Clinical Profile of Adolescents With Delayed Puberty

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ABSTRACT
One year study on forty-eight adolescents with delayed puberty revealed etiology of constitutional delay, hypogonadotrophic hypogonadism (HH), hypergonadotrophic hypogonadism, chronic systemic disease, hypothyroidism and sex reversal in 14 (29.2%), 13 (27%), 12 (25%), 5 (10.4%), 3 (6.3%) and 1 (2.1%) cases, respectively. Earlier presentation, male preponderance, significant normal variants and utility of GnRH analogue testing observed.

Delayed puberty has heterogeneous etiology in adolescents. Data on delayed puberty are available from the Western world [1-3] and from some parts of India [4]. Hence, we conducted this study between June, 2017 and May, 2018 to describe the clinical, biochemical and radiological profile of adolescents with delayed puberty in a tertiary care hospital in Southern India.

After approval from the institutional ethics committee, adolescents referred to an endocrine clinic with delayed puberty or delayed sexual maturity rating were recruited. Delayed puberty was defined as absence of thelarche by 13 years or no menarche 5 years after thelarche (girls) or no progression of secondary sexual characters for 18 months after onset of puberty [5], or no testicular enlargement (≥4mL) by 14 years (boys). Details of age, sex, history of pubertal onset, growth, systemic disease, family history of delayed puberty and previous illnesses were retrieved. Anthropometric measurement and sexual maturity rating (SMR) assessments were performed on girls with minimal clothing in complete privacy with a female staff nurse and mother, for boys in the presence of father. Breast stage and pubic hair (in girls) and testicular volume (using Prader orchidometer) and gonadal stage (in boys) were classified into stages described by Tanner [6].

Subjects underwent baseline biochemical evaluation for systemic diseases, thyroid profile, bone age assessed using the Greulich Pyle atlas in those with short stature, and ultrasound to assess pelvic organs in girls [7]. Hypothalamo-pituitary gonadal (HPG) axis was assessed by luteinizing hormone, follicle stimulating hormone and serum estradiol (in girls) and serum total testosterone (in...
boys). Serum estradiol >10pg/mL and testosterone >25ng/dL was considered as pubertal onset. Those with inconclusive LH (<0.65 IU/L) and FSH (<1.2 IU/Litre) underwent Gonadotrophin analogue (GnRHa) stimulation test to distinguish hypergonadotrophic hypogonadism (HH) from constitutional delay of growth and Puberty (CDGP) [8,9]. Children with HH also underwent MRI brain. Human chorionic gonadotrophin stimulation test (hCG) was performed to assess leydig cell function in males with dysgenic gonads. Pubertal induction with testosterone (50 mg intramuscularly) and estrogen (2.5mcg ethinyl estradiol or 0.25mg estradiol valerate on alternate days) was done in hypogonadism and subjects were followed-up.

A total of 48 adolescents (27 males) with mean age (SD) of ___ years (males, 15.3 year and females 15.8 years) were studied. Delayed sexual maturation, no progress of maturation and no menarche, was noted in 77.1%, 10.4% and 12.5%, respectively. The etiology was CDGP, HH, hypergonadotrophic hypogonadism, chronic systemic disease, primary hypothyroidism and sex reversal in 14(29.2%), 13(27%), 12(25%), 5(10.4%), 3(6.3%) and 1(2.1%) cases, respectively.

GnRH analogue testing was performed in twelve subjects (68% had flat gonadotrophin response suggesting HH and 34% had normal pubertal response suggesting CDGP). An increment in height Z-score of +0.4 was seen in three subjects with CDGP treated with intramuscular testosterone (owing to significant psychological distress) versus +0.3 in eight with spontaneous puberty after 12 month follow-up. Pubertal progression was noted in all on follow-up. One patient each with Crohns disease, type-1 diabetes mellitus, congenital adrenal hyperplasia (CAH), systemic lupus erythematosus (SLE) and primary immunodeficiency had delayed puberty where control of the primary disease was the primary strategy. Oral estrogen was initiated in one adolescent with SLE, steroid dose modification in CAH and thyroxine replacement in primary hypothyroidism.

Thirteen (27%) subjects (10 boys) had HH (9 with panhypopituitarism). The etiological profile was non-syndromic in 9. Kallman syndrome 2, Prader Willi syndrome 1 and Bardet Biedl syndrome 1. Multiple pituitary hormone replacement (sex hormone, growth hormone, cortisol, thyroxine and desmopressin) and pubertal induction, resulted in height Z-score increment of +0.6 and +0.15 in subjects with multiple pituitary hormone deficiency and isolated HH, respectively.

Hypergonadotrophic hypogonadism was seen in 12 adolescents (median age 15.4 years; 8 females) with mean (SD) height SDS of -3.2 (0.9). These included Turner syndrome in 5, Klinefelter syndrome in 2, bilateral anorchia in 1, primary gonadal dysgenesis in 3 and post intracranial tumor therapy in 1. Three subjects with Turner syndrome had co-morbidities (solitary left kidney, horse shoe kidney and aortic valve abnormality in one subject each). One adolescent with delayed puberty had complete androgen insensitivity syndrome and was initiated on oral estrogen.

In our series, normal variants predominated among the cases. A similar prevalence of 17.9% to 68% of normal variants was observed earlier [1,4]. Puberty being an important milestone in southern India leads to increased health seeking behavior of families. Boys with delayed puberty have low self- esteem and reduced peer contact leading to earlier health seeking behavior [10]. Hence, we
observed a higher male preponderance in HH. Need for pituitary hormone replacement in majority of subjects with HH and significant co-morbidities in few with hypergonadotrophic hypogonadism, highlights the need for detailed systemic evaluation in delayed puberty.

*Ethics clearance: Mehta Multispeciality Hospitals IEC; No. IRB-MCH/10/2017, dated April 4, 2018.*

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