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Testotoxicosis: gonadotrophin - independent male sexual precocity

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Summary: In this era of rapidly developing investigational tools and pharmacology, the pathophysiology of precocious puberty is becoming well defined. What was previously thought to be a form of gonadotrophin releasing hormone (GNRH)-dependent central precocious puberty is now classified as GNRH-independent familial testotoxicosis. We present two such cases and review the clinical features, pathophysiology and treatment of testotoxicosis.

Introduction

Sexual precocity is defined as the appearance of physical signs of puberty before 8 years of age in females or 9 years of age in males. The clinical disorders that induce sexual precocity can be classified as gonadotrophin releasing hormone (GNRH) dependent or GNRH independent.[1]

Male sexual precocity first described as a form of central precocious puberty has recently been characterized as a familial intratesticular disorder.[2,3] Sexual development, symmetrical testicular enlargement and accelerated rate of growth are noted by 3-4 years of age.[1,3] The pulsatile pattern of luteinizing hormone (LH) secretion and the immunoreactive and bioactive LH responses to GNRH are similar to these seen in prepubertal children despite markedly elevated concentrations of serum testosterone.[1] We describe two sporadic cases and will review clinical features, diagnosis and treatment of testotoxicosis.

Case report

Case 1

The first patient, born in December 1986, the product of normal pregnancy delivered by Caesarean section due to transverse lie, weighed approximately 6 lb at birth. The mother took no medications during pregnancy. He was noted to have a rather large penis at 6 weeks of age when he was circumcised. At the age of 6-9 months pubic hairs were noted. At age 2 years his height was 99.7 cm and weight was approximately 15 kg both being above 97th percentile. He had a bone age of 6.4 years. He had stage IV genital development, Stage IV pubic hair and testicular volume of 8 ml (Figures 1 and 2). His voice was husky and he was extremely hirsute. There was no family history of precocious puberty. Reports of hormonal assays are shown in Table I. An overnight gonadotrophin profile showed low level pulsatility of LH but no measurable follicle stimulating hormone (FSH). Testicular biopsy showed Leydig cell hyperplasia. An injection of Lupron (LHRH agonist) increased serum testosterone to 1064.8 ng/dl. Computed tomographic (CT) scan of the brain and adrenal was normal as was ultrasound of the testes and adrenals.

Case 2

This patient presented to us at 8 years of age. He was born full term and there was no history of any drug intake except diazepam by his mother. At 3 years of age he was found to have enlargement of the penis and appearance of pubic hair. At presentation his height was 135 cm and weight was 32 kg. There were downy facial hairs. Axillary hairs were present. The penis was 7-8 cm in length and pubic hair was Tanner Stage IV. The right testis was 10 ml in volume and the left was 12 ml. Investigations revealed a bone age of 14 years. X-ray skull and CT scan of brain were normal. Hormonal assay results are shown in Table I.

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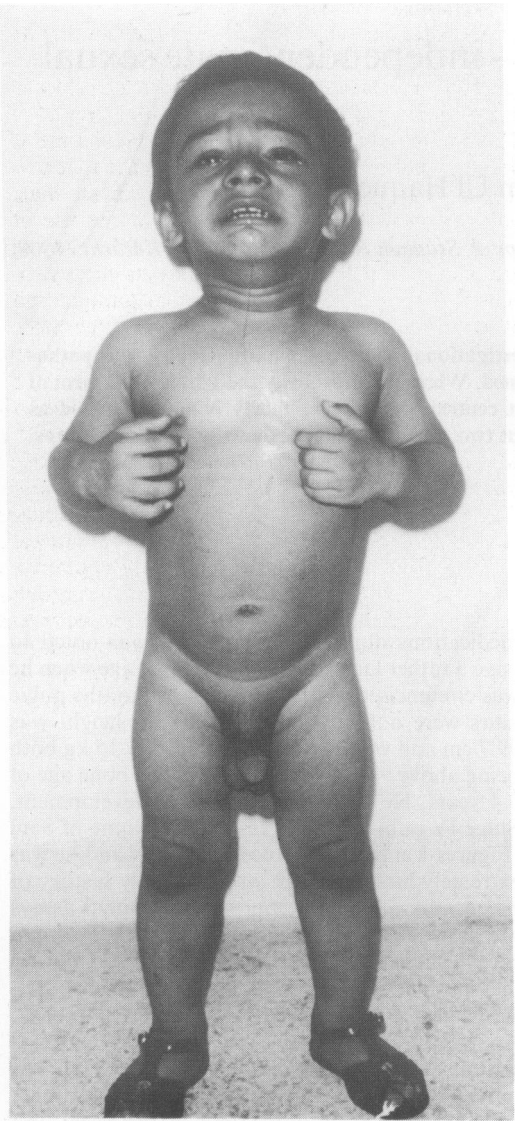

Figure 1 Case 1. The patient aged 2 years.

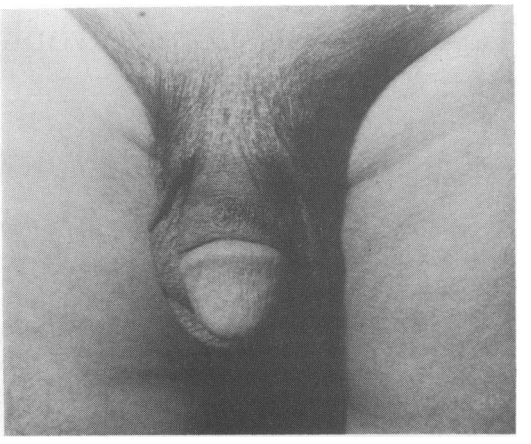

Figure 2 Case 2. The patient aged 2 years.

Table I Endocrine screening

Hormone	*Case 1*	*Case 2*	*Normal range*
Serum testosterone (ng/dl)	598.0	631.0	4.1–9.1
Dehydroepiandrostenedione (μg/dl)	21.4	310.5	60–254
Serum follicle stimulating hormone (mIU/ml)	<1.5	<1.7	1–16
Serum luteinizing hormone (mIU/ml)	<2.8	<1.0	1.8–6.0

Discussion

Testotoxicosis or familial male precocious puberty is a form of isosexual precocious puberty, that is independent of gonadotrophin releasing hormone. The pattern of inheritance is autosomal dominant, although sporadic cases can occur.[4] Transmission is through affected males or carrier females to their sons.

Clinical features are characterized by sexual development, symmetrical testicular enlargement and acclerated rate of growth seen by 3–4 years of age. Enlargement of external genitalia may be noted as early as birth.[5] The testes may be appropriate in size or slightly small in relation to the stage of sexual maturation. Rapid virilization and premature epiphyseal fusion results in short adult stature.[6,7]

The hypothalamic–pituitary gonadotrophin unit operates at a prepubertal level in these patients.[8] The characteristic findings are low basal gonadotrophin levels, absence of sleep-associated LH pulses and lack of a pubertal-type rise in LH concentration after luteinizing hormone releasing factor (LHRF). However, affected adults show a mature LH response to LHRF, whereas FSH is elevated in adults with seminiferous tubule damage, provding evidence that central regulatory pathways are intact. There is lack of excessive testosterone response to administration of human chorionic gonadotrophin (HCG) in boys and absence of testosterone increase after LHRF in adults, despite substantial rises in plasma LH levels. All the above findings are consistent with a primary testicular defect.[1] Testicular histology

shows hyperplasia of Leydig cells.[9] In some affected adults, germ cell degeneration, progressive dysfunction of spermatogenesis and elevated levels of FSH have been observed.[9,10]

The pathophysiology of premature Leydig cell activation has still not been clearly elucidated. Salient features of various hypotheses are as follows. Negative LH–HCG activity by bioassay argues against the presence of a circulating gonadotrophin-like factor.[3,5] In addition, indirect immunofluorescence studies have been unable to identify a serum immunoglobulin in these patients, comparable to thyroid stimulating hormone immunoglobulin in thyrotoxic patients. Derangement of an intratesticular regulatory mechanism that inhibits Leydig cell function leading to unrestrained activity of these cells has also been proposed.[3,11–13] Premature Leydig cell activation may also result from local production of a stimulatory factor not detectable in the circulation that stimulates CAMP-dependent kinase to induce testosterone secretion. For example, immunoreactive HCG-like material has been identified in extracts of human testes and other tissues,[3,14] and human fetal testes appear able to synthesize HCG.[3,15]

Various treatment options have been proposed for testotoxicosis. Initial reports showed that medroxyprogesterone acetate and anti-androgen cypropterone acetate may have some therapeutic benefit.[5,10] The mode of action of ketoconazole is inhibition of synthesis of both adrenal and gonadal steroids.[10,16,17] The disadvantages of ketoconazole are its potential hepatotoxicity and the fact that its use is limited to those patients whose bone age has reached pubertal age.[10] Another approach is blockade of androgen action with spironolactone.[4,18–21] The commonest problem with spironolactone is development of gynaecomastia. Evidence that oestrogens may have an important role in the male pubertal growth spurt[22–24] has led to the use of testolactone, a competitive inhibitor of the enzyme aromatase, which converts androgens to oestrogens.[25–27] There is recent evidence that combination of spironolactone and testolactone may be more beneficial than either alone.[4]

In conclusion familial testotoxicosis is a disorder of male isosexual precocity that is inherited as an autosomal dominant condition (although sporadic cases can occur) characterized by gonadotrophin-independent testicular hypersecretion. This condition should be differentiated from gonadotrophin-dependent true precocious puberty as treatment with LHRH analogues may aggravate testotoxicosis. Treatment has not yet been well defined and should be individualized for each case. We believe our two cases either represent sporadic cases or may be a new gene mutation in these two families; long-term follow-up may answer the issue.

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