

Prevalence and etiology of male hypogonadism

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ABSTRACT

Introduction: Hypogonadism manifests clinically as defects of sexual differentiation, sexual development or infertility.

Material & Methods: We screened a total of 8,844 patients attending our endocrine clinic between June 2000 - May 2001 to assess the frequency and etiology of male hypogonadism.

Objectives: To evaluate the frequency of male hypogonadism among patients attending the endocrine clinic and to assess the clinical, hormonal and genetic profile of men with hypogonadism.

Material & Methods: Patients referred to the endocrine clinic of AIIMS hospital between the period of 1st June 2000 to 31st May 2001 were screened for male hypogonadism. All patients underwent detailed history, physical examination, hormonal analysis and genetic studies.

Results: The prevalence of male hypogonadism was found to be 1.2%. Out of these 6(5.45%) patients had ambiguous genitalia. Among the 6 patients with ambiguous genitalia 4 had 46, XY karyotype and 2(siblings) had 46, XY/47, XXY mosaic karyotype. Three cases had dysgenetic male pseudo hermaphroditism and one had 5 α reductase deficiency. Twenty eight (25.45%) had gynecomastia, 15(13.63%) had hypergonadotrophic hypogonadism, 36(32.72%) had hypogonadotrophic hypogonadism, 11(10%) had azoospermia and 16 (14.54 %) had delayed puberty.

Conclusion: We conclude that the male hypogonadism constituted 1.2% of referrals to our clinic. Age at presentation was quite variable. Some cases were more than 40 years at the time of diagnosis which could be because of lack of awareness / inadequate medical facilities. [IJEM 2007;(3&4):3-5]

Key words: Male hypogonadism, male pseudo hermaphroditism, ambiguous genitalia, mosaic Klinefelter syndrome, gynecomastia.

INTRODUCTION

Hypogonadism is a complex disorder manifesting as disorder of sex differentiation or development and or infertility. This condition is expressed in two ways depending on which portion of the hypothalamopituitary gonadal axis is affected. In hypogonadotropic hypogonadism, the gonadotrops are low, implying an abnormality at the level of hypothalamus or pituitary or both, while in hypergonadotropic hypogonadism, luteinizing hormone (LH) and follicle stimulating hormone (FSH) are elevated, indicating a lack of negative feedback by androgens produced by testes.

The pathway from cholesterol to androstenedione is the same in the testis and adrenal and uses the same enzymes

encoded by single genes(1). The enzyme of 3 β -hydroxysteroid dehydrogenase (3 HSD) converts pregnenolone to progesterone, 17-hydroxypregnenolone (17OH-pregnenolone) to 17-hydroxyprogesterone (17OH-progesterone), dehydroepiandrosterone (DHEA) to androstenedione, and androstenediol to testosterone. Defects in 3 HSD would lead to an increase in pregnenolone, 17OH-pregnenolone, DHEA, and androstenediol. P450c17 is also necessary in the proximal stages of testosterone synthesis. P450c17 catalyzes the 17 -hydroxylation of pregnenolone to 17OH-pregnenolone and progesterone to 17OH-progesterone. The 17, 20 lyase activity of P450c17 converts 17OH-pregnenolone to DHEA, but very little 17OH-progesterone is converted to androstenedione, so that 17OH-progesterone is not a precursor of human androgen synthesis(2,3). Defects in either 17-hydroxylation or 17, 20 lyase activity of P450c17 will lead to an increase in respective steroid hormone precursors. The conversion of androstenedione to

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testosterone in the testis is catalyzed by type 3 17 HSD (17 HSDIII), but this reaction can also be catalyzed by 17 HSD type V, which is widely expressed in extraglandular tissue(4,5). In the present study, an attempt has been made to evaluate the frequency of male hypogonadism among patients attending the endocrine clinic and to assess the clinical, hormonal and genetic profile of men with hypogonadism.

MATERIAL AND METHODS

Patients referred to the endocrine clinic of AIIMS hospital between the period of 1st June 2000 to 31st May 2001 were screened for male hypogonadism. All patients underwent detailed history and physical examination. Those with disorders of sexual differentiation (46, XY karyotype,) lack of secondary sexual development or infertility (with azoospermia) were included for further evaluation.

Genetic analysis

Conventional cytogenetic analysis was done on peripheral blood using standard techniques. Karyotyping was done on G-banded metaphases obtained from 72-hour cultures.

Hormonal analysis

Testosterone was estimated by radioimmunoassay method with IMMUNOTECH Radioimmunoassay kit (France). Human Luteinizing Hormone (hLH), Human Follicle-stimulating hormone (hFSH), and Human Prolactin (hPRL) levels were estimated by Immunoradiometric method from MEDICORP kits (Canada). DHT was estimated in these samples by radioimmunoassay method after celite chromatography.

HCG stimulation test

hCG stimulation test was done for children with ambiguous genitalia or undescended testes who had LH, FSH levels in the normal range. 2000 IU (500 IU for children less than 5 years) of hCG intra-muscularly was given for 3 days and the blood sample was collected on the 4th day for testosterone estimation. Same sample was used for DHT also as and when required.

GnRH stimulation test

GnRH stimulation was done for children with ambiguous genitalia. 100µg of Gonadotrophin releasing hormone (GnRH) was injected intravenously and samples were collected for LH & FSH -15, 0, 30, 60, 120 minutes. Samples were stored at -20°C till assayed.

RESULTS

8,844 new patients were registered in the Endocrine clinic during a one year period (from 1st June 2000 to 31st May 2001). Male hypogonadism accounted for 110 referrals. Age of patients ranged from 4 months to over 40 years. There were 6 children with ambiguous genitalia (age 4 months to 14 years), 93 complained of disorders of pubertal development

11 had infertility due to azoospermia. Among them with disorders of pubertal development, 15 were hypogonadotropic hypogonadism, 36 were hypergonadotropic hypogonadism, 11 had idiopathic gynecomastia and 14 had constitutional delay in growth and development. Dysgenetic male pseudo hermaphroditism was diagnosed in 3 of the 6 cases with ambiguous genitalia. Two had 46, XY/47, XXY karyotype and these were siblings. The degree of deficit correlated with the percentage of abnormal (47, XXY) cell lines. While the elder sibling with 30% 47, XXY cell lines had the urethral opening over the distal 3rd of the phallus, the younger sibling with 70% abnormal cell lines had perineal urethral opening. The testosterone response to hCG was also greater in the older sibling.

One patient was diagnosed to have 5 reductase 2 deficiency. His history was remarkable as he was reared as a girl till puberty, when male secondary sexual development was noticed; this patient opted for a male gender. His LH, FSH, testosterone levels were within normal male range, but T/DHT ratio was 37 and raised to 85 following hCG stimulation.

DISCUSSION

Patients with hypogonadism exhibit a wide spectrum of phenotypes, ranging from disorders of sexual differentiation to infertile or impotence. Prevalence of hypogonadism was found to be 38.7% in men of 45 years or above who visited primary care practices in the United States(6). In a five years (1999–2004) clinical and inheritance study of Kallmann syndrome from twelve Jordanian and Palestinian families (age 4 - 46 years) were evaluated. Among 26 males, nine boys aged 4 - 14 years presented with cryptorchidism and microphallus, all other males presented with delayed puberty, hypogonadism and/or infertility(7).

In an epidemiological study, the incidence of ambiguous genitalia in neonates from Germany, 80 cases were identified within a 2-year study period(8). They reported an incidence of 2 per 10,000 births with ambiguous genitalia per year in Germany. Prevalence was higher in infants from non-German family background. In more than 50% of infants a definite diagnosis was lacking even at the age of 6 months.

A retrospective gender assessment study of 250 patients in Seattle, WA, from January 1981 through December 2005 evaluated the frequency of disorders of sex development. They observed, 177 were infants, 46 were children or adolescents, and 27 had a multisystem genetic condition. The most common disorders were congenital adrenal hyperplasia (14%), androgen insensitivity syndrome (10%), mixed gonadal dysgenesis (8%), clitoral/labial anomalies (7%), hypogonadotropic hypogonadism (6%), and 46, XY small-for-gestational-age males with hypospadias (6%) respectively(9).

Though there is a paucity of data on the prevalence and

etiology of male hypogonadism from India, six cases of true hermaphroditism were reported from North India in one and a half decades period(10). The authors reported that the age at presentation varied from 2 months to 41 years and symptoms ranging from ambiguous genitalia to a lower abdominal mass. All patients had perineoscrotal hypospadias with varying degrees of labioscrotal fusion. Age at presentation for the present study ranged from 2 months to 40 years for the 110 males with hypogonadism. Among them, 33 % were cases of hypogonadotrophic hypogonadism while 28% had isolated (idiopathic) gynaecomastia with normal gonadal functions. Six patients had ambiguous genitalia. Among them was a pair Siblings with 46, XY / 47, XXY karyotype and genital ambiguity, a rarer occurrence (11). One patient with DSD and virilized at puberty and changed to male gender(12).

CONCLUSION

We conclude that the male hypogonadism constituted 1.2% of referrals to our clinic. Age at presentation was quite variable. Some cases were more than 40 years at the time of diagnosis which could be because of lack of awareness / inadequate medical facilities.

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