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A slight variability in anthropometric parameters but a significant delay in sexual maturity rating and decreased hormonal parameters in patients with delayed puberty

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Abstract--- The present study was designed to compare anthropometric parameters, sexual maturity rating (SMR) and plasma follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone (T) levels in male delayed puberty patients and age matched healthy controls and determine whether a difference exists between these parameters before and after 18 years of age in delayed puberty patients. Anthropometric parameters (height, weight, body

mass index (BMI), bone age), SMR (penile length, testicular volume, pubic and facial hair stage) and plasma concentrations of FSH, LH and T were determined through respective ELISA in 37 sporadic delayed puberty male patients of 14-23 years and 55 age matched controls visiting Shifa International Hospitals Ltd., Islamabad, Pakistan Institute of Medical Sciences, Islamabad and Military Hospital, Rawalpindi, Pakistan. Data were interpreted using Student's t-test and ANOVA. The height of delayed puberty patients was lower than controls from 14-17 years, whereas weight of delayed puberty patients was slightly more than controls from 17-23 years; most of patients were over-weight. Bone age of most of patients was slightly delayed than chronological age. SMR of patients showed significantly lower penile length, testicular volume, pubic and facial hair stage than controls. Plasma FSH, LH and T concentrations were significantly decreased in patients than controls. In conclusion, we demonstrate a slight difference in anthropometric parameters of controls and delayed puberty patients during later stages of puberty while SMR and hormonal parameters were significantly reduced in delayed puberty patients than controls throughout puberty.

Keywords---Delayed puberty, Hypogonadism, Male puberty, Sexual maturity rating, Testosterone

Introduction

Delayed puberty in boys is typically described by the deficiency of masculinization and reduced volume of testes (<4 mL) in combination with absent or low sperm count until fourteen years of age (Kim, 2015). The disorders, which are most important causes of delayed puberty include constitutional delay in growth and puberty (CDGP) and hypogonadotropic hypogonadism (HH). CDGP is not a disorder but a common condition in which puberty and its associated growth spurt occurs near the upper level of normal age range (Howard, 2019), while HH is a disorder caused by decreased release or action of gonadotropin releasing hormone (GnRH), which in turn decreases luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone (T) (Nalbantoglu et al., 2019).

Delayed puberty can be diagnosed by complete medical check-up of a new-born baby, which may include decreased genital size (micropenis) or undescended testes (cryptorchidism) (Xu & Pitteloud, 2019). The physical examination such as height, weight and growth velocity and bone age of boys with delayed puberty may give some idea about the causes that might have delayed their puberty (Kim, 2015). In addition, the delayed puberty is carefully confirmed using Tanner staging that determines precise sexual maturity (Dwyer & Hayes, 2019). Dysfunction of hypothalamo-pituitary-gonadal (HPG) axis can be further confirmed by determining the levels of FSH, LH and T in plasma (Kim, 2015).

Puberty is a period of biological, physical, psychological, cognitive and social transformations, which affect his/her personal life and interaction with other members of the society. Moreover, the society determines the socio-economic contribution of an individual through his appearance and behaviour (Wolfenden &

Ryan, 2013). The children with symptoms of delayed puberty are considered behind their peers and hence their socio-economic contribution is misdiagnosed, which may cause psychological problems (Laronda & Woodruff, 2017). The diagnosis of delayed puberty at an earlier age (14-16 years) is very important in order to start the treatment for induction of puberty, however, the differentiation between CDGP and HH is very difficult (Xu & Pitteloud, 2019). The age of 18 years was set as a cut off value to differentiate between CDGP (<18 years) and HH (>18 years) (Swee & Quinton, 2019). Therefore, the present study was designed to:

- Compare anthropometric parameters including height, weight, body mass index (BMI) and bone age, sexual maturity rating (SMR) including penile length, testicular volume, pubic hair and facial hair and plasma FSH, LH and T levels in delayed puberty patients and age matched healthy controls.
- Determine whether a difference exists between these parameters before and after 18 years of age in delayed puberty patients.

Methods

Subjects

Thirty-seven sporadic male patients, who did not grow at puberty and show signs of pubertal development by the age of 14/15 years from Shifa International Hospitals Ltd. (SIH), Islamabad, Pakistan, Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan and Military Hospital (MH), Rawalpindi, Pakistan, comprised the study group in this investigation. A questionnaire was developed to acquire relevant information from the patients and blood sampling was carried out at the respective hospitals. Fifty-five age matched healthy individuals constituted the control group. The study was conducted from August, 2016 to July, 2017.

The study was approved by University and Hospitals' Ethics Committees and an informed written consent was obtained from the patients and/or their guardians. The male patients with late/absent sexual maturation and previous history of mumps, having abrupt weight changes, eating disorders, neurological pathology and/or androgens exposure were not included in the study. Patients diagnosed with other illnesses like hypothyroidism, hyperprolactinemia, growth hormone deficiency and with syndromic conditions like Turner syndrome, Bardet Biedl syndrome (BBS), Klinefelter syndrome, Prader Willi syndrome (PWS) were also not included in the study.

Assessment of Anthropometric Parameters

The height of delayed puberty patients and normal subjects was measured using Harpenden Stadiometer with the precision of 0.1 cm. The weight of the boys was determined through digital weight scale as close as 0.1 Kg. The determination of BMI was carried out through equation:

$$\text{BMI (Kg/m}^2\text{)} = \frac{\text{Weight in Kilograms}}{(\text{Height in meters})^2}$$

Bone age of males with delayed puberty was assessed through Greulich and Pyle, (1971) procedure and was compared with their chronological age.

Determination of SMR

Penile length, testicular volume, pubic and facial hair were determined through Tanner & Whitehouse, (1976) criteria to find the stage of pubertal development. Prader's orchidometer was used for measurement of testicular volume.

Hormonal Analysis

Analysis of plasma samples was carried out at the Shifa Clinical Laboratory, SIH, Islamabad through respective ELISA systems for analysis of FSH, LH and T levels.

Statistical Analysis

The statistical tools like Student's t-test and ANOVA were used for data analysis. The value of p was set at <0.05 . The mean values for each group were obtained and were given along with their standard error of mean (SEM).

Results and Discussion

Comparison of Anthropometric Parameters of Controls and Delayed Puberty Patients

The comparison of mean height, weight, BMI and bone age of controls and delayed puberty patients when diagnosed for disorder is presented in Table 1. The mean height of patients was found to be reduced significantly when compared with controls at 14 ($p = 0.001$), 15 ($p = 0.000$) and 16 ($p = 0.000$) years but non-significantly ($p = 0.11$) at 20 years. Similarly, the mean height of patients was slightly lower than control subjects at the ages of 17, 18, 19, 22 and 23 years but the sample size was small for these age groups. The mean weight of delayed puberty boys was lower than the controls at 14 ($p = 0.11$), 15 ($p = 0.53$) and 16 ($p = 0.09$) years but markedly ($p = 0.3$) more than controls at 20 years of age. In contrast, the mean weight of delayed puberty patients was marginally more than controls at the ages of 17, 18, 19, 22 and 23 years. The mean BMI of delayed puberty patients was non-significantly ($p = 0.5$) lower than controls in 14 years' age group. However, mean BMI of delayed puberty patients was higher at 15 ($p = 0.26$), 16 ($p = 0.54$) and 20 ($p = 0.09$) years of age. Furthermore, mean BMI in delayed puberty patients was evidently higher at the ages of 17, 18, 19, 22 and 23 years. Our results revealed that the difference was significant between chronological age and bone age of patients at 14 ($p = 0.001$), 15 ($p = 0.02$) and 16 ($p = 0.002$) years but non-significant ($p = 0.14$) at 20 years of age. Moreover, the bone age was also delayed at 17, 18, 19, 22 and 23 years of chronological age.

Comparison of SMR of Controls and Delayed Puberty Patients

The comparison between mean penile length, testicular volume, pubic hair stage and facial hair stage of controls and delayed puberty patients is presented in Table 2. The mean penile length of delayed puberty patients was significantly lesser than controls at 14 ($p = 0.000$), 15 ($p = 0.01$), 16 ($p = 0.008$) and 20 ($p = 0.000$) years of age. Furthermore, the mean penile length of delayed puberty patients was evidently lesser than controls at the ages of 17, 18, 19, 22 and 23 years. The patients with delayed puberty had significantly lower mean testicular volume than controls at 14 ($p = 0.000$), 15 ($p = 0.000$), 16 ($p = 0.000$) and 20 ($p = 0.000$) years of age. In addition, the patients with delayed puberty had markedly

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Table 1: Mean height, weight and BMI of controls and delayed puberty patients at diagnosis and number (n) of delayed puberty patients having normal and delayed bone age

Age of diagnosis of patients (years)	Number (n)		Height (cm)		Weight (Kg)		BMI (Kg/m ²)		Bone age (years)	
	Controls	Patients	Controls (Mean±SEM)	Patients (Mean±SEM)	Controls (Mean±SEM)	Patients (Mean±SEM)	Controls (Mean±SEM)	Patients (Mean±SEM)	Normal (n)	Delayed (n)
14	10	9	154.9±1.26	143.56±4.7	43.5±1.31	36.4±5.6	18.12±0.47	17.06±1.77	2	7
15	7	6	160.3±1.33	145.6±4.6	47.2±1.51	44.8±6.61	18.44±0.82	20.57±1.89	2	4
16	7	6	167.9±1.29	150.75±2.44	52.28±2.63	45.5±7.22	18.6±1.02	19.77±2.8	1	5
17	5	2	169.1±1.72	157.5±2.5	55.4±2.77	60±2	19.39±1.06	24.18±0.04	0	2
18	5	1	174.9±1.93	163±0	60.2±1.02	60±0	19.68±0.35	22.58±0	0	1
19	5	1	175.1±1.73	165±0	61.8±2.82	63±0	20.19±1.09	23.14±0	0	1
20	6	3	176.2±1.82	168.3±1.7	63.33±2.02	70±4.2	20.47±0.92	24.66±1.03	1	2
22	5	1	177±1.8	168.5±0	67.2±2.46	72±0	21.44±0.69	25.8±0	0	1
23	5	2	178.7±1.26	170.5±2.5	69.2±2.46	71±11	21.68±0.73	24.33±3.07	0	2

Table 2: Mean penile length and testicular volume of controls and delayed puberty patients at diagnosis and number (n) of delayed puberty patients having different stages of pubic and facial hair at diagnosis along with normal Tanner stage

Age of diagnosis of patients (years)	Penile length (cm)		Testicular volume (mL)		Pubic hair stage		Facial hair stage	
	Controls (Mean±SEM)	Patients (Mean±SEM)	Controls (Mean±SEM)	Patients (Mean±SEM)	Normal	Patients	Normal	Patients
14	9.56±0.28	6.11±0.89	13.7±0.29	2.77±0.4	Stage 3	Stage 1(n=9)	Stage 3	Stage 1(n=9)
15	10.01±0.41	7.42±0.64	17.29±0.61	4.5±1.26	Stage 4	Stage 1(n=4) Stage 2(n=2)	Stage 3	Stage 1(n=6)
16	10.87±0.58	8.08±0.64	21.42±0.48	6.83±1.7	Stage 5	Stage 1(n=3) Stage 2(n=1) Stage 3(n=2)	Stage 4	Stage 1(n=4) Stage 3(n=2)
17	11.96±0.74	6±1	21.6±0.93	4±2	Stage 5	Stage 2(n=2)	Stage 4	Stage 1(n=2)
18	13.52±0.91	7±0	22.4±1.04	10±0	Stage 5	Stage 2(n=1)	Stage 5	Stage 1(n=1)
19	14.12±0.96	8±0	22.6±0.87	3±0	Stage 5	Stage 1(n=1)	Stage 5	Stage 1(n=1)
20	14.62±0.88	7.33±0.88	22.8±0.7	2.33±0.67	Stage 5	Stage 1(n=1) Stage 2(n=2)	Stage 5	Stage 1(n=3)
22	14.7±0.97	4±0	23.2±0.86	2±0	Stage 5	Stage 1(n=1)	Stage 5	Stage 1(n=1)
23	15.04±0.95	6±1	23.4±0.93	4±2	Stage 5	Stage 2(n=2)	Stage 5	Stage 1(n=1) Stage 3(n=1)

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lower mean testicular volume than controls at the ages of 17, 18, 19, 22 and 23 years. Our results revealed that pubic hair and facial hair stages of delayed puberty patients were significantly ($p < 0.05$) delayed at 14, 15, 16 and 20 years of age. Likewise, the pubic and facial hair stages of 17, 18, 19, 22 and 23 years of delayed puberty patients were also markedly delayed.

Hormonal Analysis of Controls and Delayed Puberty Patients

The difference between mean FSH, LH and T levels in controls and delayed puberty patients at the age of diagnosis is presented in Table 3. Our results revealed that the mean FSH levels were significantly lower in delayed puberty patients than controls at the ages of 14 ($p = 0.000$), 15 ($p = 0.001$), 16 ($p = 0.000$) and 20 ($p = 0.001$) years. Furthermore, the mean FSH levels were greatly decreased as compared to controls at the ages of 17, 18, 19, 22 and 23 years. In a similar manner, the results of our study showed significantly lower mean LH levels in delayed puberty patients than controls at the ages of 14 ($p = 0.03$), 15 ($p = 0.001$), 16 ($p = 0.000$) and 20 ($p = 0.001$) years. Mean LH levels were markedly reduced in patients as compared to control subjects at the ages of 17, 18, 19, 22 and 23 years. Our results indicated significantly decreased mean T concentrations in delayed puberty patients than controls at the ages of 14 ($p = 0.001$), 15 ($p = 0.000$), 16 ($p = 0.001$) and 20 ($p = 0.001$) years. Moreover, mean T levels were markedly decreased as compared to controls at the ages of 17, 18, 19, 22 and 23 years.

Table 3: Mean FSH, LH and T concentrations in controls and delayed puberty patients at diagnosis

Age of diagnosis of patients (years)	Plasma FSH concentrations (mIU/mL)		Plasma LH concentrations (mIU/mL)		Plasma T concentrations (nmol/L)	
	Controls (Mean±SEM)	Patients (Mean±SEM)	Controls (Mean±SEM)	Patients (Mean±SEM)	Controls (Mean±SEM)	Patients (Mean±SEM)
14	7.51±0.27	1.91±0.53	2.18±0.37	1.2±0.4	12.04±1.17	2.85±0.85
15	6.75±0.38	1.49±0.45	2.59±0.43	0.64±0.26	13.77±0.81	1.52±0.8
16	7.47±0.42	1.25±0.38	3.24±0.47	0.59±0.31	16.64±0.86	1.84±0.55
17	8.26±0.41	1.5±0.5	4.13±0.32	0.85±0.15	19.5±0.59	0.77±0.31
18	8.89±0.55	0.9±0	4.59±0.54	0.8±0	21.68±0.72	0.46±0
19	7.44±0.43	0.4±0	4.18±0.41	0.1±0	20.27±0.95	0.4±0
20	7.84±0.39	0.37±0.07	4.79±0.44	0.4±0.25	21.23±0.75	0.53±0.26
22	8.19±0.38	0.02±0	5.49±0.31	0.14±0	24.08±1.01	0.46±0
23	8.36±0.4	0.97±0	6.306±0.38	0.33±0.2	26.15±1.11	0.38±0.28

Our results indicated that the anthropometric parameters such as height and weight of delayed puberty patients were significantly lower than controls at earlier ages of 14 to 17 years but the difference was not significant at the later ages and these patients attained their target values of height. However, bone age and BMI were found to be important parameters as delayed puberty patients had significantly delayed bone age from 14 to 16 years of age and most of them were over-weight. Furthermore, SMR and hormonal levels were significantly lower than controls in patients of all age groups, which indicated that these two criteria need to be focused during diagnosis of delayed puberty.

Our findings showed significantly decreased mean height in delayed puberty patients between 14 and 17 years of age, while the decrease in the mean height was non-significant between 18 and 23 years of age as compared to age matched controls. Similar to results of our study, a recent study observed a decrease in the height of boys with HH at pubertal age (Reinehr et al., 2019). In addition, another study indicated that boys having HH lack the pubertal growth spurt (Marshall-Andon, 2016) but they grow at a steady speed and reach their final height, which is close to their target height (Satoh, 2015). It has been suggested that delayed puberty patients have longer pre-pubertal period during which the length of their legs increases that enables them to attain their final height (Satoh, 2015).

The growth rate and maturity of a child can be assessed by using bone age, which tells the maturity of a child's skeletal system. Our study observed that the bone age of boys with delayed puberty was years behind their chronological age. We witnessed a delayed bone age of about 2-3 years as compared to chronological age in delayed puberty patients. A previous study has also demonstrated a delayed bone age of about 2.5 years in delayed puberty patients as compared to their chronological age (Zucchini et al., 2008).

Our research revealed reduced mean weight in delayed puberty patients than controls at the ages of 14, 15 and 16 years and mean weight of patients was higher than controls from 17 to 23 years of age. A previous study has also demonstrated increased weight in HH patients (Martin & Martin, 2005). The correct measurement of body size is through BMI, which tells whether a person's weight is correct for his height. In our study, most of the delayed puberty patients were in the underweight category of BMI from 14 to 16 years age while most of the patients were in the over-weight category of BMI between 17 and 23 years of age. In line with our observations, a number of recent studies have also indicated a higher percentage of over-weight and obesity in HH patients with advanced age as compared to HH patients with age around 14 years (Reinehr et al., 2019; Bonomi et al., 2018). It has been observed that obesity and hypogonadism are strongly correlated with each other although, the mechanism is not yet fully described (Zouras et al., 2017).

Our results witnessed significantly smaller mean penile length and decreased testicular volume of delayed puberty patients than controls in all age groups from 14 to 23 years. Similarly, some recent and previous studies have also observed a decreased penile length and testicular volume in patients with absent pubertal development (Kulshreshtha et al., 2013; Shiraishi et al., 2014; Bonomi et al., 2018; Jin et al., 2018). An earlier study also showed that increased BMI causes hypogonadism and small genital size (Moriarty-Kelsey et al., 2010). This condition was also observed in our patients, who were mostly over-weight and had

significantly small penis length. Furthermore, Bonomi et al. (2018) revealed the presence of cryptorchidism in patients with complete pubertal failure. In the present study, cryptorchidism was also observed in three out of thirty-seven patients. Our study identified that delayed puberty patients had significantly delayed pubic hair and facial hair stages as compared to controls in all age groups from 14 to 23 years. In line with these observations, a recent and some previous studies have also shown delayed Tanner stages in delayed puberty patients before any treatment (Kulshreshtha et al., 2013; Shiraishi et al., 2014; Jin et al., 2018).

The present study revealed very low FSH, LH and T levels in patients with pubertal delay than controls in all age groups from 14 to 23 years indicating dysfunction of HPG axis. The results of our study are supported by some recent and previous studies, where low levels of FSH, LH and T in HH patients than controls were observed (Kulshreshtha et al., 2013; Shiraishi et al., 2014; Bonomi et al., 2018; Jin et al., 2018).

Conclusion

Our results revealed a slight decrease in anthropometric parameters of delayed puberty patients as compared to controls during later stages of pubertal development and these patients attained their target height values. However, BMI was found to be an important parameter as most of patients were over-weight. Furthermore, sexual maturity rating and hormonal parameters were significantly reduced in delayed puberty patients than controls throughout the pubertal period, which indicated that these two criteria need to be focused during diagnosis of delayed puberty.

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