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ORIGINAL RESEARCH

Clinical spectrum and treatment outcome of 5 alpha reductase deficiency in resource limited setting

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ABSTRACT

Background: 5-alpha reductase deficiency is a rare etiology of 46, XY disorders of sex development (DSD), with a prevalence estimated between 1 in 100,000 to 1 in 1 million live male births. Diagnosis in resource-limited settings can be challenging due to the high cost of genetic testing. **Clinical Description:** The cohort consisted of 14 patients, with a mean age of 9.70 ± 5.06 years and a median age of 11 years. Six patients presented during puberty, while eight were prepubertal, including four below five years of age. Presentations varied from isolated small phallus to proximal hypospadias and cryptorchidism. **Management and Outcome:** Karyotyping confirmed 46 XY in all patients, and ultrasound showed no Mullerian structures. HCG stimulation test was done using standardized protocol in all patients; revealing high (>27) testosterone: dihydrotestosterone ratio. Treatment with DHT gel resulted in significant increases in phallic length, especially in younger patients. Stage-wise surgical interventions were planned for patients with varying degrees of proximal hypospadias. **Conclusion:** Diagnosis and management of 5-alpha reductase deficiency in resource-limited settings can be effectively approached using clinical evaluation, hormonal assays, and imaging studies. HCG-stimulated testosterone to DHT ratio is a useful diagnostic tool, with higher cut-offs may improve specificity in the absence of genetic testing. DHT gel treatment significantly improves phallic length, demonstrating its efficacy in managing this condition.

Key Words: 5-alpha reductase deficiency, 46, XY DSD, Testosterone to dihydrotestosterone (DHT) ratio, DHT gel treatment, Micropenis, HCG stimulation test

INTRODUCTION

5-alpha reductase deficiency is one of the etiologiesof46, XY DSD (disorders of sex development). Its prevalence is estimated to be quite low, around 1 in 100,000 to 1 in 1 million live male births.[1] The condition can lead to ambiguous genitalia at birth and can be challenging to diagnose without genetic testing especially in a resource limited setting where cost of genetic testing is a big hurdle.Diagnostic approaches in resource-limited settings may include clinical evaluation, measurement of the testosterone to dihydrotestosterone (DHT) ratio, and imaging studiesto assess internal reproductive organs. The testosterone to DHT ratio is crucial for diagnosis, with a high ratio suggesting the deficiency due to impaired conversion of testosterone to DHT. However Falsely high testosterone to DHT ratios can occur in partial androgen insensitivity syndrome (PAIS) and other conditions affecting androgen metabolism, which can complicate the diagnosis.Here we are describing fourteen patients withpresumptive 5 alpha reductase deficiency cases where treatment with DHT cream lead to significant improvement.

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CLINICAL DESCRIPTION

Total 14 patients were diagnosed with 5 alpha reductase deficiency. Among the 14 patients, the mean age at presentation was 9.70 ± 5.06 years, with a median age of 11 years. Six patients presented during puberty, while eight were prepubertal, including four who were below 5 years of age. Youngest patient was 6 months, while the oldest patient was 20 years old. Clinical phenotype varies among patients from isolated small size phallus (8 patients) being the most common presentation, while other presentations were small size phallus with varying degree of proximal hypospadias and cryptorchidism. Case2, 11 and 14 had penoscrotal hypospadias while case 10 and 13 had perineo-scrotal hypospadias. There was history of small for gestational age at birth in case 2 and 9, while others have appropriate birth weight for gestational age. Anthropometric evaluation revealed obesity in case 1, 2, 4 and 9. (Table 1) None patient had any obvious dysmorphic features.

Table 1: Clinical history and anthropometry details

Case Number	Family history	Consanguinity	Birth H/o	Development H/o	Weight (kg); z score		Length/Height (cm); z score		Body Mass Index (kg/m^2); z score		Any dysmorphic feature/Other associated congenital anomalies
1	Not significant	No	AGA	Normal	48	0.55	141	-1.48	24.14	1.48	obese
2	Not significant	No	SGA	Normal	56	1.97	150	0.91	24.89	1.97	Obesity + Penoscrotal Hypospadias
3	Not significant	No	AGA	Normal	27	-0.87	134	-0.77	15.04	-0.70	None
4	Not significant	No	AGA	Normal	43.9	1.43	138.5	0.01	22.89	1.77	Obese
5	Not significant	No	AGA	Normal	6	-1.13	63	-1.53	12.85	N/A	B/L Undescended Testis
6	Not significant	No	AGA	Normal	68	1.56	170	1.91	23.53	0.71	None
7	Not significant	No	AGA	Normal	48.5	0.87	146.5	-0.32	22.60	1.26	overweight
8	Not significant	No	AGA	Normal	38.69	0.26	148	0.48	17.66	0.08	None
9	Not significant	No	SGA	Normal	80	2.59	165	1.52	29.38	2.36	Obesity
10	Not significant	No	AGA	Normal	15.4	-0.29	100	-0.48	15.40	#N/A	Perineo scrotal Hypospadias with Small Phallus with Chordee
11	Not significant	No	AGA	Normal	58	1.70	162	1.99	22.10	1.16	Penoscrotal Hypospadias operated with Small Phallus
12	Not significant	No	AGA	Normal	48	1.36	148	0.69	21.91	1.35	None
13	Not signific	No	AGA	Normal	19	0.80	119	1.95	13.42	-0.60	Perineo scrotal Hypospadias with

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	ant										Small Phallus with Chordee
14	Not significant	No	AGA	Normal	10	-1.25	82	0.00	14.87	#N/A	Penoscrotal Hypospadias with Small Phallus with Chordee

Stretched penile length (SPL) was measured using the Schoenfeld method [2]. The subjects were positioned in a supine position with the perineum properly exposed. Penile length (PL) was measured to the nearest 0.1 cm using a disposable ruler. SPL was determined by measuring the stretched distance from the pubic symphysis to the tip of the glans penis.Small size phallus was defined as SPL below -2SD for that age as per Indian study [3].All these patients were reared as male at birth. None of families reported history of consanguinity. All these patients belong to northern India. Three patients had history of previous administration of testosterone injection which did not lead to any improvement in phallic length.

Management and outcome: The karyotype analysis for all 14 patients revealed a 46 XY chromosomal pattern. Ultrasound examinations of the abdomen and pelvis showed no presence of Mullerian structures and were consistent with the presence of male internal organs.

Baseline hormone levels (testosterone, androstenedione, and dihydrotestosterone) were measured between 8 AM and 9 AM on the first day. After the baseline sample collection, an HCG stimulation was done using an intramuscular injection of HCG: 500 IU for patients weighing less than 5 kg, 1000 IU for those weighing 5-10 kg, 1500 IU for those weighing 10-15 kg, and 3000 IU for those weighing over 15 kg. Post-stimulation hormone levels were collected 72 hours later [4].

Testosterone was measured using enzyme linked fluorescent assay by biomerieux VIDAS system and Dihydrotestosterone was measured using Chemiluminescence Immunoassay analyser by Maglumi. Values of testosterone was converted into nmol/L by using Conversion factor 3.47 (ng/mL × 3.47 = nmol/L), while Dihydrotestosterone was converted into nmol/L by using conversion factor 0.00344 (pg/ml x 0.00344=nmol/L) to calculate Testosterone: Dihydrotestosterone ratio. A post stimulation Testosterone: Dihydrotestosterone ratio of >27 was considered positive for diagnosis of 5-alpha hydroxylase deficiency [4-6]. Genetic testing could not be performed due to financial constraints.

All patients were started on Dihydrotestosterone gel (Andractim (androstanolone 2.5%))to be applied locally over required area of skin after washing, patients were also advised to left it to dry for 5 minutes before wearing clothes.Patients were followed up every monthly to see clinical response. Patient presented in early childhood (<5 years age) had good clinical response over period of 3-7 months where 75-600% increase in phallic length was seen.older age patients (10-14 years age) follow up data is available from 6 months to 1.5 year where 57-124% increase in phallic length over this period was seen (Table 2). Stage wise surgical intervention was planned in consultation with pediatric surgeon for patients with varying degree of proximal hypospadias.

Table 2: Clinical characteristics and outcome of 5 alpha reductase deficiency patients

Case. No.	Age at Presentation (years)	Tanner Staging at Presentation	Stretched Penile Length (cm (SD as per Indian Study [3])	T/DHT Post Stimulation	Stretched Penile Length (Post Treatment) (cm) (SD as per Indian Study [3])	Clinical Features	Duration of Treatment	Previous administration of injection Testosterone
1	12.8	G1A2P2R2L2	4.2 (<-2SD)	142	8.5 (b/w 0 to +1 SD)	Small Size Phallus	1.5 Year	No
2	11.10	G1A1P1R4L4	2 (<-2SD)	86	3.2 (<-2SD)	Penoscrotal Hypospadias	1.2 Year	No
3	10.4	G1A1P1R3L3	3.2 (<-2SD)	28.8	6.2(b/w 0 to +1 SD)	Small Size Phallus	1 Year	No
4	10.2	G1A1P1R2L2	3 (<-2SD)	35.7	6.5(b/w 0 to +1 SD)	Small Size	1.1 Year	No

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						Phallus		
5	0.5	G1A1P1	0.3 (<-2SD)	33.5	2.5 (b/w -1 to -2 SD)	B/L Undescended Testis	7 Months	No
6	20	G3A3P3 R18L18	5 (<-2SD)	34	10 (b/w to -1 SD)	Small Size Phallus	1.5 Year	No
7	12.1	G1A1P1 R3L3	3.5 (<-2SD)	35	5.9 (-1 SD)	Small Size Phallus	11 Months	No
8	11.3	G1P2A2P 2R4L4	3 (<-2SD)	40	6 (b/w 0 to -1 SD)	Small Size Phallus	1 Year	No
9	14	G3P3A3R 10L10	3.5 (<-2SD)	34.7	5.5 (b/w -1 to -2 SD)	Obesity with Small Size Phallus	3 Months	No
10	4	G1P1A1R 2L2	2 (<-2SD)	34.17	4.0 (b/w -1 to -2 SD)	Proximal Hypospadias with Small Phallus with Chordee	3 Months	Yes (3 doses of 25 mg)
11	12	G3P3A3R 12L12	3.5 (<-2SD)	31.4	5.5 (b/w -1 to -2 SD)	Proximal Hypospadias operated with Small Phallus	1 Year	Yes (3 doses of 50 mg)
12	13	G1A1P1 R4L4	3 (<-2SD)	32.5	5.5 (b/w -1 to -2 SD)	Small Size Phallus	6 Months	No
13	5	G1P1A1R 2L2	2 (<-2SD)	33.3	4 (b/w -1 to -2 SD)	Proximal Hypospadias with Small Phallus with Chordee	3 Months	Yes (3 doses of 25 mg)
14	1.5	G1P1A1R 2L2	2 (<-2SD)	94.66	4 (-1SD)	Proximal Hypospadias with Small Phallus with Chordee	4 Months	NO

Pubertal Staging expressed as G: Genital stage, P: Pubic hair, A: Axillary Hair, R: Right testicular volume, L: Left Testicular volume, T: Testosterone, DHT: Dihydrotestosterone, SD: Standard Deviation

DISCUSSION

In this case series, 14 patients diagnosed with 5-alpha reductase deficiency and noted a bimodal age of presentation during early childhood and early adolescence, which reflects the age at which symptoms become apparent and medical attention is sought. Other studies, such as those conducted in Turkey and the Dominican Republic, have reported similar age distributions where diagnosis often occurs during young age or early adolescence when the differences in poor phallic development become more noticeable [7,8].

In this case series, most common presentation was an isolated small size phallus, followed by associated conditions including proximal hypospadias and cryptorchidism. This spectrum of presentations is

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consistent with global findings [5]. Studies in the Dominican Republic, where 5-alpha reductase deficiency is more prevalent, also report a range of genital ambiguity, with many patients presenting with small phallic size and hypospadias [7]. The study in Turkey noted varied presentations from severe undervirilization to milder forms [8].

In the Indian cohort, all patients were reared as male at birth despite ambiguous genitalia. This practice varies globally based on cultural and medical guidelines, however lack of medical facility and counselling at birth leads to rearing of sex assignment without investigations. Gender assignment should be delayed till adequate testing is done and parents should be counselled. The absence of consanguinity in this case series suggests a sporadic occurrence or possible de novo mutations [9].

The diagnostic approach for disorders of sex development (DSD) typically includes karyotyping and ultrasound (USG) of the abdomen and pelvis. These methods are essential for approach to a case of 46 XY DSD and are standard in evaluating patients with ambiguous genitalia and suspected DSDs. They provide crucial information about internal reproductive anatomy and chromosomal sex. [10,11].

The use of the HCG test is well-documented in diagnosing conditions like 5-alpha reductase deficiency, as it helps differentiate between various forms of intersex conditions by assessing the ability of the testes to produce androgens [12].Testosterone was measured using enzyme-linked fluorescent assay (ELFA) and DHT using chemiluminescence immunoassay (CLIA). These methods are reliable and widely used in clinical laboratories [13]. However newer methods Liquid Chromatography with tandem mass spectrometry (LC-MS/MS) is gold standard method [14], which is not readily available in India. A post-stimulation ratioof >27 while using immunoassay for measurement was considered indicative of 5-alpha reductase deficiency [12].There are several newer studies which describes different testosterone: Dihydrotestosterone cut-offs (≥ 8.5 for minipuberty, ≥ 10 for prepuberty, ≥ 17 for puberty) to be used for diagnosing 5 alpha reductase deficiency (4,5,15), however some of these studies used LC-MS/MS method for hormonal estimation. Few studies recommend to use cutoff >10 to improve sensitivity [16], however it will lead to decrease in specificity.These different cut-offs are probably due to variation of methodology in testosterone and dihydrotestosterone measurement. Few studies have shown that DHT measurement is hindered by testosterone while using RIA or CLIA methods while it doesn't interfere with LC-MS/MS method [14], however LC-MS/MS isnot widely available.

Genetic testing, though definitive, could not be performed due to financial constraints. It's a common challenge in resource-limited settings, where comprehensive genetic analysis may not be feasible. Despite this, biochemical and clinical evaluations remain crucial for diagnosis and management in a resource limited setting [10].There are several studies which have shown high testosterone: Dihydrotestosterone ratio with negative genetic testing [16] suggesting that there might be unknown mutations/mechanisms which were leading to clinic-biochemical picture suggestive of 5 alpha reductase deficiency.

All patients were treated with dihydrotestosterone gel (Andractim) applied locally. The treatment showed significant improvement in phallic length, especially in younger patients. The use of DHT gel is supported by clinical evidence suggesting its efficacy in promoting penile growth in patients with 5-alpha reductase deficiency [17]. Significant Improvement in penile length also strongly corelate with the diagnosis of 5 alpha reductase deficiency.

Management of 5 alpha reductase deficiency required a multidisciplinary approach to ensure comprehensive care, addressing both hormonal and anatomical aspects of the condition. Surgical correction of hypospadias is often necessary to improve urinary and reproductive function and is a standard practice in managing DSDs [11].

CONCLUSION

Diagnosis of 5 alpha reductase deficiency remains a challenge, where clinical, biochemical and genetic evaluation is needed to confirm the diagnosis, however in a resource limited setting, we should focus to a better outcome for our patients while judiciously using our limited resources. HCG stimulated Testosterone: Dihydrotestosterone ration remains a good diagnostic tool in a resource limited setting. Higher cut-offs (>27) could be used to obtain a high specificity for diagnosis in absence of genetic testing. Dihydrotestosterone gel provides significant improvement in phallic length leading to good outcome in 5 alpha reductase deficiency.

LEARNING POINTS

- Identification, counselling and investigations of case of DSD at birth is must before moving forward with gender assignment.
- In absence of genetic testing, clinical and biochemical criteria become important to diagnose 5 alpha reductase deficiency.
- Biochemical testing involving HCG stimulated testosterone: Dihydrotestosterone ratio should be interpreted according to method used for hormonal estimation.
- Patient with diagnosis and treatment at younger age have better clinical outcome.

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