INTRODUCTION

The prevalence of Idiopathic Hypogonadotropic Hypogonadism (IHH) is approximately 1 in 10,000 men.¹ A study on Sardinian military recruits reports the prevalence of hypogonadism associated with anosmia (Kallmann syndrome) as 1 in 86,000 men.² Classic Kallmann syndrome and idiopathic hypogonadotropic hypogonadism are congenital genetic disorders.³⁻⁶ Genetic transmission appears to be autosomal dominant (approximately 64% of families), autosomal recessive (about 25% of families), or X-linked (about 11% of families).⁷ Male to female ratio ranges 4:1⁻⁵:1. Condition is present at birth although an adult variety presenting at 30⁻40 has recently been described.⁸ Patients with either classic Kallmann syndrome or IHH report with delayed onset of puberty; however, occasionally individuals have a history of partial progression through puberty. These male patients were previously labelled fertile eunuchs. Height for age is normal in these patients, distinguishing them during adolescence from individuals with constitutional delay in growth and development because adolescents in the latter group tend to be short for chronological age. IHH is a form of hypogonadism that is due to a problem with the pituitary gland or hypothalamus. In this condition the male testes or female ovaries produce little or no hormones. IHH is caused by a lack of secretion of the gonad stimulating pituitary hormones, i.e., follicle stimulating hormone (FSH) and luteinising hormone (LH).

Normally, the hypothalamus in the brain releases gonadotropin-releasing hormone (GnRH). This hormone stimulates the pituitary gland to release other hormones, including FSH and LH. These hormones stimulate the female ovaries and male testes to release hormones that lead to normal sexual development in puberty. Any change in this hormone release chain causes a lack of sex hormones and prevents normal sexual maturity.

Keywords: Hypogonadotropic hypogonadism, Constitutional delayed puberty, prolactin, FSH, LH
Failure of the hypothalamus is usually the result of Kallmann syndrome. Kallmann syndrome is an inherited form of hypogonadotrophic hypogonadism that can occur with a loss of smell. In the absence of smell disorder hypogonadotrophic hypogonadism is labelled as idiopathic hypogonadotrophic hypogonadism. An adult form of IHH that is a treatable cause of infertility has also been described.

Short stature, lack of development of puberty, inability to smell, failure of enlargement of testes, penis, deepening of voice and facial hairs are some of the features in male. In females, absence of breasts development and menstruation are common presentations.

IHH mimics CDP and hypothalamic amenorrhoea due to anorexia nervosa, severe stress and exercise in female. Delayed puberty is defined in girls by the absence of breast development beyond 13 years old and in boys by the absence of testicular enlargement (>4 ml) beyond 14 years old. Conceptually, pubertal maturation can be described in terms of sequence, timing, and tempo. (Puberty consists of a series of predictable events, and the sequence of changes in secondary sexual characteristics has been categorised by several groups. The staging system utilised most frequently is that published by Marshall and Tanner and the sequence of changes, commonly referred to as Tanner scale. Unfortunately CDP cannot be differentiated from IHH merely on the basis of symptoms or serum gonadotropins and testosterone levels. Response of pituitary gonadotropins to GnRH is also same in both conditions. Nevertheless, the advent of highly sensitive immunoassay and radiometric immunoassay systems for LH, FSH and testosterone has not entirely solved the problems, since their values may overlap between normal and pathological conditions. Serum prolactin in IHH is often low and fails to increase following provocative tests like TRH and chlorpromazine challenge. Patients with anorexia nervosa, stress and exercise induced syndromes are often reversed by pulsatile GnRH treatment. Failure of puberty in IHH patients is the dominant and worrying symptom with which patient or parents seek advice. Once the diagnosis has been made pulsatile GnRH treatment is the preferred treatment. High cost of GnRH pump, problem of constant wearing it, GnRH availability and cost are the main obstacles in successful outcome of treatment. Gonadotropins in the form of injection LH and FSH given for 6–12 months or injection testosterone in low dose intermittently are alternative regimens that induce puberty in majority of the cases and are cost effective.

MATERIAL AND METHODS

After informed consent 20 patients who reported in OPD either at their own or brought by the parents for small sized testes and subsequent failure of development of secondary sexual characters were enrolled for the study. Patients with known pituitary or hypothalamic disorder or raised gonadotropins signifying damaged gonads were excluded from the study. Important parameters evaluated in patients were age at presentation, weight, height, any abnormal preterm or term event, change in weight and height, anosmia, presence of facial, pubic and axillary hairs, size of testes, baseline hormonal profile including basal LH, FSH, Testosterone, basal and provocative increase in Prolactin and clinical examination to exclude pituitary or hypothalamic disorder. X-rays hand for bone age and lateral view x-rays skull for hypothalamic/pituitary disorders were also included in the baseline investigations.

On the basis of above findings patients were assigned a Marshal and Tanner stage and were followed by progress of this staging. Genetic studies and MRI brain and GnRH stimulation of pituitary were omitted considering the cost.

Twenty patients were divided into two groups based on serum prolactin levels, i.e., IHH group (n=9) and CDP (n=11) group. Two patients in CDP group were lost in follow-up leaving nine patients in each group. Initially patients in both groups were followed at 6 monthly intervals for 2 year without any treatment. At the end of two years all patients of IHH group with no pubertal features were given intermittently 50 mg injection testosterone weekly for 4 weeks. Only those CDP cases who lagged behind by more than 2 years as per Tanner scale or by more than 4 years by bone age especially having psychosocial or psychosexual problems were also given intermittently short courses of 50 mg injection testosterone weekly for 4 weeks to induce secondary sexual characters. Again all cases were followed-up at 6 monthly intervals for 2 more years or till completion of puberty whichever was earlier. At each follow-up visit patients were evaluated for progress in weight, height, appearance of axillary and pubic hairs, facial hairs, change in the size of testis and phallus, deepening of voice, bone age and other signs of puberty.

RESULTS

Nine patients were provisionally diagnosed as IHH and 11 as cases of CDP. Patients with IHH had low basal and provocative serum prolactin levels as compared to patients diagnosed as CDP. (Figure-1 & 2). All patients presenting with delayed puberty in our study were male. Age of presentation varied between 14 and 23 years with mean of 15 years. Height of all patients varied between 112 and 123 Cm with a mean of 115 Cm. Two patients from CDP group were lost in the follow-up leaving 9 patients in each group (Table-1). Total of 10 (50%) patients (3 patients from IHH and 7 patients from
CDP group) achieved stage 4 puberty spontaneously in a variable duration spanning from 6 to 36 months. Eight (44%) patients from IHH group with failed induction of puberty were put intermittently on short courses of Testosterone 50 mg weekly for 4 weeks each to induce pubertal features. This attempt was successful in 6 (67%) patients who achieved stage 4 puberty. Two (22%) patients of IHH failed to achieve any pubertal features despite 4 years follow-up and repeated attempts to stimulate hypothalamus-pituitary-testis axis by low dose testosterone. Despite low testosterone and gonadotropin levels their testes sizes did not increase from pre-pubertal level. Both these patients were inducted in study when their ages were 20 and 23 respectively. Ultimately they were placed on full dose of testosterone 100 mg monthly to induce secondary sexual characters. Two patients with an initial diagnosis of CDP were also placed on short testosterone regime. Their puberty stages lagged behind by more than two years or bone age by more than four years and had psychosocial or psychosexual problems at school or at home. This group also successfully achieved stage for puberty.

DISCUSSION

Approximately 75% of patients with Kallmann syndrome have abnormal olfactory systems on MRI, including complete agenesis of olfactory bulbs and sulci, shallow olfactory sulci, or medial orientation of the olfactory sulci. In our study none of the patient had any olfactory disorder.

Delayed epiphyseal maturation is nonspecific and is present in individuals with idiopathic hypogonadotropic hypogonadism. Bone age lagged behind the chronological age by 2 years in 6 patients and by 1 year in 3 patients with IHH and this lagging continued till induction of puberty by high dose testosterone therapy. Androgen replacement in males with IHH restores libido, improves erectile dysfunction, increases muscle strength, and develops secondary sex characteristics. A short course of androgens in infancy leads to penile growth in infants with micropenis. Androgen replacement also improves bone density and may prevent osteoporosis. Classically low prolactin basal and post-TRH or post-chlorpromazine test have been done traditionally to segregate normal puberty from IHH but our study failed to support this observation. Raivio et al described a variety of reversal of IHH in which patients with IHH during treatment with androgen or other drugs undergo spontaneous remission of disease with spontaneous cure. Therefore treatment needs to be stopped to observe this phenomenon. None of our patient demonstrated this phenomenon. Despite success claimed by many authors, Delemarre et al observed that pulsatile GnRH cannot distinguish between a normal delayed puberty and a hypothalamic defect in still prepubertal patients. Pulsatile GnRH however offers an appropriate way to initiate testicular growth including virilization and fertility in males with hypogonadotropic hypogonadism. Liu L et al demonstrated a two-year comparison of testicular responses to pulsatile gonadotropin-releasing hormone and exogenous gonadotropins therapy in men with IHH that there is no difference in outcome with these two regimens. Our patients were treated with LH and FSH due to non-availability of GnRH. Most of them achieved grade 4 puberty with this regimen alone. IHH is not all or none phenomena but is characterised by various grade of severity of GnRH deficiency. Moreover, the hormone responses to GnRH in IHH patients depend on the magnitude of the underlying GnRH secretory defect. No such grade of severity was observed in our study. Finkelstein JS et al concluded that long term exogenous GnRH administration induces pituitary and gonadal priming, which subsequently enables them to sustain normal pituitary and gonadal function in response to their own enfeebled GnRH secretion. Pitteloud N et al concluded that 1) pulsatile GnRH therapy in IHH men is very successful in

Table 1: Results of patients in four year follow up

<table>
<thead>
<tr>
<th>Description</th>
<th>Result</th>
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<tbody>
<tr>
<td>Total number of patients</td>
<td>20</td>
</tr>
<tr>
<td>Number of patients lost in follow-up</td>
<td>2 (11%)</td>
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<tr>
<td>Number of patients in IHH group based on clinical examination and basal and post stimulation serum prolactin level</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>Number of patients in CDP group based on relatively normal basal and post stimulation serum prolactin level</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>Ages of 2 patients with failed induction of puberty with low dose gonadotropin therapy</td>
<td>22, 23 year</td>
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<tr>
<td>Number of patients from IHH group requiring high dose testosterone therapy</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>Number of patients from CDP group requiring high dose testosterone treatment</td>
<td>2 (22%)</td>
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inducing androgen production and spermatogenesis; 2) normalization of the LH-Leydig cell-T axis is achieved more uniformly than the FSH-Sertoli cell axis during GnRH therapy; and 3) favourable predictors for achieving an adult testicular size and consequently optimizing spermatogenesis are prior history of sexual maturation, a baseline testosterone level >60 pg/ml, and absence of cryptorchidism. Segregating cases of CDP from IHH is an uphill task. Only adequate and prolonged follow-up can resolve and unfold this diagnostic dilemma.

CONCLUSION

Discriminative value of basal and provocative serum prolactin in differentiating IPP from CDP reported in several studies could not be substantiated by our study.

REFERENCES


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