17 Alpha-Hydroxylase/17,20-Lyase Deficiency

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17 alpha(α)-hydroxylase/17,20-lyase deficiency is a condition that affects the function of certain hormone-producing glands called the gonads (ovaries in females and testes in males) and the adrenal glands. The gonads direct sexual development before birth and during puberty and are important for reproduction. The adrenal glands, which are located on top of the kidneys, regulate the production of certain hormones, including those that control salt levels in the body. People with 17α-hydroxylase/17,20-lyase deficiency have an imbalance of many of the hormones that are made in these glands. 17α-hydroxylase/17,20-lyase deficiency is one of a group of disorders, known as congenital adrenal hyperplasias, that impair hormone production and disrupt sexual development and maturation.

genetic conditions

1. Introduction

Hormone imbalances lead to the characteristic signs and symptoms of 17α-hydroxylase/17,20-lyase deficiency, which include high blood pressure (hypertension), low levels of potassium in the blood (hypokalemia), and abnormal sexual development. The severity of the features varies. Two forms of the condition are recognized: complete 17α-hydroxylase/17,20-lyase deficiency, which is more severe, and partial 17α-hydroxylase/17,20-lyase deficiency, which is typically less so.

Males and females are affected by disruptions to sexual development differently. Females (who have two X chromosomes) with 17α-hydroxylase/17,20-lyase deficiency are born with normal external female genitalia; however, the internal reproductive organs, including the uterus and ovaries, may be underdeveloped. Women with complete 17α-hydroxylase/17,20-lyase deficiency do not develop secondary sex characteristics, such as breasts and pubic hair, and do not menstruate (amenorrhea). Women with partial 17α-hydroxylase/17,20-lyase deficiency may develop some secondary sex characteristics; menstruation is typically irregular or absent. Either form of the disorder results in an inability to conceive a baby (infertility).

In affected individuals who are chromosomally male (having an X and a Y chromosome), problems with sexual development lead to abnormalities of the external genitalia. The most severely affected are born with characteristically female external genitalia and are generally raised as females. However, because they do not have female internal reproductive organs, these individuals have amenorrhea and do not develop female secondary sex characteristics. These individuals have testes, but they are abnormally located in the abdomen (undescended). Sometimes, complete 17α-hydroxylase/17,20-lyase deficiency leads to external genitalia that do

not look clearly male or clearly female (ambiguous genitalia). Males with partial 17α-hydroxylase/17,20-lyase deficiency usually have abnormal male genitalia, such as a small penis (micropenis), the opening of the urethra on the underside of the penis (hypospadias), or a scrotum divided into two lobes (bifid scrotum). Males with either complete or partial 17α-hydroxylase/17,20-lyase deficiency are also infertile.

2. Frequency

17α-hydroxylase/17,20-lyase deficiency accounts for about 1 percent of congenital adrenal hyperplasia cases. It is estimated to occur in 1 in 1 million people worldwide.

3. Causes

17α-hydroxylase/17,20-lyase deficiency is caused by mutations in the *CYP17A1* gene. The protein produced from this gene is involved in the formation of steroid hormones. This group of hormones includes sex hormones such as testosterone and estrogen, which are needed for normal sexual development and reproduction; mineralocorticoids, which help regulate the body's salt and water balance; and glucocorticoids, which are involved in maintaining blood sugar levels and regulating the body's response to stress.

Steroid hormones are produced through a series of chemical reactions. The CYP17A1 enzyme performs two important reactions in this process. The enzyme has 17 alpha(α)-hydroxylase activity, which is important for production of glucocorticoids and sex hormones. CYP17A1 also has 17,20-lyase activity, which is integral to the production of sex hormones.

17α-hydroxylase/17,20-lyase deficiency results from a shortage (deficiency) of both enzyme activities. The amount of remaining enzyme activity determines whether a person will have the complete or partial form of the disorder. Individuals with the complete form have *CYP17A1* gene mutations that result in the production of an enzyme with very little or no 17α-hydroxylase and 17,20-lyase activity. People with the partial form of this condition have *CYP17A1* gene mutations that allow some enzyme activity, although at reduced levels.

With little or no 17α-hydroxylase activity, production of glucocorticoids is impaired, and instead, mineralocorticoids are produced. An excess of these salt-regulating hormones leads to hypertension and hypokalemia.

Loss of 17,20-lyase activity impairs sex hormone production. Shortage of these hormones disrupts development of the reproductive system and impairs the onset of puberty in males and females with 17α-hydroxylase/17,20-lyase deficiency.

3.1. The gene associated with 17 alpha-hydroxylase/17,20-lyase deficiency

- CYP17A1

4. Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

5. Other Names for This Condition

- 17-alpha-hydroxylase deficiency
- 17-alpha-hydroxylase-deficient congenital adrenal hyperplasia
- adrenal hyperplasia V
- combined 17 alpha-hydroxylase/17,20-lyase deficiency
- congenital adrenal hyperplasia due to 17-alpha-hydroxylase deficiency
- congenital adrenal hyperplasia type 5
- deficiency of steroid 17-alpha-monooxygenase

References

1. Kim YM, Kang M, Choi JH, Lee BH, Kim GH, Ohn JH, Kim SY, Park MS, Yoo HW. Areview of the literature on common CYP17A1 mutations in adults with17-hydroxylase/17,20-lyase deficiency, a case series of such mutations amongKoreans and functional characteristics of a novel mutation. Metabolism. 2014Jan;63(1):42-9. doi: 10.1016/j.metabol.2013.08.015.
2. Marsh CA, Auchus RJ. Fertility in patients with genetic deficiencies ofcytochrome P450c17 (CYP17A1): combined 17-hydroxylase/17,20-lyase deficiency and isolated 17,20-lyase deficiency. Fertil Steril. 2014 Feb;101(2):317-22. doi:10.1016/j.fertnstert.2013.11.011. Review.
3. Miller WL. The syndrome of 17,20 lyase deficiency. J Clin Endocrinol Metab.2012 Jan;97(1):59-67. doi: 10.1210/jc.2011-2161.
4. Rosa S, Steigert M, Lang-Muritano M, l'Allemand D, Schoenle EJ, Biason-Lauber A. Clinical, genetic and functional characteristics of three novel CYP17A1mutations causing combined 17alpha-hydroxylase/17,20-lyase deficiency. Horm ResPaediatr. 2010;73(3):198-204. doi: 10.1159/000284362.