Etiological Diagnostic Difficulties in Peripubertal Hypogonadotropic Hypogonadism

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Abstract

Late pubertal sexual development may be constitutional delayed puberty (CDP) or hypogonadotropic hypogonadism (HH). In order to differentiate the two phenotypes, the test with analogues of Gonadotrope Releasing Hormone (GnRH) may offer some additional information. CDP is suggested by increased levels of LH (above 8 mUI/mL), after a low dose of analogue of GnRH. On the contrary, low levels of gonadotropes are found in case of either GnRH or gonadotropes deficiency, with an overlapping type of response. We report a case with peripubertal hypogonadism where triptorelin test was performed.

Keywords: *hypogonadotropic hypogonadism, delayed puberty, triptorelin, magnetic resonance*

Introduction

The causes of delayed puberty associated with low values of gonadotropes raise important issues, since if hypogonadotropic hypogonadism (HH) is diagnosed, the patient is a candidate to long term estrogen or testosterone therapy in different manners probably a long life period. On the contrary, if constitutional delayed puberty CDP is most probable, after a short term substitution, the patient will no longer need it. In order to have an early diagnosis, different tests are practiced, including hormonal (stimulation with GnRH), genetic or imagistic assessment.

Case report

A 17 years old female presents primary amenorrhea. The medical history is unremarkable. From her family medical history she mentions that her mother had menarche at the age of 16 years, her maternal aunt had constitutional delayed puberty, with spontaneous menses at the age of 18 years. Her four sisters started menstruating between 12 and 13 years.

The clinical examination reveals a normal weight patient (BMI - 19.45 kg/m^2), with a height of 165 cm (+ 0.5 SD), an arm span of 165 cm, upper/lower body ratio of 0.85 (characteristic of eunuchoid proportions). Tanner stage is B2, P2. The smell sense is normal. The rest of the physical examination is unremarkable. Her complete blood count is within normal range, and so is the other biochemical parameters investigated. Her hormonal profile shows low levels of gonadotropes and estradiol (LH - 0.52 mUI/mL, FSH - 0.6 mUI/mL, Estradiol - 14 pg/mL). No other causes of hypogonadism are identified: she had normal levels of prolactin (4.43 ng/mL, normal ranges between 2.8-29.2), normal thyroid function (TSH - 1.3 μUI/mL, normal range: 0.5-4.5), normal levels of testosterone (0.58 ng/mL, normal range: 0.14-0.79 ng/mL). During an insulin tolerance test, performed with 0.1 units of insulin per kilogram of body weight, she presents normal increases of growth hormone (maximum GH - 29.4 ng/mL) and cortisol (maximum cortisol - 25.67 ng/mL).

The cerebral magnetic resonance exam reveals a pituitary micro-adenoma of 2 by 3 mm, without any other pathological changes.

The pelvic computed tomography showed a hypoplastic uterus, of 2.5 by

7.5 cm and small ovaries, with fatty degeneration (a medium density of 0.7 Hounsfield Units) (Figure 1). The X-Ray exam of the hand showed open growth cartilages. The breast ultrasound showed only small amounts of glandular tissue, of 0.46 cm on the right and 0.56 cm on the left.

Differential diagnosis

Several disorders should be considered in the differential diagnosis in this patient as sporadic or familial CDP or, on the other hand, peripubertal HH as hyperprolactinemia, pituitary tumors, genetic defects regarding gonadotropes, infiltrative disorders of the pituitary region.

In order to differentiate between CDP and HH, a stimulation test with a GnRH (Triptorelin, 100 μg/m^2 of body surface, s.c.) was performed. The levels of LH and FSH increased only slightly after 4 hours (from an undetectable basal LH to 0.57 mUI/mL, and from a basal FSH of 0.47 mUI/mL to 5.64 mUI/mL). The level of estradiol after 24 hours was low (12.55 pg/mL).

Even if her family history suggested constitutional delayed puberty, the GnRH test indicated HH. The pituitary micro-adenoma was considered an incidentaloma, too small to cause hypopituitarism. The hypogonadism probably has a genetic cause, the Kallman syndrome being unlikely because of normal sense of smell. Estrogen therapy was started, in low dose (estradiol, 1 mg per day, p.o.), in order to induce the development of secondary sexual characteristics and to increase peak bone mass. The patient will be monitored every tree months by pelvic ultrasound. The development of the uterus and of the endometrium will determine the moment of introduction of progestative therapy.

Discussion

Delayed puberty is characterized by the absence of signs of sexual maturation at an age that is 2.5 SD above the median age for puberty start for that population. Generally, the lack of pubertal development at the age of 13 for girls and 14 for boys suggests that investigations are necessary.

The causes for delayed puberty with low levels of gonadotropes are CDP and HH. A large retrospective study of 232 patients, both males and females, which presented for delayed puberty identified as the most common cause constitutional delayed puberty, in 53% of the subjects, followed by functional delayed puberty, caused by a primary non endocrine condition in 19% of the cases. The rest of the patients had HH (12%), hypergonadotropic hypogonadism (13%), or no clearly classified pathology, in 3% of the cases[1].

Patients with CDP display a normal but delayed peak of growth and development, with delayed adrenarche and bone age. The condition is much more frequent in boys than in girls. The family medical history usually reveals first or second degree relatives with delayed puberty, like in presented case, in some studies, up to 80% of cases, but no specific genes mutations have been yet identified, suggesting a complex polygenic pattern[2,3]. Whether or not patients reach their target or predicted height is still a matter of debate because the lack of most accurate formula for height prediction. Some, especially those with early growth deficit, do not attain their full potential, and treatment with growth hormone or testosterone/estrogen does not seem to alter the final height[4-7].

Usually, pubertal development begins in 12 to 18 months after the levels of gonadotropes or sexual hormones increase spontaneously of after a stimulation test. HH is caused by a quantitative or qualitative deficiency of the GnRH or gonadotropes. Even if a mutation in GnRH has been described in mice, no such mutation has been identified yet in humans. On the other hand mutations of GnRH receptor are the cause of about half of the familial cases of HH without anosmia. The type of mutation correlates with the clinical manifestations, which range from total resistance to GnRH with total absence of pubertal development or cryptorchidism in males to only partial loss of function of the receptor. In these cases, there is some incomplete pubertal development, like in our patient, which presented some breast growth[8]. The majority of cases are sporadic, but there are familiar cases, usually autosomal recessive or dominant and in rare instances X-linked[9,10]. Other studies have identified mutations at the level of LH β subunit, or FSH β subunit[11]. The Kalmann's syndrome, in which HH is associated with anosmia, may be transmitted in an X-linked, autosomal dominant or

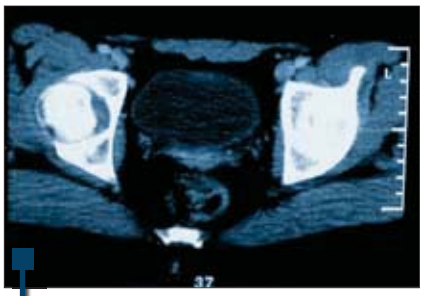

Figure 1. Pelvic computed tomography

recessive pattern. Mutations in the KAL1 gene, located on the chromosome X determines the malfunction of a extra cellular matrix glycoprotein, anosmin 1, which influences the development of the olfactory lobes and the migration of GnRH neurons to the pituitary gland. Since in our case, the patient had normal sense of smell and the cerebral magnetic resonance exam was normal, a Kallman syndrome is unlikely.

Patients with HH usually have normal height for age during childhood and develop into tall adults, with eunuchoid body proportions (increased arm span and decreased upper/lower ratio). There are some cases described especially in males, where idiopathic hypogonadism was reversible after treatment and so the estro-progestative or testosterone therapy will be stopped from time to time[2].

In common medical practice, the GnRH agonists are widely used since the last three decades. In pediatrics, their place is related to the treatment of precocious puberty. In adults, there are useful in inducing temporary hypogonadism as required in endometriosis, protection of ovaries during chemotherapy or prostate cancer[12-14].

The GnRH analogues also mark a point in diagnosis test as seen in hypogonadism. If delayed puberty caused by primary gonad failure is relatively simple to diagnose because of increased levels of LH and FSH, the differential between HH and CDP is not easily achieved. There are differences in the growth pattern and family history, but the hormonal panel is similar, with abnormally low or normal prepubertal levels of LH and FSH. The secretor pattern of LH during a GnRH analogue stimulation test is relatively easy to perform. After basal morning levels of LH, FSH and testosterone/estradiol were obtained, a GnRH analogue, in our case triptorelin 100 μg per square

meter of body surface was injected s.c. Gonadotropes were measured again 4 hours after the injection and after 24 hours, estradiol or testosterone were determined. The cut off value for LH at was considered 8 mUI/mL. The levels below that value suggest HH, as in our case. Patients with constitutional delayed puberty usually have an increase LH more than 8 mUI/mL.

The cut off value for LH is still under debate. There are different opinions regarding the exact values of the gonadotropes.

For example, a study using a LH threshold of 12 mUI/mL, correctly identified all patients with HH (who had levels of stimulated LH below 8 mUI/mL), but three patients with CDP out of 37 were misdiagnosed[15].

In another study on 31 prepubertal males, followed for a mean period of 4.2 years, all 8 hypogonadic patients had stimulated levels of LH below 5 mUI/mL and only one patient with CDP reached that level of 5 mUI/mL. The sensitivity of the test was 100%, with a specificity of 96% and a positive predictive value of 89%[16].

Using a 14 mUI/mL threshold a study including over 33 patients with delayed puberty obtained a positive predictive value of 100% and a negative predictive value of 72% for congenital delayed puberty. 5 patients with constitutional delayed puberty were initially diagnosed as HH[11]. Some authors, in order to avoid the lack of a conventional threshold, use the triptorelin test as a confirmation of the diagnosis already done by proving a statistically significant difference in gonadotropes levels between CDP and HH[17].

Some, but not all, consider the test with GnRH analogue less reliable than the hCG test[11,18]. The levels of FSH after 4 hours overlap in patients with CDP and HH and so do not differentiate between the two entities[15,16]. The increase in testosterone levels is greater in subjects with CDP than HH, but there is a great overlap of values so most authors do not recommend a cut off level. A small Turkish study obtained a statistically significant difference in the levels of testosterone at 24 hours[19].

The triptorelin test is also used in functional hypothalamic amenorrhea (FHA), a condition where gonadotrophin deficiency has a nutritional origin, For example, in one study over 12 women with FHA and 12 control normal menstruating women but also 6 more patients with congenital hypothalamic hypogonadism, the basal estradiol was low, as well as the LH pulse frequency and amplitude in all FHA women. After performing a triptorelin test, FSH/LH ration increased rapidly, as well as estradiol. In contrast, no significant response was observed to the 6 hypogonadic patients[20].

Conclusion

Even there is still a matter of debate regarding the cut off value during the GnRH stimulation test; this represents a very useful tool in differential diagnosis between constitutional delayed puberty and hypogonadotropic hypogonadism. The test represents a staring point not only in searching more complications of the possible maladies associated but also in timing of periodic check up in order to appreciate the sexual development and adverse reactions of the substitution therapy, and in choosing long term formula therapies if long time substitution is required. ■

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