydroxylase deficiency and the rarer 17 hydroxylase deficiency. Gonadal dysgenesis is a rare form of congenital adrenal hyperplasia with defect in cortisol and sexual steroid biosynthesis resulting in excess mineralocorticoids, hypokalemic hypertension, and sexual abnormalities. It presents in genetic males with complete female phenotype or less frequently with ambiguous external genitals. It is correlated with enzymatic activity and phenotypic variability or less frequently with ambiguous external genitals. There is a greater prevalence in certain ethnic groups such as Canadian Mennonites and Brazilians. Physiologically, adrenal steroidogenesis is a complex and sequential process involving a series of enzymes that act on cholesterol, producing a wide variety of steroids that are essential for life. The first step in the biosynthesis of all the adrenal hormones is cholesterol conversion into pregnenolone through cytochrome P450scc action. This enzyme is the point of departure for glucocorticoid and mineralocorticoid synthesis. Its function is to hydroxylate pregnenolone and progesterone in position 17 and at the same time it acts as a lyase, breaking the bond between carbon 17 and 20, thus allowing for sexual androgen synthesis.

Congenital adrenal hyperplasia has a recessive autosomal pattern and is caused by mutations in the cytochrome P450c17 (CYP17) gene that mediates 17 alpha-hydroxylase and 17,20-lyase activity. Enzymatic activity analysis shows that more than 25% of normal activity is necessary in order for normal masculinization of the external genitals to take place. When there is 17alpha-hydroxylase deficiency, cortisol secretion reduction causes an increase in ACTH production resulting in overproduction of 17-deoxy steroids by the adrenal cortex. Serum progesterone is a diagnostic marker. After ACTH stimulation the progesterone level is altered. Many patients have low or abnormal aldosterone production. Diagnosis is usually made at puberty with the presence of high blood pressure (although 10-15% of patients can have normal blood pressure), hypokalemia (with neuromuscular and intestinal symptoms), and hypergonadotrophic hypogonadism (primary amenorrhea and absence of secondary sexual characteristics in women and pseudohermaphroditism in men). There are usually no symptoms of adrenal insufficiency. The patient in Case Presentation 1 had the characteristic symptoms but the patient in Case Presentation 2 had no symptomatology. Female patients have external female genitals at birth but there is no sexual development at puberty. Male patients have external female genitals, a blind vaginal canal, and absence of uterus and Fallopian tubes, as observed in the cases presented here. Diagnosis can be established based on elevated levels of 17-deoxy-C21 steroids, progesterone, pregnenolone, serum deoxycorticosterone (DOC) and corticosterone and an increase in urinary excretion of their metabolites by means of radioimmunoassay (RIA) and chromatography/spectroscopy.

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**CONCLUSION**

Newborns presenting with abnormal external genital development should be diagnosed early to minimize medical, psychological, and social complications. 17 alpha-hydroxylase deficiency is a rare condition that should be suspected in patients presenting with hypokalemic hypertension and delayed development of secondary sexual characteristics so that appropriate therapy is implemented. Female sex was assigned to the Case Presentation 1 patient and she was managed with...
estrogen hormone replacement to induce secondary sexual characteristics. Prophylactic gonadectomy is indicated in genetic men with 17 alpha-hydroxylase deficiency due to malignization risk. Gonads can be intra-abdominal, located in the inguinal canal or labioscrotal fold.

BIBLIOGRAPHY