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Late onset Congenital Adrenal Hyperplasia

(Non classic CAH)

What is late onset CAH?

Late onset or non-classic congenital adrenal hyperplasia is an uncommon genetic disorder that is frequently due to mutations in 21-hydroxylase gene leading to reduced levels of the 21 hydroxylase enzyme. Late onset CAH due to deficiencies or mutations in other genes such as 11 β -hydroxylase (*CYP11B1*) and 3 β -hydroxysteroid dehydrogenase (*HSD3B2*) are extremely rare.

Late onset CAH should not be confused with the more serious and early onset condition of newborns called congenital adrenal hyperplasia (CAH) or classic CAH. Women with late onset CAH develop signs and symptoms of the condition later in life as opposed to the first few weeks and months of life.

What is the cause of Late onset CAH?

One of the most common causes of late onset CAH is so called 21-hydroxylase deficiency. This is caused by mutations in the *CYP21A2* gene. To date, 127 mutations have been reported in *CYP21A2*. This particular gene provides instructions for making an enzyme called 21-hydroxylase (located in the hormone producing adrenal glands). Mutations in *CYP21A2* lead to reduced or low levels of 21-hydroxylase enzyme activity (activity about 50-80% of normal) which then result in low levels of hormones such as cortisol and/or aldosterone and high levels of androgens (male hormones such as testosterone and androstenedione).

As a result of low cortisol, patients may experience changes in energy levels, blood pressure, blood sugar levels, as well as impaired ability of the body to respond to stress, illness, and injury. Aldosterone plays a key role in helping the body maintain the proper level of sodium and water and helps maintain blood pressure. The amount of functional 21-hydroxylase enzyme determines the severity of the disorder. Patients with late onset CAH have *CYP21A2* mutations that lead to reduce levels on the enzyme but not a complete absence.

How is late onset CAH inherited?

Late onset CAH is usually inherited in an autosomal recessive (AR) manner. What this essentially means is that for a patient to be affected by the condition they need to have both copies of the affected gene - one gene from mom and one gene from dad. The parents of a person with late onset CAH are said to be 'carriers' and typically have only one mutated copy of the gene. The parents usually don't have any symptoms or signs of the disease themselves.

How is late onset CAH diagnosed?

The patient's signs and symptoms may point to a possible diagnosis. Generally speaking, the clinical features of late onset CAH reflect an excess of male hormones (androgens) rather than adrenal insufficiency.

Children with late onset CAH may present with premature pubarche (i.e. the development of pubic hair, axillary hair, and/or increased apocrine odor prior to age 8 years in girls and age 9 years in boys). Affected children may be tall and have accelerated linear growth velocity, and advanced skeletal maturation.

About 2-9 % of all women with hyperandrogenism may have late onset CAH. Women with late onset CAH may develop a variety of symptoms including frontal baldness, hirsutism, acne, irregular periods, a delay in the timing of the very first period, early onset of pubic hair, accelerated growth, reduced final height and infertility.

In a multicenter study by Moran and colleagues, the most common symptoms among adolescent and adult women were hirsutism (59%), oligomenorrhea (54%), and acne (33%). Studies by Bidet and colleagues suggested that the initial presenting symptoms in 161 women with late onset CAH were hirsutism (78%), menstrual dysfunction (54.7%), and decreased fertility (12%). Therefore, for most women with late onset CAH presentation to a hair specialist regarding hair loss may not occur until later. Of course, it can be the presenting symptom.

Generally, additional testing is ordered to help confirm the diagnosis. These tests may include a blood test to measure the concentration of 17-hydroxyprogesterone (17-OHP) on day 3-5 of the menstrual cycle. Levels of 170–300 ng/dL have been found to be useful as a screening tool. These should be obtained in the morning and during the follicular (pre-ovulatory) phase of the menstrual cycle.

The clinical features of late onset CAH in post pubertal adults may be difficult to differentiate from those of the polycystic ovary syndrome (PCOS). Even 17 OHP concentrations may be within the normal range for individuals with late onset CAH. An adrenocorticotrophic hormone (ACTH) stimulation test may also be ordered which involves measuring the concentration of 17-OHP in the blood before ACTH is administered and 60 min after ACTH is given. This test is typically conducted through an endocrinologist. *The acute ACTH stimulation test remains the gold standard to confirm decreased 21-hydroxylase activity.*

To perform the ACTH stimulation test, a blood sample is first collected to measure baseline hormone concentrations. Then, synthetic ACTH (Cortrosyn, 0.25 mg) is administered. A second blood sample is collected 30–60 minutes later. When the ACTH-stimulated 17-OHP value exceeds 1500 ng/dL a mutation is likely. In few late onset CAH patients ACTH-stimulated 17-OHP levels will be between 1000 and 1500 ng/dL.

A common error in investigating CAH is having the patient perform the blood test on any day of the menstrual cycle. 17-OHP levels normally rise in the second part of the menstruate cycle and if the test is done during this phase of the menstrual cycle falsely high levels will be recorded. the 17OHP test must be done on day 3-5.

Other tests

In addition to 17 OHP, other tests may be recommended by the physician caring for the patient. These are normally done in the MORNING and on day 3-5 of the menstrual cycle. They include cortisol, androstenedione, testosterone, free testosterone, DHEAS, progesterone, sodium, potassium, creatinine, glucose, hemoglobin A1C. LH and FSH, estradiol, SHBG, cholesterol and prolactin may also be measured. Aldosterone may be tested. Blood pressure measurements will also be obtained.

What is the treatment for late onset CAH?

For some patients affected with late onset CAH, treatment is not needed. Most endocrinologists agree that treatment is geared towards *treating symptoms* rather than simply helping bring lab tests into more normal ranges.

Symptoms of late onset CAH may develop at various points in life, including puberty, after puberty, post part and during times of illness or increased stress. If symptoms are present, a physician may prescribe a glucocorticoid, often dexamethasone. Dexamethasone is commonly used to treat irregular menstruation, acne, and excess body hair (hirsutism). Anti-androgens are also frequently used, especially by the hair specialist. Oral contraceptives are sometimes used as treatment for adult women or adolescents with irregular periods, acne or hirsutism who are not seeking to become pregnant

If identified early, treatment of children is geared towards helping with a normal linear growth velocity and a normal timing and progression of puberty. For adolescent and adult women, the goals of treatment goals are to help regulate menstrual periods, prevent excess hair growth on the face, stopping hair loss and help with fertility.

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