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Delayed Puberty in Male: A Review and Cases Reports

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Abstract

Is considered delayed puberty in the boy when the testis are less than 4 ml at 14 years of age or need more than 5 years for genital development. The three main causes of delayed puberty are: constitutional delay of growth and sexual maturation, hypo and hypergonadotropic hypogonadism. The clinical history and the physical examination can lead us to the etiological diagnosis. Complementary diagnostic tests are essential for therapeutic orientation. The treatment should be specific for each disease. Testosterone at low dose 50 mg/month, can physically improve and psychologically recover a teenager with low self-esteem caused by pubertal delay. We report 3 cases with delay puberty caused by growth hormone deficiency, Kallmann syndrome and testicular regression syndrome.

Keywords: *Delay; Puberty; Male*

Introduction

Is considered delayed puberty, when we found no secondary sexual characteristics at an age when 97% of the same sex and culture began sexual maturation. In the boy, the onset of puberty is characterized by the presence of 4 ml testicular volume, when this volume is not reached at 14 years of chronological age or need more than 5 years for genital development, we are in the presence of delayed puberty [1-5].

Classification

They are classified into 3 large groups: constitutional delay of growth and sexual maturation (normal variant), hypogonadotropic hypogonadism (hypothalamic-pituitary axis insufficiency) and hypergonadotropic hypogonadism (primary gonadal insufficiency).

Constitutional delay of growth and sexual maturation (normal variant)

Is the most frequent cause (60%). Is characterized by delayed growth, puberty, bone age and frequent family history (60 - 90%). The adolescents later achieve sexual maturation and most of them have a normal and adequate final height for their genetic height.

The differential diagnosis is made with hypogonadotropic hypogonadism. Is difficult to distinguish in some situations and only can clarify through clinical evolution and repeat of blood tests. Constitutional delay may have a transient growth hormone deficit that normalizes after puberty.

Hypogonadotropic hypogonadism

Is classified as congenital or acquired. In congenital form, we have gonadotrophin deficit, LHRH isolated deficit with anosmia (Kallmann syndrome) or no anosmia (idiopathic) - mutations that inactivate the LHRH receptor gene, X-linked suprarenal hypoplasia, isolated LH deficit, isolated FSH deficit, deficit of CNS development (septo-optic dysplasia, midline defect), panhypopituitarism, associated with obesity by mutations of the leptin gene or its receptor, polymalformative syndromes (Prader-Willi, Laurence-Moon-Bardet-Biedl, others).

In acquired type, we have organic: hypothalamic-pituitary lesions, tumors (craniopharyngiomas, gliomas, astrocytomas), infiltrative processes (histiocytosis, sarcoidosis, hemochromatosis), inflammatory lesions (meningitis), iatrogenic, surgery of the hypothalamic-pituitary region, head trauma, radiotherapy and functional: malnutrition, chronic disease like gastrointestinal, chronic renal failure, etc., hormonal disorders (growth hormone deficit, hypothyroidism, diabetes, hypercortisolism, hyperprolactinemia), excessive physical exercise, stress and eating behavior disorder (anorexia nervosa, bulimia).

Hypergonadotropic hypogonadism

Is classified as congenital or acquired. The congenital group include sexual chromosome abnormalities like Klinefelter syndrome, 47XYY and Y chromosome changes, testicular regression syndrome (congenital anorchia, 5α reductase deficiency, rudimentary testis), androgen insensitivity syndrome and mutations that inactivate the genes of LH and FSH receptors. The acquired group are: surgical or traumatic castration, bilateral orchitis, immunosuppressants, chemotherapy, radiation therapy, oligoespermia or idiopathic azoospermia.

Diagnosis - physical examination

We should evaluate: secondary sexual characters (Tanner Stage), height 2 SD below average, volume and testis symmetry (> 4 ml suggests evolving puberty), use of Prader orchidometer, study of smell and vision, eunuchoid proportions suggestive of hypogonadism, wingspan>height more than 6 cm and proximal/distal segment < 1.

Laboratory diagnostics

Depending on the clinical signs and history, we need to check the: karyotype, molecular study - KAL1, leptin, Prop1 and HESH1. Hormonal study may indicate the etiological diagnosis: If LH and FSH are increased, we have a hypergonadotropic hypogonadism. On the other hand, if LH and FSH are decreased, hypogonadotropic hypogonadism or constitutional delay of growth and sexual maturation should be considered. When prolactin level is high, probably will have a patient with prolactinoma. When TSH is high and FT4 decreased, the diagnosis is either a primary or secondary hypothyroidism. If S-DHEA showed low values, is suggestive of constitutional delay. The basal testosterone is increases when testis volume reaches 8 - 10 ml.

LHRH test

The normal response after injection of 0.1 mg / m2 (maximum 100 μg EV of LHRH) consists in increase 3-6x over baseline LH, increase 1.5 to 2x compared to baseline FSH. In constitutional delay, the response is normal/prepubere. In hypogonadotropic hypogonadism the response is weak or normal and in hypergonadotropic hypogonadism, the response is increased.

hCG test

It measures the testosterone response by stimulation of the Leydig cells and by this way to evaluate the testicular function. The response depends on age: in childhood increases from 2-20 x. On puberty increases 2 - 3 x. There are multiple protocols using different doses: 1000 U x 3 with daily intervals, 2000 U at intervals of 72h, 1500 U x 7 at 48h intervals and 5000 U / m^2 with testosterone measurement 24 h later.

In hypergonadotropic hypogonadism the basal value is normal or weak (decreased in anorchia). After hCG, the result is same with normal or weak response (no response in anorchia). In hypogonadotropic hypogonadism, the basal result is decreased and after hCG, still is decreased. In constitutional delay, the basal value is normal as same as after hCG.

Diagnostic Imaging

The imaging exams that need to request are x-ray of hand and left wrist for bone age, testicular ultrasound to exclude anorchia or athrophy and brain CT or MRI if the clinical history and analyzes are consistent with pathology of the hypothalamus or pituitary region.

Treatment

We prescribe L-thyroxine if the child have hypothyroidism and growth hormone in growth hormone deficiency. In severe pubertal delay and psychological implications, we give testosterone - 50-100 mg/month intramuscularly - short cycles of 3 to 6 months. Some authors use oral testosterone undecanoate - 40 mg/day. We give dopamine agonist if the patient have prolactinoma. In others cases like craniopharyngioma, surgery is indicated and when the patient showed anorchia, testicular prosthesis is recommended.

Clinical Cases

Case 1: Growth hormone deficiency

We describe a 14 years old male with short stature and delay puberty. On physical examination showed infant face, A1, P1, testis 3 ml, height - 135.5 (P3), Growth velocity -1,5 cm /year. Bone age: 10 years. Additional tests revealed: FSH - 3.84 mIU/mL (1.5 - 12.4), LH - 0.1 mIU/ml (1.7 - 8.6), testosterone - 0.23 ng/ml (0, 28 - 11.1), clonidine: basal - 0.3 ng/ml and peak -2.3 ng/ml, L-Dopa: basal - 0.2 ng/ml and peak -1.7 ng/ml, Igf1- 222 ng / ml (200-850), brain MRI – normal. We start treatment with growth hormone, with growth velocity up to 14.4 cm , A3, P4 and testis 10 ml after one year.

Case 2: Kallmann syndrome

Is a 15 years old, male, with absence of ejaculation during the act of masturbation. The physical examination showed micropenis, A1, P2, testis 2 ml. Bone age: 15 years. Further examination: LHRH test revealed LH: basal - 0.1 mIU/mL and at, 120m, peak of - 0.9 mIU/mL. The FSH showed: basal value of - 0.1 mIU/mL and at 120 m, peak of 2.0 mIU/mL. Total testosterone: at basal time -315 ng/ml and 223 ng/ml at 120 m. Brain MRI showed absence of bulb and olfactory grooves on both sides, compatible with Kallmann syndrome. The KAL 1 gene was negative. Start treatment with testosterone.

Case 3: Testicular regression syndrome

A 15 years old male, with micropenis, also have A2, P2. Bone age 14 years. Supplementary exams showed: karyotype: 46XY, FSH - 136.60 mIU/ml (1.5 - 2.4), LH 26.21 mIU/ml (1.7 - 8.6), total testosterone 0.21 ng/ml (0, 28-11, 1). Testicular ultrasound revealed bilateral cryptorchidism (intra-abdominal? atrophic?). The LHRH test showed: basal LH - 20.7 mIU/ml, with peak of 103 mIU/ml. The basal FSH was high - 98.8 mIU/ml, with peak at 120 m of 206 mIU/ml. Total testosterone revealed at basal time -12 ng/dl, and at 120 m - 17 ng/ml. Abdominal/testicular MRI confirmed the diagnosis of anorchia. Scrotal biopsy revealed fibrovascular tissue without the presence of testicular parenchyma. Start treatment with testosterone and need testicular prosthesis.

Conclusions

Is considered delayed puberty in the boy when the testis are less than 4 ml at 14 years of age or need more than 5 years for genital development. Constitutional delay of growth and sexual maturation, hypo and hypergonadotropic hypogonadism are the main causes. Testosterone at low dose 50 mg/month, can physically improve and psychologically recover a teenager with low self-esteem caused by pubertal delay.

Bibliography

1. Schwartz B., *et al*. "Variants of pubertal progression". In: Sarafoglou K,Hoffmann GF, Roth KS, eds. Pediatric endocrinology and inborn error of metabolism. New York: McGraw Hill (2009): 513-523.

2. Zeitler PS., *et al*. "Endocrine disorders". In: Hay WW, Levin MJ, Sondheimer JM, Deterding RR, eds. Current diagnosi and treament in pediatrics, eighteenth edition. New York: McGraw Hill (2007): 966-967.

3. Cohee L. "Endocrinology". In: T schudy MM, Arcara KM, eds. The harriet lane handbook, nineteenth edition. Philadelphia: Elsevier Mosby (2012): 259-261.

4. Aoyama K., *et al*. "Molecular genetic and clinical delineation of 22 patients with congenital hypogonadotropic hypogonadism". *Journal of Pediatric Endocrinology and Metabolism* 30.10 (2017): 1111-1118.

5. Carel JC., *et al*. "Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or child short stature: preliminary report of the French SAGhE study". *Journal of Clinical Endocrinology and Metabolism* 97.2 (2012): 416-425.