

Response to short course androgenisation in late reported cases with micropenis

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Abstract

Background and objectives: Micropenis is an abnormally short penis and its treatment should begin in infancy or in very early childhood. The present study investigated the response of short term testosterone therapy in late reported cases of micropenis.

Methods: A total of 17 cases of micropenis between the age of 8 and 15 years were included in the study. Standard criteria for the diagnosis of micropenis were followed. All cases were treated with intramuscular testosterone 50 to 75 mg once every 21 days. Response to testosterone treatment was measured by the absolute and percent increment in stretched penile length (SPL). Response was considered adequate if final SPL crosses the average SPL for age. We also compared the response of treatment of cases reported before and after 11 years of age.

Result: A total of 17 micropenis cases were included in the study. Out of total 17 boys, 10 were between 8 to 11 years (Group 1) and 7 were between 12 to 15 years (Group 2) of age. The mean pre-treatment SPL of 17 micropenis cases was 3.1 ± 0.2 cm (CI: 2.83, 3.43 cm). The mean initial SPL of Gr1 and Gr2 was not significantly different (3.2 ± 0.3 cm vs 3.0 ± 0.1 cm; $p > 0.248$). The mean post treatment SPL of 17 cases increased significantly ($p < 0.001$) compared to their initial SPL. The range of percentage increment in SPL was 100%-400%. Higher testosterone doses were required in Gr2 cases compared to Gr1 (360 ± 20.8 mg vs 260.7 ± 38.5 mg).

Conclusion: Micropenis in boys with palpable gonads responded to short term testosterone treatment in late reported cases and we termed these cases as simple micropenis.

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Introduction

Micropenis is an abnormally short penis and is defined as stretched penile length (SPL) of < 2.5 standard deviations below the mean SPL for age [1,2]. Micropenis should be treated shortly after birth to prevent its consequences. Appropriate evaluation is required to exclude few potentially serious diseases like panhypopituitarism, isolated growth hormone deficiency, androgen insensitivity states, congenital adrenal hyperplasia (CAH) in a girl or developmental anomaly [1,2]. The cases with palpable testes are likely to have intraabdominal sex organs and are of male pattern and most of

them respond well to short term androgenisation therapy [3,4]. It is important that treatment of these cases should begin in infancy or in very early childhood. But in practice, we come across such cases who seek treatment late. In this paper, we present our experience of 17 cases of micropenis who sought treatment from 8 to 15 years of age.

Material and method

Cases of micropenis reporting to the outpatient department after their 8th birthday from January 2015 to December 2018 were enrolled in the study.

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Diagnosis of micropenis was made by measurement of SPL which was either equal or less than that for his age by using table described by Custer & Rau [1]. Exclusion criteria included hypothyroid, suspected hypopituitarism, growth hormone deficiency, any syndrome related to microphallus or developmental anomaly, family history of androgen insensitivity, bilateral cryptorchids and one or both testicular volume > 4 ml [1,2]. All cases were treated with intramuscular testosterone 50 to 75 mg once every 21 days until SPL reaches or cross the average SPL for his age up to the age of 11 and for age 11 thereafter or total 6 times which ever came first. Total increment and percent increment were calculated by formula (Last SPL – Initial SPL) and [(Last SPL – Initial SPL)/ Initial SPL] x100 respectively. The response of treatment was considered adequate if last SPL of the case reached or crossed

the average SPL for his age up to age of 11 years and for age 11 years thereafter. To assess obesity we used BMI-for-age by calculating BMI Percentile Calculator for Child and Teen [5]. Statistical analysis was done with IBM SPSS package version 24.

Result

A total of 17 micropenis cases were included in the study. Out of total 17 boys, 10 were between 8 to 11 years (Group 1) and 7 were between 12 to 15 years (Group 2) of age. All the 17 boys were treated with injection testosterone. Their pre and post treatment detail profile namely age, height, weight, BMI, puberty stage, testosterone dose and SPL are shown in Table-1. Age adjusted % BMI showed 10 (59%) were obese; 3 (17.5%) over weight and 4 (23.5%) were of normal weight. The mean (±SE)

Table-1: Profile of study population and change of stretched penile length (SPL) and other parameters before and after testosterone therapy

Case no.	Age	Ht	Wt	BMI	Puberty	TT(n)	SPL1	MP	SPL2	AP	HG	WG	% increment
1	8	116	21	37 th	T1	300(6)	3.0	3.7	6.5	6.2	4	3	116.67
2	8	137	44	99 th	T1	250(5)	3.0	3.7	6.5	6.2	3	5	116.67
3	8	142	38	90 th	T1	350(6)	3.0	3.7	10.0	6.2	3	2	233.33
4	8	136	41	98 th	T1	300(6)	2.5	3.7	8.0	6.2	5	3	220.00
5	9	151	61	99 th	T1	375(6)	3.5	3.8	8.5	6.3	3	5	142.86
6	9	137	45	98 th	T1	100(2)	3.0	3.8	9.0	6.3	2	2	200.00
7	9	122	22	18 th	T1	150(6)	3.0	3.8	8.0	6.3	7	3	166.67
8	11	140	50	97 th	T1	350(6)	3.5	3.7	7.0	6.4	4	4	100.00
9	11	141	30	11 th	T1	350(6)	2.0	3.7	10.0	6.4	4	3	400.00
10	11	144	36	48 th	T1	250(5)	3.0	3.7	9.0	6.4	0	4	200.00
11	12	144	52	96 th	T1	350(6)	3.0	9.3	10.0	13.3	2	4	233.33
12	12	150	58	97 th	T1	450(6)	2.2	9.3	10.0	13.3	4	2	354.55
13	12	146	60	98 th	T1	300(6)	4.5	9.3	9.5	13.3	2	1	111.11
14	12	155	62	97 th	T1	400(6)	4.0	9.3	9.5	13.3	1	3	137.50
15	14	157	58	88 th	T1	400(6)	3.0	9.3	10.5	13.3	3	4	250.00
16	14	165	70	94 th	T1	450(6)	4.0	9.3	10.0	13.3	1	2	150.00
17	15	162	72	96 th	T1	300(4)	3.0	9.3	10.0	13.3	2	1	233.33

Note: SPL1: pre-treatment SPL (cm); SPL2: post treatment SPL (cm); MP: micropenis for the age (cm); AP: average phallus for the age; Ht: height (cm); Wt: weight (kg); HG: height gain during treatment (cm); WG: weight gain during treatment (kg); Puberty T1: compatible with Tanner’s stage 1 means TV = testicular volume <4 ml, PH = Pubic Hair Stage 1 and serum testosterone < 20 ng/d; TT (n): Total Testosterone in mg (number of shots) used; % increment: % increment in SPL; BMI: BMI-for-age calculated by BMI Calculator for Child and Teen as in www.cdc.gov/healthyweight/bmi/resultgraph.html; MP and AP columns are according to the table published by Custer JW & Rau RE. In: The Harriet Lane handbook, 18th ed., p 269-300.

Table-2: Change of SPL and percent increment of SPL following testosterone treatment of micropenis cases

Study population	No of case	Mean \pm SE (cm) of		p value	SPL gain (cm) mean \pm SE	% increase in SPL mean \pm SE	TT dose (mg) mean \pm SE
		SPL1	SPL2				
Gr1 Age: 8-11 yrs	10	3.2 \pm 0.3 (CI:2.73, 3.71)	9.6 \pm 0.3 (CI:8.94, 10.15)	<0.001	6.3 \pm 0.5	216.9 \pm 100.0	260.7 \pm 38.5
Gr2 Age:12-15 yrs	7	3.0 \pm 0.1 (CI:2.79, 3.22)	8.1 \pm 1.3 (CI:7.12, 9.01)	<0.001	5.1 \pm 0.5	170.9 \pm 48.0	360 \pm 20.8
Total	17	3.1 \pm 0.2 (CI: 2.83, 3.43)	8.9 \pm 0.3 (CI:7.51, 8.76)	<0.001	5.8 \pm 0.4	198.0 \pm 20.4	319.1 \pm 22.8
P value Gr1 vs. Gr2		0.248	0.008	-	0.391	0.139	0.013

Note: SPL1: pre-treatment SPL; SPL2: post treatment SPL; TT: testosterone; CI: confidence interval; p value calculated by student's t test; CI: confidence interval; SE: standard error

Table-3: Change of height and weight of micropenis cases following testosterone treatment

Study population	Pre-treatment	Pre-treatment	Post treatment	Post treatment
	Ht (cm) mean \pm SE	Wt (kg) mean \pm SE	Ht gain (cm) mean \pm SE	Wt gain (Kg) mean \pm SE
Gr1 Age: 8-11 yrs	136.6 \pm 3.3	38.8 \pm 3.9	3.9 \pm 0.6	3.3 \pm 0.5
Gr2 Age:12-15 yrs	154.1 \pm 2.9	61.7 \pm 7.1	2.3 \pm 0.5	2.8 \pm 0.4
Total	143.8 \pm 3.1	48.2 \pm 3.8	2.9 \pm 0.4	3 \pm 0.3
p value Gr1 vs Gr2	0.0009	0.0002	0.0280	0.2193

Note: Ht: height; Wt: weight; p value calculated by student's t test.

BMI of 17 cases was 22.6 \pm 1 Kg/m². Mean BMI of Gr1 and Gr2 cases was 23.9 \pm 1.3 Kg/m² and 20.8 \pm 1.7 Kg/m² respectively (p=0.08). Their pubertal parameters were compatible with Tanner's stage I: testicular volume (TV) range: (1–4 ml) and pubic hair (PH) stage 1 and serum testosterone level were < 20 ng/dl (Table-1). The SPL increased in all cases after testosterone treatment compared to pre-treatment length. The mean post treatment SPL of 17 cases increased significantly (p<0.001) compared to initial SPL (Table-2). The mean increase of SPL of younger boys (Gr1) was significantly more (p=0.008) compared to that of older boys (Gr2; Table-2). The range of percentage increment in SPL was 100%-

400%. No significant (p=0.139) difference in percentage increment of SPL occurred between Gr1 and Gr2 cases. Higher testosterone doses were required in Gr2 cases compared to Gr1 (360 \pm 20.8 mg vs. 260.7 \pm 38.5 mg). Table-3 shows the change of height and weight of micropenis cases following testosterone treatment.

Discussion

Micropenis means abnormally small penis and is defined by stretched penile length less than 2.5 standard deviations below the average stretched length for their age [1,2]. Micropenis has psychological stress to both family and individual and also has

medical challenges. The condition may be a presenting feature for underlying hormonal disorders like panhypopituitarism, isolated growth hormone deficiency, hypogonadism, hypothyroidism, testosterone insensitivity in boys or CAH in girls or of a part of syndrome like Prader-Willi syndrome and Laurence-Moon syndrome [1,2]. Usually a person with micropenis has internal genitalia and normal testicles. Testosterone treatments can often help the penis to grow. Applying testosterone cream to the genitals during infancy was tried with variable response but intramuscular testosterone injections are very effective [6-8]. It is advocated to treat early and at least before the age of onset of puberty e.g. before 8th birthday. In practice, some cases report late and clinician has to offer testosterone therapy. Our study is with 17 cases between their 8th and 15th birthday and 10 of them are after their 10th birthday. We administered 50 to 75 mg of testosterone at an interval of 3 weeks until target SPL was achieved or total dose of 450 mg was administered. In literature, a good response to testosterone treatment has been described as 100 percent increase in the SPL while an adequate response as a 3.5 cm increase in length [3,4,9]. All our cases attained the normal SPL for that age after testosterone treatment. We were also able to assess the amount of testosterone required to reach the mean SPL for age. All our cases had bilateral palpable gonad which means their karyotype was likely to be of male pattern (XY) and the response to such a dose of testosterone apparently excluded them as cases of androgen insensitivity syndromes (AIS). We, therefore, term this condition as simple micropenis. It is characterized by a) SPL < 2.5 SD below the mean for age, b) bilateral palpable gonads and c) response to testosterone treatment. All our cases were in per pubertal stage and during treatment there was no change in TV and PH. Out of 17 cases, 13 (76.5%) cases were either obese or overweight and

that might have delayed the diagnosis of micropenis by failing to differentiate them from buried penis. The study emphasizes that physicians should be made aware that micropenis is a treatable condition with good outcome even if diagnosed late.

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